DO ENVIRONMENTAL FACTORS PLAY A SIGNIFICANT ROLE IN THE AETIOLOGY OF PRIMARY SYSTEMIC VASCULITIS ?

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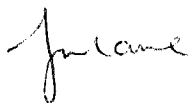
DECLARATION

The work described in this thesis was carried out unaided except where stated. The work of collaborators is acknowledged in the text and summarised in the acknowledgement section. Informed consent was obtained from patients involved in the case-control study.



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SYNOPSIS

The primary systemic vasculitides are rare disorders characterised by inflammation and necrosis of small and medium blood vessels. Their aetiology is unknown. The aim of this thesis was to examine the hypothesis: 'Environmental factors play a significant role in the aetiology of primary systemic vasculitis (PSV)'.

The definition of systemic vasculitis is not straight-forward. The literature review describes historical aspects and the evolution of accepted classification criteria. The clinical features, relationship to antineutrophil cytoplasmic antibodies (ANCA), treatment and outcome of the three clinico-pathological syndromes studied in this thesis (Wegener's Granulomatosis-WG, microscopic polyangiitis-mPA and Churg Strauss syndrome-CSS) are reviewed. Environmental and genetic factors which may be important in the pathogenesis of PSV are discussed.

Norfolk is favourable for epidemiological study because of its geographical location. The clinical features of the cohort of PSV patients studied, classified according to accepted criteria, were similar to published series. A new classification system proposed by Sorensen et al was also evaluated. Mortality has improved considerably with the use of immunosuppressive treatment, especially cyclophosphamide. In keeping with published reports, the standardised mortality rate for PSV was 4.78 in Norfolk compared to the denominator population and is similar for each age group. mPA was associated with poorer prognosis but there were no other significant differences in terms of organ involvement, sex or ANCA type. Cyclophosphamide (CYC) therapy is associated with significant side-effects including infection and malignancy. The use of intravenous pulses of CYC appears to be associated with less toxicity than oral CYC regimens. This might be explained by the higher cumulative doses of CYC received in the latter regimens.

The introduction of accepted classification systems has allowed evaluation of the incidence of PSV and comparison between centres. The mean annual incidence of PSV in Norfolk over 11 years was 20.7/million and 18.0/million for primary renal vasculitis over 5 years, which are higher than most previous European reports. WG was the most common diagnosis (12.1 /million/year) and the annual incidence for mPA and CSS was 8.8/million and 3.3/million respectively. As previously reported, PSV was more common in men than

women but the peak incidence of disease occurred in an older age group (65-74 year-olds) compared to earlier studies from tertiary referral centres. There was a non-significant trend towards increasing incidence of PSV in Norfolk with time but no significant fluctuation in annual and seasonal variation. The incidence of PSV was similar when comparing population-based cohorts in Spain and Norway but there appears to be a trend towards increasing incidence of WG with latitude and an excess of CSS in Norfolk. A non-significant trend towards a higher incidence of WG and CSS in rural residents compared to urban dwellers is noted in Norfolk. These results suggest that PSV affects an older age group than traditionally perceived, the incidence of PSV may be increasing with time and may vary between geographical locations. This might reflect the influence of environmental factors although genetic factors may also be important.

A case-control study comparing 75 PSV patients with 220 age-sex matched non-vasculitis controls found significantly raised ORs for a number of environmental factors. For the first time an association was found between exposure to farming and PSV, in particular WG and mPA. Livestock appeared to be of particular importance which may reflect an infectious aetiology. Associations were also found between high occupational silica exposure and PSV, WG, CSS, mPA and pANCA, whilst jobs with high solvent exposures were associated with PSV, WG and cANCA. In keeping with the literature there was no trend towards increasing risk with increasing exposure duration in either case. Drug allergies, especially antibiotics (predominantly penicillin) gave significantly raised ORs for PSV, WG and cANCA. Comparison of PSV with systemic rheumatoid vasculitis and CSS with asthma yielded no significant results important to the hypothesis.

In summary the clinical characteristics and epidemiology of a well-defined population-based cohort of PSV patients has been described. Geographical variation in the incidence of PSV supports the hypothesis that environmental factors might be important. A case-control study has found a significant association between PSV and farming for the first time and supports previous reports of a link between PSV and drug allergies, silica and solvents. Environmental factors therefore do seem to play a significant role in the aetiology of Primary Systemic Vasculitis but further study is required to establish the exact nature of the association.

DO ENVIRONMENTAL FACTORS PLAY A SIGNIFICANT ROLE IN THE AETIOLOGY OF PRIMARY SYSTEMIC VASCULITIS?

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CHAPTER 1

Literature Review

I. INTRODUCTION TO PRIMARY SYSTEMIC VASCULITIS

The systemic vasculitides (SV) are a heterogeneous group of multi-system disorders characterised by inflammation and necrosis of the blood vessels. They can occur as primary disorders, arising de novo, where the aetiology is unknown or secondary to other diseases e.g. infection, malignancy and autoimmune conditions including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The range of manifestations of SV is extensive and clinical features reflect the size, site and extent of blood vessel involvement. The differential diagnosis of SV is problematic because individual types are often indistinguishable at presentation although their disease course, treatment and prognosis vary considerably. Vasculitis is also a great mimic and the clinical picture may resemble numerous other disorders, resulting in mistaken or delayed diagnosis. The classification of disease remains controversial and is complicated by the fact that pathogenetic mechanisms and disease precipitants have not been clearly defined. However some distinct clinico-pathological syndromes have been recognised and classification criteria have been developed for use in research and allow valid comparisons between centres. The subjects of this thesis are the primary systemic vasculitides (PSV) affecting small and medium blood vessels: Wegener's Granulomatosis (WG), microscopic polyangiitis (mPA) and Churg-Strauss syndrome (CSS). At present the aetiology of these disorders is largely unknown.

Historical Perspective

The first description of a primary systemic vasculitis (PSV) may have been as early as 1755 (Michaelis and Matani) but the first published report is attributed to Kussmaul and Maier.[1, 2] Many reports have followed but few as florid as this classical description of the disease they christened 'periarteritis nodosa'. A twenty-seven year old man presented with an acute onset of severe malaise, fever and diarrhoea. Subsequently he developed

abdominal pain, myalgia, muscular weakness and sensory disturbance. On admission he had renal disease and a persistent tachycardia then developed a hoarse voice and palpable subcutaneous nodules. Death occurred within six weeks of symptom onset and post mortem revealed 'peculiar mostly nodular thickening of countless arteries of and below the calibre of the liver artery'. The selective involvement of organs (kidney, intestine, heart, spleen, stomach, voluntary muscles and to a lesser extent the liver, subcutaneous tissues, bronchial and phrenic arteries) and the predilection of the disease for certain sized arteries but not veins was noted. The reason for these characteristics remains to be elucidated. [3]

Hypotheses as to the cause of disease were formed from an early stage. In 1887 Eppinger postulated that a congenital cause was the predominant factor whilst by 1892 Fletcher suggested that infection was responsible, supported by Kahlden in 1894. He also reviewed the literature, including a case report by Gee at St Bartholomew's, probably the first in the English Literature, and others predating 1866. Ferrari introduced the term polyarteritis nodosa in 1903, which became the generic name used for a wide variety of vasculitides.[4] In 1921 Wohlwill recognised a periarteritis only visible on microscopy in a 53-year-old woman with myalgia, transient eosinophilia, fever, proteinuria and haematuria. Disease remitted spontaneously but one year later she developed rapidly progressive haemorrhagic nephritis. At post mortem vessels were macroscopically normal but widespread arteritis was seen on microscopy.[5,6] By 1950 Wainwright and Davson introduced the term microscopic polyarteritis to describe patients with polyarteritis dominated by segmental necrotizing glomerulonephritis and a propensity to rapidly progressive renal failure.[7,8] These represent early reports of microscopic polyangiitis.

Wegener, Churg and Strauss described their eponymous syndromes as distinct entities in 1936 and 1951.[9,10] The former reported on 'a remarkable rhinogenic granulomatosis with particular involvement of the arterial system and the kidneys' following the death of a 38-year-old truck driver with maxillary pain, arthralgia, pulmonary infiltrates and

glomerulonephritis characterised by fibrinoid necrosis, crescents and periglomerular granuloma. He recognised WG to be a distinct clinical syndrome characterized by both systemic polyarteritis and granulomatosis and recommended that it be distinguished from other SV. [11]

Churg and Strauss reviewed the growing evidence for a relationship between allergy, asthma and vasculitis which had been noted by a number of investigators including Cohen, Kline and Young (1936) who had suggested a causal relationship and Wilson and Alexander (1945) who found an association between periarteritis and allergy in 18% of cases reviewed. A number of reports had already described an extravascular lesion comprising of a necrotizing eosinophilic inflammatory exudate with a granulomatous reaction that accompanied vascular lesions in these cases. They reviewed 14 patients who had presented with severe asthma, fever, hypereosinophilia, cardiac failure, renal damage and peripheral neuropathy (a clinical syndrome previously reported by Rackmann and Greene - 1939). 13 demonstrated a characteristic lesion with eosinophilic, necrotizing, granulomatous (epitheliod and giant cell) infiltration and fibrous scarring whilst the remaining case revealed fibrosed scars. No such lesions were found in 15 cases of periarteritis without asthma. They concluded that there was indeed a distinct clinical syndrome consisting of severe asthma, fever and hypereosinophilia with angiitis, which was set apart from classical polyarteritis nodosa by extravascular granulomata and granulomatous vascular lesions. [10]

Although the distinctions between mPA, WG and CSS remain valid today, similarities and the overlapping nature of disease suggest that they may belong to a spectrum of disease. Therefore although it is appropriate to investigate them as independent entities it is also important to consider them as a group.

II. DIAGNOSIS OF PRIMARY SYSTEMIC VASCULITIS

There is no pathognomonic test for any of the vasculitides and diagnosis is based upon a combination of clinical, radiological, histological and laboratory findings. In general men are more commonly affected than women and patients reported in the literature are predominantly Caucasian.

Clinical Features

Wegener's Granulomatosis

WG is characterized by necrotizing granulomatous vasculitis and occurs as both a systemic and limited disease. The former affects the respiratory tract and kidneys predominantly and follows a progressive, destructive course, which is fatal without treatment.[12] Limited WG is more indolent, involving only the upper airways[13] although some may progress to systemic disease.[14] Wegener first described the syndrome in 1936 [9] but Klinger (1931) had already reported a case illustrating most characteristic features.[15] He described a 70-year-old physician with fever, nasal discharge and deformity, arthritis, sinusitis, pulmonary vasculitis, otitis, proptosis, laryngeal ulceration, nephritis and terminal broncho-pneumonia. Necrotizing granulomatous vasculitis of the upper and lower airways and crescentic glomerulonephritis were found at post mortem. WG has mostly been described in Caucasians (96.5-100% of study cases) although it can occur in other ethnic groups.[16,17,18] Tables 1.1 and 1.2 illustrate the spectrum of symptoms and signs at presentation and throughout the course of disease. Table 1.3 describes patients included in these studies.

ENT Disease

The most common presentation of WG is with features of ENT involvement, which occurs in 78-100% of cases during the course of their disease. Sinusitis, rhinitis and nasal obstruction may at first be attributed to allergy causing a delay in diagnosis until epistaxis,

nasal crusting, deformity or even septal perforation occurs. Otitis media and hearing loss are relatively frequent whilst subglottic stenosis is reported in <20% of patients. Although 76% of patients reviewed by Luqmani et al presented with ENT disease the proportion was significantly less for those with renal disease compared to those without (p=0.004).[13] Rasmussen suggested that variation in ENT assessment might explain the lower percentages described in some studies, implying that ENT disease is usual at presentation but may be unrecognised.[19] Other reasons for variation include the criteria used to select patients, referral bias and environmental differences which may influence the expression of disease. The relatively low percentages reported by Carruthers and Salvadori[16,20] but not Hoffman and Romas,[18,21] may be explained by the high proportion of patients with renal disease. Referral bias may account for the difference between the Norwich report[16], which included population-based cases, and the other university or tertiary referral centres.

Lower Respiratory Tract Disease

Lower respiratory tract disease is also frequent at presentation. Symptoms include shortness of breath, dyspnoea, cough and haemoptysis. Fixed pulmonary infiltrates or classical cavitating nodules may be seen on X-ray (Figure 1.9). Even asymptomatic patients may have significant lung involvement demonstrated by neutrophilic alveolitis and pulmonary production of ANCA on bronchoalveolar lavage.[22] In one study less than half of patients with pulmonary infiltrates had significant symptoms[17] and 34% of radiographic, biopsy proven pulmonary abnormalities were asymptomatic in another.[23] Most series describe between 55-80% lung involvement at presentation with relatively high percentages of radiographic infiltrates but <20% clinical haemoptysis. Luqmani et al found that only 36.4% of patients without renal disease had respiratory manifestations, perhaps reflecting a limited form of vasculitis, whilst Salvadori report 100% involvement, probably due to the small number of cases (5).[13,20]

Kidney Disease

In most reports kidney disease occurs in the majority of cases. Hoffman et al reported that kidney involvement was relatively rare at presentation (11%) but increased to 77% of cases over 2 years.[17,18] Therefore monitoring of urinalysis is essential in all patients. The higher percentages of renal disease reported in other studies at presentation could reflect a longer prediagnostic phase or differences in classification.

Other Organ Manifestations

Musculoskeletal (arthralgia and myalgia) and constitutional symptoms (malaise, fever, weight loss) are common and may cause early confusion with rheumatoid or other inflammatory arthritis although erosive disease is rare.[24] Ocular manifestations occur in 40-60% but are mainly non-specific. Proptosis caused by inflammatory, fibrotic and necrotic tissue in the retroorbital space, is suggestive of WG but occurs rarely. It can be complicated by visual loss[25], diplopia and gaze abnormalities due to optic nerve or muscle entrapment respectively and may prove resistant to treatment.[17] Cutaneous disease including palpable purpura, ulcers and nodules occur in 40-50% of cases. Nervous system involvement although less frequent is wide-ranging from mononeuritis multiplex to cerebral mass lesions, meningitis, infarction or bleeds and other manifestations including headache, confusion, dementia, seizures, temporal pain, stroke, diabetes insipidus and pan-hypopituitarism.[26] Cardiac involvement although reported infrequently can be serious e.g. pericarditis, myocarditis or cardiomyopathy.[17]

Therefore although WG is often regarded as a classical triad of ENT, respiratory and kidney disease the diagnosis is not straight-forwards. Any organ system may be involved in combination or isolation and there are many reports of unusual presentations in the literature.[27,28,29,30,31,32]

Table 1.1
Clinical features at presentation in Wegener's Granulomatosis (%)

	Salvadori [20]	Hoffman [18]	Anderson [33]	Carruthers [16]	Luqmani [13]		Reinhold Keller [34]
No. Patients	5	158	265	21	Renal (28)	Non-renal (22)	155
ENT	80	73		71	60.7	95.5	93
• Saddle nose	-	-		-	-	-	12
• Sinusitis	-	50	75	-	-	-	-
• Epistaxis	-			-	-	-	-
• Nasal disease	-	35-40		-	-	-	-
• Otitis media	-	20-25		-	-	-	-
• Hearing loss	60	10-15	7	-	-	-	-
• Ear pain	-	10		-	-	-	-
• Subglottic stenosis	-	<5	-	-	-	-	-
• Oral lesions	-	<5	-	-	-	-	-
Lung	100	-	63	67	60.7	36.4	55
• Infiltrates	-	45	-	-	-	-	37
• Nodules	-	-	-	-	-	-	17
• Haemoptysis	-	12	-	-	-	-	7.7
• Pleuritis	-	10	-	-	-	-	-
• Dyspnoea	-	-	-	-	-	-	-
Kidney	80	18	60	86	100	0	54
Eye Disease	60	15	14	33	32.1	40.9	40
• Proptosis	-	2	-	-	-	-	-
• Conjunctivitis	-	<5	-	-	-	-	-
• Scleritis	-	5	-	-	-	-	-
• Eye pain	-	<5	-	-	-	-	-
• Visual loss	-	0	-	-	-	-	-
• Retinal	-	0	-	-	-	-	-
• Cornea	-	0	-	-	-	-	-
Others							
• Joints/myalgia	-	40-45	20	57	64.3	59.1	25(61)
• Fever	-	23	-	-	-	-	-
• Cough	-	20	-	-	-	-	-
• Skin	-	13	-	43	42.9	18.2	23.2
• Weight loss	-	15	-	-	-	-	-
• PNS	60	<5	-	5	10.7	4.5	20.6
• CNS	-	<5	-				-
• CVS	-	<5	-	-	10.7	0	12.9

PNS = Peripheral Nervous System; CNS = Central Nervous System; CVS = Cardiovascular system

Table 1.1(cont.) Clinical features at presentation in WG (%)

	Vassallo [35]		Westman [36]
No patients	29 (<60yrs)	22 (> 60yrs)	56
ENT	100	68.1	55
• Saddle nose	-	-	-
• Sinusitis	-	-	-
• Epistaxis	-	-	-
• Nasal disease	-	-	-
• Subglottic stenosis	-	-	-
• Otitis media	-	-	-
• Hearing loss	-	-	-
• Ear pain	-	-	-
• Oral lesions	-	-	-
Lung	79.3	77.2	70
• Infiltrates	-	-	-
• Nodules	-	-	-
• Haemoptysis	-	-	-
• Pleuritis	-	-	-
• Dyspnoea	-	-	-
Kidney	89.6	86.3	100
Eye Disease	48.2	18.2	20
•	-	-	-
• Conjunctivitis	-	-	-
• Scleritis	-	-	-
• Eye pain	-	-	-
• Visual loss	-	-	-
• Retinal	-	-	-
• Cornea	-	-	-
Other manifestations			
• Joints/myalgia	58.6	31.8	48
• Fever	-	-	-
• Cough	-	-	-
• Skin	51.7	18.2	5
• Weight loss	-	-	-
• PNS • CNS	10.3	21.7	12
• Pericarditis/CVS	-	-	-

PNS = Peripheral Nervous System; CNS = Central Nervous System; CVS = Cardiovascular System

Table 1.2.
Clinical Features of Wegener's Granulomatosis throughout disease course (%)

	Cohen Tervaert [37]	Hoffman [18]	Romas [21]	Koldingsnes [38]
No. Patients	58	158	37	11
ENT	90	92	78	100
• Saddle nose	-	-	-	100
• Sinusitis	-	85	41	-
• Epistaxis	-	-	-	100
• Nasal disease	-	65-70	54	63.6
• Subglottic stenosis	-	15-20	19	-
• Otitis media	-	40-45	-	-
• Hearing loss	-	40-45	-	-
• Ear pain	-	10-15	-	9.1
• Oral lesions	-	10	-	36.4
Lung	66	85	70	90.9
• Infiltrates	-	65-70	-	-
• Nodules	-	55-60	-	-
• Haemoptysis	-	30	-	-
• Pleuritis	-	28	-	-
• Dyspnoea	-	-	-	90.9
Kidney	81	77	51	45.5
Eye Disease	60	52	43	-
• Proptosis	-	15	22	-
• Conjunctivitis	-	15-20	-	-
• Scleritis	-	15-20	-	-
• Eye pain	-	10	-	-
• Visual loss	-	5-10	-	-
• Retinal	-	<5	-	-
• Cornea	-	<5	-	-
Other manifestations		-	-	100
• Joints/myalgia	78	67	35	-
• Fever	-	50	-	-
• Cough	-	45-50	-	63.6
• Skin	50	46	19	-
• Weight loss	-	35		27.3
• PNS	48	15	8	0
• CNS		8	-	18.2
• CVS	-	6	-	-

PNS = Peripheral Nervous System; CNS = Central Nervous System; CVS = Cardiovascular System

Table 1.3. Comparison of WG patients between studies

	Year	Author	No. patients	Follow-up (years) mean(range)	M:F	Classification	Age at diagnosis (Years) Mean (range)	Time to diagnosis (months) Mean (range)
T	1983	Fauci[17]#	85	4.2 (<1-13.2)	1.6:1	-	40.6 (14-75)	8.3 (0.5-120)
T	1990	Cohen Tervaert[37]	58	-	1.2:1	Fauci[17]	56.3 (22-77)	N/A
-	1991	Salvadori[20]	5	(1-8)	4:1	-	-	-
M	1992	Anderson[33]	265	-	1.2:1	Clinical diagnosis	50.0(10-83)	7.0(<1-132)
T	1992	Hoffman[18]#	158	6 (<1-24)	1:1	-	41(9-78)	4.7 (<1-192) median = 15m
-	1993	Romas[21]	37	6 (N/G to >7)	1.3:1	De Remee[39]	48 (21-82)	12 (1-48)
T	1994	Luqmani[13]	Renal (28)	1.8*	2.1:1	ACR	59* (18-84)	4.5* (1-99)
			Non-Renal (22)	2.8*			43.5* (20-65)	8* (1-366)
D	1994	Carruthers[16]	21	-	1.6:1	ACR	61(33-87)	3.5(0.5-40)

* Median # These series include the same patient cohort

Table 1.3. cont. Comparison of WG patients between studies

	Year	Author	Number	Follow-up (years) mean(range)	M:F	Classification	Age at diagnosis (Years) Mean (range)	Time to diagnosis (months) Mean (range)
T	1997	Westman[36]	56	5.6 (<1-14)	2.7:1	ACR	58 (30-77)	
-	1997	Vassallo[35]	51	3.6 (<1-15.6)	1.2:1 1.4:1	ACR	42.2(19-59) 68.0(60-83)	-
T	1998	Schleiffler[40]	15	2.3 (<1-5)	3.7:1	ACR	51(23-77)	53(1-240)
T	1998	Koldingsnes[38]	11	4.3 (1-8.2)	1.7:1	ACR	47(21-63)	5(1-15)
T	2000	Reinhold-Keller[34]	155	7 (0.3-27.3)	1:1	ACR/CHCC	48(13-74)	-

T=Tertiary or University hospital, D= District General Hospital, M=multi -centred
ACR = American College of Rheumatol ogy Classification [41]
CHCC= Chapel Hill Consensus Conference Definitions [42]

Churg-Strauss Syndrome

Rackemann and Greene first described a form of polyarteritis nodosa characterised by allergic disease in 1939. Subsequently Harkavy recognised an association with asthma, eosinophilia, pulmonary infiltrates and reported a single granuloma (1941).[43] However in 1951 Churg and Strauss established the syndrome as a distinct entity characterized by asthma, hypereosinophilia, fever and systemic vasculitis. They described the main histological finding in the autopsies of 13 cases to be a granulomatous, necrotizing vasculitis with extravascular eosinophils.[10] Case reports and a series of 30 patients revealed a disease pattern.[43,44] Churg-Strauss Syndrome (CSS) can be thought of as three phases: an initial phase of atopic symptoms including allergic rhinitis, nasal polyposis and the onset of asthma; a stage of recurring peripheral and infiltrating tissue eosinophilia which can resemble Loffler's syndrome, eosinophilic pneumonia or gastroenteritis or hypereosinophilic syndrome; and finally systemic vasculitis (SV).[43] Table 1.4. gives clinical features detailed in CSS series and Table 1.5. gives patient characteristics.

Prodromal Atopic Phase and Asthma

The duration of the atopic prodrome is variable and may last for many years or occur simultaneously with vasculitis. Asthma is the most common manifestation of CSS (96-100% in most series). It is almost always present at the onset of SV but can develop afterwards.[45] Rhinitis is also common (52-75 % cases) and although usually present prior to SV may occur at any stage of disease. The atopic phase in CSS is unusual in that it develops in an older age group than is usual for atopy in general (e.g. adult-onset asthma) and can be resistant to treatment, e.g. CSS patients have more polypectomies than 'simple' asthma patients and asthma may be difficult to control and steroid dependent.[45]

Neurological involvement

In contrast to WG, neurological involvement is a prominent feature and mononeuritis multiplex is the second most common manifestation (70 – 92% cases). It can develop acutely with sudden onset of symptoms or have a gradual subacute course. Many nerves may be affected with the peroneal, ulnar, internal popliteal and radial nerve commonly involved and occasionally the cranial nerves. Polyneuropathy may also occur. Nerve damage can cause considerable disability and recovery is often slow and incomplete.[46]

Other Manifestations

Arthralgia and myalgia are relatively common manifestations of disease (40-70% cases in most studies) although fewer cases were noted in the early reports (Churg, Strauss and Chumbley - 31% and 20% respectively). Cardiac involvement is an especially important manifestation of disease and has been reported to cause approximately half of all deaths from CSS. Cardiac failure is usually caused by eosinophilic granulomatous myocarditis.[8]

All series report asthma in 100% of cases during the course of illness except for an earlier study from Norfolk by Reid et al who recorded one patient with eosinophilic granulomatous vasculitis but no history of asthma.[47] Guillevin also noted a single patient who did not have asthma at presentation although it developed later.[45] Apart from asthma, pulmonary infiltrates are the most common respiratory manifestation although pleural effusions and haemorrhage also occur. Renal disease is relatively infrequent (8-26%) and usually mild. Renal failure was reported in a single patient each in Lanham and Chumbley's reviews (6% and 3% respectively).[43,44] The majority of patients describe constitutional symptoms, up to 70 % have cutaneous features and abdominal involvement is also reported relatively frequently.

Table 1.4. Clinical features associated with CSS (%)

		Guillevin [45]		Abu-Shakra [48]	Reid [47]	Lanham [43]	Chumbley [44]	Churg-Strauss [10]	Literature [43]
		Presentation	Over Disease Course						
No. Patients		96	96	12	23	16	30	13	
Asthma		97.9	100	100	96	100	100	100	100
Mononeuritis multiplex /PNS		77.1	78.1	92	70	75	-	-	65
Central nervous system		8.3	8.3	13.5	39	25	-	-	27
Rhinitis		61.1*	61.1*	83 (URTI)	52	75	70	77	69
Constitutional	Weight loss	70.8	70.8	100	-	-	-	-	-
	Fever	57.3	57.3		-	-	-	-	-
Cutaneous	Nodules	49.0	51	67	9	13	27	54	33
	Purpura				26	56	-	62	46
Myalgia		54.2	54.2	33 (myositis)	57	69	-	-	33
Arthralgia		40.6	41.7	42	57	69	20	31	46
Lung	Infiltrates	37.5	37.5	58	48	63	27	39	74
	Effusion	-	-	-	17	25	-	-	30
	Haemorrhage	3.1	4.2	-	-	-	-	-	-
G.I.T.	Abdo. pain	31.2	33.3	8	17	44	17	-	62
	Diarrhoea				17	31	-	-	33
	Bleeding				9	25	-	-	16
Kidney		26	26	8	48	88-93	-	31	46
Hypertension		-	-	0	26	75	-	54	39
C.V.S	Cardiac Failure	-	-	-	17	25	-	39	52
	Pericarditis	21.9	22.9		26	13	-	-	37
	Myocarditis	12.5	13.5	42	-	-	-	-	-
Ophthalmic		3.1	-	3.1	-	-	-	-	-
History of allergy		-	100	63.8	-	-	-	-	-

* 'paranasal sinusitis'; URTI = Upper respiratory tract involvement; PNS = Peripheral Nervous System; GIT= Gastrointestinal Tract; CVS = Cardiovascular system

Table. 1.5 Churg Strauss Studies – patient details

	Year	Author	No. patients	F/U (yrs) Mean(range)	M:F	Classification	Age (Yrs)at onset Mean (range)	Yrs asthma to SV Mean (range)
T	**1951**	**Churg-Strauss** [10]	13	-	1:2.3	Own	Asthma - 30	-
T	**1977**	**Chumbley** [44]	30	-	2.3:1	-	Asthma – 39 SV – 47	-
T	**1984**	**Lanham** [43]	16	3.4(0.5-11.7)	3:1	Own	Rhinitis – 25 Asthma – 33 SV - 38	-
T	**1994**	**Abu-Shakra** [48]	12	5.5(0.25-15)	1:1	ACR	SV – 48 (28-70)	-
D	**1998**	**Reid**[47]	23	Up to 14 yrs	1.9:1	19/23 - Lanham 14/23 - ACR 4/23 - CS 2/23 - CHCC	Rhinitis – 29 Asthma – 50 SV –57(19-85)	-
T	**1999**	**Guillevin**[45]	96	2.7	1.2:1	Own (79.2%ACR)	48.21 (14-74)	8.8 (0-61)

F/U= Follow-up; T= Tertiary or University hospital, D= District hospital M= Male, F= Female; Yr= Year
SV = systemic vasculitis, ACR = American College of Rheumatology Criteria [49] CHCC= Chapel Hill Definition [42]
Lanham = Lanham criteria[43]; CS = Original criteria[10]

Microscopic Polyangiitis

Microscopic polyangiitis (mPA) was defined by a consensus conference (CH CC) in 1994 as 'necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e. capillaries, venules and arterioles) although small and medium sized arteries may also be affected.' Necrotizing glomerulonephritis and pulmonary capillaritis were recognised to occur often. mPA was differentiated from 'classical' PAN by the presence of small vessel involvement, which by the CHCC definition excluded a diagnosis of PAN. [42] Previously this type of vasculitis had been termed microscopic polyarteritis although it had not been included independently in classification schemes. The CHCC consensus group replaced the term polyarteritis with polyangiitis to reflect the fact that arteries are not necessarily involved. Because this definition is recent there have been relatively few reviews of mPA patient series. Cases of microscopic polyarteritis described by Savage et al would probably now be termed mPA[50] but earlier series are harder to compare.Guillevin et al reviewed 85 patients who they felt fulfilled the CHCC definition for mPA but excluded other cases with granulomatosis, ENT or nodular lung disease, i.e. they excluded patients who fulfilled criteria for both WG and mPA, limiting the spectrum of clinical findings. 80% of patients had renal disease, 25.4% of whom required dialysis and 70.1% had raised serum creatinine greater than 1.36mg/dl. Lung involvement, particularly haemorrhage was relatively infrequent (11.8%) but neurological features, especially mononeuritis multiplex and cutaneous disease occurred in more than half of the cohort and the majority of patients suffered with constitutional symptoms.[51] Savage et al found similar constitutional, cutaneous and musculoskeletal findings but markedly less cardiac and neurological disease and more haemorrhage and eye involvement than Guillevin et al. This cohort may be biased as all patients had renal disease when referred to the centre although a similar percentage (23.5%) required haemodialysis. [50] Similarly all the patients studied by Westman et al had renal involvement and approximately

one third had lung involvement. The relatively high numbers with ENT disease probably reflects differences in patient selection.[36] An unusually high percentage of the ten patients described by Li et al had lung haemorrhage (70%), which may be explained by selection bias because this group had a particularly high mortality.[52] Musculoskeletal disease occurred in between 30 and 65% of cases, similar to WG.

Table 1.6. Clinical features of Microscopic Polyangiitis

	Guillevin [51]	Westman [36]	Li [52]	Fuiano [53]	Savage [50]
	Overall	Referral	Overall	Presentation	Presentation
No. Patients	85	67	10	26*	34
Renal	78.8%	100	90	-	100%
- Hypertension	34.1	-	80	-	29
Constitutional	-	-	-	77	76
- Weight loss	72.9	-	-	-	-
- Fever	55.3	-	40	20	41
Cutaneous	62.4	3	30	29	-
- Purpura	41	-	-	-	44
Neurological		16	-	7	
- PNS	57.6	-	-	-	27
- CNS	11.8	-	-	-	18
Musculoskeletal		33	-	59	
- Arthralgias	50.6	-	30	-	65
- Myalgias	48.2	-	-	-	50
CVS		9	-	-	
- Cardiac failure	17.6	-	-	-	3
- Pericarditis	10.6	-	-	-	3
- Myocardial infarction	2.4	-	-	-	0
Lung	24.7	33	-	37	-
- Haemorrhage	11.8	-	70	-	29
- Pneumonitis	10.6	-	-	-	-
- Pleuritis / pleural effusion	5.9	-	-	-	15
- Haemoptysis	-	-	-	13	32
GIT	30.6	16	30	26	-
Others		-	-		
- Eye involvement	1.2	12	-	11	24 (episcleritis)
- Orchitis	2.1	-	-	-	-
ENT	-	28	-	41	-
- Sinusitis	1.2	-	-	-	9
- Epistaxis	0	-	10	-	0

* may include some WG patients

CVS= Cardiovascular System, GIT = Gastrointestinal tract, ENT = Ear, nose and throat; MI = Myocardial infarction

Table. 1.7 Microscopic polyangiitis studies – patient details

	Year	Author	No. Cases	F/U (months) mean(range)	M:F	Classification	Race	Age at diagnosis (Years)	Symptom onset to Diagnosis (months)
								Mean (range)	Mean (range)
T	**1985**	Savage[50]	34	47(3-120)	1.8-1	Own *	94.1C 5.9 O	50 (14-73)	3.7 (<1-120)
T	**1988**	Fuiano[53]	26	20.6(3-60)	1.1:1	Own**	-	53.4(19-76)	5.1 (0.5-48)
T	**1995**	Li[52]	10	-	1:1	Own#	100% Chinese	61 (40-86)	2(<1-20)
T	**1997**	Westman[36]	67	47.3(<1-273)	1.3:1	CHCC	-	65 (11-85)	-
-	**1998**	Schleiffer[40]	8	61.2	1.7:1	CHCC	-	56 (46-71)	9 (1-40)
T	**1999**	Guillevin[51]	85	69.9	1.2:1	CHCC	96.5% C 3.5% O	56.8 (16-86)	-

* micropolyarteritis – clinical or histological evidence of a small vessel systemic vasculitis associated with focal segmental necrotizing glomerulonephritis who do not have clinical or pathological evidence of WG, neoplasia or other disease associated with small vessel vasculitis and necrotizing GN

** microscopic polyarteritis – Cellular infiltration within and around the vessel walls with fibrinoid necrosis, in glomerular capillaries (necrotizing glomerulitis) and/or arterioles. This study probably includes some patients classifiable as WG.

Multisystem vasculitis involving small vessels, with prominent involvement of the kidney, but without granulomata.

C = Caucasian, O=Other

Histological Features

The histological findings associated with vasculitis are no less diverse than the clinical features. Histology is not pathognomonic and similar appearances can be found in other diseases. Findings may also vary between sites in an individual. Biopsy results depend upon timing (earlier, acute lesions generally have more specific appearances than late biopsies), location (a particular organ may be unaffected), sample size (the biopsy may not be representative), treatment prior to biopsy and interpretation of histological appearances.

In WG the upper and lower respiratory tracts are classically associated with necrotizing granuloma. In the lung, nodules containing granulomata of histiocytes, epitheloid and giant cells may undergo necrosis and cavitation. Necrotizing granulomatous vasculitis affects small arteries and veins and ENT biopsies may show focal necrosis (microabcesses). (Figure 1.1-1.4) Renal findings are usually of a focal, segmental, necrotizing glomerulonephritis (GN) - Figure 1.5. Extracapillary proliferation and crescent formation are seen and are associated with rapidly progressive glomerulonephritis (RPGN). Interstitial infiltration is common and its importance may be underrecognized. Immunofluorescence usually shows little evidence of immune complex and complement deposition and many authors favour the term 'pauciimmune' to describe this appearance. However some immune complex deposition may be present, especially in early lesions. Renal appearances may be identical to mPA. Eosinophils can be found in the inflammatory infiltrate of both WG and mPA but are rarely as prominent as CSS (Figure 1.6).[54,55,56]

CSS is characterised by the presence of extravascular granulomata and pulmonary /systemic granulomatous or eosinophilic necrotizing vasculitis. Acute lesions show a predominantly eosinophilic infiltrate but chronic lesions demonstrate granulomata although these are present on less than 50% of biopsies (Figure 1.7-1.8). The gastrointestinal tract, spleen and heart are the predominant extra-pulmonary organs affected.

mPA is characterized by necrotizing vasculitis affecting arterioles, capillaries, venules and occasionally small arteries and is usually associated with pauciimmune focal segmental necrotizing and crescentic GN (see above).

Some investigators consider idiopathic focal necrotizing and crescentic GN to be a renal limited form of vasculitis.[11] Andrassy et al investigated the prevalence and clinical course of rapidly progressive GN (RPGN) and noted difficulty in the clinical distinction between WG, mPA and 'idiopathic' RPGN. They failed to observe a single case of idiopathic RPGN following the routine use of anti-neutrophil cytoplasmic antibody testing (see later) which they regarded as an indicator of vasculitis and postulated that all such cases were in reality mPA.[57] This hypothesis is also supported by the results of a study of the clinical features of 40 patients with pauciimmune necrotizing crescentic GN selected upon histological appearances alone. Either SV or histologically proven renal angiitis was determined in all but 6 cases (5 of whom had extrarenal symptoms not confirmed to be caused by vasculitis). 3 of the 6 were MPO positive.[58]

Classical PAN (cPAN) is characterized by a systemic necrotizing vasculitis affecting small and medium muscular arteries. Controversially the CHCC definition excludes the involvement of arterioles and glomeruli although glomerular involvement was evident in Kussmaul and Maier's classic report.[1] Larger vessels, e.g. the aorta, are not involved. Historically lesions have demonstrated a predilection for vessel bifurcations but this is rarely of importance on isolated biopsies. The distinctive feature of PAN is that healing and acute lesions, and affected and unaffected arterial sections are found side by side in a biopsy specimen.[3,54,56,59]

Figure 1.1 Parotid Biopsy – Fibrinoid necrosis of vessels in a patient with WG who presented with painful parotid swelling

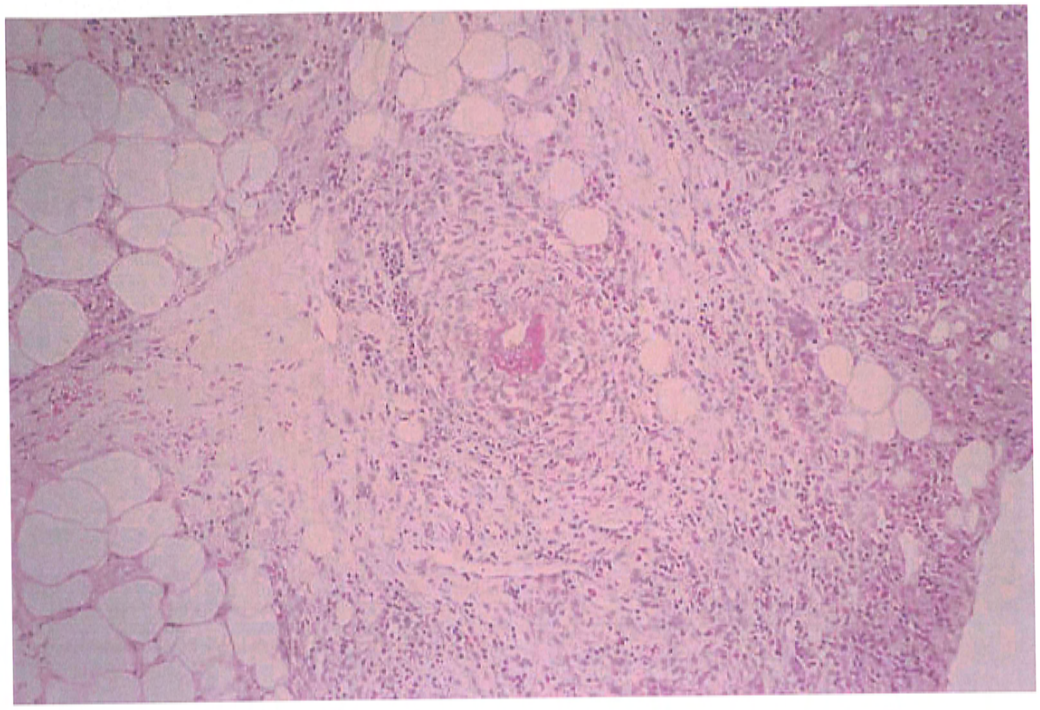


Figure 1.2 Lung biopsy in WG – Necrotizing granuloma with giant cells within the lung interstitium (same patient)

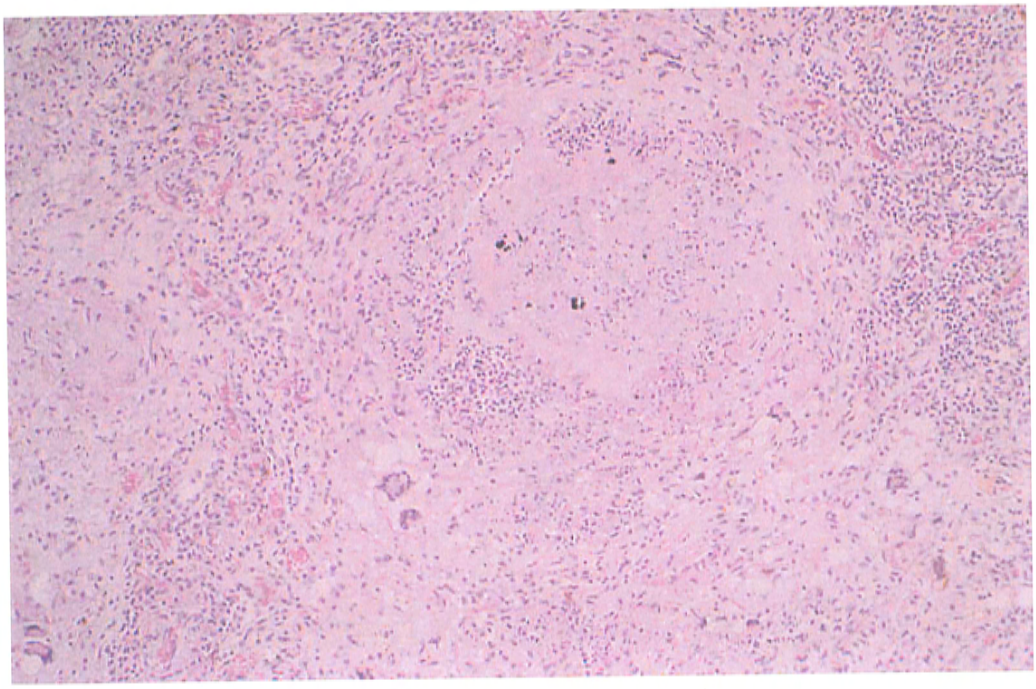


Figure 1.3 Lung Biopsy in WG – Granulomatous reaction with parenchymal haemorrhage (same patient)

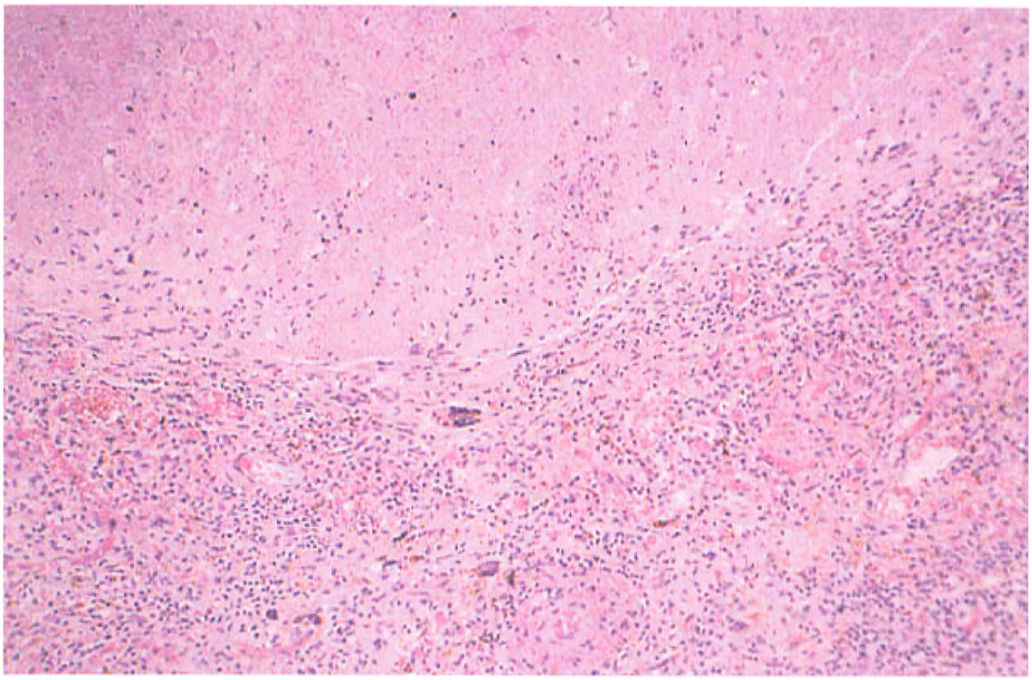


Figure 1.4 Nasal granuloma in WG

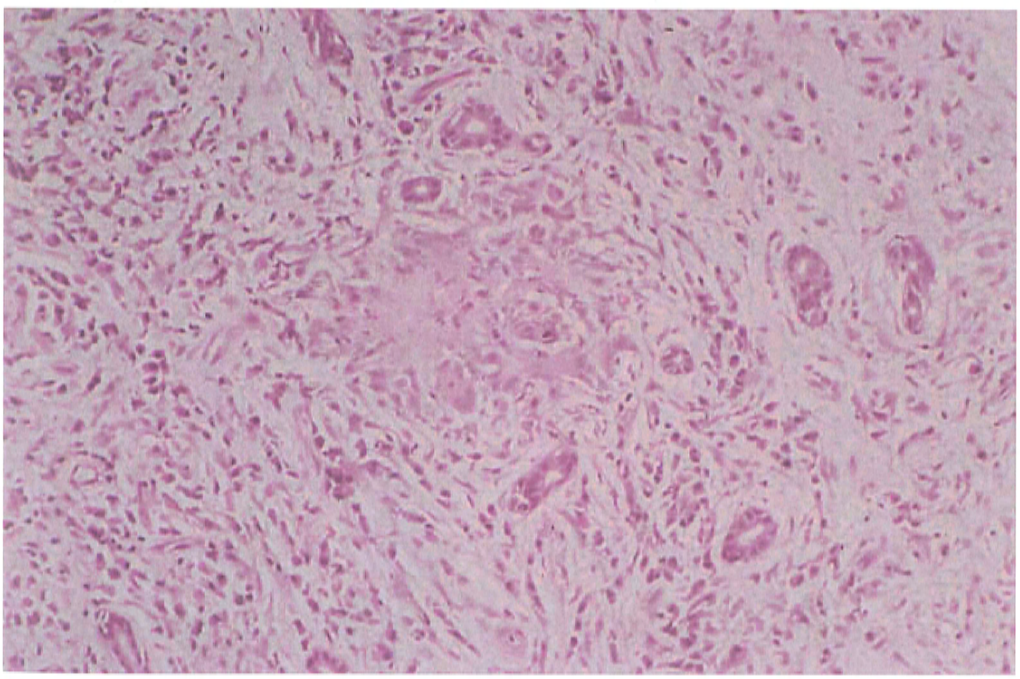


Figure 1.5
Focal Segmental Proliferative Glomerulonephritis in WG

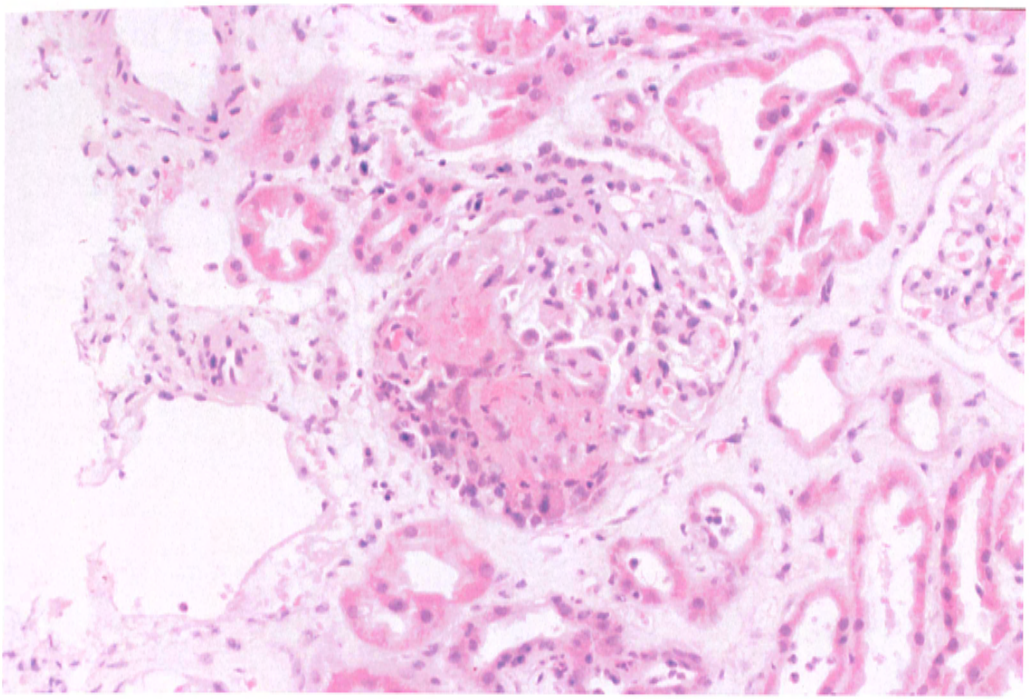


Figure 1.6 Kidney Biopsy in WG- Interstitial eosinophils and blood within the tubules

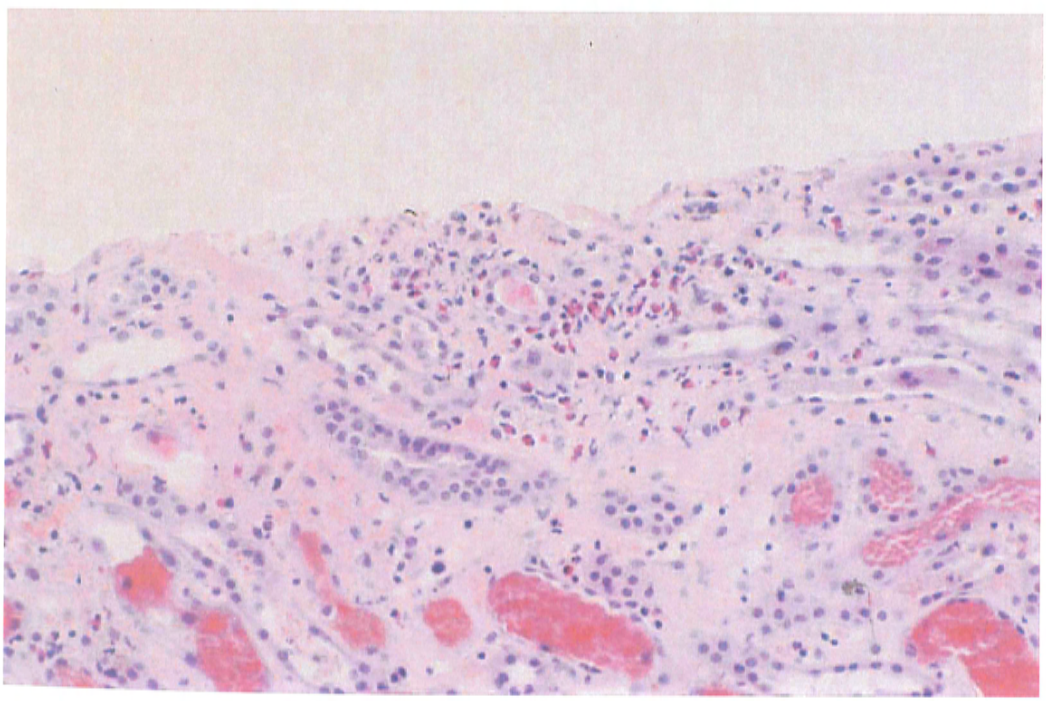


Figure 1.7 Kidney Biopsy in CSS – Granulomatous vasculitis and eosinophilia (Patient initially diagnosed as CSS but subsequently classified as WG after progression of clinical features)

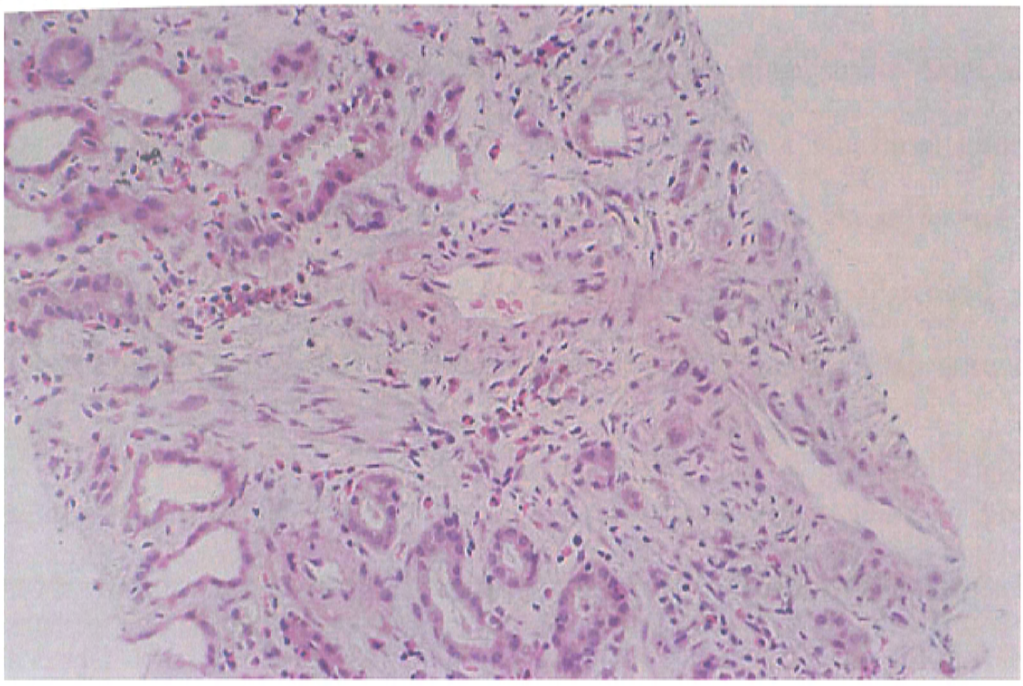
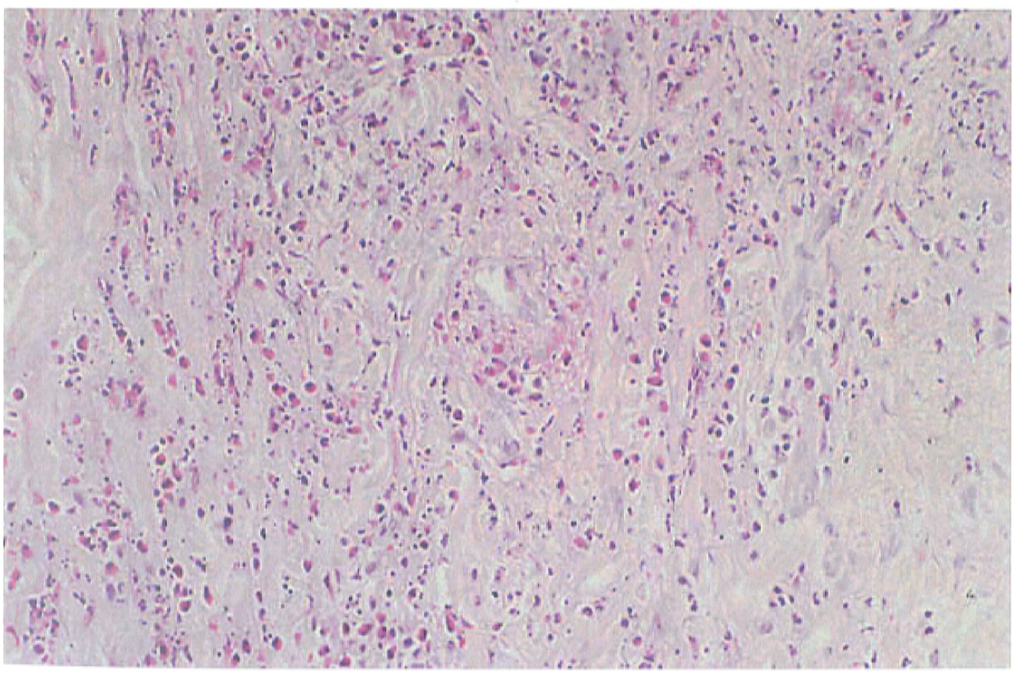


Figure 1.8 Skin Biopsy in CSS – Severe acute leukocytoclastic vasculitis with eosinophilic infiltrate



Radiological Features of PSV

Chest X–ray can be useful in distinguishing disease types. WG may give a characteristic nodular appearance with or without cavitations (Figure 1.9). The differential diagnosis of these appearances includes tuberculosis, aspergillosis, metastases and abcesses. However alveolar haemorrhage may give interstitial shadowing indistinguishable from mPA, pulmonary oedema and infection. CSS can demonstrate transient interstitial infiltrates associated with eosinophilic infiltration (Figure 1.10). None of these features are pathognomonic but can be useful when taken in clinical context. Paranasal sinus abnormalities can be seen in CSS and WG and are one of the ACR (1990) criteria for classification.[60]

Angiography is useful in the demonstration of microaneurysms and stenoses in medium sized vessels characteristic of cPAN. They may rarely be seen in mPA, WG and CSS but some investigators suggest that their presence excludes a diagnosis of mPA.[61] Indium-labelled white cell scanning can be useful in evaluating disease activity and locating areas of inflammation in known vasculitis, however its use in initial diagnosis is limited.[62] Magnetic Resonance Imaging (MRI) may be of particular benefit in central nervous vasculitis and anti-adhesion molecule monoclonal antibodies have been used to image vasculitic inflammation although they are not used routinely in diagnosis.[63]

Figure 1.9
Chest X-ray showing characteristic nodules in WG

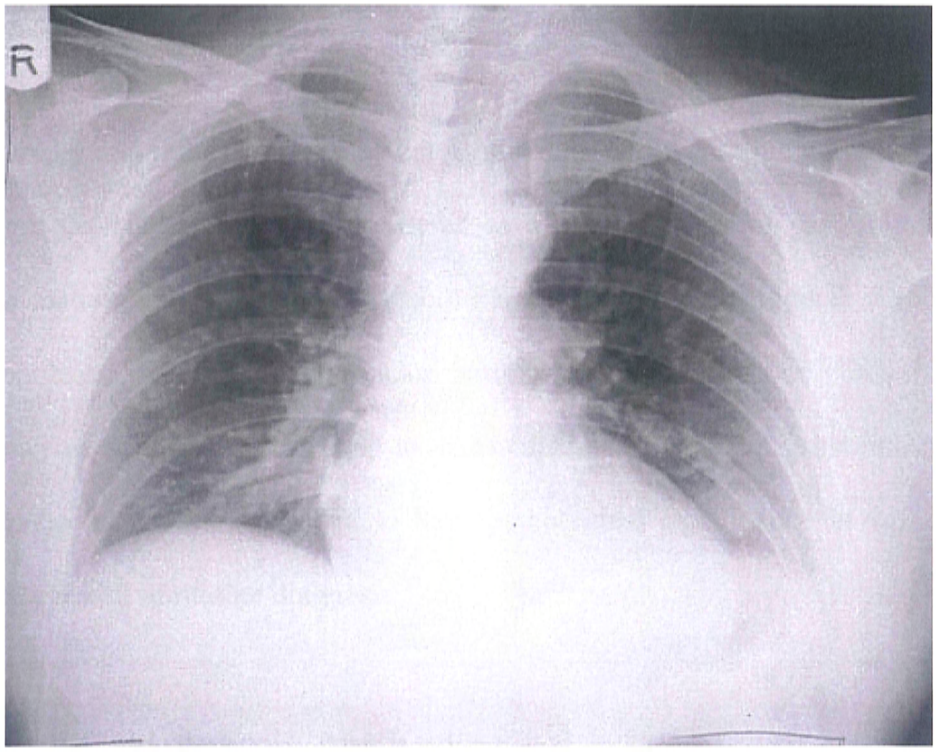
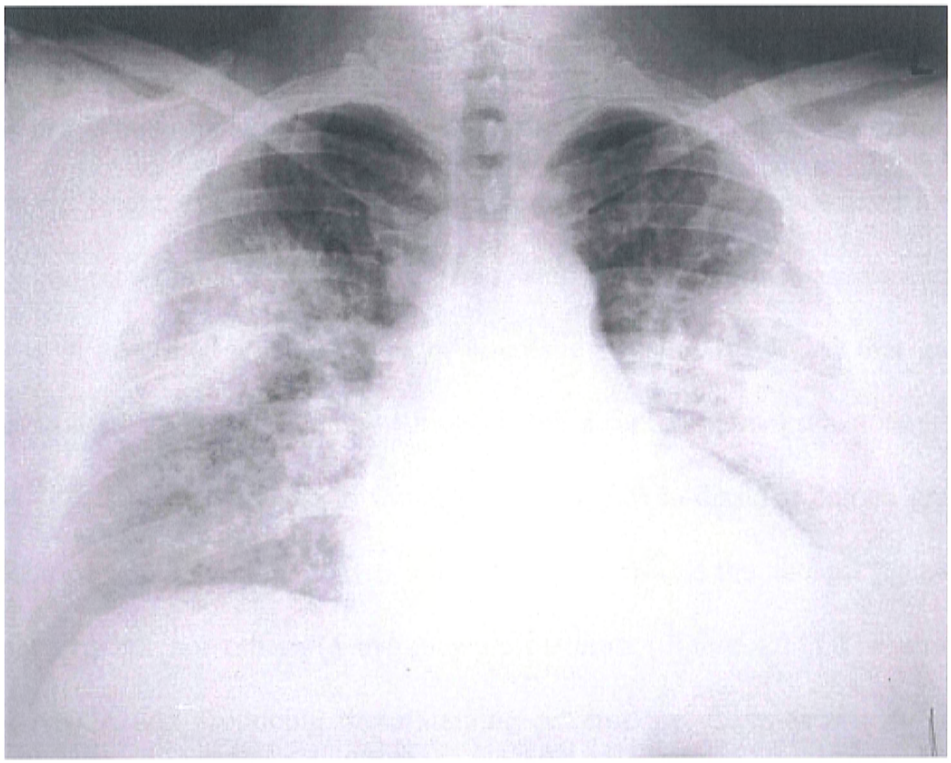


Figure 1.10
Chest X-ray with dffuse inflammatory infiltrate in mPA



Laboratory investigations in PSV

Active vasculitis is associated with non-specific markers of inflammation including raised erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), alkaline phosphatase and reduced albumin although rarely active disease has been reported with a normal ESR. CRP changes most rapidly and reflects disease activity. Anaemia (normochromic normocytic) is common but iron deficiency must be considered as a cause in case of gastrointestinal bleeding. These features are however non-specific and do not help distinguish vasculitis from other disorders. Von Willebrand factor antigen (released from endothelial cell granules on injury or stimulation) can help to assess disease activity.[64,65] Although other serological markers have been suggested to have pathological significance in vasculitis none are currently useful in routine diagnosis.[64]

Antineutrophil Cytoplasmic Antibodies

In 1982 Davies et al detected a previously unreported autoantibody, the antineutrophil cytoplasmic antibody (ANCA) in the serum of eight patients with suspected arbovirus infection and necrotizing GN.[66] Hall et al described the antibodies in four patients with SV[67] and Van der Woude hailed them as a specific marker for WG.[68] These antibodies gave characteristic bright, central, granular cytoplasmic staining of ethanol-fixed human neutrophils by indirect immunofluorescence (IIF), and are now known as classical or cANCA. Falk et al described a second type of circulating ANCA (pANCA) that gave a perinuclear stain on ethanol-fixed human neutrophils but a central pattern when they were formalin fixed.[69] This effect was due to the ability of ethanol to dissolve certain granule membranes allowing some granular enzymes to redistribute around the nucleus (causing a peri-nuclear pattern) but not others (a cytoplasmic pattern). (Figure 1.11) The antigens recognised by ANCA and producing these staining patterns are enzymes present in the primary or azurophilic granules of human neutrophils. Subsequent studies described

several enzymes recognised by both pANCA and cANCA. (Table 1.8) Neutrophil substrates prepared with formalin can be used to distinguish true pANCA from antinuclear antibodies (ANA) although they can occur simultaneously.[70]

Methods of ANCA detection.

IIF was the original method used to detect the pattern of ANCA but not the specific antigen responsible. Enzyme-linked immunosorbant assay (ELISA) is used to determine antigen-specific ANCA. Two types of solid state assay are used commercially. In one the target antigen is coated directly onto a plastic reaction well (standard assay) and in the other it is linked to the well by antigen-specific mouse monoclonal or rabbit polyclonal antibodies (Capture or Sandwich ELISA). Other detection methods include radioimmunoassay, immunoblotting and immunoprecipitation techniques but they are not routinely used.[70] Each technique has limitations that must be considered when interpreting results in a clinical context. The specificity of ANCA to a certain type of vasculitis depends upon both the accuracy of clinical diagnosis and the particular technique. IIF depends upon the experience of laboratory personnel in interpreting the results, e.g. false positive cANCA results may result from autoantibodies against other cytoplasmic antigens and false pANCA results can arise from misinterpretation of ANA. The specificity of direct ELISA depends upon the purity of the antigen preparation. Coating of the antigen onto plastic can itself affect the conformation of the protein. The sensitivity for PR3 ANCA in particular can be affected. The use of capture ELISA molecules prevents significant conformational change and reduces contamination with other proteins.[70] Therefore the meaning of ANCA results can vary between laboratories. For this reason a standardised assay has been established for use in clinical trials by a European multicentre collaborative study.[71]

Table 1.8 Target antigens for ANCA and associated immunofluorescence patterns on ethanol fixed neutrophils.[70]

ANCA target antigen	Associated IIF pattern on ethanol-fixed PMN
Proteinase 3 (PR3)	cANCA; very rarely pANCA
Myeloperoxidase (MPO)	pANCA; very rarely cANCA
Elastase	pANCA
Cathespin G	pANCA
Azurocidin	pANCA
Lactoferrin	pANCA
Lysozyme	pANCA, atypical cytoplasmic
BPI	Atypical cANCA or pANCA

ANCA= Anti-neutrophil cytoplasmic antibody
BPI= Bactericidal/permeability-increasing protein
IIF = Indirect Immunofluorescence
PMN = Polymorphonuclear cell
PR3-Proteinase 3
MPO= myeloperoxidase

ANCA in systemic vasculitis

Some investigators refer to ANCA-associated small vessel vasculitides as a distinct disease group in view of the strong relationship of the antibody. WG, mPA and CSS are all associated with ANCA, which appears to distinguish them from other forms of vasculitis. ANCA has been documented infrequently in cases of PAN (possibly due to disease definition), Kawasaki disease, Giant-cell arteritis, cryoglobulinaemic vasculitis and HSP but no significant association with disease severity or course has been noted.[59,72] The strongest relationship is for WG with 85-90% of patients reported to be ANCA positive (Table 1.9). 80-95% of ANCA in WG are cANCA, which is almost always associated with anti-PR3 (90%). The remaining pANCA cases are mostly directed against MPO but other antigens including PR3 and elastase have been reported.[70] ANCA has been shown to vary with disease activity, organ involvement and a rise in titres has been shown to precede relapses (Table 1.9).[13,73,74,75] However Hoffman et al noted the rise in cANCA titre may precede a relapse by more than 2 years indicating that in the absence of symptoms it is not a guide to increase treatment.[18] Recently a French group has also concluded that although ANCA positivity is associated with relapse in WG, its relationship with disease activity is not precise and in the absence of clinical manifestations ANCA titres are not sufficient to guide treatment.[76]

Previously Guillevin et al reported ANCA in 75% of mPA. pANCA is found most frequently in mPA and about 70% are directed against MPO but PR3 has been reported in 27-45% of mPA in some series.[65,69] A smaller percentage of CSS patients have ANCA and both PR3 and MPO have been described as target antigens.[45,64,70]

ANCA in other diseases

ANCA has also been detected in other diseases including autoimmune disorders (rheumatic disorders, sclerosing cholangitis and autoimmune hepatitis), inflammatory bowel disease, infections, Hodgkin's disease, monoclonal gammopathies, myelodysplasia, hypereosinophilic syndromes and nasal septal perforation (Table 1.10).[64,66,72,77] Certain drugs have also been linked to ANCA (described later). Usually the immunofluorescence of ANCA associated with other diseases demonstrates pANCA and in contrast to vasculitis associated ANCA target antigens are rarely PR3 or MPO.

The role of ANCA in diagnosis

The relationship of ANCA with PSV makes it a potentially useful diagnostic tool. Its use is complicated because it also occurs in diseases relevant to the differential diagnosis of PSV, target antigens overlap between mPA, WG and CSS and its precise role in pathogenesis is unknown. Early reports of IIF for cANCA detection in WG gave high levels of sensitivity (80-90%) and specificity up to 95% whilst subsequent studies found lower sensitivities. Rao et al described only 28% sensitivity in WG using the American College of Rheumatology classification criteria and 66% in a later metaanalysis.[77,78] The former result is probably due to the criteria employed and the latter increased to 91% when only active WG was considered. The specificity of disease may have been falsely raised in some studies due to controls selected. Hagen et al evaluated the diagnostic value of ANCA in WG, mPA, idiopathic RPGN and classical PAN using IIF and the recently standardised ELISA. This study obtained specificity for disease controls relevant to the differential diagnosis of PSV. They confirmed a high sensitivity for cANCA in WG (64%) and found a specificity of 95%. PR3 ELISA alone produced similar sensitivity (65-67%) but reduced specificity (86-89%). However, in combination cANCA and PR3 achieved 99% specificity but at 10% expense in sensitivity (54-56%). This suggests that IIF and ELISA combined

may be useful in differentiating WG from disease controls. pANCA can occur in a wide variety of diseases and although a sensitivity of 58% was achieved on pANCA IIF and MPO ELISA for mPA, specificity was only 81% and 91% respectively. The combination of IIF and ELISA techniques improved specificity to 99% but sensitivity fell to 49%. ANCA detected by IIF and ELISA may therefore be a useful tool in differentiating vasculitis from other diseases but its role in distinguishing vasculitis subtypes is less clear. The high percentage of pANCA positive WG patients in this study may have been a reflection of the method of classification.

Similarly Gross et al found a high sensitivity (81%) and specificity (99.5%) for WG using cANCA but combining IIF and ELISA increased sensitivity to nearly 100% and reduced specificity to 69% in their selected population.[72]

Despite encouraging data, ANCA can at present remain only an adjunct to diagnosis used in the context of clinical, radiological and histological findings and a knowledge of the ANCA laboratory's experience and techniques.

Table 1.9 Studies of ANCA in WG, mPA and CSS

Year	Author	Diagnosis	No. cases	Method	ANCA (%)	cANCA (%)	pANCA (%)	PR3 (%)	MPO (%)
1992	Hoffman[18]	WG active	106	IIF	-	88	5	-	-
		WG remission				43			
1993	Romas[21]	WG	9/37	IIF ELISA	89	66.7	22.2	-	-
1994	Luqmani[13]	Renal WG	20/22	IIF	88.9	61	0	-	-
		Non-renal WG	18/28		55	30	0	-	-
1997	Westman[36]	WG MPA	54/56 66/67	IIF	Total 97	-	-	87 39	11 56
1999	Guillevin[45,51]	mPA	51/85	ESW	74.5	9.8	64.7	7.8	60.8
		CSS	42/96	IIF ESW	47.6 (20/42)	2.4 (1/42)	35.7	--	90.9 (10/11)
2000	Reinhold-Keller[34]	WG	-	-	-	84	-	84	-
2001	Girard[76]	WG	55	IIF	87.2	80	7.3	-	-
2001	Schonermarck[72]	WG	312	IIF ELISA	-	81.3	3.6	69.0	1.8
		mPA	40		-	2.5	65.0	0	47.5
		CSS	46		-	6.5	6.5	6.5	4.3

ANCA=Antineutrophil cytoplasmic antibody; PR3 = Proteinase 3, MPO = Myeloperoxidase IIF = Immunofluorescence
ELISA = Enzyme linked immunosorbant assay; ESW= European Standardisation Workshop recommended

Table 1.10 Other disease associated with ANCA[70,71]

	IIF pattern	Target antigens	Relationship to disease
Rheumatic Disease • Rheumatoid arthritis • SLE • Sjogrens syndrome • Polymyositis • Dermatomyositis • Juvenile Chronic Arthritis • Antiphospholipid syndrome • Scleroderma • Sarcoidosis • Temporal arteritis • Spondyloarthropathy • Psoriatic Arthritis	pANCA most common IIF pattern observed. Up to 30% in SLE and RA cANCA - infrequent - atypical	• LF • elastase • lysozyme • cathepsin G • MPO • Undefined	Possible increase in risk of vasculitis (results contradictory) No correlation with • disease activity • severity • chronicity
Inflammatory bowel disease	pANCA - most common IIF pattern observed cANCA - infrequent - atypical	• LF • elastase • lysozyme • cathepsin G • BPI • Undefined	40-80% ulcerative colitis 10-40% Crohn's disease bacterial enteritis possible increase in certain subsets Unreliable correlation with disease activity

SLE=Systemic lupus erythematosus, IIF= immunofluorescence, RA= rheumatoid arthritis
LF= lactoferrin; MPO = myeloperoxidase

Table 1.10 (cont.) Other disease associated with ANCA

Infection			
• Endocarditis	-	-	
• Respiratory Tract Infection	-	-	
• Cystic fibrosis	-	BPI	
• Fungal infection	• atypical cANCA	-	
• HIV	• pANCA, atypical cANCA	• MPO PR3	
• Malaria	-	• Cathepsin G	
• Invasive amoebiasis	-	• PR3	

HIV = Human immunodeficiency virus; BPI- bactericidal/ permeability-increasing protein
ANCA = Antineutrophil cytoplasmic antibody

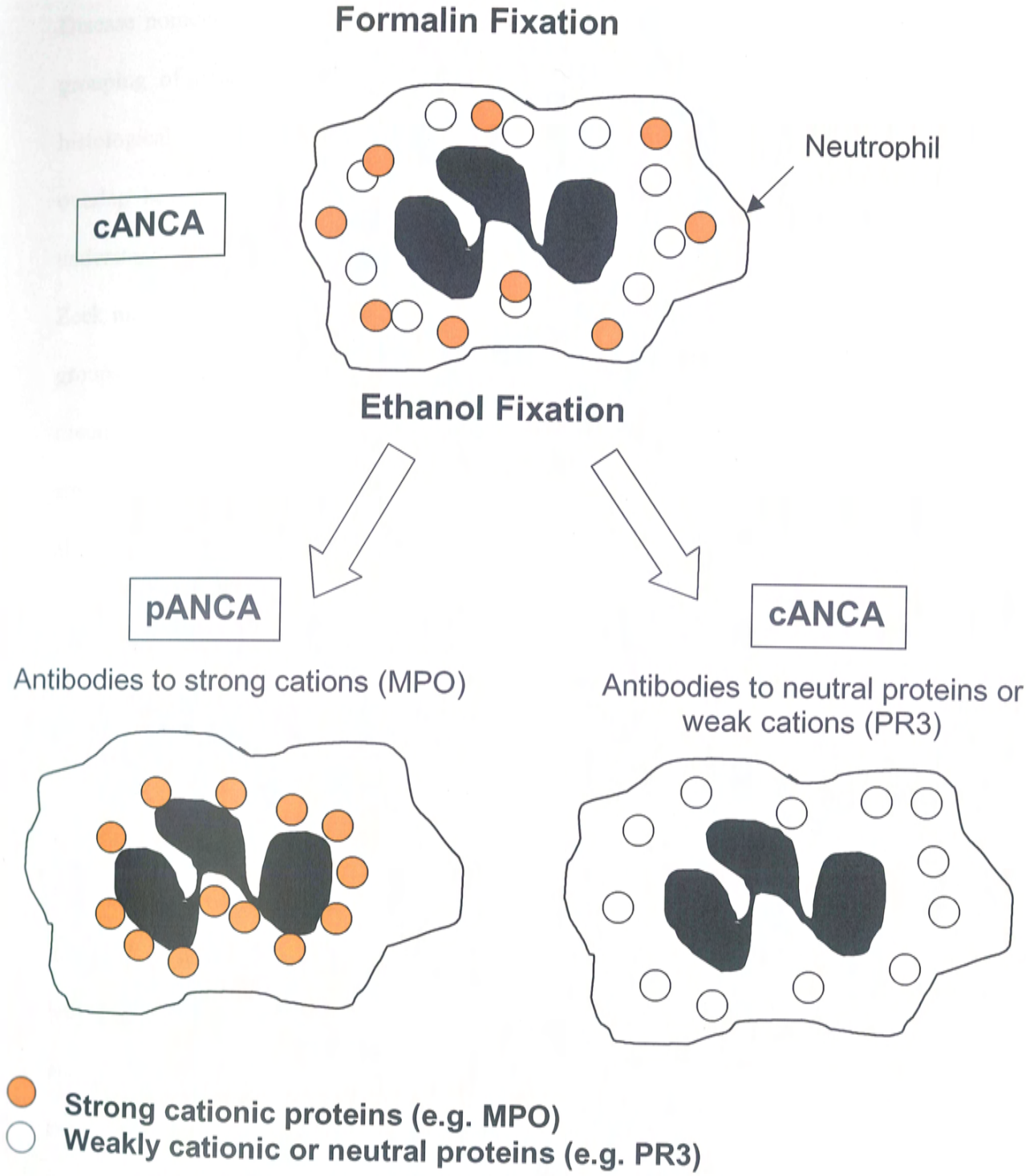


Figure 1.11 Cytoplasmic and perinuclear staining patterns on Indirect Immunofluorescence - cANCA and pANCA appearances of antibodies to myeloperoxidase and proteinase 3 on Formalin and Ethanol Fixation

III. CLASSIFICATION OF PRIMARY SYSTEMIC VASCULITIS

Disease nomenclature and classification has evolved from early descriptions to the formal grouping of disease according to clinical features, vessel size, response to therapy and histological appearances. Classification however remains controversial with considerable overlap between different vasculitic syndromes and will certainly continue to evolve as understanding of disease pathogenesis improves.

Zeek made the first formal attempt to classify vasculitis in 1952 and suggested five distinct groups: hypersensitivity angiitis, allergic granulomatous angiitis (now recognised as CSS), rheumatic arteritis, periarteritis nodosa and temporal arteritis. Her classification distinguished small vessel necrotizing vasculitis (hypersensitivity vasculitis) from classical PAN and although limited and notably omitting Wegener's granulomatosis and Takayasu's arteritis (reports had not reached the English literature) it was the basis for future classifications.[4] Alarcon-Segovia et al expanded upon her ideas in 1964, maintaining the basic scheme but adjusting terminology (e.g. replacing hypersensitivity with allergic vasculitis) and including WG for the first time. They suggested that the vasculitides represented 'a continuous spectrum of tissue changes from pure necrosis and granuloma formation to pure angiitis'.[79] Terminology evolved with further reclassifications and De Shazo et al (1975) introduced HSP and WG as a separate entities and relegated hypersensitivity vasculitis to a subgroup of leukocytoclastic vasculitis.[80] Lie reviewed the classification of vasculitis in 1994.[81] Guilliam and Smiley produced a hybrid classification highlighting the overlapping of vessel size between the major syndromes (Table 1.11). Fauci et al extended the classification to include Beurger's disease and lymphomatoid granulomatosis (soon known to be a T-cell lymphoma) and combined classical PAN, CSS and a catchall 'over-lap' syndrome. Alarcon-Segovia (1980) attempted to classify vessels by size using three groups: the giant cell arteritides, polyarteritis nodosa and small vessel vasculitides. In 1983 Mc Clusky et al proposed an extended classification based on pathogenesis (Table 1.12) and Churg, Churg and Walder et al

contributed with similar systems. In 1988 Lie et al attempted to simplify classification concentrating on the size of vessels involved and dividing the vasculitides in primary and secondary disease.[81] However after thirty-five years, although much expanded due to increased recognition of vasculitic syndromes and improved understanding of causality, Zeek's early suggestions remained the backbone for classification.

Subsequently Scott and Watts (1994) recognised the need to encompass developments in the clinical diagnosis of SV and especially to acknowledge the increasing evidence for the ANCA-associated vasculitides as a distinct group. They developed a classification that addressed clinical aspects of disease and reflected dominant vessel size, ANCA associations and broadly correlated with treatment strategies. WG, CSS and mPA were separated from other forms of vasculitis on the rationale that they often involved small arteries, are the diseases most commonly associated with ANCA, are associated with a high risk of GN and are the diseases that respond best to cyclophosphamide (Table 1.13).[82]

Similarly Lie et al (1994) revised their 1986 classification of vasculitis into primary and secondary vasculitis. They also divided primary disease according to vessel size. (Table 1.14) However they did not address therapeutic or serological differences and argued that classical polyarteritis nodosa affected both small and medium arteries, therefore grouping cPAN with CSS and WG. Despite criticism of the CHCC definition (Table 1.15) they also used microscopic polyangiitis rather than polyarteritis in the context of small vessel vasculitis.[81]

Table 1.11 Classification by Gilliam and Smiley 1976*

1. **Leukocytoclastic, hypersensitivity or allergic vasculitis**
   A. Schonlein-Henoch purpura
   B. Hypocomplementaemic vasculitis
   C. Essential mixed cryoglobulinaemia
   D. Other disease-related dermal vasculitides

2. **Vasculitis associated with rheumatic disease**
   A. Systemic Lupus Granulomatosis
   B. Rheumatoid Arthritis
   C. Scleroderma
   D. Dermatomyositis

3. **Allergic granulomatous angiitis**
   A. Churg-Strauss syndrome
   B. Wegener's granulomatosis

4. **Polyarteritis nodosa**
   A. Classic type
   B. Cutaneous type
   C. Associated with hepatitis B antigen
   D. Vasculitis in drug addicts

5. **Giant cell arteritis**
   A. Temporal arteritis
   B. Polymyalgia rheumatica
   C. Takayasu's disease

* From Lie [81]

Table 1.12
Classification of vasculitis by McCluskey and Fienberg 1983*

1. Primary vasculitides of unknown cause

A. Periarteritis nodosa (polyarteritis nodosa, classical polyarteritis nodosa, systemic necrotizing vasculitis)

B. Small vessel vasculitis (hypersensitivity or allergic vasculitis, leukocytoclastic vasculitis, allergic vasculitis)

1.Cutaneous vasculitis (cutaneous necrotizing vasculitis , cutaneous venulitis; involvement apparently confined to skin)

2. Small vessel vasculitis with cutaneous and visceral involvement

3.Hypocomplementaemic (urticarial) vasculitis

C. Unclassified vasculitis (or overlap) with features of periarteritis nodosa and small vessel vasculitis

D. Henoch-Schonlein purpura (anaphylactoid purpura)

E. Essential mixed cryoglobulinaemia

F. Giant cell arteritis and aortitis

G. Localized forms of polyarteritis nodosa

II. Connective tissue diseases in which vasculitis occurs

A. Rheumatoid arthritis

B. Systemic lupus erythematosus

C. Dermatomyositis

D. Rheumatic Fever

E. Sjogren's Syndrome

III. Diseases with known causative agents in which vasculitis sometimes occurs

A Hepatitis B infection (various forms of vasculitis including polyarteritis nodosa)

B. Bacterial infections (Pseudomonas, Streptococcus, endocarditic bacteria)

C. Drug addiction (amphetamine)

D. Rickettsial infections

E. Drug reactions – small vessel vasculitis

IV. Wegener's Granulomatosis (pathergic granulomatosis)

V. Allergic granulomatosis (Churg Strauss syndrome)

* From Lie [81]

Table 1.13 Classification of vasculitis – Scott and Watts 1994[82]

Dominant vessels involved	Primary	Secondary
Large arteries	Giant cell arteritis Takayasu arteritis Isolated CNS angiitis	Aortitis associated with RA Infection (e.g. syphilis)
Medium arteries	Classical PAN Kawasaki disease	Infection (e.g. hepatitis B)
Small vessels and medium arteries	Wegener's Granulomatosis * Churg Strauss syndrome* Microscopic polyangiitis*	Vasculitis due to RA and SLE Sjogren's Syndrome Drugs, Infection (e.g.HIV)
Small vessels (leukocytoclastic)	Henoch-Schonlein purpura Essential mixed cryoglobulinaemia Cutaneous leukocytoclastic angiitis	DrugsΨ Infection (e.g. hepatitis B and C)

PAN= polyarteritis nodosa; RA = Rheumatoid arthritis; SLE = Systemic lupus erythematosus.

- Diseases most commonly associated with ANCA, which have a significant risk of renal involvement and which are most responsive to immunosuppression with cyclophosphamide

Ψ e.g. sulphonamides, penicillin etc

Reproduced from Scott et al [82]

Table 1.14
Revised 'practical classification of vasculitis by Lie et al 1994[81]

Primary vasculitides

Affecting large, medium and small sized blood vessels
- Takayasu's arteritis
- Giant cell arteritis
- Isolated angiitis of the central nervous system

Affecting predominantly medium and small sized blood vessels
- Polyarteritis nodosa
- Churg Strauss syndrome
- Wegener's Granulomatosis

Affecting predominantly small-sized blood vessels
- microscopic polyangiitis
- Henoch-Schonlein purpura
- Cutaneous leukocytoclastic angiitis

Miscellaneous conditions
- Buerger's disease
- Cogans Syndrome
- Kawasaki disease

Secondary vasculitides
- Infection related vasculitis
- Vasculitis secondary to connective tissue disease
- Drug hypersensitivity related vasculitis
- vasculitis secondary to essential mixed cryoglobulinaemia
- Malignancy related vasculitis
- Hypocomplementaemic urticarial vasculitis
- Post-organ transplant vasculitis
- Pseudovasculitis syndromes (myxoma, endocarditis, Sneddon syndrome)

Table 1.15 Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis for small vessel vasculitis and polyarteritis nodosa[42]

Type of vasculitis	Definition
Medium sized vessel vasculitis	
Polyarteritis nodosa** (classic PAN)	Necrotizing inflammation of medium sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Small vessel vasculitis	
Wegener's Granulomatosis #	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessls (e.g. capillaries, venules, arterioles and arteries), *Necrotizing glomerulonephritis is common.*
Churg-Strauss syndrome #	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium sized vessels and associated with asthma and eosinophilia.
Microscopic polyangiitis** # (Microscopic polyarteritis)	Necrotizing vascultiis with few or no immune deposits affecting small vessels (i.e. capillaries, venules or arterioles) . *Necrotizing arteritis involving small and medium sized arteries may be present. Necrotizing glomerulonephritis is very common.Pulmonary capillaritis often occurs.*
Schonlein –Henoch purpura	Vasculitis with immunoglobulin A-dominant immune deposits , affecting small vessels (i.e. capillaries, venules or arterioles)*Typically involves skin, gut and glomeruli, and is associated with arthralgia or arthritis*
Essential cryoglobulinaemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e. capillaries, venules or arterioles) , and associated with cryoglobulins in serum. Skin and glomeruli are ofen involved.
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

*Medium sized vessels refer to the main visceral arteries (e.g. renal, hepatic, coronary and mesenteric arteries); small vessel refers to venules, vcapillaries, arterioles and the intraparenchymal distal arterial radicals that connect the arterioles. Some small and large vessel vasculitides may involve medium sized arteries but large and medium sized vessel vasculitides do not involve smaller vessels than arteries. Essential components are represented in normal type, italicized type represents usual but not essential components ** preferred term # Strongly associated with antineutrophil cytoplasmic antibodies

Reproduced from Jennette et al [42]

Classification of Individual Disease Subtypes

1990 ACR Classification Criteria

The American College of Rheumatology (ACR) proposed classification criteria for seven types of SV: Giant cell arteritis (GCA), Takayasu arteritis (TA), polyarteritis nodosa (PAN), WG, CSS, HSP and hypersensitivity vasculitis. Their aim was to establish classification criteria to improve communication between researchers and provide a standard method of describing groups of patients in therapeutic, epidemiological or other studies.[49] The ACR criteria were developed and validated using data collected over 5 years by rheumatologists from forty-eight centres in the United States, Mexico and Canada. 1020 consecutive patients with a diagnosis of vasculitis were accumulated (Kawasaki disease, connective tissue disease associated vasculitis and inconclusive cases were excluded). Details recorded were clinical diagnosis, symptoms, physical findings and relevant results of biopsies, laboratory tests and angiography. The gold standard for developing criteria was clinical diagnosis and although most patients had biopsy data this was not necessary for classification. Criteria formulated were intended to distinguish one type of vasculitis from another but not between vasculitis and other disorders i.e. they were not intended for diagnosis. For each diagnosis a short list of clinical criteria were drawn up and comparisons made between patients with the selected diagnosis and the remainder. Final classification criteria were selected according to their sensitivity and specificity and presented in a traditional table format and a classification tree.[83] Table 1.16 gives details of the number of patients, sex, age and sensitivity and specificity of criteria for WG, CSS and PAN and tables 1.17-1.19 give the actual criteria.[41,60,84] Criteria for CSS were the most specific and sensitive with eosinophilia and asthma the best discriminators of disease. PAN was the least specific and misclassification occurred for a wide range of diagnoses. More complete clinical data, especially biopsy and angiography results, may have lead to an improvement. 10 patients with WG could also be classified as PAN and a surprisingly high

number of cases of CSS and WG overlapped. These criteria provided the first method of uniformly comparing patients but even at inception it was apparent that individual patients might fulfil more than one set of criteria. The authors made it clear that clinical diagnosis was paramount. For example if a patient is clinically suspected to have WG and fulfils that set of criteria, he must be classified as WG irrespective of any other criteria set he may also fulfil. However it seems appropriate to identify patients who fulfil more than one set of criteria to allow comparison of research findings especially in epidemiological study. Rao et al confirmed that the criteria are not suitable for use as a diagnostic tool in their prospective study in which they applied the criteria for WG, GCA, PAN and hypersensitivity vasculitis to 198 consecutive patients referred to their unit for assessment for possible vasculitis. At case note review 2 to 8 months later they found that 26% of the initial patients had a diagnosis of one of these vasculitides. However 35% had initially fulfilled criteria. Only 75% of those with a final diagnosis fulfilled criteria. This gave predictive values that ranged from 29-75% in vasculitis patients but only 17-19% in all comers.[85]

The Chapel Hill Consensus Conference Definitions (1994)

In 1993 an international consensus conference at Chapel Hill, North Carolina, USA (CHCC) convened with the goal of reaching a consensus on the names of the major non-infectious vasculitides and to provide definitions for each of these. They specifically stated that their intent was not to formulate criteria for diagnostic or classification purposes but to standardise disease nomenclature.[42] However they stated that direct histopathological evidence was not necessarily required for diagnosis and suggested disease parameters; e.g. proteinuria, haematuria and red cell casts to represent glomerulonephritis (GN) and radiographic demonstration of aneurysms in the main visceral arteries to represent arteritis affecting medium sized vessels. Table 1.15 gives the agreed definitions. Points of

particular note include the distinction made between classical PAN and mPA. By their definition, a diagnosis of cPAN was limited to medium sized and small arteries and was excluded by the presence of GN or small vessel vasculitis. In effect this makes classical PAN an extremely rare disorder. The number of cases defined as WG is also limited because inflammation can be absent on a single specimen and in practice not all patients require a biopsy. Application of these definitions as classification criteria would therefore lead to an excess in mPA The authors note however that other causes of pulmonary-renal, or presumably single organ, disease must be ruled out, including immune complexes and cryoglobulins prior to a diagnosis of mPA. They acknowledged the complexities of distinguishing between mPA, WG and respiratory infection and informally introduced the potential value of ANCA.

Although not intended as classification criteria they have been adapted for use in several studies. Hagen et al successfully devised a patient classification system in their study of ANCA in idiopathic systemic vasculitis using the nomenclature (Table 1.20).[71] Sorensen et al evaluated the use of the definitions supplemented by surrogate parameters for vasculitis over 5 years in a prospective study of mostly tertiary referrals of primary and secondary vasculitis. They found that CHCC definitions were fulfilled in only 10 of 27 WG and 3 of 12 mPA patients and surrogate markers were useful in only 11 WG and 9 mPA patients. They concluded that the CHCC nomenclature was unsuitable as diagnostic criteria even when supplemented by surrogate markers.[86]

Other Significant Disease Classification Systems

Lanham et al (1984) suggested that CSS might be under-diagnosed due to overemphasis on a classical histological picture. They recommended a clinical approach to classification where patients must fulfil three criteria based upon the distinctive disease pattern. For a diagnosis of CSS, patients are required to have asthma, a peak peripheral blood eosinophil

count in excess of 1.5 X 10^{9} / L and systemic vasculitis affecting two or more extra-pulmonary organs. This provided a method of defining CSS patients without the need for histology.[46] Similarly De Remee et al proposed a unifying classification for WG in 1985 (the ELK system).[39] WG was defined as necrotizing granulomatous vasculitis of small vessels and involvement of one or more of the anatomical sites ear, nose, throat, orbit or other head and neck site (E), lower respiratory tract (L) or kidney (K). Isolated renal disease was not included and implied that the disease process commences with E and L then progresses to K. However in practice kidney involvement may precede E and L.[87] Neither the ACR nor the CHCC definitions included pathogenic mechanisms in their criteria, in particular ANCA. Over the past twenty years ANCA have been associated with WG, mPA and CSS but not the large vessel vasculitides or classical polyarteritis nodosa. Guillevin et al therefore suggested that ANCA may be useful in differentiating between mPA and cPAN.[88]

Following their evaluation of the CHCC nomenclature Sorensen et al proposed diagnostic criteria for mPA and WG using biopsy data, surrogate parameters and ELISA for PR3 ANCA (Table 1.21).[86] The clinical relevance of ANCA has been discussed and cANCA with PR3 target antigen in WG noted to be most clinically relevant. The aim of diagnostic criteria is to distinguish vasculitis from other types of disease. To achieve this it seems likely that a more exhaustive list of variables may be necessary. Their proposed criteria seem more suitable for use in classification, especially to distinguish WG from mPA. However their exclusion of WG by the presence of blood or tissue eosinophilia challenges accepted definitions of WG as eosinophilia is well documented in WG classified by other means although to a lesser extent than CSS.[55,56]

In conclusion although current systems for the classification of vasculitis allow meaningful comparison of results between studies, areas of controversy remain. Currently no criteria are suitable for sole use in diagnosis in the clinical setting and physicians must continue to

rely upon clinical judgement. However, once a diagnosis of vasculitis has been made, classification allows comparison of patient series, e.g. in the evaluation of treatment and outcome, which may help in prognostic decision-making. The role of ANCA in the clinical setting is becoming more defined and it seems likely that its use, particularly cANCA / PR3, will improve disease definition and classification.

Table 1.16 Details of patients included in ACR Classification of WG, CSS and PAN[49,60,84]

Diagnosis	No. patients	M:F	Age	Traditional format	
				Sensitivity (%)	Specificity (%)
WG	85	1.7:1	45.2+/- 1.8 SEM	88.2	92.0
CSS	20	1.9:1	50+/1 13.2 SEM	90.0	99.7
PAN	118	1.6:1	48.4 +/1 17 SEM	82.2	86.6

SEM= Standard error of the mean

Table 1.17 ACR (1990) criteria for classification of Polyarteritis nodosa (traditional format)* [84]

	Criterion	Definition
1.	Weight loss>4 Kg	Loss of 4kg or more body weight since illness began, not due to dieting or other factors
2.	Livedo reticularis	Mottled reticular pattern over the skin of proportions of the extremities or torso
3.	Testicular pain	Pain or tenderness of the testicles, not due to infection, trauma or other causes
4.	Myalgias, weakness or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
5.	Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies or polyneuropathy
6.	Diastolic BP>90mmHg	Development of hypertension with diastolic BP higher than 90mmHg
7.	Elevated blood urea or creatinine	Elevation of blood urea nitrogen > 40 mg/dl or creatinine > 1.5mg / dl, not due to dehydration or obstruction
8.	Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
9.	Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to atherosclerosis, fibromuscular dysplasia, or other non-inflammatory causes.
10.	Biopsy of small or medium sized artery containing PMN	Histological changes showing the presence or granulocytes or granulocytes and mononuclear leukocytes in the artery wall

* For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%

BP=blood pressure; PMN = polymorphonuclear neutrophils; BUN = blood urea nitrogen

Reproduced from Lightfoot et al [85]

Table 1.18 ACR (1990) criteria for the classification of Churg Strauss Syndrome (traditional format)*[60]

	Criterion	Definition
1.	Asthma	History of wheezing or diffuse high-pitched rales on expiration
2.	Eosinophilia	Eosinophilia >10% on white blood cell differential count
3.	History of allergy*	History of Seasonal allergy (e.g. allergic rhinitis) or other documented allergies including food and others *except* for drug allergy
4.	Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to a systemic vasculitis
5.	Pulmonary infiltrates, non-fixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates) attributable to a systemic vasculitis
6.	Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
7.	Extravascular eosinophils	Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas

* History of allergy, other than asthma or drug related , is included in the tree classification criteria set and not in the traditional format criteria set . 4 or more of the 6 other criteria listed give a sensitivity of 85.0% and a specificity of 99.7%
Reproduced from Masi et al [60]

Table 1.19 ACR (1990) Criteria for classification of Wegener's Granulomatosis (traditional format)* [49]

	Criterion	Definition
1.	Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2.	Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3.	Urinary sediment	Microhaematuria (>5 red blood cells per high power field) or red cell casts in the urinary sediment
4.	Granulomatous inflammation on biopsy	Histological changes showing granulomatous inflammation within the wall of an artery or in a perivascular or extravascular area (artery or arteriole)

* For purposes of classification, a patient shall be said to have Wegener's Granulomatosis if at least 2 of these four criteria are present. The presence of two or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%

Reproduced from Hunder et al [49]

Table 1.20 Diagnostic patient classification system used by Hagen et al [71]

Diagnosis	Definition
Wegener's Granulomatosis a)	Histologically proven vasculitis with granuloma and/or giant cells in a biopsy (with or without nephritis)
or b)	Clinical evidence of at least one airway symptom or sign, compatible with WG (pulmonary nodules or fixed infiltrates, sinusitis, purulent or bloody discharge from the nose, saddle nose, otitis media, orbital pseudotumour, tracheal stenosis). Renal histology – crescentic and/or necrotizing glomerulonephritis with few or no immune deposits
or c)	Clinical evidence of airway symptoms compatible with WG (see b.). Vasculitis present on histology of any organ. No evidence of glomerulonephritis.
or d)	Clinical evidence of airway symptoms compatible with WG (see b). No histological evidence of vasculitis available.
Microscopic polyangiitis*	Histologically proven crescentic and/or necrotizing glomerulonephritis with few or no immune deposits, or histologically proven vasculitis of small vessels. Systemic manifestations compatible with vasculitis. No airway symptoms compatible with WG (see above).
Churg-Strauss syndrome	Histologically proven vasculitis or crescentic glomerulonephritis or giant cells/granuloma formation in combination with asthma and eosinophilia
Classical polyarteritis nodosa*	Proof of arterial vasculitis (angiography or biopsy) . Small vessel vasculitis at any biopsy location moves the patient in to diagnosis of mPA.

* All patients hepatitis B negative

Reproduced from Hagen et al [71]

Table 1.21 Proposed diagnostic criteria for WG and mPA – Sorensen et al[86]

Diagnosis	Criteria
Wegener's Granulomatosis	
1.	Biopsy or surrogate parameter for granulomatous inflammation in the respiratory system
2.	Biopsy verified necrotizing vasculitis in small to medium sized vessels or biopsy/ surrogate parameter for glomerulonephritis or positive PR3-ANCA test
3.	Lack of eosinophilia in blood and biopsy samples
Microscopic polyangiitis	
1.	Biopsy verified necrotizing vasculitis in small vessels and/or glomerulonephritis with few or no immune deposits
2.	Involvement of more than one organ system as indicated by biopsy verified vasculitis in small to medium sized vessels or surrogate parameter for glomerulonephritis
3.	Lack of biopsy and surrogate parameter for granulomatous inflammation in the respiratory system.

IV. ASSESSMENT OF DISEASE ACTIVITY AND DAMAGE

Effective intervention in PSV has reduced mortality dramatically and disease is usually characterised by an acute severe illness followed by a chronic course with periods of remission and relapse. During remission, disease may be entirely quiescent but more commonly there is grumbling low-grade activity. At presentation and during relapses there is a risk of permanent damage to an organ (e.g. irreversible kidney damage or neurological defect). Clinically it can be difficult to distinguish between persistent activity and damage caused by a prior insult. Infection, a risk of immunosuppressive treatment, can also mimic active vasculitis. Misdiagnosis can have fatal consequences illustrating the importance of accurate disease assessment. The importance of clinical and laboratory features has been described.

Assessment of morbidity caused by PSV is complicated and should include details of current disease activity, cumulative damage caused by non-healing scars and consequent functional status. A number of tools have been developed to assess these features of vasculitis. They allow the prospective monitoring of individual patients but also provide suitable measures for research (e.g. when characterising patients or as outcome measures in therapeutic trials).

Measurement of Disease Activity

The Groningen Index and Disease Extent Index (ELK) were developed for use in WG. [89, 90] The former requires biopsy data so although it provides a precise measure of activity it is unsuitable for monitoring disease. The second is based upon the clinical status of patients, is limited to WG and assesses the extent of disease rather than activity per se. The Birmingham Vasculitis Activity Score (BVAS) was developed for use in a variety of SV. It consists of a checklist of clinical features, identified by consensus, divided into 10 organ-system groups. It is intended that the user should establish whether each abnormality is

present, can be attributed to vasculitis and if so, whether it is new, worse or reflects ongoing, grumbling activity. The presence or absence of an item is recorded and scored. Each item and system group is weighted to reflect clinical priorities and a maximum score determined for each group.[91] The original BVAS form was adapted by the European Union Study Group of Therapeutic Trials (ECSYSVASTRIAL), reducing the number of items and modifying some definitions. They introduced the use of two scores. BVAS 1, the original score, referred to new or worse active vasculitis occurring within four weeks of BVAS completion. BVAS 2 referred to chronic low-grade disease activity that had persisted for more than 4 weeks. Initially inter-observer agreement for BVAS1 and 2 was found to be poor but improved with training.[92] Disease that persisted beyond three months was regarded as permanent damage and excluded.[93] Appendix 2 gives full details of the new form and definitions. The score has also been shown to correlate with serological and cellular markers of inflammation, have some prognostic value for mortality and morbidity and has been used to define treatment responses in patients with ANCA associated vasculitis.[94] The Vasculitis Activity Index was developed in 1992 and has recently been validated.[95,96] It utilises rating scales for organ systems similar to the BVAS in combination with ESR to assess activity within the previous four weeks and users must score only items attributable to vasculitis. Scores were reported to correlate with the Physicians Global Assessment but with reduced inter-observer variation.

Assessment of Damage

Two measures were developed to aid the separation of damage from disease activity. The Systemic Necrotizing Vasculitis Damage Index (SNVDI) was derived from the ACR SLE Damage Index and applied in a cohort of 'polyarteritis' and Churg-Strauss patients. However it excluded ENT disease, limiting its usefulness in WG.[48] The Birmingham Vasculitis Damage Index (VDI) assessed damage (defined as non-healing or fixed scars as

a result of disease activity or any event occurring since the onset of disease including treatment complications). VDI items were divided into organ systems and scored individually.[97] The VDI form and definitions are given in Appendix 2. Scores were designed to be applied as a total VDI score or could be divided into critical damage (items associated with significant organ failure), treatment related damage and major vascular damage (items of damage to major blood vessels attributable to disease).[98]

To combine the assessment of all aspects of morbidity in vasculitis the Vasculitis Integrated Assessment log (VITAL) was devised for use by ECSYSVASTRIAL. It incorporates BVAS, VDI and the Short-form-36, a widely used functional assessment.[99,100] It is also available to download at www.vasculitis.org.

V. TREATMENT AND OUTCOME OF PRIMARY SYSTEMIC VASCULITIS

PSV is a severe illness which, untreated, is rapidly fatal in the majority of cases. In one series 80% of WG patients died within one year (mean survival - 5 months) and only 7% survived to 2 years.[12] Limited disease with prolonged survival has however been recognised and may not require treatment, although in some cases it progresses to severe systemic disease.[13,33] The introduction of effective treatment revolutionised the course of PSV, in one series survival for WG was 99% and 88% at 1 and 10 years respectively.[34] Unfortunately the cost of survival is significant morbidity caused by both vasculitis and side-effects of treatment.

TREATMENT OF PRIMARY SYSTEMIC VASCULITIS

Corticosteroids were first used in the treatment of PSV but although survival improved marginally (mean survival - 12.5 months in WG) it remained mostly fatal.[101] In 1954 Fahey et al reported improvement in a WG patient following the use of nitrogen mustard.[102] Subsequently cytotoxic agents including alkylating agents, folic acid and purine antagonists were tried either alone or with corticosteroids producing some good clinical responses and significant long-term remissions.[17]

Cyclophosphamide

Cyclophosphamide (CYC), an alkylating agent derived from nitrogen mustard, emerged as the main-stay of treatment and a regimen of daily oral low dose CYC (2mg/kg) was reported to induce remission in 90% of WG cases[17] and approximately 80% of mPA.[50] Unfortunately its use is accompanied by significant morbidity.

Haemorrhagic cystitis is a particular risk associated with CYC caused by the excretion of the toxic metabolite acrolein through the bladder and has been reported in 43% of patients

in one study.[18] Later series however have noted lower percentages of 12% and 1.9% (metaanalysis).[34,103] Similarly bladder cancer has been reported in 1, 2.4 and 2.5% of cases, corresponding to a standardised ratio of 4.8 and a 33-fold increased risk compared to the denominator population in the latter two studies.[18,34,36] Infection is a complication of all types of immunosuppression. 46% of 158 WG cases required hospitalisation for infection in one study and 69.6% in another where patients received oral CYC but also high dose steroids.[18,103,104] Elsewhere a high mortality rate caused by sepsis within the first three months of CYC treatment has been reported.[105] Another complication is amenorrhoea, reported to occur in 50-70% of female SLE patients and elevated FSH has also been noted.[106,107] Bone-marrow suppression also occurs and lymphopenia and leucopenia are commonly seen. Most cases are reversible with reduction or cessation of treatment but myelodysplastic syndromes have been reported in 3.3-8% of cases.[18,36] Additionally an increased risk of malignancy overall has been demonstrated although it is unclear whether all cases are associated with immunosuppression. Hoffman et al reported a 2.4 fold increase in all malignancies and an 11-fold increase in lymphomas whilst Westman et al noted solid tumours in 12.2% of cases (SMR 1.6) and non-hodgkin lymphoma in 0.8% (SMR 3.7).[18,36] No specific cancer type has been associated with PSV although 5 cases of skin cancer, giving a SMR of 10.4 occurred in the latter study and Tatsis et al reported an odds ratio of 1.79 (95% C.I. 0.92-3.48) for malignancies in WG with an unusually high occurrence of renal cell carcinoma.[108] Many other types have been reported including breast, vulva, prostate and testicular tumours. Less severe side-effects of CYC include nausea and malaise at the time of administration and alopecia. The development of treatment regimens was therefore aimed towards maintaining an effective response but minimising side-effects.

A course of intravenous (IV) CYC pulses gives lower cumulative doses and potentially reduces toxicity. However, although it had been used successfully in SLE[109] and rheumatoid vasculitis[110] IV CYC was widely considered to be less efficacious in PSV. This

was mainly due to a study by Hoffman et al in which only 2 of 11 PSV patients maintained remission after an initial response to IV therapy. However 12 of the 14 patients included in the study had previously suffered relapses with oral CYC.[111] Additionally the Hoffman protocol used monthly pulses of CYC with daily prednisolone as described in the SLE protocol rather than the two-weekly pulses used to treat rheumatoid vasculitis. This difference in pulse interval may be important in determining the success of treatment in PSV. Reinhold Keller et al found that only 42% of 43 WG patients treated with monthly IV CYC (dose 667mg/ m^2) responded to treatment. The non-responders were reported to have more extensive disease and higher cANCA levels than responders but it should be noted that cANCA levels were higher in non-responders at baseline. They therefore concluded that IV therapy was unsuitable in severe and rapidly progressive forms of WG but suggested a role for its use in patients who: had moderately extensive disease with a low cANCA titre (<1:64); were in remission; or who discontinued oral CYC because of significant side-effects e.g. leukopenia or haemorrhagic cystitis.[90]

In contrast, Falk et al found no significant difference in patient or renal survival in ANCA-positive necrotizing and crescentic GN cases who had received monthly IV pulses compared to oral daily CYC, both with oral prednisolone.[112] Haubitz et al also found that IV and oral CYC were equally efficacious in their cohort of 23 WG patients with renal involvement.[113] In view of these findings they carried out a randomised control study comparing daily oral with monthly IV CYC in 47 mPA and WG patients. They found no significant difference between groups with regard to patient survival, remission rate, time to remission, relapses, renal function and renal survival. However there was significantly more toxicity experienced by those receiving oral treatment (Table 1.22) which led them to stop the study early.[107] The conclusion that both treatments were similarly efficacious based upon these results has been challenged due to the relatively small number of cases recruited and the need for a longer period of follow-up to establish renal outcome (there was a trend towards improved renal outcome with oral treatment CYC).[114] However as

there were no significant differences between age, clinical manifestations, disease extent or base-line BVAS and no significant difference in prednisolone dose between groups, the higher toxicity experienced by the oral group could be explained by the higher total and mean monthly doses of CYC received.

A case-control study by Adu et al compared IV pulse CYC plus pulsed IV methylprednisolone with continuous oral CYC and prednisolone for 3 months followed by Azathioprine maintenance. They found no difference in the frequency of deaths, relapses, treatment failures, improvement in disease activity and renal function between groups after a mean follow-up of 40.4 months. Survival was not significantly different at 3 years (77% for pulse CYC compared to 90% for continuous CYC). There was a trend to greater CYC-related toxicity in the continuous group (87%) compared to the pulse group (71%).[115]

Koldingsnes et al followed 11 patients who had received IV CYC for up to 9 years and described remission induction even in severe progressive disease although 60% relapsed, higher than reported for oral CYC. Because pulse intervals were shorter than other studies they suggested that the timing of pulses might be critical for IV CYC to be effective.

Guillevin et al carried out a prospective randomised trial of newly diagnosed WG patients and concluded that IV pulse CYC was as effective in achieving remission as oral CYC, was associated with lower side-effects and mortality but was less effective at maintaining remission or preventing relapses.[104] The European Vasculitis Study Group (EUVAS) was initiated following the discovery of the association of WG and cANCA to standardize ANCA assays and investigate its diagnostic role. Once standardisation had been achieved it became possible to carry out multicentre therapeutic trials in PSV. The results of the large ECSYSVASTRIAL randomised control trial of daily oral versus pulsed oral therapy (CYCLOPS) are awaited.[116] Details of studies are given in tables 1.23 and 1.24

In summary oral daily CYC appears to be effective in inducing and maintaining remission in a substantial proportion of patients but is associated with significant side-effects. Studies support the hypothesis that pulse IV CYC causes less toxicity but those comparing the

efficacy of IV and oral CYC have presented conflicting results and comparison is made difficult by varying treatment regimens and follow-up. Overall, results suggest that IV and oral CYC are equally efficacious in inducing remission but that oral CYC is superior in its maintenance.

OTHER IMMUNOSUPPRESSIVE TREATMENT

Azathioprine

An alternative approach to reducing side-effects is to use shorter courses of CYC to induce remission then to introduce alternative maintenance therapy. The results of an ECSYSVASTRIAL study, CYCAZAREM, which compares CYC with azathioprine (AZA) in disease maintenance were promising. All patients received the same regimen of oral CYC and prednisolone until remission at 3-6 months then randomised to either AZA or CYC up to 1 year. After 18 months follow-up there was no significant difference in relapse rate and there was a non-significant trend towards lower toxicity with AZA. Mortality and relapse rates were overall better than expected and remission occurred in 93% at 6 months.[116] Westman et al also reported no significant difference in mortality between WG and mPA patients who received AZA as induction treatment compared to CYC.[36]

Methotrexate

The NIH group has described the use of combined daily steroids and methotrexate (MTX) in WG. Patients were excluded if serum creatinine levels exceeded 2.5mg/dl due to the increased risk of MTX toxicity in renal failure or had significant lung disease. An analysis of 42 patients showed remission in 71% of patients in a median period of 4 months and prednisolone could usually be discontinued by 7 months. However this protocol was not without toxicity, 9.5% developed opportunistic infection including pneumocystis carinii

pneumonia (PCP) with infection reported to contribute to 2-3 deaths. In addition although cystitis and bladder cancer are not associated with MTX there is a small increased risk of other malignancies. MTX can also cause pneumonitis, dose-related bone-marrow suppression, liver dysfunction and may affect fertility. Some of the main side-effects associated with MTX may be attributable to accompanying steroids. Unfortunately a similar percentage of remissions achieved by MTX also relapse, in one study 36% who achieved remission relapsed after about 29 months, usually when MTX dose was tapered.[117] Similarly Stone et al described the use of MTX and prednisolone in 19 cases of non-life-threatening WG. 17 of the 19 showed improvement and 14 achieved remission, but all relapsed.[118] MTX may therefore be a suitable alternative to CYC in the initial treatment of patients without immediate life-threatening disease but the problems of toxicity and relapses remain.

Steroids

Most treatment regimens include the use of steroids to variable degrees. It is well known that steroids are associated with significant side-effects, including osteoporosis, hypertension, induction of diabetes and potentially increasing infection risk, and may contribute to toxicity reported in studies. For example the cohort reported by Guillevin et al experienced a very high incidence of severe infections 40.7 and 69.6% in the IV vs oral group. The treatment regimen included high doses of steroids (Table 1.24).[104] In general the aim is to keep the use of steroids to a minimum although high dose IV methylprednisolone may have a particular role in refractory renal disease (see below).

Trimethoprim / sulfamethoxazole

De Remee et al first observed beneficial results of trimethoprim and sulphamethazole (T/S) in 1985 but subsequent reports produced conflicting results as to its efficacy.[119] Studies were difficult to compare because most reported cases received different additional immunosuppressive drugs. Reinhold-Keller et al carried out a prospective study of 72 WG patients at various disease stages comparing the use of T/S alone or T/S and prednisolone. They found that neither was effective in sustaining remission in generalized WG.[120] More recently the same group assessed the effectiveness of MTX in maintaining remission in patients with generalized WG and compared results. They found that low dose MTX was superior to T/S in retaining remission and therefore recommended that neither T/S alone or T/S plus prednisolone were suitable in the maintenance of remission in WG.[121] However T/S may have a place in the treatment of WG affecting the upper airways and has been shown to reduce relapses of nasal and upper airway disease in WG patients in remission.[122] An explanation for this effect is the eradication of nasal staphylococcus aureus, which may be responsible for precipitating relapses. Therefore another potential treatment option is the application of nasal mupirocin ointment, which is being studied by the ECSYSVASTRIAL group in the MUPIBAC study.[116]

Treatment of Refractory Vasculitis

Intravenous immunoglobulin (IVIG), plasmapheresis and high dose IV methylprednisolone are treatment options in resistant cases of PSV. Most data is available as case-reports and uncontrolled trials but Jayne et al carried out a placebo-controlled trial of IVIG. This suggested that a single course of IVIG reduced disease activity in ANCA-associated vasculitis with persistent disease, although the effect did not extend beyond 3 months.[123] Plasmapheresis and high dose IV methylprednisolone are thought to be of particular benefit in renal disease. These two treatment modalities are being evaluated in a

randomised controlled trial (MEPEX) by the ECSYSVASTRIAL group. A trial initiated to investigate IVIG however did not go ahead due to the expense and availability of IVIG and concerns about the transmission of prion disease. An additional trial (SOLUTION) has commenced to assess the role of polyclonal anti-thymocyte globulin in active refractory vasculitis.[116]

Prevention of Toxicity

In addition to refining treatment regimens for PSV, measures to reduce known side-effects can be instituted. To reduce the risk of the bladder toxicity associated with CYC patients should be asked to have a high oral intake of fluids and to take mesna (sodium 2-mercaptoethane sulphonate). Mesna is oxidised in the body and binds to acrolein the toxic metabolite of CYC responsible for haemorrhagic cystitis, in the bladder.[93] However as it has only a short half-life its use is probably only practical with pulsed therapy. Three doses are administered; one at the time of the pulse if given IV or 2 hours prior to administration if given orally, then 2 others 2 and 4 hours post infusion.

Some centres use septrin as prophylaxis for pneumocystis carinii pneumonia but the incidence of this complication varies. Guillevin et al reported a high incidence of PCP in their cohort and recommend routine use of septrin but few cases are seen in other centres. It is interesting to note the relatively close proximity in HIV positive patients with PCP to the vasculitis patients in the French centre[104] but a low incidence of CYC related PCP in Norwich (2 cases in 11 years amongst patients treated with CYC- one oral and one IV pulsed therapy). The risk of PCP in patients treated with CYC may therefore be related to the background level of infection. A history of varicella zoster infection in individuals receiving CYC should also be sought and vaccination considered in those without a positive history. Premature ovarian failure is another possible side-effect of CYC and the

option of ovarian biopsy and storage may need consideration as advancing technology may offer a second chance of fertility in affected women in the future.[124]

Survival in PSV

As described, survival in PSV has improved dramatically with 1-year survival figures of up to 99% reported in WG.[34] Table 1.23 compares survival figures and standardised mortality ratios (SMRs) reported in various studies. Early survival appears to be worse in mPA compared to WG with 1-year survival reported as 10-70% compared to 84-99% in WG. However 5-year survival is similar with reported figures of 65% in mPA compared to 57-88% in WG. Reported survival in CSS was 76% at approximately 18 months.[45]

Differences noted between cohorts may be caused by variation in classification, referral patterns and treatment regimes. For example Guillevin et al described an unusually high mortality amongst their cohort (20% at 6 months and 38% by a mean follow–up of 31month) compared to 20% mortality within the NIH cohort at 8 years follow-up. This difference may be explained by the case-mix in the NIH cohort, which was recruited from a wider area and included patients fit to travel long distances. Additionally some early deaths may have been excluded if they occurred prior to referral. Treatment regimes also differed and the French group aimed to induce a least a mild leucopenia following CYC and used higher doses of steroids, which may have increased treatment-related deaths.[18,104]

Genetic factors may also contribute to variations. Nine out of ten Chinese patients who presented to a tertiary referral centre over 3 years died, with a mean survival of only 9 months (range 1-33). A high proportion (70%) had pulmonary haemorrhage compared to other series but treatment regimes seem comparable. The poor outcome could be attributed to race although unknown environmental factors could predispose these patients to lung involvement, there may have been unknown referral biases and in at least one case the cause of death was miliary T.B. so a misdiagnosis of TB is possible.[52]

The relatively high survival rates of 35 WG patients with GN and ESRF (93% at 2 years and 79% at 5 years) may reflect the exclusion of severely ill patients who died prior to the initiation of chronic dialysis.[125]

It has also been suggested that PSV may be more aggressive and have a poorer outcome in the elderly. Vassallo et al compared 29 WG patients aged less than 60-years-old with 22 over 60-years-old. They found a reduced survival for the older patients despite similar treatment regimes. Causes of death did not suggest that these individuals were more vulnerable to immunosuppression but reflected active vasculitis in most cases. The authors suggested that the elderly experience more severe, treatment-resistant disease than younger patients although they found no significant differences in clinical features between the groups. They did not attempt to adjust these figures for the expected difference in mortality between the age groups within their denominator population.[35] Westman et al found that age and serum creatinine at the time of referral were significant prognostic factors for death (p=0.028 and 0.0002 respectively) in their cohort of 56 WG and 67 mPA patients. They found no significant difference between gender and clinical diagnosis (32% WG died vs 30% mPA) but a non-significant trend towards mortality with high titres of PR3-ANCA was noted.[36]

Hoffman et al also found no difference in survival between men and women.[18] In a review of the long-term survival of the 85 patients enrolled in the ACR classification cohort women had a higher SMR than males (6.81+/- 1.57 compared to 4.00 +/- 0.69) although the difference was not significant (p=0.068). Overall the mortality of WG patients exceeded that of the US and Canadian populations with an SMR of 4.69 +/- 0.65. A rapid decrease in survival was noted in the first year of disease and at five years survival was only 75% of that expected for the general population. Apart from the presence of an abnormal chest X-ray they found no associations of any clinical features with mortality and they found no significant differences in mortality according to age at disease onset using the Cox proportional hazards model.[126] Luqmani et al found significantly higher mortality

amongst 28 WG patients with renal involvement, especially with renal failure at presentation, compared to 22 with non-renal WG (there were no deaths in this group). There were no other poor prognostic indicators.[13]

In summary, survival has improved amongst PSV patients. Outcome appears to be worse in mPA in the early stages of disease compared to WG but is similar later on. Patients with renal involvement, infiltrates on chest X-ray and females have been reported to have a poorer prognosis. Elderly patients also have a higher mortality than the younger group although this difference may reflect the expected excess of mortality between age groups rather than variation in disease severity or response to treatment.

Table 1.22 Comparison of toxicity between pulse IV and daily oral CYC [107]

Side-effect	Oral CYC	IV CYC	p-value
Leucopenia (<3,000/μl)	60%	18%	p<0.01
Lymphopenia<400/μl	86%	47%	<0.01
Thrombocytopenia<80000/μl	14%	0%	-
Infection	47.6%	15%	p<0.056
Haemorrhagic Cystitis	0%	0%	-
Nausea	24%	55%	-
FSH levels	40.2 IU/l	10.1 IU/l	-

FSH = Follicle stimulating hormone

Table 1.23 Comparison of Relapse, Survival and Death in PSV

Study	Year	No. patients	Diagnosis	Relapses % cases	Survival	Cause of deaths
Savage[50]	1985	34	mPA	35.3%	70% 1 year 65% 5 years	Early - 1 sepsis (no Rx), 3 lung haemorrhage, 1 sepsis, 1 MI, 2 pneumonia Late - 2 unrelated, 1 PCP, 1 CVA, 1 subarachnoid
Fuiano[53]	1988	20 26	'Acute' mPA$^{\phi}$ All mPA$^{\phi}$	-	77% 5 years 80% 5 years	4 early – 1 septicaemia, 1 pneumonia, 2 cardiorespiratory failure
Falk[112]	1990	70	ANCA +ve ncGN	-	75% 1yr	Early – 4 pulmonary haemorrhage, 1MI, 1GIT and sepsis; Late-1 MI, 1 bladder Ca (no CYC), 3 infection
Hoffman[18]	1992	158	WG	-	80% 8 years	13% WG, 2.5% malignancy, 3% infection
Abu-Shakra[48]	1994	13 12	PAN CSS	83% 42%	69% mean 4.2 months 92% mean 5.5months	3 active disease (2 GIT, 1 CNS); 1 TB 1 pulmonary embolism
Luqmani[13]	1994	22 28	Non-renal WG Renal WG	31.8% 39.3%	100 % 1 year 78.6% 1 year	3 early deaths- active disease 3 late deaths- 1 relapse, 1 sepsis, 1 unknown
Li[52]	1995	10	MPA	40.0%	10 % mean 9 months	4 pulmonary haemorrhage, 1 miliary TB, 1 IHD, 1 uraemia, 1 CVA, 1 E coli sepsis, 1 pulmonary oedema
Matteson[126]	1996	85**	WG	-	SMR- 4.69+/-0.65 SMR F 6.81 +/1 1.57 SMR M 4.00 +/-0.69	8 Infection, 5 cardiac disease, 5 renal failure, 4 malignancy, 3 unspecified, 2 pulmonary disease, 1 stroke
Vassallo[35]	1997	29	WG (<60yrs)		73.4(3-93)	8 early vasculitis, 2 vascular events 4 ESRD, 1 septicaemia, 1 bronchopneumonia, 1 Ca uterus, 3 unknown
		22	WG (>60yrs)		8.9(<1-65)	

$^{\phi}$ Some patients probably classifiable as WG;* Haemorrhagic cystitis, amenorrhoea, nausea, transient aplasia, dysmyelopoiesis
diabetes, glaucoma, osteoporosis with fractures **Patients from the ACR classification cohort

Table 1.23 (Cont.) Comparison of Relapse, Survival and Death in PSV

Study	Year	No patients	Diagnosis	Relapses % cases	Survival	Cause of deaths
Guillevin[104]	1997	23	WG (Oral CYC)	48.0%	57% 5 year	2 alveolar haemorrhage, 4 PCP, 1 bacterial pneumonia, 1 septic shock, 1 suicide, 1 CVA
		27	WG (IV CYC)	37.0%	66% 5 year	1 lung haemorrhage, 1 renal & 2 multi-organ failure, 2 PCP, 1infection, 1 suicide, 1 CVA
Westman[36]	1998	56 67	WG mPA	40% CYC 89% AZA	91% 3 months 69% overall	-
Haubitz[125]	1998	35	WG ESRF	-	93% 2 years 79% 5 years	2 bone marrow insufficiency, 1 sepsis post leucopenia, 2 IHD, 1 IHD+/- vasculitis
Haubitz[107]	1998	21	WG / mPA (Oral CYC)	28.6%	84% 2 years 78% 3 years	1 pulmonary vasculitis + sepsis 2 sepsis (by 2 years)
		20	WG / mPA (IV CYC)	40.0%	100% 2 years 90% 3 years	-
Guillevin[45]	1999	96	CSS	-	76.0% ~18mnths	11 vasculitis (5 CVS, 2 GIT, 4 sudden death), 2 anticoagulant overdose, 1 septicaemia, 1 diverticulitis, 2 respiratory failure, 2 asthma, 2 Ca stomach/colon, 1 anaphylaxis, 1 unknown
Koldingnes[127]	2000	56	WG	57%	93% 1 year 79% 5 years 75% 10 years	Early – 4 active disease Later 6 active disease, 2 MI
Reinhold-Keller[34]	2000	155	WG	64.0%	99% 1 year 97% 2 years 88% 10 years	19 related to WG and / or Rx (7 MDS, 5 infection, 6 other) 2 Ca (lung- no CYC / metastatic adenoca) 1 MI, no active WG

SMR = standardised mortality ratio; ncGN = necrotising crescentic glomerulonephritis; Rx = treatment; CYC=cyclophosphamide, AZA= azathioprine, ESRD= End-stage renal disease, Ca= cancer; PCP = Pneumocystitis carinii pneumonia, CVA = Cerebrovascular accident, IHD = Ischaemic heart disease, CVS = cardiovascular system, GIT = gastrointestinal system, MI = Myocardial infarction, MDS = myelodysplastic syndrome

Table 1.24 Comparison of Treatment Regimens Between Studies in PSV

Study	Year	No.	Diagnosis	Cyclophosphamide & Other Immunosuppressants	Steroid Use	Prophylaxis	Renal Reduction
Savage[50]	1985	34	mPA	CYC 3mg/kg/day for 8 weeks (27cases) + AZA in 17 cases AZA alone (3 cases)	32 cases oral prednisolone 60mg/day reduced to 30 mg/day by four weeks and then slower to maintenance dose 5-10mg for 1 year or longer	N	N/A
Fuiano[53]	1988	19	mPA/WG	IV CYC 1.87 mg/kg/d (10cases) and maintenance AZA. 1.97 mg/kg/d (8 cases) + plasma exchange in 7 cases	IV methylprednisolone 1g for 3 days (15 cases) followed by oral prednisolone maintenance	-	-
Reinhold-Keller[90]	1994	43	WG	IV CYC (mean 667mg/m^2) every 4 weeks. N.B. 31 had previous daily po CYC	IV 100mg prednisolone with pulse CYC 27/43 also oral prednisolone	Mesna	N
Guillevin[104]	1997	50	WG	IV CYC 0.7g/m^2 every 3 weeks until 1 year post remission. Intervals then increased to 4 weeks for 4 months then 6 months up to 2 years duration. Oral CYC 2 mg/kg/day. 1 year after remission dose reduced by 25% every 3 months until discontinuation	IV MP 15mg/kg for first 3 days. Oral prednisolone 1mg/kg/day for 6 weeks. If remission taper 2.5mg / day to reach half starting dose. After 3 weeks reduce 2.5mg / 10days to 20mg/day then 1mg / 2 weeks to 10mg then 1mg / month and stop	PCP after 12 patients	Y
Adu[115]	1997	54	cPAN (8) mPA (17) WG (29)	A. IV CYC 15mg/kg/day 2 weekly, oral CYC 5mg/kg, 3 consecutive days, three weekly B. Continuous oral CYC 15mg/kg reduce with renal disease	A. Pulse prednisolone B. Continuous prednisolone 10mg/kg	-	-

Table 1.24 (cont.) Comparison of Treatment Regimens Between Studies in PSV

Study	Year	No.	Diagnosis	Cyclophosphamide & Other Immunosuppressants	Steroid Use	Prophylaxis	Renal Reduction
Koldingsnes[38]	1998	11	WG	IV CYC15mg/kg 2/52 until remission then less frequently for 1 yr or remission. From 1990 oral Rx after 3-6 pulses	Initial Rx 0.75-1g MP 3/7 then 1987-90 7.5-1g MP with each treatment 1990- 50mg prednisolone orally on day of treatment	PCP post 1992	Y
Cohen-Tervaert[36]	1998	56 67	WG mPA	Oral CYC 2mg/kg/day AZA 1-2 mg/kg after 3-6 months remission	Prednisolone 1mg/kg/day, taper to 15-20mg by 3 months		
Haubitz[107]	1998	47	WG	IV CYC 0.75 g/m2 for 4 weeks Oral CYC 2mg/kg/day CYC stopped at 1 year if 6 months remission	0.5g MP first 3 days next 4-14 days 1mg/kg/day next 15 days taper 10mg /week at 30mg taper 5mg/week at 15mg taper 2.5mg/week.	N	Y
Reinhold Keller[34]	2000	142 155	WG	2-4 mg/kg/day p.o (severe disease) CYC pulses for less severe disease Maintenance MTX or AZA after remission	Oral prednisolone 1mg/kg/day reduced to 5-10mg/day in first 3-6months then taper 1mg/month	Mesna	N

CYC=Cyclophosphamide, AZA=Azathioprine, MP= Methylprednisolone, PCP = Pneumocystis carinii pneumonia, Rx = treatment,

VI. Epidemiology of Primary Systemic Vasculitis

Introduction

Historically it was difficult to study the epidemiology of PSV due to the heterogeneous classification of disease and the fact that they are relatively rare disorders. Tertiary referral centres with a special interest in PSV have carried out most studies and as a result the denominator populations were usually poorly defined. These studies were also prone to referral bias which suggests that figures obtained may not be representative of the full clinical spectrum of disease seen in the community. Early reports of incidence figures must therefore be interpreted cautiously, especially in the case of polyarteritis nodosa, which was used as a generic term for any form of necrotizing vasculitis in many older studies. The introduction of the ACR (1990) classification criteria and CHCC definitions has allowed uniformity in classification, so valid comparisons may be attempted between more recent studies. However inter-observer variation in the application of criteria remains a limitation.

Annual Incidence of Primary Systemic Vasculitis

We have prospectively studied the incidence of PSV in the adult population of Norfolk over a ten-year period to obtain annual incidence figures in a well-defined, stable population. This work was directly related to the thesis and full details are provided in Appendix 3 / Chapter 4. Overall the annual incidence of PSV in Norfolk was found to be 19.8 /million /year (95% C.I. 15.8-24.6) for individuals classified as WG (ACR 1990), mPA (CHCC 1994), CSS (ACR 1990) and PAN (ACR 1990).[41,42,60,84,128] PSV was more common in males (23.5/million; 95% C.I. 17.3-31.3) than females (16.4/million; 95% C.I. 11.4-22.8) and the peak age was in the 65 to 75 year-old age group for both men and women.[128]

The annual incidence was higher than for previously published results and the peak age was higher. More recent reports from Sweden (WG, mPA and renal limited vasculitis) and Norway (ACR 1990 PAN, WG and CSS) however give similar annual incidence figures [16.0 (95% C.I. 12.0-31.0) and 17.2 (95% C.I. 9.2-29.6) respectively] but peak age was 55-64 in the first case and not given in the second.[129,130] Unpublished data (presented at 'Vasculitis – Aims of therapy', September 1999) from Crete and Exeter report similar incidence figures and age distribution in their population based cohorts. Daphnis et al found an annual incidence of 20.0/ million in Crete with a peak incidence at 63-years whilst Satchell et al reported an incidence of 12.0/million/year with peak age 69-years.[131,132] The most likely explanation for the lower average age of patients in earlier studies is the effect of referral bias because most were carried out in tertiary referral centres. Most studies suggest that PSV of all classifications is more common in men than women.

Temporal changes in Incidence of PSV

The higher incidence noted in recent studies compared to earlier reports might be caused by an increase in the incidence of disease over time. Several studies have noted a trend towards an increasing incidence of PSV within a study population including a non-significant trend in the Norwich cohort.[128] Andrews et al noted a significant increase ($p<0.0001$) in the combined incidence of WG and mPA between the first and second half of their study period [Annual incidence, 1980-86 1.5/million compared to 6.1/million between 1987-89].[133] Similarly an increase was noted in WG in Norway with an increase in annual incidence from 5.2/million (95% C.I. 2.7-9.0) for the years 1989-93 to 15.6/million (95% C.I. 8.0-17.3) for the period 1994-98.[134] These findings may be attributable to a real increase in disease which could represent a cohort effect with some change in environmental factors either in utero or at birth or immediately prior to the onset

of vasculitis. Alternatively they could be explained by the improved recognition of PSV by physicians, especially with the introduction and increasing use of ANCA testing over the period in question, and changes in the nomenclature of disease. There may also have been under-ascertainment of cases within a population in the early years of a study compared to more recent years, especially when cases were reviewed retrospectively.

Tidman et al described a periodic fluctuation in the incidence of ANCA positive vasculitis with peaks every three to four years between 1975–95 which is suggestive of an infectious trigger of disease but no specific infection was detected and to date these findings have not been reproduced.[130] Seasonal variation in disease, which may also indicate an infectious or other environmental trigger factor, has been described but reports are not consistent. (Table 1.25) Studies varied in terms of geographical regions, duration (from 5-21 years), patient numbers and disease definition. Most were tertiary centres so results might be affected by referral bias but the Norwich and Swedish studies were population based. Most studies defined winter as December to February (inclusive) but once again this varied between reports. All, except Duna and Koldingnses et al[134,135], reported a winter peak although results were not significant in two studies.[136,137]

Table 1.25 Studies of Seasonal Variation in Primary Systemic Vasculitis

	Population	TR / DH	Years F/U	No. Patients	Diagnosis	Findings
Tidman[130]	Orebro, Sweden	1TR 2DH	21	83	cANCA SVV	Winter Peak* p=0.011
				10	WG (CHCC)	Nil significant
				70	mPA (CHCC)	Nil significant
Falk[112]	North Carolina, USA	MixΨ	5	70	ANCA +ve SVV renal biopsy proven	Winter peak* p<0.05
Duna[135]	N.I.H. & C.C.F, U.S.A	TR	6	101	WG (ACR)	Nil significant**
Raynauld[137]	U.S.A, Mexico, Canada	48TR	5	84	WG(ACR)	Winter Peak*, p=0.04 Summer trough
				118	PAN(ACR)	Nil significant
				213	GCA(ACR)	Nil significant
Geffriaud-Ricouard[136]	Paris, France	Unknown	4	98	ANCA +ve	50% Oct-Jan; 24% June-July 12% 'Spring'
Carruthers[16]	Norwich, UK	DH	5	21	WG(ACR)	Winter Peak* Autumn Trough
Koldingsnes[134]	Tromso, Norway	TR/DR	15	55	WG (ACR)	Nil significant

* Dec – Feb Ψ120 university and private nephrologists +ve = positive
TR = Tertiary referral centre; DH = District hospital; SVV = small vessel vasculitis ; N.I.H. = National Institutes of Health
C.C.F = Cleveland Clinic Foundation

Epidemiology of Polyarteritis Nodosa and Microscopic polyangiitis

Polyarteritis Nodosa

Several early studies estimated the incidence of PAN to be between 2.0 and 9.0 million/ year.[138,139,140,141] These studies included patients who would now be termed 'classical PAN' (cPAN) and/or ACR (1990) PAN but also those who would be defined as mPA. In addition other types of vasculitis including CSS may have been included, suggesting that these figures were overestimates.[2] One early study by McMahon et al stands out, with an estimated incidence of 77/million /year.[142] This unusually high figure was detected in a population of 14,000 Alaskan Indians who had a very high incidence of hepatitis B and were hepatitis B surface and e antigen positive at diagnosis. This finding contributed towards establishing the association between cPAN and hepatitis B.

More recently the annual incidence of PAN defined by the ACR (1990) criteria has been described as 8.0/million (95 % C.I. 5.5-11.2) in Norwich and 6.9/million (95% C.I. 3.2-10.6) in Lugo, Spain.[128,143] Cases in the Norwich study were aged over 15-years-old compared to over 20-years-old in the Lugo study. These results are in keeping with previous reports but include individuals who can also be classified as WG and CSS by the ACR (1990) criteria. There does not appear to be a trend towards increasing incidence of PAN and it may in fact be reducing. It has been suggested that this reduction is due to a concurrent reduction in hepatitis B infection although data about hepatitis B status is not available for patients in earlier studies.[45]

Classical PAN as defined by the CHCC (i.e. similar to the original description by Kussmaul and Maier and characterised by organ infarction) appears to be much less common than previously reported. No cases have been detected in the Norfolk population

over a twelve year period and the annual incidence in Spain was only 1.1/million/year (95% C.I. 0.1-3.8). This reduction in incidence is probably due to reclassification.[144] One report gives an unusually high figure for cPAN[145] (defined as 'either renal histology showing necrotizing inflammation of small and/or medium sized arteries without glomerulonephritis (GN) or renal arteriography showing microaneurysms, stenoses or occlusions in the coeliac and/or renal arteries, not due to atherosclerosis, fibromuscular dysplasia or Takayasu's disease'). Eight cases were detected between 1993-96 in their Kuwaiti National population (ex-patriates were excluded) giving an annual incidence of 16.3/million (95% C.I. 7.1-32.1). This population did not have a high incidence of hepatitis B so an alternative explanation is needed. A higher number of cases may have been detected compared to other studies because of the frequent use of angiography but this is unlikely to fully explain the excess. Alternatively the Kuwaiti nationals may have a genetic preponderance to develop cPAN or some environmental factor may have made them more susceptible, e.g. exposure to silica in sandstorms, hydrocarbons from the oil industry or pollutants associated with the Gulf War (just prior to the study).[145]

Microscopic Polyangiitis

The annual incidence of mPA was found to be 8.0/million/year (95% C.I. 5.5-11.2) in the Norfolk population[128] which is comparable to the figure obtained by the Spanish group of 5.8 (95% C.I. 2.9-10.4) over the same period but higher than earlier reports (Table 1.26). An earlier report from Norwich also gave a lower result of 2.4 /million/year (95% C.I. 0.9-5.3).[146] This discrepancy is explained by an extended search of the histopathology database for renal biopsies leading to the identification of additional cases e.g. previously diagnosed as rapidly progressive GN and also the reclassification of all patients in the study, highlighting the problem of applying subjective definitions.

There have been few reports of the incidence of mPA from non-Western countries but unpublished estimates from Japan suggest an annual incidence for mPA of 10 /million/year compared to 1/million per year for cPAN.[2] In the Kuwaiti population the annual incidence of mPA was also unusually high with an annual incidence of 24.7/million (95% C.I. 12.7-42.8). In contrast it is thought to be very rare in the Chinese, although when it does occur it may be more severe.[52] It has also been reported in patients of many ethnic groups including the Indian sub-continent, Phillipines, Indonesia, Somalia, Egypt, Iraq and Syria.[147,148]

Renal Limited Vasculitis and Pauciimune Rapidly Progressive GN

Pauciimmune rapidly progressive glomerulonephritis (RPGN) is regarded by some investigators to be a limited or localised form of mPA. Prior to the introduction of the CHCC definition of mPA several studies have investigated the epidemiology of renal vasculitis using various histological and laboratory definitions. Andrassy et al studied the annual incidence of crescentic GN and RPGN in Heidlberg, Germany between 1984-89 and found an annual incidence of 7.0/million in their population of 930 000. This figure included patients with SLE, Goodpastures and IgA nephropathy in addition to HSP, mPA and WG.[57] In Huddinge, Sweden 71 new cases of pauci-immune necrotizing and crescentic GN between 1986 and 1992 in their adult population of 1.2 million giving a mean annual incidence of 6.0/million.[149] They also noted that the incidence doubled from 6.0/million in 1986 to 12.0/million in 1992. Both reports suggested that the incidence of renal vasculitis was increasing. In contrast a study in Wessex, U.K., (1986 to 1996) found an annual incidence of biopsy proven RPGN of only 3.5/million, which was stable throughout the period and the Italian Registry of renal biopsies reported an annual incidence of only 1.6/million for necrotizing vasculitis in 1993.[150,151]

Table 1.26
Comparison of Annual Incidence of mPA Between Studies

Study	No. Cases	Years	Place	A.I./ million	95% C.I.
Westman[36] *	67	1971-93	Lund, Sweden	2.4	1.9-3.1
Andrews[133] **	18	1980-89	Leicester, UK	1.38	8.2-21.9
Andrassy[57] *	7	1984-89	Heidlberg,Germany	1.3	0.5-2.74
Watts[128] **	33	1988-97	Norwich,U.K.	8.0	5.5-11.2
Gonzalez-Gay[143] *	11	1988-97	Lugo,Spain	5.8	2.9-10.4
El-Reshaid[145] **	12	1993-96	Kuwait	24.5	12.7-42.8

* Renal involvement only; **CHCC consensus defi nition [42]

Table 1.27
Comparison of Annual Incidence of WG Between Studies

Study	No. Cases	Years	Place	A.I./ million	95% C.I.
Westman[36] *	56	1971-93	Lund, Sweden	2.0	1.5-2.6
Andrews[133] **	18	1980-89	Leicester, UK	1.38	8.2-21.9
Andrassy[57]	13	1984-89	Heidlberg,Germany	2.5	1.3-4.2
Watts[128] *	40	1988-97	Norwich,U.K.	9.7	7.1-13.5
Gonzalez-Gay[143] *	9	1988-97	Lugo, Spain	4.8	1.7-7.9
Haugeberg[129]	9	1992-96	Kristiand, Norway	11.9	5.5-22.7
Koldingsnes[134] *	55	1984-1998	Tromso, Norway	9.3	7.0-12.2

* ACR (1990) WG[41] **Fauci definition of WG[17]

Epidemiology of Wegener's Granulomatosis

The annual incidence of WG (ACR 1990) in Norfolk (1988 -1998) was 9.7/million (95% C.I. 7.1-13.5), which is higher than almost all previous reports. (Table 1.27). [128] The exception is a report from Tromso, Norway, which described an annual incidence of 9.3/million (95% C.I. 7.0-12.2) for 1984-1998 (Table 1.27).[134] In both studies an increase in the incidence of WG with time was noted. In the former the annual incidence was 10.3 (95% C.I. 6.4-15.5) for 1993-1997 compared to 14.4 (95% C.I. 9.5-21.0) in the latter, which is the highest published incidence figure for WG. Anecdotally WG has been thought to be more common in the North compared to the South of Europe but a study compari ng the incidence in the North with South of Germany failed to find a difference.[152] Although Gonzalez-Gay et al did not report incidence figures for the later part of their study comparison of the incidence figures for WG from Norway, Norwich and Lugo suggests a trend towards increasing incidence with latitude.[128,134,143] If this trend could be confirmed it would certainly provide support for a hypothesis that environmental factors are important in the aetiology of WG and attention could be focused upon differences in lifestyle between regions, e.g. diet, industry, pollution or amount of ultraviolet light exposure. The difference in the incidence of PSV between these regions was formally examined and the study is discussed in Chapter 4/ Appendix 3

Cotch et al estimated the prevalence of WG to be 26.0/million individuals between 1986 and 1990[153], Haugeberg et al reported a prevalence of 53/million in Norway in 1996 [129] and the point prevalence in Norwich on 31 December 1997 was estimated to be 63.8/million. [128] The differences may be explained by a geographical variation in disease or differences in case ascertainment (the population based study in Norwich is likely to have better capture than the estimate based upon hospitalisations in the first report). No stud ies have formally reported the incidence of WG in non-Western regions but anecdotally its incidence seems rare. In Japan and India it was estimated to be approximately 1/million/year[148] and only 20 cases were seen

in 10 years at the Apollo hospitals, Chennai, India although the population served is not reported.[154] Case series suggest that WG is becoming more frequently recognised in India.[155] The low incidence in developing countries may be due to true geographical variation but under- recognition of disease is also likely to contribute significantly due to differences in the provision of healthcare and the potential for misdiagnosis in areas where tuberculosis is common are also likely to contribute considerably.

Early data from Norwich suggested a weak trend towards increased incidence of WG in the built up areas of Norfolk compared to rural areas.[156] However Cotch et al noted that the prevalence of WG based upon hospitalisation data in New York State, adjusted for population density was highest in counties without a large metropolitan area, which may lead to speculation that in fact rural factors may be of more importance. However these findings were confused by the fact New York City itself also had a high prevalence.[153]

Epidemiology of Churg Strauss Syndrome

Few studies have estimated the annual incidence of CSS. The first incidence figure was estimated as 4.0/million/year in Olmstead County, Minnesota but this result was based upon a single case seen between 1976-79.[138] CSS does appear to be the rarest of the primary systemic vasculitides. In Norfolk we estimated the annual incidence of CSS (ACR 1990) to be 2.7 (95% C.I. 1.3-4.8) and Gonzalez-Gay estimated an annual incidence of 1.1/million (95% C.I. 0-2.5) in their adult population, based upon 2 observed cases.[128,143]

Similarly Haugeberg et al found only 2 cases in their population between 1992-96 giving an annual incidence of 2.7 /million (95% C.I. 0.3-9.6).[129] Early data from Norwich found that CSS was more common in the rural population compared to those living in built up areas although significance was not reached which suggested that a rural environmental factor may be of importance.[156]

Summary

It has recently become possible to estimate the incidence of PSV and make valid comparisons between studies using the ACR 1990 classification criteria and CHCC definitions. WG is more common than mPA and CSS occurs least frequently. The annual incidence of PSV may be increasing with time (especially WG and mPA), which could be due to a real increase in disease but could also be explained by changes in the classification of disease and increasing recognition by physicians, especially with the introduction of ANCA testing. Observation over longer periods will be necessary to confirm this trend. The onset of disease has also been noted to vary with the seasons and in periodic peaks but no definite link with infection of a particular seasonal risk factor has been detected.

Apparent geographical differences between regions also suggest that environmental and / or genetic factors may contribute to the onset and expression of PSV although some differences may be accounted for by variation in the application of classification criteria. Further studies using standardised methods are needed to advance our understanding of these observed differences.

VI. Environmental Factors and Primary Systemic Vasculitis

Introduction

Evidence supporting a role for environmental factors in the aetiology of primary systemic vasculitis (PSV) is growing including the temporal and geographical variations in disease previously described. Several factors have been reported in the literature to be associated with the development of vasculitis. These include silica, hydrocarbons, inhaled fumes and particulates, infections, drugs, allergy, vaccinations and desensitisation procedures.

Silica

Silicon is one of the earth's most abundant elements and exists in a wide variety of forms.[157] The major absorbable form encountered by man is soluble silicic acid, a principle solute in many natural waters in its monomeric form. Silica is ubiquitous worldwide but concentrations vary between areas in both water and soil.[158] It is thought to be an essential trace element in animals and humans playing a role in the normal development of bone and connective tissue. The soluble form has not been associated with toxicity.[159]

Plants absorb and accumulate silica to varying degrees via both active and passive mechanisms. High accumulators include rice, wheat and sugarcane. Silicic acid polymerises at solutions >2mM concentration to form insoluble silica, which has structural properties in some plants (e.g the epicarp hairs of wheat).[160] Humans may be exposed to these particles in agricultural environments, e.g. grain dust at harvesting and food processing.[161]

There are two forms of solid-state silica – amorphous and crystalline. Amorphous silica is favoured at low temperatures and pressures and crystalline at high temperatures. The resulting structures are determined by various factors including degree of hydration (glass vs sand) and age (quartz vs amorphous). Aluminium and other cations (e.g. Sodium,

Potassium, Magnesium) also become incorporated in silica matrices to form aluminosilicates with varying crystal structures and properties.[162] Silica and silicates therefore occur naturally in many forms including quartz, flint, granite, sandstone and slate. Silica is also used in industrial synthetic organic chemistry producing alternative silica polymers. Exposure to insoluble particulate silica is therefore inherent to many occupations including mining, quarrying, building, agricultural work, dentistry, industrial cleaning, ceramic and cement manufacture. It is these crystalline forms of silica, which pose a health hazard.

Silica and Disease

It is probable that silica per se does not cause lasting adverse effects. For example a nettle sting introduces amorphous silica protected by an organic layer into the skin. Irritation occurs whilst enzymes clear the foreign object but no ill effects persist once the silica has dissolved.[160] However insoluble crystalline silica cannot be removed in this way and adverse effects are thought to arise from the perpetuation of the immune response mounted in the attempt to do so. Crystalline silica has been directly associated with pulmonary silicosis (PS), strongly linked to oesophageal and other cancers[163,164,165,166] and reported to be associated with a variety of autoimmune diseases including systemic sclerosis, rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus.[167,168,169,170,171] Evidence for an association with glomerulonephritis (GN) and vasculitic syndromes will be reviewed.

The precise effects of silica on the immune system are not fully understood. In PS and scleroderma it has been suggested that alveolar macrophages become stimulated following the ingestion of crystalline silica particles causing inflammation and activation of fibroblasts.[161,172] When lysozymal enzymes fail to break down the silica, the macrophage is destroyed and a cycle of production and destruction results leading to a focus of

inflammation and fibrosis. In addition the immune system may become activated by the transport of silica particles to lymph nodes resulting in T-helper and B-cell production.[167] Experimental data supports an adjuvant effect of silica on the immune system[173], which is consistent with the hypothesis that it promotes autoimmune disease, requiring another event to actually break tolerance and initiate autoimmunity. The activated macrophage may upregulate cytokine production including IL1 and TNFα, which escalate the inflammation by stimulating other cells, and may activate T-helper cells, which in turn facilitate B-cell antibody production.[174] Silica may act via a Vβ-specific pathway in a superantigen-like mechanism and in vitro it has been shown to activate monocytes and macrophages, producing IL1, TNF α, O_2 radicals and lysosomal enzymes e.g. PR3 and MPO.[174] In vitro data supports the inactivation of alpha-1 antitrypsin (α-1AT), the natural inhibitor of PR3 by silica which may also induce the apoptosis of monocytes, macrophages or neutrophils. Apoptotic antigens would then become the natural targets for autoantigens. These findings support the hypothesis that silica may be involved in the generation of vasculitis.

Silica may also have a direct nephrotoxic effect.[175] Silica content of control kidneys was reported to be 21.6mg/kg dry body weight but was increased in a patient with idiopathic rapidly progressive GN (RPGN) and a tile factory worker with focal segmental necrotizing GN (264 mg/kg and 150mg/kg respectively).[175,176] Silica-induced cell injury has also been described to be dose dependent and site specific within the kidneys of transgenic mice.[177]

Renal Disease, Systemic Vasculitis and Silica

Renal disease associated with pulmonary silicosis and silica exposure

PS has been associated with renal disease including rapidly progressive renal failure characterised by crescentic GN and angiitis in coal miners, a crystal cutter and a tombstone sandblaster.[178,179,180] 7/17 PS patients described by Slavin et al had focal segmental necrotizing GN or proliferative GN with mesangial hyperplasia.[167] GN has also been described in individuals who did not have PS but had a history of prolonged occupational exposure to silica, including a 54-year-old foundry worker and a 44-year-old bricklayer.[181] Subclinical renal dysfunction, in terms of the urinary excretion of albumin, retinol-binding protein and beta-N-acetyl-D-glucosaminidase, has also been demonstrated in 116 male PS patients and 86 silica exposed workers without PS compared to controls.[182,183] Dysfunction was unrelated to the duration of exposure. Serum beta-2 microglobulin also showed a tendancy to rise in the PS group. Ng et al reported similar findings in 33 male silica exposed workers and 7 PS patients.[184] PS-associated GN is generally reported to be pauciimmune on immunofluorescence although non-specific granular IgM or C3 deposits and IgA and C3 deposits compatible with IgA nephropathy have been described.[174] It is possible that these early reports included ANCA-associated vasculitis including RPGN.

Several case-control studies support the association between renal disease and occupational silica exposure. An odds ratio (OR) of 1.67 for end-stage renal failure (ESRF) compared to the normal US population was reported amongst 325 men in Michigan (1976-84) following occupational silica exposure. ORs reported were 1.92 for exposure in foundries or brick factories and 3.83 for sandblasting. A later study (1987-95) found that 10% of 583 PS patients had evidence of chronic kidney disease whilst 33% had serum creatinine >1.5 mg/dl, significantly higher than age-race matched controls. No relationship was found between renal disease and duration of silica exposure or scarring on chest X-ray.[185] A significantly increased risk of ESRF was reported in 2980 male Italian ceramic

workers with or without PS and 2412 white male gold miners from South Dakota who had worked underground for at least one year (1940-65).[186,187] The standardised incidence ratio (SIR) for the exposed cohort compared to the US population was 1.37 (95%C.I. 0.68-2.46). The highest risk was associated with ESRF caused by GN (SIR= 4.22) and risk increased with duration of exposure. (SIR 7.70 in men working underground for 10 years or more). Standardised mortality ratios of 1.19 and 1.25 were found for acute and chronic kidney disease respectively amongst 3,328 miners.[188]

Various other reports suggest an increase in renal disease in populations exposed to high levels of silica. A review by Goldsmith et al described an excess mortality due to renal disease in construction trade and farm workers in California between 1979-81 and farmers between 1959-61.[189] In addition they noted that granite workers in Singapore excreted more albumin than controls and that in Negev, Israel, Beduins who have greater exposure to dust storms compared to their Jewish neighbours (whose housing affords greater protection) have a higher incidence of PS and ESRF in their elderly population.[189] Balkan nephropathy has also been associated with consumption of well water with high silica content.[190]

Systemic vasculitis and ANCA positive renal disease associated with silica

Case reports have also associated systemic vasculitis (SV) with PS. Michel et al reported a pulmonary renal syndrome characterised by haemoptysis and RPGN in two miners with PS. Alveolar haemorrhage and focal segmental, proliferative GN were found at autopsy.[174] A young woman developed SV with arthralgia, renal and cutaneous features fifteen years after silicosis of the lungs and liver caused by the intentional inhalation of commercial silica containing scouring powder. She relapsed when high dose steroids controlling her disease were reduced.[191] In the Spanish literature severe alveolar haemorrhage and RPGN

with necrotizing crescentic GN and arteritis complicated the PS of a quarryman and a granite mineworker and Susovik et al reported steroid responsive SV in a crystal cutter after forty years exposure to silica dust.[192,193]

A 55-year-old miner with a ten-year history of PS developed fever, weight loss, arthralgia, neuropathy and renal insufficiency. Arteriography showed multiple aneurysms and treatment with prednisolone and cyclophosphamide was successful.[194] In addition two of the PS patients with biopsy proven renal arteriolitis described by Dracon et al had haemoptysis and arthralgia compatible with mPA.[178] Siebels et al reported 2 cases of mPA and 1 limited WG in PS patients.[195] Neyer et al described a miner with PS for 7 years who developed fevers, arthralgias, necrotizing tonsilitis, pulmonary infiltrates and cANCA positive pauciimmune necrotizing crescentic GN.[196] MPO ANCA associated systemic illness has also been reported.[197,198] Wichmann et al measured autoantibodies to MPO in 52 people exposed to silica for a mean duration of 7 years using ELISA. 27% had positive MPO, significantly higher than in 15 healthy individuals ($p<0.01$) but not disease controls comprising SLE and progressive systemic sclerosis.[199] A causal association has been suggested between exposure to high levels of silica dust in the aftermath of the 1995 Great Earthquake in Kobe, Japan and an increase in MPO-ANCA associated angiitis and/or nephritis in the 3 years following the event.[147] Investigators from the medical centre serving the immediate area affected noted 4 new cases in 1995, 7 in 1996 and 3 in 1997 in contrast to 15 cases seen over 8 years in the Kyoto University Hospital, a tertiary referral centre serving a wider population in a geographically distinct area. The vasculitic diseases seen after the earthquake had significantly more upper respiratory symptoms and required more emergency haemodialysis and courses of methylprednisolone than those seen previously. However there were no differences in MPO-ANCA or outcome of PSV pre or post the earthquake.[147]

Three case control studies describe significant associations of silica with ANCA positive renal disease and PSV. A group from Chapel Hill compared 65 patients with ANCA

positive SV (8 necrotizing and crescentic GN, 36 mPA and 21 WG) with 65 age/sex-matched controls with other renal disease. Significantly more ANCA positive SV patients reported silica exposure compared to controls giving an OR (95%CI) of 4.6(1.8-12.1). This remained statistically significant when controlled for exposure to smoking, pesticides, fuels and solvents. The OR for WG patients was 3.5 (p=0118) and 5.0 for mPA and GN combined (p=0.011). There was no significant difference in results for ANCA subtypes (cANCA, pANCA, PR3 and MPO) or particular patterns of organ involvement (e.g. lung and/or sinus). In contrast they reported reduced silica exposures in SLE nephritis patients compared to renal controls.[200] Gregorini et al estimated that 16 ANCA positive RPGN patients were 14 times more likely to have been exposed to silica dust than 32 hospital controls (95% C.I. 1.7-113.8). ANCA had specificity for MPO in 6/7 exposed patients 3 of these had crescentic necrotizing GN.[201] Nuyts et al found an OR of 5 for silica (95% CI 1.4-11.6) in 16 WG cases compared to 32 age and sex matched community controls.[202]

In summary there is strong evidence for an association between silica and both clinical and subclinical renal disease and potential mechanisms of action have been described. In general the intensity of exposure appears to be important, reflected in higher ORs obtained for occupations such as sandblasting and mining. In contrast the duration of exposure is not generally reported to be influential. ANCA associated renal disease and RPGN have been found to have significantly more exposure to silica compared to other types of renal disease, which may suggest a specific influence of silica in renal disease associated with vasculitis.

Hydrocarbons and Vasculitis

Hydrocarbons (HC) are widely used in industry and the term encompasses a wide range of substances including aliphatic, alicyclic, aromatic and halogenated HCs; glycols and organic solvents.[203] An association with renal disease has been postulated for many years and it has been suggested that the male predominance in patients with GN may reflect the influence of occupational HCs.[204] It therefore seems reasonable to hypothesise that HC exposure plays a role in renal vasculitis. HCs can be absorbed by the lung, skin and gastrointestinal tract and have been identified in many body compartments including the brain, adrenals, kidney, blood, bone marrow, spleen, liver and fat at post mortem.[205] Acute renal failure has been directly linked with exposure to high levels of HC within hours, for example in a patient immersed in seawater polluted by diesel fuel.[206] These cases are usually due to acute tubular necrosis with complete recovery of renal function.[207] Chronic and end-stage renal failure including GN has also been associated with hydrocarbon exposure although the association remains controversial with studies presenting conflicting results and methodological limitations.[205,208,209,210,211] One possible mechanism of action is that chronic HC exposure could cause low-grade tubular damage and the production of antigens, GN may then result from local autoimmunity induced by these antigens.[212] Associations have also been reported between HCs and GN caused by systemic vasculitis, Goodpasture's Syndrome and Behcets disease.[213,214,215]

Much other evidence for the role of HC in PSV comes from occupational studies. One cross sectional study investigated the prevalence of clinical and subclinical renal disease in subjects chronically exposed to HCs at work. Three groups were compared: 112 paint sprayers exposed to paint based HCs, 101 transmission area workers exposed to petroleum based mineral oils and 92 automated press operators with minimal exposures as internal controls. Markers of renal dysfunction (serum creatinine, urinary total protein, N-acetyl-

glucosaminidase (NAG), gamma-glumyl transferase and leucine-amino-peptidase excretion) were significantly higher in paint sprayers compared to the other groups. Although serum creatinine was normal, other markers of renal dysfunction were raised in those exposed to mineral oils compared to internal controls.[218] A case-control study by the same group compared 55 patients with ESRF due to biopsy proven GN with 55 normal subjects and 45 controls with renal disease of other causes e.g. diabetes. Compared to both control groups, patients with GN had significantly higher exposures to HC products ($p < 0.001$), petroleum products ($p<0.001$, RR 15.5), greasing/degreasing agents ($p<0.01$, RR 5.3) and paints/glues ($p<0.05$, RR 2.0).[219] These results suggest that occupational HC exposure is related to both clinical and subclinical renal dysfunction and the risk of GN is higher than other types of renal disease.

A study of 59 shoe-factory workers exposed to naphtha and toluene, compared urinary excretion of total protein, beta-2-microglobulin, retinol-binding protein, albumin, transferrin, lysozyme, lactate dehydrogenase and NAG with 24 age-matched controls. Only NAG was significantly different and the conclusion was that long-term moderate exposure to solvents did not carry significant risk for of nephrotoxicity.[220]

A case control study from Brazil compared 17 patients with biopsy-proven crescentic GN and renal failure with 34 matched hospital controls and found a relative risk of 5.0 (95% C.I. 1.14-22.0) for solvent exposure but no significant increased risk for fuels (RR 3.25, 95% C.I. 0.76-13.89). They reported that renal histologic findings suggested immune complex mediated injury in addition to a direct glomerular toxic effect.[221]

Ongoing HC exposure may be linked to progressive renal failure.[222] Yaqoob et al found that HC exposure scores were significantly higher in a group of progressive biopsy-proven primary GN patients compared with non-progressive.[223] A recent meta-analysis of case-control studies supported these findings and concluded that HCs are associated with deterioration in GN but that this effect is inversely proportional to the stage of disease (i.e. if exposure is eliminated at an early stage then progression to renal failure may be

prevented).[224] Furthermore a study of an experimental rat model of adriamycin nephrosis described disease progression (histopathological and microproteinuria) in rats exposed to styrene in addition to adriamycin but not in those given adriamycin alone.[225] These results suggest that patients with renal disease should avoid occupational HCs.

Nuyts et al investigated various occupational risk factors for chronic renal failure by comparing 272 cases with chronic renal failure (including 9 with WG and 38 proven GN) with controls with normal renal function. They found a significant OR of 5.45 (95% C.I.; 1.84-16.2) for oxygenated hydrocarbons. The average duration of exposure was 20 years.[226] Another case control study looked at exposures associated with male ESRF and reported an OR of 2.50(95% C.I.; 1.56-3.95) for solvents in cleaning agents or degreasers.[227]

Pai et al tested the hypothesis that the inhalation of volatile substances are involved in the development of WG and mPA with renal involvement by comparing 28 mPA and WG patients with blood donors matched for age, sex and social class. HC scores based upon occupational and recreational exposures were significantly higher for male patients compared to controls. Female patients and those with pulmonary haemorrhage also had greater HC exposures but differences were not significant.[213] However an abstract presented at the 9th ANCA workshop failed to find any statistical difference in occupational and domestic exposure to HCs in 42 WG or mPA patients compared to neighbourhood controls. Results for renal vasculitis were not reported separately.[228]

There have been no case reports of SV associated with HCs although toxic oil syndrome (a multisystem disease made famous by an outbreak in Spain in 1981 following widespread ingestion of rapeseed oil denatured with 2% aniline) has many features in common with CSS in its acute phase. The basic lesion is a non-necrotizing vasculitis accompanied by thrombotic events with peripheral eosinophilia, pulmonary oedema and endothelial damage. The course of disease differs to CSS with an intermediate phase of severe myalgia, sensory neuropathy, liver damage, skin oedema and sicca and a chronic phase

involving a peripheral neuropathy, muscle wasting, scleroderma and hepatopathy. An extensive review of other mineral oils did not report any associated vasculitis although Methazolamide (used in the treatment of glaucoma), which contains thiazoles has been associated with rashes with perivascular lymphocytic and eosinophilic infiltrates. Renal toxicity, pulmonary and pericardial haemorrhage have been related to some types of mineral oils (petroleum distillates, anthracenes, nitrosamines, silicone and polymers) following ingestion but pulmonary haemorrhage was due to local damage by the inhalation of the substance rather than vasculitis. Subcutaneous injections of mineral oil for cosmetic purposes had been linked with panniculitis, autoimmune thyroiditis and Sjogren's syndrome but not vasculitis.[229] Finally butylhydroxytoluene, an antioxidant in chewing gum, has been causally associated with cutaneous urticarial vasculitis in a 30-year-old female following its daily consumption.[230]

In conclusion, although evidence is conflicting, HCs may play a role in primary vasculitis, particularly with renal and possibly respiratory disease. One hypothesis is that exposure may render the individual more susceptible to renal involvement rather than actually triggering the onset of vasculitis, perhaps by facilitating the deposition of glomerulotoxic mediators in the renal tissue.[231] A modulatory role such as this could also account for the association of HCs with progressive renal disease and its relative improvement after cessation.

Inhaled Fumes and Particulates

An inhaled agent could trigger systemic vasculitis, especially where respiratory involvement is predominant. As early as 1931 Klinger speculated that 'inhaling a sensitising agent or various 'noxa' might have precipitated a particular reactivity of the vessels' in WG.[15] Duna et al compared exposure to six categories of inhaled agents [Occupational exposure to inhaled fumes or particulates and construction; avocational exposures (hobbies); residential exposure to construction; residential proximity to factories; and farm exposure] in 101 WG patients compared to 54 healthy controls, 24 respiratory patients with sarcoidosis or pulmonary fibrosis and 45 patients with inflammatory rheumatological diseases (e.g. RA). Significant findings were that WG patients reported more avocational exposure to fumes or particulates than healthy or rheumatological controls ($p<0.01$) but not respiratory controls and were exposed to pesticides more commonly than normal and rheumatic controls ($p=0.046$ and 0.013 respectively) but not respiratory controls ($p=0.053$).[134] Henoch Schonlein Purpura has been described in association with tetramethylthiuram disulfide (an agricultural agent) exposure and Parks et al reported an increased risk of SLE with pesticides but they have not been associated with other forms of PSV.[232,233]

Exposure to metal fumes has also been associated to vasculitis. Lung biopsies from six Russian brass bronze smelters obtained by diagnostic thoracotomy demonstrated vasculitis.[234] Nuyts et al also reported increased ORs for various metal and welding fumes in their case control study of chronic renal failure, WG and glomerulonephritis. ORs (95% C.I.s) were as follows: lead -OR 2.11(1.23-4.36), copper-2.54 (1.16-5.53), chromium-2.77 (1.21-4.36), tin-3.72 (1.22-11.3), mercury-5.13 (1.02-25.7), welding fumes- 2.06(1.05-4.60). Trends suggested a dose related response except for welding fumes and they reported that blood lead concentrations were significantly higher in cases than controls ($p<0.001$).[202] However Steenland et al failed to find significant associations for exposure to lead, iron/steel or welding fumes or to metal particles in their study of ESRF. Their study

differed included GN, hypertensive kidney disease and interstitial kidney disease but excluded disease thought to be unrelated to occupation (e.g. diabetic nephropathy, Alport's Syndrome, malignancy) compared to all causes of renal disease in the study by Nuyts et al.[202,227]

The effect of particulate matter containing soluble metals from three emission sources was studied in a rat model of pulmonary vasculitis / hypertension. Tracheal administration caused a significant increase in mortality and airways responsiveness and the authors concluded that soluble metals from the particulate matter mediate cardiopulmonary injury in both the healthy and at risk host.[235] Direct contact with cobalt has been reported to precipitate an allergic cutaneous vasculitis and vasculitis has been reported in lead toxicity.[236,237]

An interesting case report links behenic acid fumes (produced when heat-activated photocopier paper is developed) with recurrent palpable purpura affecting the legs of a librarian. Purpura occurred during the working week and challenge studies showed that purpura formed with exposure to developed photocopy paper and behenic acid but not control and undeveloped paper or direct contact testing. Because fumes were never in contact with the subject's legs the authors surmised that inhalation of fumes was the most likely cause. Biopsy showed a necrotizing cutaneous venulitis with immunofluorescence positive only for C3. Immune complex deposition may have explained such a reaction but none were detected. A delayed cell mediated response by sensitised T-cells seems unlikely due to rapid recurrence of symptoms on re-exposure and negative patch tests. Symptoms disappeared with a change in working environment and to the authors' knowledge she has never had a recurrence or developed systemic vasculitis. (personal communication).[238,239]

The inhalation of solvent fumes and the ingestion of mineral oils (presumably associated with some inhalation) have been reported to cause alveolar haemorrhage but vasculitis per se has not been documented.[229,240]

There is only sparse evidence that inhalation of metals either as particulates or fumes are important in vasculitis and no studies have described an association with metal industries in the same way as silica. Metals could directly cause vasculitis through an immunological mechanism or a localised alveolar effect or may act as an immunological adjuvant. Reports also suggest that exposure to lead may increase risk of infection, which may in turn render the individual vulnerable to an infectious trigger of vasculitis.[241]

Infection and Vasculitis

Fletcher suggested that an unknown infectious process was responsible for vasculitis in 1892, finding early support for his theory from Kahlden in 1894 and subsequently many other investigators.[4] They have been proven at least partially correct and many infections have been associated with small vessel vasculitis, especially leukocytoclastic vasculitis. Table 1.28 lists reported pathogens.[242] Infections may involve blood vessels in several ways: they may invade the vascular endothelial cells directly (rickettsia, bartonella, CMV); lead to the formation of immune complexes including cryoglobulins; infect pre-existing aneurysms during bacteraemia or fungaemia; or contribute to the progression of atherosclerosis. Aortitis may rarely be caused by a contiguous infection directly invading the vessel wall.[243]

An interesting hypothesis is that an infectious trigger may lead to the onset or exacerbation of PSV. Giant cell arteritis and polymyalgia rheumatica have been temporally associated with epidemics of Mycoplasma pneumoniae, Chlamydia pneumoniae and Parvovirus B19 in Denmark and period peaks of GCA occurring every seven years have been noted over a forty year period in Olmstead county.[244,245] Rosso et al also showed a correlation between GCA and infection.[246] However a study from Sweden failed to significant disease fluctuations over twenty years.[247] WG, CSS and mPA have not been directly linked to infections although Tidman et al described a periodic fluctuation in the incidence of

ANCA positive vasculitis with peaks every three to four years between 1975–95.[130] Seasonal variation in disease, which may suggest an infectious trigger, has previously been described (Table 1.25).

Table 1.28
Pathogens reported to be associated with small vessel vasculitis*

Common associations	Occasional associations
Bacterial pathogens	
Neisseria gonorrhoeae	Anaerobes (Bacteroides fragiles)
Neisseria meningitidis	Borrelia burgdorferi
Staphylococcus aureus	Brucella species
Streptococcus	Campylobacter jejuni
β-Haemolytic	Escherichia coli
equisimilis	Haemophilus influenzae
pneumoniae	Klebsiella species
viridans	Lactobacillus species
	Mycobacterium tuberculosis
	Mycobacterium leprae
	Mycoplasma pneumoniae
	Pseudomonas aeruginosa
	Salmonella hirschfeldii
	Salmonella typhimurium
	Yersinia enterocolitica
Viral pathogens	
Cytomegalovirus	Epstein-Barr virus
Hepatitis B virus	Hantavirus
Hepatitis C virus	Herpes simplex virus
Human immunodeficiency virus	Influenza virus
Parvovirus B19	Rubella virus
Helminths and other parasites	
	Ascaris species
	Acanthamoeba species
	Microfilariae
	Strongyloides stercoralis

*From Somer et al [242]

Viruses and Vasculitis

Three types of disease course can follow acute viral infection: clearing of the pathogen e.g in influenza; viral latency with periodic reactivation, e.g. herpes zoster; and persistent viral replication with a stable or progressive course.[248] A seasonal onset of PSV would favour an acute viral infection being responsible for triggering disease. In fact vasculitis has been most frequently associated with chronic viral illnesses although self-limiting and relapsing viruses have also been reported.

Hepatitis and Systemic Vasculitis

Hepatitis B was first reported to be associated with a necrotizing vasculitis mimicking polyarteritis nodosa in 1970.[249] Subsequently 15-30% of cases of PAN have been associated with acute hepatitis B infection (HBV) and up to 75% of patients have been found to be HBV positive, indicating previous exposure and suggesting a causal relationship.[141] The illness is clinically similar to classical PAN, characterized by medium-sized vessel involvement and microaneurysms and / or stenoses on angiogram.[250] However orchitis, renal failure due to infarcts and malignant hypertension may occur more commonly in virus associated PAN and the disease course tends to be remitting with a better prognosis.[251] Recurrence of acute vasculitis is unusual. However as PAN is only found in < 2% of HBV populations suggesting that it is not solely responsible for precipitating disease.[252] It is important to identify virus-associated vasculitis because treatment regimes may vary. The aim is to treat both the vasculitis and the underlying infection. Conventional treatment including steroids and cyclophosphamide allow the virus to continue replicating. Therefore a treatment regimen may comprise of high dose steroids to control the life-threatening mainifestations of vasculitis, antiviral therapy to halt viral replication and plasma exchange to remove circulating complexes.[250] Early reports

suggesting that giant cell arteritis may also be associated woth Hepatitis B have not been confirmed.[253]

Hepatitis C has been linked to essential mixed cryoglobulinaemic vasculitis, the prevalence of which is similar to hepatitis B associated PAN. 80-90% of patients have hepatitis C antibodies.[243] The role of HCV is supported by the presence of the virus within cryoprecipitates and some cutaneous vasculitic lesions. Both hepatitis viruses are thought to cause vasculitis via immune complex formation.[254]

HIV and vasculitis

Systemic and localised vasculitis has also been associated with HIV infection. Small vessels are more commonly affected compared to medium or large vessels and clinical presentation is heterogeneous.[248] The role of HIV is unknown, circulating immune complexes are found in HIV but there is little evidence for involvement in vasculitis lesions.[248] The virus may act directly on the endothelial cells and it has been suggested that the mechanism is one of persistent immune activation.[250] However evidence for a pathogenic role of HIV is complicated by the presence of opportunistic infections including cytomegalovirus and hepatitis and complicated drug therapy, both of which may be responsible for vasculitis.[250,255,256]

Other Viruses

CMV has been reported in some cases especially involving medium and small calibre vessels of the gastrointestinal tract and central nervous system.[257] CMV was reported to mimic relapse in a WG patient when it responded to Ganciclovir treatment[258] and CMV inclusions have been found in the endothelium suggesting a direct mode of action.[242,259,255] Herpes viruses have also been associated with vasculitis. A temporal relationship of varicella zoster was reported with granulomatous cerebral vasculitis and varicella DNA

and specific antigen has been described in arteries from a patient with primary granulomatous angiitis of the CNS.[243]

Parvovirus B19 has been associated with systemic vasculitis. Aleutian mink are known to carry chronic Parvovirus B19 and develop a systemic necrotizing vasculitis associated with immune complex deposition.[260] Case reports suggest a role for Parvovirus B19 in human vasculitis including PAN and HSP.[261,262] Two children diagnosed with PAN and one with WG were described to have serological evidence of Parvovirus B19 and a causal association was proposed. It is noteworthy that these cases were atypical in that the patients were young and did not respond to conventional immunosuppression but rather IVIG and plasmapheresis. This may suggest an immune complex mechanism although none were detected.[263] However a study of a cohort of PAN patients did not support a role for Parvovirus B19 nor in 42 WG patients with new onset of diseas.[264,265] Epstein Barr Virus has also been associated with vasculitis but mostly affecting large vessels.[266,267]

Bacteria and Vasculitis

Bacterial infections are well known to cause vasculitis, including leukocytoclastic vasculitis and GN, for example meningococcal septicaemia. WG has been associated in particular with staphylococcus aureus and clinical impression often suggests that infection can trigger relapses in almost any type of vasculitis. Staphylococcus aureus has been cited as the predominant cause of nasal or sinus infection in a WG cohort.[17] Nasal carriage of staphylococcus aureus has been associated with clinical relapse in WG patients[122,268] and some studies of nasal eradication of the organism with cotrimoxazole and trimethoprim did suppress disease activity although the success of treatment may have been due to their immunosuppressive effect, perhaps related to folate suppression.[269,270,271,272] As previously discussed treatment with trimethoprim/ cotrimoxazole alone is insufficient to prevent systemic relapses but may be useful in preventing relapse of nasal disease. Molecular data

suggests that Staphylococcus aureus cationic protein can bind to endotheial cells and that this interaction stimulates the release of interleukins 6 and 8 which are markers of endothelial cell activation. This supports a role for SAcp in vasculitis.[273] It is important to remember that some systemic bacterial infection may occasionally mimic Wegener's granulomatosis e.g Nocardia can cause sinusitis, ENT, pulmonary and musculoskeletal disease and Fusobacterium necrophorum can produce pulmonary infiltrates, haemoptysis, mastoidosis and otitis media.[243]

Other Infections and vasculitis

Various other agents have been reported in patients with PAN including Streptococcus, Klebsiella, Pseudomonas and Yersinia.[242,274] Giannico et al reported positive chlamydia pneumoniae serology in 7 WG and 7 mPA patients but Haubitz et al failed to find an increased incidence in a case-control study of 40 ANCA positive mPA patients before immunosuppression compared to 160 healthy staff members.[275,276] HSP has been described following cat scratch fever (Bartonella henslae infection) and toxocara canis infection after contact with a puppy.[277] Toxocara has also been implicated in cerebral vasculitis.[243]

The unequivocal association of infection with some types of vasculitis raises the possibility that undetected infection could be responsible for PSV. An outbreak of viral encephalitis associated with widespread vasculitis-induced thrombosis causing microinfarction of the CNS and other organs occurred in Malaysian pig farmers in 1999. The causative agent was a previously undescribed paramyxovirus related to Hendra virus and close contact to infected pigs was thought to be responsible.[278] Similarly six of seven male Behçets patients were reported to have jobs with close contact to pigs or pork in another report. Although no organism was identified an infective agent transmitted from the pigs was thought a possibility.[279] In a similar way to human reports, a number of pathogens are linked to

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limited vasculitis in pigs e.g. porcine reproductive and respiratory syndrome and hog virus.[280,281] Some syndromes do occur in pigs which are similar to human PSV with GN and although specific organisms have not been identified if present they could potentially be transmissible.[282,283,284] Transmission of agents between species has also been demonstrated, for example a pseudorabies virus causing vasculitis in pigs then subsequently exposed lambs.[285]

Conclusion

There is strong evidence for an association of PAN and cryoglobulinaemic vasculitis with Hepatitis B and C, which has led to important advances in treatment. Although other infections have been associated with SV the evidence is less clear-cut. Most infections thought to be important are common and the great majority of infected individuals do not develop vasculitis. This suggests that infection may trigger vasculitis only in susceptible individuals. It is important to consider infection in the assessment of a patient with PSV because less conventional treatment may be of particular benefit (e.g. IVIG) and because a currently unidentified infection may be important.

Allergy and Vasculitis

Allergy has also been associated with PSV. Clinically CSS is characterised by late-onset asthma, eosinophilia and frequently allergic rhinitis and most classification criteria include asthma, eosinophilia and a history of allergy. Often symptoms are treated as allergic phenomenon for years prior to the onset of SV although they may occur simultaneously or even following diagnosis.[45] Atopic symptoms appear to be more common and severe in CSS patients compared to those with simple asthma e.g. polypectomies were reported in 56% vs 7-15% of patients respectively.[46] However less than 50% had positive skin and IgE RAST tests for atopy in one study.[286] Up to 90% of WG patients present with upper or lower respiratory tract symptoms and about 70% have ENT involvement at SV onset.[18] Initial ENT symptoms may precede SV by years and are often attributed to allergic rhinitis. It is difficult to determine whether they represent unrecognised WG or are indeed allergic in nature.

Case-Control Study of Allergy in Primary Systemic Vasculitis

Cuadrado et al carried out a case-control study using a validated questionnaire to investigate the link between vasculitis and allergy in a case-control study. They recruited 60 consecutive patients attending a vasculitis clinic at St Thomas' Hospital, a tertiary referral centre. These included 20 WG, 8 CSS, 12 PAN and 20 unclassifiable SV according to ACR 1990 classification criteria. Two control groups were recruited, the first comprising of rheumatology outpatient attendees and the second healthy hospital workers. They reported significantly more allergic rhinitis, asthma and plant allergy in PSV compared to non-vasculitis patients and more skin, drug, insect and food allergy than healthy individuals. Rhinitis, skin, drug and insect allergy were significantly more common in WG patients; asthma, food and skin allergies were associated to CSS; but no significant results were reported for PAN or unspecified vasculitis.[287] In addition they

reported a significant association between a family history (FH) of atopy and PSV (45% cases) compared to both sets of controls. Elsewhere FH has also been reported in 19.7-44.2% of CSS cases.[46,288]

Allergy

Atopy is generally defined as asthma, hayfever / allergic rhinitis and atopic eczema, either alone or in combination and the term allergy is often used synonymously with type 1 hypersensitivity reactions. Four types of hypersensitivity reactions are described and may occur simultaneously in some allergies, e.g. drug allergies (Table 1.29).

Type 1 Hypersensitivity

Type 1 or immediate hypersensitivity is characterised by an immediate reaction following allergen exposure with symptoms of urticaria, maculopapular rash, localised swelling, bronchial spasm and anaphylaxis. Ig E, mediated by T helper cells, is responsible for these effects.[289] Two T-helper subsets have been identified and are associated with different cytokine profiles. Th1 cells promote inflammatory cellular immune responses and are biased to the production of interferon (IFN)γ, interleukin (IL) 2 and tumour necrosis factor (TNF)β whilst Th2 cells favour the secretion of interleukins 4,5,6,10 and 13. The Th1 pattern has been associated with organ specific autoimmunity (e.g. multiple sclerosis, Hashimoto's thyroiditis and primary biliary cirrhosis) whilst a Th2 cytokine profile is associated with atopic disorders.[290] Several autoimmune diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have been associated with a heterogeneous T-helper cell cytokine profile with proinflammatory cytokines (IL6, IL8 TNFα) in addition to IFNγ , IL2, IL4 and IL10.[290] Evidence supports a Th1 dominant environment in RA[291,292,293], and there is evidence for both Th1 and Th2 dominance at various stages and severity of SLE.[294,295,296,297,298] Similarly Behcets disease has been reported to have a strong Th1 immune response, with high IL12 but a mixed response with

Th2 dominance in another report.[299,300,301] Spondyloarthropathies have been associated with a Th2 type response.[302,303]

In type 1 hypersensitivity an environmental allergen enters via a mucosal surface and is taken up by local antigen presenting cells. It is then presented to Th0 precursor cells which are triggered into clonal expansion down one of two differentiation pathways according to the surrounding cytokine environment (Figure 1.). IL4 is secreted and in the absence of regulatory cytokines Th2 cells are produced which secrete IL4, 5 and 10. These cytokines induce B cell proliferation with the subsequent production of Ig E that binds to Fcγ receptors and sensitises mast cells. Sensitised mast cells release pre-formed (histamines and proteases) and newly formed mediators (e.g. leukotrienes and prostaglandins). ILs 3, 4, 8, 9 and TNFα are also released or upregulated. Th1 and Th2 cell responses are mutually antagonistic with IL4 and IL13 cytokine environment augmenting a Th2 response and IL10 inhibiting Th1 effects. Similarly IL 12 promotes a Th1 response whilst IFNγ inhibits Th2 cells.[289] Individuals are thought to develop an equilibrium between Th1 and Th2 cell memory with a dominant Th–cell phenotype which determines their response to environmental antigens e.g. re-exposure to pollen in an individual with pollen allergy causes allergic phenomenon via the secretion of IL4 and 5 whilst a non-allergic individual responds to the same allergen by the secretion of Th1 cytokines and little IL4 or 5 activity. Animal models suggest that T-cell memory is determined by early exposures encountered in infancy. The foetal environment is constitutively skewed away from the Th1 phenotype and the placenta secretes ILs 4 and 10.[304] This Th2 bias is thought to persist postnatally and peripheral blood leukocytes in humans have been shown to have a poor IFN γ secreting capacity up to five years of age which may explain the transient high-risk window for allergic sensitisation in infancy and children exposed to high levels of inhalant allergens.[305] Those with a FH of atopy are reported to have a higher risk of adult allergic respiratory disease although these findings are not universally accepted. Some studies

suggest an association between allergy and date of birth close to the pollen season and others that initial priming of the foetal immune system occurs in utero via allergen specific IgG antibodies and allergen from the mother.[306]

Evidence for a Th2 cytokine profile in vasculitis

Evidence suggests that an 'atopic' Th2 cytokine profile and raised serum IgE may be associated with active PSV. Tomer et al described an experimental mouse model of vasculitis mediated by a Th2 response. They induced pulmonary vasculitis in mice using a pathogenic human IgG enriched ANCA derived from a WG patient and compared serum levels of IL1β, 2, 4, 6, TNF α and IFNγ with controls. After two weeks IL4, IL6 and TNFα were significantly elevated in the immunised mice whereas IL2 and IFNγ did not differ. By three months immunised mice had developed pulmonary vasculitis. However a full cytokine profile was not assessed (e.g. IL10) so a heterogeneous T-cell profile in vasculitis could not be excluded.[290] Another animal model of vasculitis is the Brown Norway rat. In this case Gold, D-Penicillamine (disease modifying agents used in RA) and mercuric chloride induce a Th2 dominated autoimmune syndrome with an upregulation of IL4 mRNA and vasculitis. Mercuric chloride induced vasculitis is also associated with MPO antibodies.[307]

Evidence for a Th1 cytokine profile in vasculitis

Evidence for this is conflicting. Csernok et al evaluated IFNγ and IL4 in biopsies, bronchoalveolar lavage fluid and peripheral blood in WG patients, chronic rhinitis and healthy controls. WG and disease controls demonstrated in situ production of mRNA for IFNγ but only 2 WG patients expressed IL4 compared to all of the rhinitis patients. T-cells from the WG granulomas produced only IFNγ.[308] In addition Ludviksson et al compared peripheral blood from 12 patients with active WG, 7 with inactive disease and 12 healthy donors and found increased secretion of IFN γ and TNFα but not IL4, IL5 or IL10 in the

WG patients. They also reported increased levels of IL12 in both active and inactive disease and therefore hypothesised that, in WG, T-cells overproduce IFNγ and TNFα in response to dysregulated IL12.[309] Both these studies suggest that a Th1 cytokine pattern predominates in WG. Additionally Dixon et al described a murine model of Th1 cell induced lung injury characterised by mononuclear cell vasculitis, alveolitis and interstitial pneumonitis.[310] Finally skin tests for delayed cutaneous hypersensitivity were found to be mostly negative in a series of WG patients.[311]

Peripheral blood lymphocytes from vasculitis patients have also been examined. PR3 stimulated cells from patients with acute systemic vasculitis produced IL4 in response to phytohaemoglutinin but not IL2 indicating a Th2 response whereas IL2 and IFN γ were produced without detectable IL4 in PR3 stimulated cells from patients in remission. These data suggest that a Th2 cytokine profile is involved in initiating vasculitis whilst a Th1 response is important in it's maintenance.[312] The acute stages of Kawasaki disease have also been associated with reduced IFN γ but not IL4, suggesting an imbalance in Th1 and Th2 subsets in the early stages of disease, which lends further supports this Th1/Th2 hypothesis.[313]

IgE in Primary Systemic Vasculitis

In support of a role for Type 1 hypersensitivity, raised serum Ig E has been reported in WG, PAN and especially CSS (when it may be used to confirm the diagnosis).[314,315,316,317] Raised IgE in five cases of WG was not related to particular clinical manifestations or eosinophilia but in a separate report was associated with SV with respiratory involvement (predominantly WG and CSS).[317,318] Several reports suggest that IgE levels vary with disease activity and eosinophilia in CSS[319,320,321] but elevated IgE was seen rarely in one series of WG.[17] Harrison et al reported that the distribution of IgE bearing mast cells in renal biopsies were located within the interstitial inflammatory infiltrate in mPA but not

WG.[322] IgE deposits have also been reported in the myelin of peripheral nerves in CSS with lymphocytic infiltrates around endoneural capillaries and the endoneurium.[320]

Type 2 Hypersensitivity

Type II hypersensitivity is mediated by IgG and IgM antibodies binding to specific cell surface or tissue antigens and interacting with complement and/or effector cells (K cells, platelets, neutophils, macrophages, eosinophils) to produce cell damage. Examples are blood transfusion reactions, haemolytic disease of the newborn and autoimmune haemolytic anaemias. The latter has been implicated as the mechanism of action of a number of drug reactions and thrombocytopaenia in immune disease.[289]

Type 3 Hypersensitivity

Type III hypersensitivity relates to the formation of immune complexes caused by persistent infection (e.g. leprosy, malaria, dengue haemorrhagic fever, staphylococcal infective endocarditis), autoimmune disease where an autoantibody to a self-antigen leads to immune complex formation (e.g. RA, SLE) and inhalation of antigenic material (e.g. farmers lung). The immune complexes trigger inflammatory processes in several ways – activating the complement system, stimulating macrophages to release cytokines (e.g. IL1, TNF alpha) and binding directly to basophils and platelets to release vasoactive amines. In serum sickness circulating immune complexes deposit in blood vessel walls leading to increased vascular permeability and inflammatory disease (e.g. glomerulonephritis.).[289] Immune complexes are known to be involved in some types of vasculitis illustrated by necrotizing vasculitis associated with serum sickness and the arthus reaction.[323,324] Immune complexes have been detected in most patients with vasculitis associated with Hepatitis B, cryoglobulinaemia, SLE, RA and bacterial endocarditis and reported to correlate with disease activity in some cases. However even in these diseases they are not detectable in

all patients and are often not seen in typical vasculitis lesions. Immune complexes are described rarely in PSV and histological lesions are classically 'pauciimmune' suggesting that their contribution to disease, if any, is small.[54,325] However some investigators have suggested that the absence of recorded immune complexes may be due to the stage of disease at investigation. Immune complexes may only circulate for a limited period and are removed quickly from tissues.[326] Brons et al detected immune deposits in a higher proportion of early cutaneous biopsies in PR3 positive WG patients than expected. Deposits were absent after four days.[327]

Type 4 Hypersensitivity

Type 4 reactions refer to delayed hypersensitivity including contact, tuberculin and granulomatous reactions. Contact hypersensitivity may cause vasculitis (e.g. cobalt) and granulomatous change can be seen on biopsies of all types of PSV although it is predominant in WG and CSS.[54,46] The formation of granulomas results from the persistence of intracellular microorganisms or particulates within macrophages, which are unable to destroy them (e.g. silica). Wegener's is characterized by the formation of granulomas with the presence of epitheliod and giant cells, macrophages and lymphocytes. Most diseases associated with granulomas are caused by infection (tuberculosis, leprosy and schistosomiasis) and may give support to an unknown infective agent precipitating WG.[289]

Table 1.29 Immunology of drug allergies*

Type I hypersensitivity reactions

ACTH
Allergens in desensitisation
Aminopyrine
Antisera
Bromosulpharein
Cephalosporins
Chymotrypsin
Dextrans
Heparin
Insulin
Meprobanate
Penicillin
Penicillinase
Procaine
Salicylates
Sodium –Dehydrocholate
Streptomycin
Sulphonamides
Tetracyclines

Type II hypersensitivity reactions

Acetazolamide
Ampicillin
Aminopyrine
Aminosalicylic Acid
Antazoline
Aspirin
Carbamazepine
Carbenicillin
Cephalosporins
Chlorpromazine
Chlorpropamide
Chlorothiazide
Digitoxon
Dipyrone
Hydralazine
Hydrochlorothiazide
Imipramine
Insulin
Iodides
Isoniazid
Levodopa
Mefenamic Acid
Melphalan
Meprobamate
Methicillin
Methimazole
Methyldopa
Novobiocin
Paracetamol
Penicillin G Phenacetin
Phenolphthalein
Phenytoin
Phenylbutazone
Probenecid
Propylthiouracil
Quinidine
Quinine
Rifampicin
Spironolactone
Stibophen
Streptomycin
Sulphonamides
Tetracycline
Thiazides
Thioguanine
Thiouracil
Tolbutamide

TYPE III Hypersensitivity Reactions

ACTH
Arsenicals
Azathioprine
Barbituates
Bismuth
Dextran iron complex
Digitalis
Penicillins
Erythromycin
Griseofulvin
Heparin
Hydralazine
Indsulin
Iodides
Isoniazid
Nitrofurantoin
Phenolphthalein
Phenylbutazone
Phenytoin
Probenecid
Procainamide
Propylthiouracil
Quinidine
Quinine
Salicylates
Serums
Streptomycin
Sulphonamidesw
Tripelenamide
Vaccines
Viomycin

Type IV Hypersensitivity

Benzylalcohol
Chromate compounds
Ethylenediamine
Formaldehyde
Lanolin
Mercury derivatives
Neomycin
Nickel
Para-aminobenzoic acid
Parabens
Peru balsam
Phenylenediamine compound:

*** From Witte et al [328]**

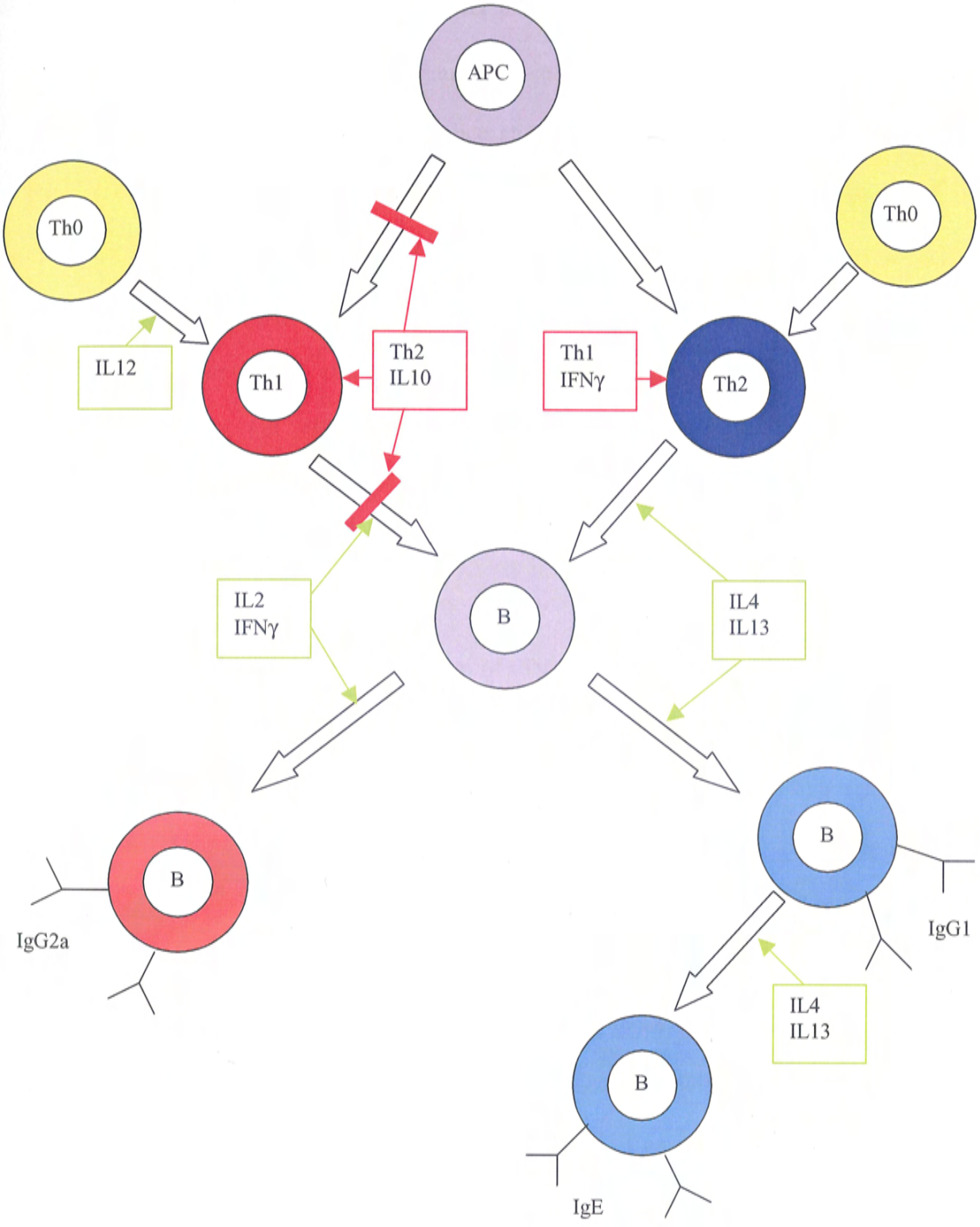

Figure 1.12 Illustration of Th1 / Th2 cytokine environment interactions*.

Th= T helper, APC = Antigen presenting cell, B= Blymphocyte Ig = Immunoglobulin IL= Interleukin, IFN= Interferon = inhibits = inhibits =promotes

* From Roitt et al [124]

Desensitisation Procedures and Vasculitis

Desensitisation / hyposensitisation therapy is a specific treatment for IgE related allergies including allergic rhinitis, asthma and bee stings and is often successful in improving clinical symptoms. It involves the administration (usually by subcutaneous injection although oral preparations are under development) of increasing doses of allergen identified by skin-prick tests. The exact mechanism of action is not known but following treatment serum levels of allergen-specific IgG and suppressor T-cell activity increase whilst IgE levels fall although this does not necessarily correlate with clinical improvement. These changes may represent a switch from a Th2 dominant environment to a Th1 predominant response.[289,329]

There have been a number of reports of SV following desensitisation procedures. Phanupak et al described twenty consecutive patients with 'polyarteritis' seen over twenty years, six of whom had developed disease following allergic hyposensitisation procedures.[330] Table 1.30 gives details of these and a further two cases reported in 1986.[331,332] Guillevin et al reported that 19 of 43 patients with necrotizing angiitis and asthma gave a history of desensitisation within four weeks of disease onset. Individual details are not recorded but they received subcutaneous doses of various antigens including dust, pollen and microbial antigens.[333] Another patient with allergic rhinitis received 7 months of treatment, which was discontinued because of anaphylaxis. 2 months later he developed a necrotizing digital vasculitis, which resolved with steroid therapy.[334]

The patients described by Phanupak and Guillevin could be classified as Churg-Strauss syndrome using modern classification. A real association between desensitisation and vasculitis seems likely as a high proportion of patients had received the treatment and in 23 cases systemic vasculitis occurred within 4 to 11 weeks of the first allergen injection. This

suggests a possible causal relationship and may lend support to the hypothesis that a switch in Th cell dominance may be important in the onset of vasculitis. A delay in the development of a Th1 response could explain the occurrence of vasculitis in cases following a prolonged course of hyposensitisation. However the persistence of raised eosinophils and IgE in active CSS appears to contradict this hypothesis. Phanupak et al suggested that immune complexes could be involved and they have been detected in some cases of vasculitis presumed secondary to immunotherapy.[330] Another explanation is that the original allergies treated with hyposensitisation were in fact prodromal symptoms of CSS and in fact the onset of vasculitis was unrelated to the injection. The authors concluded that desensitisation should be avoided in severe corticosteroid dependent asthmatics and during the first year of respiratory allergic symptoms. There have been no recent reports of an association, which could be attributed to a change in practice with the availability of newer asthma treatments.

In conclusion, allergy appears to be associated with vasculitis. The T-cell response is heterogeneous at differing stages of disease but Th2 cytokines seem to be important in active disease and a pre-existing 'atopic' Th2 dominant environment may predispose to developing vasculitis.

Table 1.30 Details of Desensitisation procedures and subsequent vasculitis

			Details of Desensitisation Procedure			Details of Vasculitis			
Sex	Age	Ref	Indication	Duration	Allergens	Organ involvement	Eosinophilia	Treatment	Outcome
F	29	1	rhinitis cough	9 weeks	tree, grass and weed pollens, dust, moulds horse & cattle dander	Nerve, Joints Lung, Kidney	Yes	Pred, CYC	Death (PCP)
F	67	1	rhinitis polyps	6weeks	dust, feathers dog dander	Skin, Nerve Kidney	Yes	Pred, Aza	Asthma, polyps, sinusitis Inhaler / Pred
M	38	1	asthma	11weeks	weed pollen, mould, house dust	Myalgia Nerve, Kidney	Yes	Pred	Asthma, rhinitis, sinusitis Prednisolone
M	72	1	rhinitis	2 years then 6months	foods, house dust bacterial antigens parakeet feathers	GIT, Kidney Lung, Heart	-	None	Death – (vasculitis of GIT, liver, kidneys, adrenals, lungs, heart, brain)
M	57	1	asthma hayfever	8 years	pollens	GIT, lung, Kidney	-	None	Death – (vasculitis of most thoracic & abdominal arteries)
M	54	1	rhinitis polyps	10 weeks	grass & tree pollen house dust, milk	Skin and mucosa Joints, Nerve, Kidney	Yes	Pred, CYC	Asthma Pred and Cyc
M	31	2	asthma	22 months	Graminaceae pollen House dust	GIT , skin	Yes	Pred	Remission on Pred
-	-	3	rhinitis	23 months	-	-	-	-	-
M	37	4	rhinitis	7 months	ragweed, mixed moulds, dust, animal dander	Digital vasculitis	-	Pred	Remission on Pred
M	26	5	asthma	24 months	'various'	Skin, Nerve, Lung, hepatic aneurysms	Yes	Pred, CYC	Remission with CYC
-	8	6	rhinitis, asthma	6 months	ragweed, pollen, ascaris	-	-	Pred	Remission
M	32	7	-	-	bacterial antigens	Joints, skin, GIT, Kidney, Lung	-	Pred	Death (vasculitis of GIT, kidneys; granulomatous meninges
-	-	7	asthma	-	ragweed, dust	Skin, CNS	-	-	-

F= Female; M=Male; Pred= Prednisolone, CYC = Cyclophosphamide, Aza = Azathioprine

Phanupak [330] 2. Berbis[332] 3. Thompson [331] 4.Cabrera [334] 5. Fauci [335] 6. Umetsu [336] 7. Winkelmann[337]

Vaccinations and Vasculitis

Vaccines are widely used to protect against a variety of infections. The underlying mechanism of vaccination is the induction of clonal expansion of T and/or B-lymphocytes by an administered antigen, which leaves behind a population of memory T cells. This primary response is slow but on subsequent exposure to the antigen a secondary response is rapid. Antigens used in vaccines may be live, attenuated or dead bacteria or viruses, toxoids, subcellular fragments, surface antigens and synthetic or gene cloned antigens (Table 1.31). The effect of vaccines may be augmented by adjuvants (aluminium hydroxide, aluminium phosphate and calcium phosphate), which improve the exposure of the antigen to lymphocytes and/or induce cytokines.[289]

Vasculitis has been associated with a number of vaccinations including those for influenza, Hepatitis A, B and C, rubella, small pox, diphtheria, tetanus and pertussis. Kelsall et al described a previously healthy 34-year-old man who developed mPA within three weeks of receiving influenza vaccination. Disease was characterized by a severe necrotizing vasculitis affecting the scrotum, perineum, inguinal region and abdominal wall and knee effusions. Necrotizing fasciitis was excluded and a causal role for the vaccine cited as titres of anti influenza A antibody were markedly higher in synovial fluid tested compared to serum whereas anti influenza B antibodies were present only in the serum.[338] They also reviewed 16 further cases, Gavaghan et al reported severe systemic vasculitis and Molina et al cutaneous vasculitis following influenza vaccination (Table 1.32).[339,340]

Somer et al reviewed the association of SV (PAN and/or HSP) and leukocytoclastic vasculitis in association with hepatitis B and C, Influenza, Rubella and small pox vaccinations[242] and Guillevin et al reported 5 cases of necrotizing angiitis (probable CSS) amongst 43 reviewed following vaccination with CCB Pasteur, Friedman and Bruschettini Staphylococcus vaccines.[333] Vasculitis came on immediately following a tetanus vaccine in one patient and another developed their disease in two phases each time after a vaccination

but no other details are recorded.[333] Table 1.33 illustrates reports of vasculitis associated to hepatitis vaccinations. Benign cutaneous polyarteritis has also been described following a diphtheria, tetanus, pertussis vaccination in a child under ten, cutaneous vasculitis with BCG and Henoch Schonlein Purpura associated with small pox vaccination.[341,342,343]

The association of vaccination and vasculitis suggests a role for T-lymphocytes. As all types of vaccine have been associated with the onset of vasculitis (live, dead, attenuated, toxoids and subcellular fragments it is more likely that the T-cell response initiated by the vaccination is responsible rather than an infection per se.

Table 1.31 Types of Vaccine*

Type of Antigen		Vaccine examples
Living organisms	Natural	small pox
	attenuated	polio (Sabin) measles, mumps, rubella, yellow fever, varicella zoster BCG** (Tuberculosis)
Dead organisms	viruses	polio (Salk) rabies influenza hepatitis A typhus
	Bacteria	Pertussis typhoid cholera plague
Subcellular fragments	capsular polysaccharides	pneumococcus meningococcus Haemophilus influenzae
	surface antigen	Hepatitis B
Toxoids		tetanus diphtheria
Recombinant DNA-based	gene cloned	hepatitis B

* From Roitt et al [289]

**BCG= Bacillus Calmette-Guerin

Table 1.32 Influenza Vaccination and Vasculitis

Date of Publication	Author	Probable CHCC Definition
1974	Wharton[344]	CSS
1980	Blumberg[345]	mPA
		LCV
1981	Cannata[346]	mPA
1983	Guillevin[347]	mPA
1987	Reizis[348]	mPA
1988	Wattiaux[349]	HSP
1990	Vial[350]	mPA
		LCV
		LCV
		CSS
		HSP/mPA
1990	Molina[340]	LCV
1993	Mader[351]	PAN/mPA
		mPA
		mPA
1993	Gavaghan[339]	---
1997	Kelsall[338]	mPA

LCV = Leukocytoclastic vasculitis

Table 1.33 Hepatitis Vaccination and Vasculitis

Year	Author	Hepatitis type	Vasculitis type
1988	Le Goff[352]	B	
1993	Allen[353]	B	Pulmonary and cutaneous
1996	Bani-Sdar[354]	A	
1999	Maillefert[355]	B	Polyarthritis, myalgia, LCV, fever
		B	Polyarthritis, urticaria, fever
		B	Neuropathy, arthralgia, back pain, lower limb parasthesis

LCV = Leukocytoclastic vasculitis

Drugs and Vasculitis

Many drugs have been associated with cutaneous and hypersensitivity vasculitis (Table 1.34) however reports of SV are less common.[356] Propylthiouracil and hydralazine have been reported most often but penicillamine, minocycline, methimazole, carbimazole, thiamazole, sulphasalazine, phenytoin and allopurinol have also been associated with SV.

Propylthiouracil (PTU)

PTU has been associated with a growing number of cases of SV in patients with hyperthyroidism. Table 1.35 details 35 case reports from the literature. ANCA was predominantly pANCA with MPO specificity although seven cases also document PR3.[357,358,359] Choi et al suggested that a sizeable number of ANCA positive vasculitis with MPO specificity may be drug related, following their review of 30 patients with the highest anti MPO titres out of 250 MPO positive cases identified at their unit over 4 years. 10 cases had received hydralazine, 3 PTU, 2 allopurinol, 2 penicillamine and 1 sulphasalazine within the nine months prior to disease onset.[360] Clinical features range from limited skin or renal disease to systemic syndromes including WG. The nature of disease appears to differ from idiopathic SV because its prognosis is generally good. Only one death and one case of ESRF have been reported.[361,362] PTU has been causally associated with SV because ANCA/MPO titres and clinical features have been reported to fall with its discontinuation (sometimes without immunosuppression) and a high number of MPO patients have been noted to have taken the drug.[360] However adverse effects of antithyroid drugs are rare and autoimmune disorders particularly unusual. Since 1945 less than 100 cases of systemic manifestations have been reported in the literature (mostly due to PTU) and in a review of 586 patients treated with PTU over eleven years only one case of vasculitis was reported.[363,364] There have also been reports of MPO antibodies arising in patients treated with PTU in the absence of vasculitis.[365,366]

Hydralazine

Hydralazine has long been associated with autoimmune syndromes and autoantibodies, e.g. drug-induced lupus and ANA but has also been associated with vasculitis (Table 1.36) Most cases are associated with MPO and clinical features range from cutaneous to systemic disease. Patients are generally older than the PTU cases, which probably reflects the indication for treatment. Disease course also seems more severe with two disease-related deaths despite immunosuppression and three cases of haemodialysis.[360] This may reflect comorbidity, pre-existing renal disease or a more aggressive form of disease.

Antielastase and antilactoferrin antibodies have also been described, not only with PTU and hydralazine but also in allopurinol and sulphasalazine related disease.[359] PTU and hydralazine are both known to induce other autoimmune syndromes and MPO has been reported in drug-induced lupus and nephritis but not idiopathic SLE or SLE nephritis.[367] A study of IgG and IgM antilactoferrin antibodies reported their presence in 100% of hydralazine-induced lupus cases, 5% and 10% respectively of SLE cases and IgG antibodies in a subset of RA (20%) with vasculitis.[368] These data suggest that MPO and antilactoferrin antibodies have a specific role in drug-induced autoimmunity and vasculitis.[367] Pillinger et al speculated about the importance of cross reactivity between thyroid peroxidase and MPO antibodies and the apparently specific association between PTU associated-vasculitis and Grave's disease.[357,369,370] They propose that the primary cause for vasculitis could equally be the underlying disease as the PTU. However the favourable disease course, particularly in PTU, indicates that drug-associated disease is different and evidence is strong that the drug is important in pathogenesis perhaps through a propensity to induce or interact with MPO, antilactoferrin and perhaps antielastase antibodies.

Minocycline, Penicillamine and Allopurinol

Minocycline, widely used for acne, is another drug known to induce autoimmune syndromes including SV after prolonged use and serum sickness reactions. Patients are usually young and disease has been associated with ANA and pANCA antibodies.[371,372,373] Penicillamine has been reported in two cases of fatal renal vasculitis, ANCA positive crescentic glomerulonephritis and associated with ANCA and MPO antibodies in three other cases.[360,374,375] Allopurinol was also associated with SV and MPO antibodies although as it is in relatively common usage this may be coincidental.[360] However it has been specifically implicated in a case of cerebral vasculitis in a 45-year-old man with no other precipitating factor and vasculitis resolved with discontinuation of the drug.[376] Allopurinol has also been linked to hypersensitivity vasculitis.[377]

Leukotriene Inhibitors and CSS

The relatively new leukotriene inhibitors used in the treatment of asthma have also provoked debate. Wechsler et al described eight patients with steroid dependent asthma who developed CSS following the discontinuation of steroids facilitated by Zafirlukast treatment. All eight cases fulfilled criteria for CSS but were unusual in that they all had dilated cardiomyopathy. Four further publications describe CSS following Zafirlukast, Pranlukast and Montelukast treatment.[378,379,380,381] The most likely explanation is that pre-existing CSS was unmasked by the reduction in steroids but it has also been reported in two patients started on zafirlukast but not taking systemic steroids.[382] Weschsler et al speculated that the cardiomyopathy may have been caused by altered biological actions of infiltrating eosinophils in the presence of leukotriene inhibitors but it seems more likely that this could be the natural course of inadequately treated CSS.[383] Alternatively the drugs could have initiated an allergic vasculitic reaction. Similar syndromes have also been

reported with macrolides, chlorothiazide, allopurinol, glibenclamide, phenytoin, carbamazepine and quinine.[384,385,386,387,388,389]

A similar case appears to have occurred with cromolyn when a 56-year-old man with a two-year history of asthma, eosinophilia and pulmonary infiltration developed sub acute multifocal sensorimotor neuropathy. Retrospective review showed that onset of the infiltration and eosinophilia had coincided with the initiation of cromolyn. The question therefore arises as to whether the cromolyn was responsible for a CSS type syndrome or whether symptoms were a prodrome to the onset of systemic disease.[390] A second case where a woman with eosinophilia and liver disease developed SV, which resolved on discontinuation of cromolyn and steroid treatment, might however indicate a causal effect.[391]

Other case reports of drug induced vasculitis

Other reports include: crescentic GN with carbamizole[392]; interstitial pneumonitis and pulmonary vasculitis in a patient taking an L-tryptophan preparation[393]; and phenytoin induced granulomatous vasculitis causing rash, fever and eosinophilia mostly in elderly black men with a high mortality.[394] Tetracycline has also been reported to cause a multisystem illness with vasculitis and ANA which reversed on discontinuation of the drug[395] whilst Barak et al described two cases of ophthalmic vasculitis following ticlodipine hydrochloride use which resolved on discontinuation.[396] Pyrithinol used for the treatment of concussion was associated with a headache and MRI findings consistent with vasculitis[397] and streptokinase implicated for a serum sickness reaction with vasculitis in a patient 9 days post-myocardial infarction.[324] Vancomycin has been associated with a lupus-like syndrome with haemorrhagic lesions of the fingertips and naproxen has also been reported to cause three cases of digital vasculitis.[398,399] Vasculitis reported with non-

steroidal anti-inflammatory drugs is usually limited to cutaneous disease but in one case diflusinal was associated with a steroid responsive eosinophilic pneumonia with vasculitis and cutaneous vasculitis, nephritis and paralytic ileus in another.[400,401] Other remarkable cases of severe cutaneous vasculitis have been reported with transretinoic acid, levamisole, an oral contraceptive pill and paracetamol.[402,403,404,405]

Substance Abuse and Vasculitis

'Recreational drugs' including cocaine, methamphetamine and heroin have been particularly associated cerebral vasculitis.[406,407,408,409,410,411] However one man, who self-administered hallucinogenic drugs, developed malignant hypertension and infarction of the renal cortex caused by arteritic changes with aneurysms in renal vessels. Symptoms responded dramatically to steroids.[412] Limited vasculitis has also been reported.[413]

Phenylpropanolamine, a drug available over-the counter as a nasal decongestants and the major ingredient for diet pills, has also been associated with cerebral vasculitis. Glick et al reported a case of biopsy proven necrotizing vasculitis of small cerebral vessels associated with cerebral infarction, intracerebral and subarachnoid haemorrhage in a 35 year old woman.[414] Symptoms came on an hour and a half after taking a diet pill containing phenylpropanolamine. A second reported case was a 27-year-old man who developed intracerebral haemorrhage and angiographic evidence of cerebral vasculitis after the ingestion of 13 nasal decongestant tablets.[415]

In conclusion, a wide variety of drugs have been related to cutaneous vasculitis, often associated with immune complex deposition. A smaller number have been associated with SV via a range of mechanisms but specific drug induced autoimmunity, possibly mediated by MPO and other autoantibodies, has been recognised to precipitate vasculitis syndromes with a superior prognosis to idiopathic vasculitis.

Table 1.34 Drugs associated with Hypersensitivity Vasculitis*

Alclofenac	Isoniazid
Allopurinol	Isoretinoin
Ampicillin	Levamisole
Aspirin	Maprolitine
Atenolol	Mefenamic Acid
Bromide	Melphalan
Busulphan	Metformin
Captopril	Methamphetamine
Carbamazepine	Methotrexate
Carbimazole	Methylthiouracil
Cefoxitin	Naproxen
Chloramphenicol	Nifedipine
Chlorothiazide	Oxyphenbutazone
Chlorpropramide	Penicillamine
Chlorthalidone	Penicillin
Cimetidine	Phenacetin
Ciprofloxacin	Phenothiazides
Colchicine	Phenylbutazone
Cotrimoxazole	Piroxicam
Dextran	Potassium Iodide
Diazepam	Procainamide
Diclofenac	Propylthiouracil
Dihydran	Quinidine
Diltiazem	Rifampicin
Diphenhydramine	Sodium cromoglycate
Erythromycin	Spironolactone
Fenbrufen	Streptokinase
Frusemide	Sulphasalazine
Griseofulvin	Sulphonamides
Haematoporphyrin	Terbutaline
Hydralazine	Tetracycline
Ibuprofen	Troxidone
Indium-113	Tryptophan
Indomethacin	Vaccines
Iproniazid	Vitamins

* from Dubost et al (1991) [356]

Table 1.35 Cases of Propylthiouracil associated vasculitis

Year	Author	No	Age/Sex	Dur.	Clinical Features	Autoantibodies	Treatment	Outcome
1982	Reidy[361]	1	46F	2w	Haemoptysis, ARF	Not done	None, PTU continued	Death
1983	Cassorla[416]	2	12F		Rash, nephritis, pulmonary cavitation, haemoptysis	Not reported	Steroid	Remission
		3	16F					
1991	Chevrolet[417]	4	56F	1y	ARDS	Not done	Immunosuppression	Remission
1992	Stankus[418]	5	73F	15d	Pulmonary and skin vasculitis	Not reported	Steroid	Remission
1993	Dolman [358]	6	37F	2y	Arthralgia, myalgia, scleritis	pANCA PR3	Nil	Remission Reduction in ANCA
		7	80F	6y	Arthralgia, skin vasculitis, microhaematuria			
		9	32F	1m	Arthralgia, myalgia, microhaematuria	pANCA		
		10	45F	18m	Arthralgia, myalgia, skin ulcer	MPO		
		11	37F	1w	Pulm vasculitis, renal	pANCA,PR3,MPO		Remission
		12	49F	6y	Fever, weight loss,haematuria	pANCA PR3	Immunosuppression	
	Frankel[364]	13	-	-	-	-	-	Good
1994	Vogt[362]	14	11M	3y	Crescentic FSGN	pANCA, MPO	Immunosuppression	Renal failure, dialysis
		15	15F	1m				Remission
		19	22m	4y			None specific	
		20	82F	3y		MPO		

Table 1.35(cont.) Cases of Propylthiouracil associated vasculitis

Year	Author	No.	Age/Sex	Dur	Clinical Features	Autoantibodies	Treatment*	Outcome
1995	Aoki[359]	16	22F	6y	Mesangioproloferative GN	pANCA MPO	Steroid	Remission
	Romas[419]	17	39F	1y	Pulmonary vasculitis	pANCA MPO	-	Improvement and decreased ANCA
	Tanemoto[420]	18	60F	3y	Pauciimmune crescentic GN	pANCA MPO	Steroid	Improvement or remission
		19	22m	4y				-
		20	82F	3y		MPO	None specific	-
	D'Cruz[393]	21	40M	11y	WG-like syndrome- arthralgia, pulmonary haemorrhage Pauci-immune crescentic GN	pANCA MPO	Continue PTU, steroids Immunosuppression	Improvement
	Ito[359]	22	82F	-	Scleritis, pachymeningitis necrotizing GN	pANCA MPO	Steroids	Remission
	Kudo[359]	23	52F	-	Purpura , Crescentic GN	MPO, PR3	Steroids	Decline in renal function
	Toda[359]	24	54F	7y	Arthralgia, crescentic GN	MPO, PR3	Nil	Improvement
	Hirana[359]	25	22F	4y	Fever, necrotizing GN	MPO	Steroids	Improvement
1996	Yuasa[421]	26	49M	3y	Pauci immune crescentic GN	pANCA	Steroids	Remission

Table 1.35(cont.) Cases of Propylthiouracil associated vasculitis

Year	Author	No	Age/Sex	Dur	Clinical Features	Autoantibodies	Treatment*	Outcome
1997	Kitharal[359]	27	39F	5y	Myalgia, scleritis, nasal disease, FSPGN	pANCA MPO, PR3 elastase, lactoferrin	Immunosuppression	Remission Reduction in ANCA
	Prasad[422]	28	39F	1m	Crescentic GN	pANCA	Immunosuppression	Remission
	Ohtsuka[423]	29	44F	7y	Pulm Haemorrhage, nec GN	pANCA	Nil	Remission
1998	Pillinger[357]	30	46M	4y	Diarrhoea, rash, fever, myalgia, haemoptysis, renal	cANCA PR3, borderline MPO	Nil	Remission
2000	Choi[360]	31	51F	-	Skin	2 elastase 1 lactoferrin	Steroids	Remission
		32	72F	-	Kidney		Immunosuppression	
		33	66M	-	Skin		Topical steroid	
	Wang[424]	34	12M	-	Anaphylactoid Purpura	ANCA	Immunosuppression	Remission
	Mathieu[363]	35		-	Systemic	-	-	-

Dur= Duration, M= male, F= female, GN = Glomerulonephritis, MPO = myeloperoxidase, PR3 = Proteinase 3, cANCA = cytoplasmic anti-neutrophil cytoplasmic antibody
ARDS = Adult Respiratory Distress syndrome
* PTU discontinued in all cases unless stated

Table 1.36 Hydralazine associated vasculitis cases

Year	Author	Age/Sex	System involvement	Antibodies	Treatment	Outcome
1987	Martinez-Veal[425]	42M	Renal, Joints, Muscle – (biopsy proven vasculitis)	ANA	Prednisolone	Well
1994	Cambridge[367]	-	Vasculitis in > 2 systems	8 MPO	-	-
1995	Short[426]	75M 76F 69F 64M 70F 65F 55F 71F 65M 70F	Renal, resp, ENT Renal, joints Renal, skin Renal, resp, skin Renal, thrombocytopenia Renal, skin, brain, heart, ENT Renal, brain Renal, skin Renal, brain Renal, skin, joints	10 MPO	9 Prednisolone 4 Cyclophosphamide 1 Azathioprine 1 HD	-
2000	Choi[360]	66M 76F 81F 76F 79M 61F 80F 67M 45F	Renal Renal, resp Skin Resp Renal, resp Renal, resp, ENT Renal Renal, resp, ENT Renal, skin	10 MPO 7 lactoferrin & antielastase 2 antielastase	10 Systemic steroids 8 Cyclophosphamide 3 HD	Died, renal failure and sepsis Died, Perforated diverticulum 7 in remission 1 HD

M= Male, F= Female, Resp = Respiratory, MPO= myeloperoxidase, CYC = Cyclophosphamide, HD = Haemodialysis

Conclusion

Many environmental factors have been linked with PSV. Where a strong association has been found (e.g. hepatitis B and polyarteritis nodosa or propylthiouracil and MPO-positive vasculitis) the resulting disease appears to be distinct from idiopathic PSV, particularly in its' response to treatment and superior prognosis. Although many factors are potentially important in the aetiology of PSV their precise role is harder to define and none seem to be a prerequisite for disease. However particular patterns can be surmised, e.g. atopy seems especially important in CSS and WG whilst occupational exposure to silica and hydrocarbons is linked with renal disease, especially GN. Genetic factors may also play a role. It seems reasonable to hypothesise that disease is multifactorial and that more than one factor may trigger SV in an individual whose immune system has been correctly primed. Immune modulation may be due to a sequence of events over time, encompassing genetic aspects, the normal ageing process (cell apoptosis has been reported to be important and disease peaks in the older years), atopic phenotype (perhaps predetermined in utero or childhood) and subsequent environmental exposures whether infectious or occupational. The expression of disease in an individual would then be determined by their combination of exposures, e.g. atopy leading to CSS, an adjunctive effect of silica particles causing renal or respiratory disease and chronic mucosal stimulation by staphylococcus promoting nasal involvement in WG.

Primary prevention of PSV seems unlikely as many implicated exposures are almost ubiquitous (silica, CMV) and others currently impossible to modify (ageing). In addition the population would be unlikely to modify lifestyle for a rare disorder. However, knowledge of agents involved in precipitating disease will improve our understanding of its pathogenesis. Identification of factors that cause relapse or are involved in disease progression (e.g. hydrocarbons in renal disease) will improve prognosis and quality of life for patients. Occupational practices can be scrutinised and improved should any specific

task be highlighted. Finally specific infectious triggers and unrecognised chronic infection should be sought because if present they could lead to improvements in management and targeted therapy.

VIII. Pathogenesis and Genetic Associations of Primary Systemic Vasculitis

Introduction

The aetiology of PSV is generally thought to be multifactorial with environmental factors inducing disease in genetically susceptible individuals. Although the precise pathophysiology of PSV is unknown, studies have provided evidence for a role for autoimmunity, T-cells, cytokines and endothelial cell interactions, especially with regard to adhesion molecules. Alpha-1 antitrypsin deficiency, complement, transforming growth factor beta (TGFβ) and particular types of T cell receptors may also be important. This chapter evaluates the evidence for a genetic contribution to PSV in the context of current understanding of the pathogenesis of disease.

Familial Vasculitis

Several case reports have described familial clustering of PSV suggesting a genetic contribution to disease. Knudson, Munian, Hay, Nowack and Murty et al reported WG occurring in close relatives; Rottem et al described WG and PAN affecting several members of two families and Mason et al described familial PAN.[427,428,429,430,431,432] In Norfolk a mother and daughter also have WG. In the daughter's case WG is limited to nasal disease and was probably only recognised as a potential problem because of the family knowledge of WG. Nowack et al also recorded mPA and RPGN occurring in HLA identical siblings.[432] Faust et al described two infants born to a consanguinous marriage with a Wegener's-like syndrome, which responded to colchicine.[433] Recently pANCA positive glomerulonephritis with MPO antibodies and systemic vasculitis has also been described in a father and daughter.[434] In addition PSV, including PAN and HSP, has been reported in association with Familial Mediterranean Fever (FMF), especially in

children.[435,436,437,438,439,440,441,442,443,444,445] One explanation is that vasculitis may be an expression of Familial Mediterranean Fever; alternatively genetic characteristics important in FMF may also be involved in the development of PSV.

Autoimmunity, T-cells and HLA associations

Circumstantial and experimental evidence supports an autoimmune mechanism for PSV.[446] Both positive and negative HLA associations have been reported in many autoimmune diseases which may be explained by inappropriate T cell recognition of the self peptide multi histocompatability complex (MHC) which is central to the generation of autoimmunity. There is substantial evidence for a role for T cells in the pathogenesis of PSV, especially in ANCA associated disease (AASV). Renal biopsies in vasculitis associated rapidly progressive glomerulonephritis (RPGN) have been shown to contain T-cells and macrophages and circulating activated T-cells have been observed in WG patients.[447,448] In WG and CSS soluble interleukin 2 receptor (IL2 R) levels, a marker of T cell activation, may correlate with disease activity[449,450], and granulomatous inflammation which is known to be mediated by CD4+ T-cells, is a feature of both diseases. Peripheral blood T cells from AASV patients demonstrate more proliferation in response to MPO and PR3 than those of healthy controls.[451,452,453] This highly specific response may be due to epitopes of PR3 being recognised by cANCA which also provides indirect evidence for T-cell activation.[454,455] Ig G class switching in ANCA, which may occur when active disease switches to remission or vice-versa, is also T-cell dependent.[456] Finally, both monoclonal and polyclonal antilymphocyte therapy has been reported to be effective in systemic vasculitis, including WG.[457]

There has been little consensus between the many studies of HLA associations with PSV, which have been reviewed by Griffiths et al.[458] Positive associations described include HLA DR2, HLA B8 and DR1 with WG, HLA DR8 with mPA and WG and negative

associations include HLA DR3, DR6 and DR13 with mPA and WG. Other investigators found no associations. This may indicate that no real HLA associations existing for PSV or alternatively reflect differences in laboratory techniques and disease classification between studies. In comparison to diseases with recognised HLA associations, numbers of PSV cases included in these studies is small, making an association more difficult to detect.

A syndrome similar to WG characterised by necrotizing granulomatous lesions of the upper respiratory tract and skin and associated with recurrent bacterial infections and skin vasculitis has been described recently. All five patients were homozygous for the HLA– locus so genetic defects within the locus were investigated by PCR and restriction fragment length polymorphism. Reduced cell-surface expression of HLA class-I molecules associated with defective expression of the transporter associated with antigen presentation (TAP) gene was found. In two cases a mutation of the TAP2 gene was noted and autoreactive natural killer (NK) cells and gamma delta T-lymphocytes were found in the peripheral blood of two other cases. The authors suggest that the pathophysiology of lesions may relate to the inability of HLA class I molecules to turn off NK responses in the light of a predominant NK population within the granulomatous lesions.[459] This study demonstrates the value of genetic studies in improving our understanding of vasculitic diseases.

Cytokines and endothelial cell interactions

Tumour necrosis factor α (TNFα), interleukin 1(IL1) and Interferon γ (IFNγ) are thought to play a role in the initiation of vasculitis by upregulation of adhesion molecules on the endothelium and priming of quiescent neutrophils and possibly monocytes. These circulating primed neutrophils / monocytes express ANCA antigens (e.g. proteinase 3-PR3) on their cell surface, adhere to the endothelium and form a complex with circulating ANCA. Exactly how activation of these primed cells occurs is not fully understood but

Fcγ receptors (FcγR) are thought to be important. Activation leads to the release of reactive oxygen species and lysosomal enzymes which results in endothelial damage and necrosis. Degranulation of PR3 and MPO by activated cells may exacerbate the damage by causing endothelial cell activation, injury and apoptosis. Recruitment may also be amplified by a direct effect of cytokines causing ANCA antigen expression on the endothelium and the production of monocyte chemoattractant protein-1 and interleukin-8 (IL-8) by activated monocytes.[446,460]

Studies of the genetic markers of relevant cytokines in PSV have generally included relatively small numbers of heterogeneous PSV cases and most have failed to find any positive associations. However a strong association was recently found in 32 WG compared to controls for CTLA–4 microsatellite but not IL-1β.[461] Liu et al found significantly increased IL-1 receptor antagonist (IL-1ra) allele frequencies in patients with Henoch Schonlein purpura and a subgroup of IgA nephropathy patients with gross haematuria compared to controls.[462] However no significant increase in IL-1ra was found in a group of 20 patients with corneal melt associated with systemic vasculitis.[463] Four studies which looked at polymorphic allele frequencies of TNF alpha in systemic vasculitis failed to find an association. These included the same 20 patients with corneal melt, two studies of WG patients (67 patients combined) and one study of 102 AASV patients.[463,464,465] Investigation of IL-2 and IL-5 ra microsatellite markers in 102 AASV patients also failed to find an association. Similarly no significant associations were found when FcγRIIa receptors were compared between 107 AASV cases and controls.[465] IL4 mRNA has however been shown to be upregulated in a rat model of vasculitis precipitated by gold and d-Penicillamine.[466]

Adhesion Molecules

Adhesion molecules appear to play a key role in the interaction of primed cells with the endothelium. Their role has been reviewed by Kevil et al.[467] Three major families of adhesion molecules have been described; the selectins, integrins and members of the immunoglobulin superfamily of adhesion receptors. In 'normal' inflammation the function of adhesion molecules is to promote leukocyte recruitment from the vasculature into the tissues. This is a regulated process in which the leukocyte adheres to the endothelium mediated by the selectins and the β_1 integrin, VLA4. Firm adhesion is achieved by the leukocyte rolling over the endothelial surface which is promoted by integrins (LFA 1, Mac-1) and the Ig G superfamily members (ICAM-1, ICAM-2, VCAM-1). Finally the leucocyte is extravasated into the tissues mediated by the integrins, IgG superfamily members and platelet endothelial cell adhesion molecule-1 (PECAM-1).

Studies suggest that some adhesion molecules are upregulated in PSV. In WG, studies have reported: reduced leukocyte expression of L-selectin; conflicting evidence for the upregulation of Mac-1 on neutrophils, upregulated ICAM-1 on lymphocytes; and increased ICAM-1, VCAM-1 but not E-selectin expression in kidney biopsies. In acute PAN (CHCC definition) VCAM-1 and E selectin were upregulated on endothelium, compared to controls, with LFA-1 and VLA-4 positive infiltrating leukocytes. ICAM, VCAM and E-selectin have been demonstrated in mPA skin biopsies but renal biopsies showed no E-selectin and little upregulation of I-CAM1. In Giant cell arteritis ICAM-1 has been shown to be upregulated in temporal artery biopsies with infiltrating T-cells expressing LFA-1.[467] No reports have found an association between adhesion molecule genetic polymorphisms and PSV.

Alpha-1 antitrypsin deficiency

Alpha – 1 antitrypsin (α-1AT) is known to be the main inhibitor of PR3 and certain genetic phenotypes causing α-1AT deficiency have been associated with systemic vasculitis. A high prevalence of medium and severe deficiency was described in cANCA positive WG.[468] In 32 cAASV patients the phenotypic frequencies for homozygous PiZZ and heterozygous PiMZ were significantly higher than expected values ($p<0.01$)and the PiZ allele was significantly increased compared to controls. However, 47 patients with severe α-1AT deficiency were cANCA negative and had no clinical vasculitis.[469] Other investigators suggested that heterozygotes for PiZ variant of α–1AT had a greater risk of developing WG than the general population and that amongst 105 PR3 positive patients this variant was a marker of poorer prognosis.[470] A high incidence of the PiZ gene in PSV irrespective of autoantibody type and a novel form of α-1 AT deficiency which manifests only during acute illness has also been reported.[471]

Complement

Complement may be involved in the pathogenesis of vasculitis via the affinity of myeloperoxidase (MPO) for C3. C3 exists in two main allotypic forms C3S and C3F distinguished at the DNA level by a single base change. The rarer C3F allele has been reported to be increased in autoimmune disease including rheumatoid arthritis and IgA nephropathy. Increased allele frequency of C3F was reported in 65 patients with SV. The relative risk of developing SV with the presence of a C3F allele was 2.6, which increased to 5.1 for homozygotes, indicating a positive association with a gene dose effect.[472] A recent study confirmed these findings with an increased gene frequency of C3F ($p<0.05$) compared to controls in 67 PR3 AASV patients.[473]

T cell receptor genes and Transforming Growth Factor- β

Increased T-cell receptor (TCR) Vβ2.1 gene expression has been described in the peripheral blood repertoire of PSV patients compared to controls($p<0.003$). This was marked in mPA patients(<0.0001).[474] TGFβ may also be overexpressed in systemic vasculitis and plays a role in angiogenesis.[475]

Summary

Familial clustering of PSV provides evidence for a genetic association. In many reports however disease presentation is unusual, e.g. WG occurring in children with an atypical response to treatment (e.g. colchicine). Specific genetic forms of PSV may therefore exist. Identification of a specific defect responsible in these cases could lead to targeted therapy in a particular cohort of patients but may not be applicable to a wider cohort. In a similar way to environmental factors the genetic contribution to PSV appears to be heterogeneous. Several genetic polymorphisms have been linked with PSV which are consistent with the current understanding of disease pathogenesis but do not occur in all cases. Improved understanding of the pathogenesis of PSV will enable genetic associations to be elucidated but conversely the identification of genetic associations may improve our understanding of disease mechanisms.

CHAPTER 2

The Norfolk Primary Systemic Vasculitis Cohort

Chapter Overview

Introduction The Norfolk and Norwich Hospital is favourable for epidemiological study because of its geographical location. It is the single central referral hospital for the former Norwich Health Authority (NHA) population. A prospective vasculitis register was established in 1988 to record all new cases of PSV presenting to the hospital. The introduction of immunosuppressive treatment, especially cyclophosphamide (CYC) has transformed PSV from an almost universally fatal disease to a chronic relapsing-remitting condition. Unfortunately treatment is associated with significant side-effects. This chapter describes the well-defined cohort of patients studied in this thesis. Mortality and toxicity associated with CYC regimens within the cohort is also investigated.

Methods Patients were identified from the vasculitis register and by review of hospital biopsy, plasmapheresis and discharge data. Case notes were reviewed and cases classified by the ACR (1990) classification criteria for WG, CSS and PAN, the CHCC definitions for mPA and the Lanham criteria for CSS. New diagnostic criteria suggested by Sorensen et al were compared to these accepted criteria. Details obtained for all cases included age, sex, date of the first symptom attributable to vasculitis, date of presentation, hospital department of first referral, symptoms at presentation and throughout illness, ANCA type, comorbidity, BVAS at presentation and VDI scores at case-note review. Comparison was made between clinical features of the Norfolk cohort and published series and the Mann-Whitney test was used to compare features between WG, mPA and CSS and between surviving and deceased patients.

Mortality within the cohort was investigated by recording the number of incident and prevalent PSV cases and deaths each year. Standardised mortality ratios (SMR) were calculated compared to the NHA population, Kaplein Meyer survival plots were constructed and the Cox proportional hazards model used to compare survival by

diagnosis, sex, age, ANCA type, presence and absence of comorbidity and renal or respiratory involvement.

The long-term toxicity associated intravenous pulse CYC therapy was compared to regimens which included oral CYC. Disease characteristics were compared between treatment groups by the Mann Whitney test and Fisher's exact test was used to compare side-effects.

Results Classification of the patients is described. All patients were Caucasian with a predominance of males for all diagnoses. The mean age was highest for mPA (64.8 years) and the mean prediagnostic period was longest for WG (8.95 months) but differences were not significant. WG patients usually presented to the ENT department, mPA to the renal team and CSS to respiratory physicians. Organ involvement of disease was described as a percentage of the total number of cases and was similar to previous studies. BVAS1 was significantly higher for WG compared to mPA (mean scores 20.6 vs 17.7 respectively, $p=0.046$) and VDI was significantly higher for CSS (mean VDI: 3.3) compared to WG (mean VDI 2.2, $p=0.04$) and mPA (mean VDI: 1.6, $p=0.0017$) for CSS. mPA cases had less organ systems affected throughout the disease course than either WG or CSS but there was no difference in the duration of follow-up between the groups. Results were similar for NHA residents alone compared to the whole cohort. Comparison of survivors with deceased patients demonstrated significantly more cutaneous, mucocutaneous and nasal disease in survivors and more abdominal involvement in deceased patients. However there was no significant difference in their BVAS or VDI scores.

The SMR for PSV cases was 4.78 (95% C.I. 2.98-6.59) compared to the NHA population and was similar for each age group (SMR < 65 years = 4.26 and >65 years = 4.92). Survival was significantly less for a diagnosis of mPA compared to WG and CSS (Log-rank $p= 0.009$ and $p=0.07$ respectively) but there was no significant difference between sexes. The risk of mortality was significantly associated with increasing age but no other factor tested by the Cox proportional hazards model.

96 patients were treated with cyclophosphamide (CYC) in the study period, 30 received intravenous pulsed CYC alone and 76 had regimens including oral CYC. The mean cumulative dose of CYC was significantly less for individuals who received only IV CYC ($p=0.034$) and there was a non-significant trend towards less toxicity in the same group.

Conclusions A number of problems associated with the classification of PSV are noted, in particular the considerable number of patients who fulfil more than one set of criteria. The potential use of the Sorensen criteria in the classification of WG, especially to distinguish between mPA and WG is highlighted but limitations are recognised including the exclusion of a diagnosis of WG by the presence of eosinophilia and the subjective nature of surrogate markers. They appeared to offer no advantage in the classification of mPA.

The mean age of patients in the Norfolk cohort is higher than other series, which may be explained by differences in referral patterns. The higher proportion of males and slightly longer prediagnostic period in WG is in keeping with previous reports and in general clinical features were similar with only minor variations. The BVAS and VDI scores are likely to be an underestimate as they were calculated retrospectively but are similar to previous series. Overall apart from a higher median age our cohort does not appear to differ substantially from previously published series.

A diagnosis of mPA was associated with reduced survival. Mortality also increased significantly with age but this is probably explained by the expected difference in mortality between age groups, reflected in the SMRs. No other factor was identified as a poor prognostic indicator. The study of toxicity associated with CYC regimens suggests that regimens of IV CYC alone may be associated with lower cumulative doses of CYC and a corresponding reduction in toxicity.

Figure 2.1 The Norfolk and Norwich Hospital

The Norfolk Primary Systemic Vasculitis Cohort

I. Classification, Patient Characteristics and Clinical Features

Introduction

All research described in this thesis was carried out at the Norfolk and Norwich Hospital (Figure 2.1.), a centre favourable for epidemiological study because of its geographical location. It is a large district general hospital which serves as the single referral centre for a well-defined, stable, homogenous (~99% Caucasian) adult population (the former Norwich Health Authority – NHA) of approximately 415 000. The area demarcated by the former NHA, an administrative grouping of 77 primary care practices, has been used successfully as the denominator population in the study of rheumatoid arthritis by the Norfolk Arthritis Register (NOAR) and in the descriptive epidemiology of PSV.[16,146,476] The NHA covers an area of 1175 square miles bordered by the coast and the only substantial urban conurbation is Norwich. (Maps 1-4, Appendix 1, illustrate the population distribution within the NHA, the location of primary care services in 1988, parts of the local government districts incorporated in the NHA and administrative areas within Norfolk). Currently acute beds are concentrated at the Norfolk and Norwich Hospital and West Norwich Hospital (which operate as a single trust) although over the early period of the studies they have also been located at Cromer, Wayland and St Michael's Hospitals (Map 5, Appendix 1). Although the health authority boundaries have changed the referral pattern of the relevant general practices to the Norfolk and Norwich Hospital is unchanged. There is little referral of patients out of district and these individuals can usually be identified because of good communication between hospital specialities, adjacent health districts and primary care. A prospective register of all patients diagnosed with vasculitis at the hospital was established in 1988 by Professor David Scott and maintained since then. This chapter

describes the classification and clinical characteristics of the PSV patients studied.

Methods

Patient Identification

Patients who had been diagnosed with PSV at the Norfolk and Norwich Hospital between May 1988 and June 2000 were identified in the following ways:

i) The prospective register was used to identify known patients throughout the study period

ii) Records of all renal biopsies performed at the Norfolk and Norwich Hospital from January 1992 to December 1999 were reviewed and all those with appearances suggestive of vasculitis were evaluated. Although focal segmental necrotizing glomerulonephritis (GN) with or without crescent formation or arteritis is the classical appearance of vasculitis on biopsy, various other appearances can occur. Therefore biopsies were included for further review where there was evidence of focal segmental proliferative GN, necrosis, crescents, mesangial proliferation, a pauciimmune appearance on immunofluorescence, arteritis or granuloma formation. Any biopsy that was reported as suspicious of vasculitis was also included for further assessment. Biopsies after January 1995 were readily identifiable through the pathology computerised records. Prior to this date patients who had undergone a biopsy were identified from ultrasound records, then biopsy results obtained through pathology computerised records or by case note review.

iii) Hospital discharge summaries were searched from January 1988 to December 1999 using the ICD9 cross Index of diseases for 1992-1995 and ICD10 for 1995-1999. Subcodes searched were (ICD9): 446.0 – Polyarteritis nodosa, 446.2 – Hypersensitivity angiitis, 446.4 – Wegener's Granulomatosis and (ICD10) M30.0 – Polyarteritis nodosa, M30.1 Polyarteritis nodosa with lung involvement (Churg-Strauss Syndrome), M31.1-31.3 – Other necrotizing vasculopathies, Wegener's Granulomatosis, I77.6- Other disorders of

arteries and arterioles, arteritis unspecified. In addition codes for percutaneous needle biopsy of lesion of kidney were searched between January 1992 and 1997.

N.B. Between 1990 and 1994 the register had also been augmented by a search of the histopathology records for cutaneous vasculitis.[476]

Case Note Review and Disease Classification

The case notes of all patients identified were reviewed and the underlying diagnosis established. For those found to have vasculitis, details of symptoms and organ involvement were recorded with a corresponding date using a BVAS form (Appendix 2.). Details relevant to the classification of PSV (results of radiology, histology, hepatitis B serology, urinalysis and eosinophil count) were also recorded. Using this information the following classification criteria were applied to each case.

Wegener's Granulomatosis: ACR (1990)[41] and CHCC (1994)[42]

Polyarteritis Nodosa: ACR (1990)[84] and CHCC (1994)[42]

Microscopic Polyangiitis: CHCC (1994)[42]

Churg Strauss Syndrome: ACR (1990)[60], Lanham (1984)[43] and CHCC (1994)[42]

Case notes were reviewed independently by two observers (SL and RW). Where a classification was disputed RW was responsible for the final decision as an external observer, uninvolved in the patients clinical care. Patients who did not fulfil classification criteria were excluded (exceptions are described where relevant). The diagnostic criteria for WG and mPA based upon the CHCC definitions, recently proposed by Sorensen et al were also applied to all cases (SL).[86]

The following details were also recorded for cases classified as PSV: The date and age at diagnosis, sex; hospital department of first referral; permanent damage of organs (recorded using a VDI form); duration of illness at case note review; and ANCA type.

The general practitioner of each patient at the time of diagnosis was used to define residence in the NHA and the postcode of residence at the time of first symptom onset was also noted. Information about clinical features and area of residence was supplemented by interview of the surviving patients who took part in the case-control study of environmental factors in PSV (Chapter 5).

Data Analysis

Patient Characteristics

The male: female ratio and mean, median and age range were calculated for total PSV, WG, mPA and CSS. Where a case could be classified as more than one diagnosis it was included in both data sets.

Clinical Features

Clinical features were documented as a proportion of the total for PSV, WG, mPA and CSS for both the time of diagnosis and throughout the disease course. The categories (systemic, cutaneous, mucocutaneous, ENT, respiratory, cardiovascular, abdominal, renal and neurological) refer to those documented on the BVAS form (Appendix 2.) and involvement was defined as the presence of one or more clinical feature. The exception was in the renal category where hypertension was excluded and documented separately.

BVAS scores were calculated for each patient at diagnosis.[92] The BVAS form (Appendix 2) was used in two ways. The first score (BVAS1) included symptoms that had developed

or deteriorated within 1 month of diagnosis only. This excluded some grumbling disease that had been present since the Index Date. Therefore a second score (BVAS (1+2)) was calculated to include all clinical features attributable to vasculitis which had occurred prior to diagnosis. VDI scores (Appendix 2) were also established where symptoms attributable to vasculitis were present for at least 3 months.[97]

BVAS and VDI were intended for prospective use in the monitoring of vasculitis and their retrospective use is likely to underestimate scores. Estimates for surviving patients who were interviewed may be more accurate which could potentially bias results.

The mean, median and range of values were calculated for total PSV, WG, mPA and CSS for the following items: BVAS; VDI; number of organ systems (defined by the BVAS categories) involved at any time during the disease course; duration of the prediagnostic symptomatic period; and duration of disease at case note review. Where a case could be classified by more than one set of criteria it was included in both data sets.

The first symptom attributable to vasculitis (Index Symptom), the hospital speciality of first referral, symptoms present at diagnosis and throughout disease course were calculated by organ system as a proportion of total PSV, WG, mPA and CSS.

Comparison was made between disease types for each item analysed using the Mann-Whitney test to obtain p values.

Results were also analysed for NHA patients alone and comparison was made between surviving and deceased patients.

Ethics

Case-note review was undertaken as part of an ongoing research project 95RH8 registered with the Norfolk and Norwich Department of Research and Development and ethical approval was confirmed.

Results

Classification of Patients

166 patients with a diagnosis of PSV were identified at the Norfolk and Norwich Hospital between May 1988 and June 2000, 99 were resident in the NHA. 18 were excluded because the original diagnosis had been made prior to May 1988 and 9 because it had made been in another region (e.g. London). Classification criteria were therefore applied to 139 patients. In 16 cases recorded details were insufficient for classification (all resident outside the NHA), so 123 cases were finally included. 70 cases fulfilled criteria for WG, 51 for mPA, 20 for CSS and 71 for PAN. Many cases could be classified by more than one set of criteria and more than one diagnosis. Tables 2.1-2.3 give details of all classification criteria fulfilled by cases in the WG, mPA and CSS groups. In addition 2 patients fulfilled PAN (ACR) criteria only. Both are included in the clinical description of disease as PSV. One (a NHA resident) was also included as WG in the case control study (Chapter 4). No patients fulfilled PAN (CHCC).

18 patients fulfilled classification criteria / definitions for both WG and mPA. For the purposes of the clinical description of disease and descriptive epidemiology these cases were included in both data sets. However in the study of mortality and the aetiology of disease 16 were allocated a diagnosis of WG and 2 mPA as follows: those with upper or lower respiratory tract disease attributable to vasculitis and/or cANCA/PR3 positive were classified as WG, the remainder were mPA. Table 2.5. details the clinical features of these patients.

66 patients of the 123 also fulfilled the diagnostic criteria proposed by Sorensen et al for WG and 6 for mPA. Table 2.4 compares the ACR and CHCC classification of patients with the Sorensen classification.

9 patients who fulfilled the ACR criteria for WG did not meet the Sorensen criteria for WG. In 8 cases this was because of the presence of eosinophilia and in one case due to limited disease. Table 2.6. gives details of the clinical features of these individuals. An eosinophilic infiltrate was present on renal biopsy in five cases (No.s 1,3,4,6,8) and occasional eosinophils were noted on skin biopsies demonstrating leukocytoclastic vasculitis in three cases (No.s 2, 5, 7). In addition case 2 had evidence of an eosinophilic infiltrate on nasal biopsy, case 4 had a mild blood eosinophilia and case 6 had significant peripheral blood eosinophilia ($7x10^9/l$; Normal range $0\text{-}0.4x10^9/l$).

7 patients who did not meet WG (ACR) fulfilled the Sorensen criteria for WG. 1 could otherwise be classified only as PAN (ACR), 3 as mPA (CHCC), 2 as both PAN (ACR) and mPA (CHCC) and one was otherwise unclassifiable. (Table 2.7).

Patient Characteristics

All patients were Caucasian and there was a predominance of males for all diagnoses. Table 2.8 gives details of the age and sex of patients. The mean age was higher for mPA than WG and CSS but the difference was not significant between any group (WG vs mPA $p=0.137$, mPA vs CSS $P=0.149$, WG vs CSS $p=0.710$).

Clinical Features

Table 2.9 describes the Index Symptoms, the first hospital speciality to review patients and the duration between the Index Symptom and the diagnosis of PSV (Prediagnostic Period). There was no significant difference in the pre-diagnostic period between any classification

although it was longest for WG (WG vs mPA p=0.20, WG vs CSS p=0.50, mPA vs CSS p=0.98).

As may be expected the highest proportion of WG cases presented initially to the ENT department, mPA to renal physicians and CSS to respiratory physicians. The first symptoms were usually ENT in WG, non-specific constitutional symptoms in mPA and respiratory in CSS.

Tables 2.10 and 2.11 describe organ involvement at presentation and throughout disease course respectively. In addition all CSS patients had asthma, 47.4% had rhinitis and 64.7% a personal history of allergy (the latter based upon 17 cases). 65% of patients had involvement of the peripheral nervous system and 25% had central nervous system involvement (1 cranial nerve palsy, 2 strokes, 1 organic confusion and 1 cord lesion). Myalgia and arthralgia occurred in 60% and 45% respectively. Cardiac involvement occurred in 25% (4 pericardial disease, 1 myocardial infarction) and resulted in one death. Table 2.12 and 2.13 describe features of NHA residents alone.

Table 2.14 gives the mean, median and range of BVAS, VDI scores, the number of organ systems ever involved and the duration of follow-up after diagnosis. BVAS1 was significantly higher in WG patients compared to mPA overall (p=0.003) and VDI significantly higher in CSS compared to WG (p=0.01) and mPA (0.0005) but no other differences were observed between diagnoses. Duration of follow-up was similar for each classification although both WG and CSS patients had significantly more systems involved throughout the course of disease than mPA (p=0.0004 and p=0.002 respectively) but there was no significant difference between WG and CSS (p=0.461). There were no significant differences between the duration of follow-up prior to case-note review between disease types although the median duration was longest for CSS. (mPA vs WG P=0.825, WG vs

CSS p=0.127, CSS vs mPA p=0.258). A similar pattern was observed for NHA residents alone (Table 2.16). There was no significant difference between BVAS1 scores but BVAS 1+2 was significantly higher for WG than mPA (p=0.046). Significantly more systems were affected in WG and CSS than mPA (p=0.03 and p=0.009) and VDI was higher for CSS than WG or mPA (P=0.04 and P=0.0017) and WG compared to mPA (P=0.043). Duration of follow-up was similar between groups.

Table 2.17 describes the clinical features experienced at presentation and during the disease course in surviving and deceased patients. There was significantly more cutaneous (p=0.03 and 0.04), mucocutaneous (p=0.009 and 0.006) and nasal disease (p=0.003 and 0.003) in survivors than deceased patients. Conversely there was significantly less abdominal involvement in survivors than deceased patients (p=0.019 and 0.017). There was no significant difference between BVAS or VDI scores between survivors and deceased cases but survivors were followed up for a significantly longer duration and had more organ system involvement (Table 2.17.)

Table 2.1 Classification of Wegener's Granulomatosis (No. patients)

WG Classification Criteria	Total WG	ACR alone	ACR & CHCC	CHCC alone
Additional Classification				
WG alone	27	13	13	1
WG & PAN (ACR)	25	13*	12	0
WG & mPA	4	4	0	0
WG, mPA & PAN (ACR)	14	14	0	0
Total	70	44	25	1

* 1 case also fulfilled criteria for CSS (ACR & Lanham)

N.B. This table refers to all cases (70) who could be classified as WG. The rows give the number of cases who could also be classified as PAN (ACR) and/or mPA and illustrates the overlapping nature of classification criteria. Column3-5 show the criteria/ definitions fulfilled to give a classification of WG.

Table 2.2 Classification of Microscopic Polyangiitis (No. patients)

	mPA (CHCC)
Additional Classification	
mPA alone	12
mPA & WG	4
mPA & PAN (ACR)	21*
mPA, WG & PAN (ACR)	14
Total	51

* 1 also fulfils criteria for CSS (Lanham)

N.B. This table refers to all cases (51) who could be classified as WG. The rows give the number of cases who could also be classified as PAN(ACR) and WG (ACR and/or CHCC).

Table 2.3 Classification of Churg Strauss Syndrome (No. patients)

Classification Criteria	Total	ACR	Lanham	ACR & Lanham	ACR, Lanham & CHCC
Additional Classification					
CSS alone	9	0	2	5	2
CSS & PAN (ACR)	11	1	2	6*#	2
Total	20	1	4	11	4

* 1 also fulfils WG (ACR), # 1 also fulfils mPA (CHCC)

N.B. This table refers to all cases (20) who could be classified as CSS. The rows give the number of cases who could also be classified as PAN (ACR) and/or mPA(no cases). Column3-5 show the criteria/ definitions fulfilled to give a classification of CSS.

Table 2.4 Comparison of established classification methods with Sorensen Criteria

Classification	No. patients	Sorensen WG	Sorensen mPA
WG (ACR)	69	60	0
CSS (ACR)	16	0	0
PAN (ACR)	71	35	3
mPA (CHCC)	51	19	6
Unclassifiable	16	1	0

Table 2.5 Clinical features of patients who fulfilled classification criteria for both WG and mPA

No	ENT Symptoms	Respiratory Symptoms	Chest X-ray	Mouth Ulcers	Renal	ANCA	Final Diagnosis
1	N/O	-	-	N	Y	cANCA/PR3	WG
2.	-	H,S,C	Infiltrates	Y	Y	cANCA/PR3	WG
3.	Sinusitis	S	nodules	Y	Y	pANCA	WG
4.	-	H,S	-	N	Y	cANCA/PR3	WG
5.	Crusting, N/O, Sinusitis	H, S	Infiltrates	Y	Y	cANCA	WG
6.	Bl/dis, Crusting	-	-	N	Y	pANCA	WG
7.	N/O	-	-	Y	Y	Not known	WG
8.	Bl/dis, N/O, Deafness	H,S	Cavitation and nodules	N	Y	Positive	WG
9.	Bl/dis, Crusting	-	Infiltrates	Y	Y	cANCA	WG
10.	N/O, Sinusitis	-	Infiltrates	N	Y	cANCA	WG
11.	Bl/dis, Deafness	-	-	Y	N	pANCA	WG
12.	-	H	CXR unavailable	N	Y	cANCA	WG
13.	Bl/dis, Crusting	H,S,C	-	N	Y	cANCA	WG
14.	Crusting	H	Infiltrates	N	Y	Negative	WG
15.	-	-	Infiltrates	Y	Y	cANCA	WG
16.	Bl/dis, N/O	S	-	N	Y	cANCA	WG
17.	-	-	-	N	Y	pANCA	mPA
18.	-	H,S,C	Infiltrates	N	Y	pANCA/MPO	mPA

N/O = Nasal obstruction, Bl/dis= bloody nasal discharge, H= haemoptysis, S= shortness of breath, C=cough, Y=Yes, N=No

Table 2.6 Clinical features of cases who fulfilled ACR but not Sorensen criteria for WG because of eosinophilia

No	ENT symptoms	Respiratory Symptoms	Chest X-ray	Mouth ulcers	Renal Disease	ANCA	Eosinophilia
1.	Crusting, N/O, sinusitis	H,S,C	Infiltrate	Yes	u, cr	cANCA	Biopsy
2.	Deafness, Bl/D	H,C	Nodules	-	u	cANCA	Biopsy
3.	Crusting, N/O, Deafness, Bl/D	H,C	-	Yes	u, cr	cANCA/PR3	Biopsy
4.	-	H	Infiltrates	-	u, cr	cANCA	Blood / Biopsy
5.	Crusting	H,S,C	-	-	u, cr	cANCA/PR3	Biopsy
6.	-	H,S,C	Nodules	Yes	cr	cANCA/PR3	Blood / Biopsy
7.	Crusting, Deafness	H,S,C	Nodules	Yes	-	negative	Biopsy
8.	-	-	Infiltrates	Yes	u, cr	cANCA	Biopsy

Bl/D = Bloody nasal discharge N/O = Nasal obstruction; H= Haemoptysis, S= Shortness of breath, C= cough
u = abnormal urinalysis; cr = raised creatinine

Table 2.7 Clinical features of patients newly classified as WG by Sorensen criteria.

	Classification	ENT symptoms	Respiratory Symptoms	Chest X-ray	Mouth ulcers	Renal	ANCA
1.	mPA	Deafness	H,C	Infiltrate	N	Y	cANCA
2.	PAN	Sinusitis, deafness	-	-	N	N	cANCA
3.	mPA	N/O	-	-	N	Y	MPO
4.	mPA	Deafness	-	-	Y	Y	PR3
5.	mPA/PAN	Sinusitis, N/O	-	-	N	N	cANCA
6.	mPA/PAN	Deafness, N/O	-	-	N	Y	cANCA
7.	Unclassified	Crusting, Bl/Dis	-	-	Y	N	negative

N/O = Nasal obstruction; Bl/Dis = Bloody Discharge; H= Haemoptysis, S= Shortness of breath, C= cough

Table 2.8 Patient Characteristics at Diagnosis

Classification	PSV	WG	mPA	CSS
Number	123	70	51	20
Males	72 (58.5%)	38 (54.2%)	27 (52.9%)	12 (60%)
Mean Age (Years)	62.55	61.20	64.80	59.95
Median Age (Years)	65	64	66	62
Age Range (Years)	15-90	15-90	15-87	30-80

N.B. Some cases fulfilled more than one classification (Tables 2.1-2.3) and are included in this table in more than one column. The numbers in column 3-5 represent this overlap and the sum of the cases exceeds that of column 1.

Table 2.9 Prediagnostic Features of PSV

Classification	PSV	WG	mPA	CSS
Prediagnostic Period (Months)				
Number cases	111	64	45	20
Mean	7.95	8.95	6.51	6.60
Median	3	4	4	2
Range	0-61	0-59	0-29	0-61
First Symptom Attributable to Vasculitis				
Number cases	120	68	50	20
Systemic (%)	28.3	29.4	34.0	15.0
Cutaneous (%)	8.3	1.5	10.0	25.0
Mucocutaneous (%)	5.0	8.8	2.0	-
ENT (%)	24.2	35.3	16.0	-
Respiratory (%)	16.7	17.6	12.0	35.0
CVS (%)	-	-	-	-
Abdominal (%)	2.5	1.5	4.0	5.0
Renal (%)	9.2	4.4	18.0	-
CNS (%)	5.0	1.5	2.0	20.0
Other (%)	0.8	1.5	-	-
Hospital Speciality of First Referral				
Number cases	114	66	45	20
General / Elderly Medicine (%)	17.5	21.2	17.8	5
ENT (%)	16.7	25.8	4.4	5
Renal (%)	16.7	9.1	26.7	5
Respiratory (%)	13.2	9.1	8.9	40
Rheumatology (%)	9.6	9.1	8.9	20
Gastroenterology (%)	8.8	6.1	15.6	5
Neurology (%)	3.5	1.5	2.2	10
Ophthalmology (%)	2.6	4.5	-	-
Urology (%)	1.8	3	2.2	-
ITU (%)	0.8	1.5	2.2	-
Other medical (%)	4.4	6.1	6.7	-
Other surgical (%)	4.4	3.0	2.2	10

Table 2.10 Clinical Features of PSV at Presentation (%)

Classification (No. cases)	PSV (123)	WG (70)	MPA (51)	CSS (20)
Systemic	93.5	94.3	94.1	95.0
Cutaneous	37.7*	42.0*	35.3	50.0
Mucocutaneous	31.4**	51.5**	23.5	15.0
• Ophthalmic	22.3**	38.2**	15.7	5.0
ENT	52.0	68.6	31.3	45.0
• Nasal disease	43.9	60.0	25.5	35.0
• Deafness / Otitis Media	21.1	25.7	9.8	20.0
Respiratory	62.0	66.7*	46.0*	100.00
• Haemoptysis	26.0	38.6	23.5	15.0
• Nodules/ Cavitation	14.6	24.3	3.9	0.0
• Infiltrates/pleural effusion	20.3	34.3	19.6	15.0
CVS	4.1	1.4	2.0	20.0
Abdominal	7.3	4.2	11.8	10.0
Renal	74.0	78.6	92.2	35.0
• Hypertension	26.2*	20.0	38.0*	20.0
Neurological	24.4	17.1	15.7	70.0
• CNS	8.1	7.1	2.0	20.0
• PNS	17.9	8.6	15.7	60.0

* In one case data not available ** In two cases data not available

Table 2.11 Clinical Features of PSV during course of disease (%)

Classification (No. Cases)	PSV (123)	WG (70)	MPA (51)	CSS (20)
Systemic	94.3	95.7	94.1	95.0
Cutaneous	40.2*	46.4*	37.2	50.0
Mucocutaneous	35.5**	55.9**	29.4	15.0
• Ophthalmic	25.6**	42.6**	19.6	5.0
ENT	56.9	74.3	35.3	55.0
• Nasal disease	47.2	64.3	29.4	40.0
• Deafness / Otitis Media	24.4	28.6	9.8	30.0
Respiratory	62.8**	68.1*	46.0*	100.0
• Haemoptysis	27.6	40.0	25.5	20.0
• Nodules/ Cavitation	15.4	25.7	3.9	5.0
• Infiltrates/pleural effusion	22.0	51.4	22*	20.0
CVS	5.7	1.4	3.9	25.0
Abdominal	8.9	5.7	11.8	15.0
Renal	79.7	85.7	96.1	35.0
• Hypertension	30.3	25.7	40.0*	20.0
Neurological	33.3	28.6	19.6	80.0
• CNS	11.4	10.0	3.9	25.0
• PNS	26.8	20.0	17.7	70.0

* In one case data not available ** In two cases data not available

Table 2.12 Clinical Features of PSV in the NHA at presentation (%)

Classification (No. Cases)	PSV (99)	WG (57)	MPA (39)	CSS (19)
Systemic	93.9	96.5	92.3	94.7
Cutaneous	37.8*	42.9*	33.3	47.4
Mucocutaneous	32.0*	52.7**	23.1	15.8
• Ophthalmic	23.7**	40.0**	17.9	5.3
ENT	58.6	75.4	38.5	42.1
• Nasal disease	48.5	64.9	30.8	31.6
• Deafness / Otitis Media	23.2	28.1	12.8	15.8
Respiratory	61.2*	64.3*	43.6	100.0
• Haemoptysis	26.3	36.8	25.6	15.8
• Nodules/ Cavitation	15.2	24.6	5.1	0
• Infiltrates/pleural effusion	21.2	36.8	20.5	15.8
CVS	5.1	1.8	2.6	21.1
Abdominal	7.1	5.3	10.3	10.5
Renal	72.7	77.2	94.9	36.8
• Hypertension	26.3	22.8	35.9	21.1
Neurological	26.3	17.5	18.0	68.4
• CNS	8.1	5.3	2.6	21.1
• PNS	20.2	10.5	18.0	57.9

* In one case data not available ** In two cases data not available

Table 2.13 Clinical Features of PSV in the NHA during course of disease (%)

Classification (No. Cases)	PSV (99)	WG (57)	MPA (39)	CSS (19)
Systemic	93.9	96.5	92.3	94.7
Cutaneous	40.8*	48.2*	35.9	47.4
Mucocutaneous	37.1**	58.2**	30.8	15.8
• Ophthalmic	27.9**	45.5**	23.1	5.3
ENT	62.6	79.0	43.6	52.6
• Nasal disease	51.5	68.4	35.9	36.8
• Deafness / Otitis Media	26.3	29.8	12.8	26.3
Respiratory	62.2**	66.1*	43.6	100.0
• Haemoptysis	28.3	38.6	28.2	21.1
• Nodules/ Cavitation	16.2	26.3	5.1	5.3
• Infiltrates/pleural effusion	22.2	56.1	20.5	21.1
CVS	7.1	1.8	5.1	26.3
Abdominal	9.1	7.0	10.3	15.8
Renal	77.8	86.0	94.9	36.8
• Hypertension	29.3	28.1	35.9*	21.1
Neurological	34.3	26.3	23.1	75.0
• CNS	9.1	5.3	5.1	21.1
• PNS	30.3	22.8	20.5	68.4

* In one case data not available ** In two cases data not available

Table 2.14 BVAS and VDI scores, Organ Involvement and Duration of Follow-up

Classification	PSV	WG	mPA	CSS
BVAS1				
Number of cases	123	70	51	20
Mean	18.4	20.1	17.8	18.7
Median	19.0	21.0	16.0	21.0
Range	2-39	2-39	4-38	7-28
BVAS(1+2)				
Number of cases	121	68	50	20
Mean	19.8	21.6	19.0	21.0
Median	20.0	21.0	16.5	22.0
Range	4-38	6-38	4-38	7-34
VDI				
Number of cases	84	47	50	16
Mean	2.3	2.1	1.6	3.6
Median	2.0	2.0	1.0	3.5
Range	0-9	0-5	0-4	1-9
Total no. organ systems affected				
Number of cases	123	70	41	20
Mean	4.3	4.7	3.8	5.0
Median	4.0	5.0	4.0	5.0
Range	1-8	1-7	1-7	2-8
Duration of follow – up (months)				
Median	36.7	34.8	35.0	43.9
Mean	24.0	22.0	22.0	41.0
Range	1-136	1-136	1-118	1-132

Table 2.15 BVAS and VDI scores, Organ Involvement and Duration of Follow-up for NHA residents.

Classification	PSV	WG	mPA	CSS
BVAS1				
Number of cases	99	57	39	19
Mean	18.7	20.6	17.7	18.6
Median	19.0	21.0	15.0	21.0
Range	4-9	6-39	4-38	7-28
BVAS(1+2)	99	57	39	19
Number of cases				
Mean	20.1	22.0	19.2	20.8
Median	21.0	22.0	16.0	22.0
Range	4-38	6-38	4-38	7-34
VDI				
Number of cases	72	41	27	15
Mean	2.3	2.2	1.6	3.3
Median	2.0	2.0	1.0	3.0
Range	0-9	0-5	0-4	1-9
Total no. organ systems affected				
Number of cases	99	57	39	19
Mean	4.3	4.7	3.8	5.0
Median	4.0	5.0	4.0	5.0
Range	1-8	1-7	1-7	2-8
Duration of follow – up (months)				
Median	39.1	36.1	40.5	43.3
Mean	26.0	24.0	23.0	41.0
Range	1-136	1-136	1-107	1-132

Table 2.16 Comparison of Clinical Features of Survivors and Deceased Patients (NHA)

	At Presentation		During Disease Course	
	Alive (68)	Deceased (31)	Alive	Deceased
Systemic	95.6	90.3	95.6	90.3
Cutaneous	44.8*	22.6	47.8	25.8
Mucocutaneous	40.3*	13.3*	46.3*	16.7*
• Ophthalmic	32.8*	3.3*	38.9*	3.3*
ENT	67.7	38.7	72.1	41.9
• Nasal disease	58.8	25.8	61.8	29.0
• Deafness / Otitis Media	23.5	22.6	27.9	22.6
Respiratory	62.7*	58.1	62.7*	61.3
• Haemoptysis	25.0	29.0	26.5	32.3
• Nodules/ Cavitation	16.2	9.7	17.6	9.7
• Infiltrates/pleural effusion	21.2**	25.8	21.2**	25.8
CVS	5.9	3.2	7.4	6.5
Abdominal	2.9	16.1	4.4	19.4
Renal	69.1	80.7	73.5	87.1
• Hypertension	27.9	22.6	30.9	25.8
Neurological	25.0	25.8	35.3	32.3
• CNS	5.9	12.9	5.9	16.1
• PNS	22.1	16.1	35.3	19.4

* In one case data not available ** In two cases data not available

Table 2.17 BVAS and VDI scores, Organ Involvement and Duration of Follow-up : Comparison of Surviving and Deceased patients.

	Survivors	Deceased	p
BVAS1			0.539
Number of cases	68	31	
Mean	19.0	18.0	
Median	19.0	19.0	
Range	6-38	4-39	
BVAS(1+2)			0.095
Number of cases	68	31	
Mean	20.9	18.3	
Median	21.0	18.0	
Range	6-38	4-32	
BVDI			0.285
Number of cases	57	15	
Mean	2.4	2.1	
Median	2.0	2.0	
Range	0-9	1-4	
Total no. organ systems affected			
Number of cases	68	31	0.005
Mean	4.5	3.8	
Median	5.0	4.0	
Range	1-8	1-6	
Duration of follow – up (months)			
Median	47.2	21.1<	0.001
Mean	37.0	13.0	
Range	1-136	1-68	

Classification

The use of classification criteria allows direct comparison between different studies of PSV however a number of problems are evident. First a considerable number of patients fulfil more than one set of criteria. It was recommended that if a case fulfils more than one set of ACR classification criteria they should be classified by those that correspond to the clinical working diagnosis.[49] However mPA was not recognised in the ACR classification so in order to explore its clinical characteristics and epidemiology, patients who fulfilled both an ACR classification and mPA were analysed in both data sets. For the other studies it was necessary to distinguish between WG and mPA so a 'working diagnosis' was allocated for the 18 patients fulfilled criteria for both mPA and WG (Table 2.7). Later interpretation of results comparing mPA and WG must therefore acknowledge this 'overlap' in disease.

Two CSS patients also fulfilled criteria for mPA and WG. The former was diagnosed with CSS on the basis of asthma, angina, pericarditis, proteinuria, elevated creatinine and an eosinophilia of 3.7 x 10^9 /l. However renal biopsy showed a pauciimmune segmental proliferative, necrotizing and crescentic GN with focal low-grade arteriolitis but no significant eosinophilia which fulfils the definition for mPA. However the classification of CSS alone was used in view of the clinical picture. The second had a forty year history of asthma and was initially classified as CSS following a presentation with a cranial nerve palsy and significant eosinophilia (7.0 x 10^9 /l: Laboratory reference range 0-0.4 x 10^9 /l). However she subsequently developed a pulmonary nodule and necrotizing GN with arteritis, eosinophilic infiltrate and granuloma which led to a classification of WG. She was included in the case-control and mortality studies as WG but as her diagnosis was in 1999 she was not included in the descriptive epidemiology.

All but 2 patients classified as ACR PAN also fulfilled other classification criteria. One of these patients (an NHA resident) was given a clinical diagnosis of WG and included in the studies of mortality, cyclophosphamide (chapter2) and environmental factors (chapter five) on the basis of his clinical features. Prior to presentation he had a 3-year history of nasal obstruction, epistaxis and sinusitis requiring subtotal maxillary resection and bilateral intranasal antrostomies. He subsequently developed otitis media and a facial nerve palsy and was successfully treated with cyclophosphamide. Following a relapse with headache, otitis, weight loss and sensory neuropathy he responded to cyclophosphamide, prednisolone and cotrimoxazole followed by 18 months of azathioprine. He remained in remission without treatment after 18 months follow-up. No biopsy material was obtained but sinus X-ray showed opacification of both the frontal and left maxillary sinus, an indium scan showed elevated uptake of white-cells in the nasal sinuses and IIF / ELISA revealed cANCA / PR3. The second individual (non-NHA) presented with malaise, fever, arthralgia, haematuria and deranged renal function. Renal biopsy showed necrotizing crescentic GN with some interstitial infiltration but no arteritis. Renal function deteriorated rapidly despite cyclophosphamide and he became dialysis dependent. He has subsequently developed no other features of SV and ANCA was equivocal. His disease may represent mPA but in the absence of definite arteritis he was excluded from all studies except the clinical description of PSV.

A second problem is that some patients who actually have PSV could be excluded by classification and therefore the clinical spectrum observed may not be wholly representative. Of the 16 unclassifiable patients 8 lived outside the NHA. Although suspected, SV could not be confirmed in 2 cases with asthma and peripheral eosinophilia and 3 with a systemic disease with cutaneous vasculitis. 2 cases had focal segmental proliferative GN (one ANCA positive, the other with cutaneous vasculitis) and the final case had ENT disease with small vessel necrosis on biopsy but no granulomas. Unclassifiable patients with a probable diagnosis of vasculitis were recorded on the

register, so their notes were reviewed to ensure that disease had not progressed to SV. However records were not routinely kept of other patients excluded from the register so it was not possible to re-evaluate them later. However following the careful review of histopathology records and discharge data we are confident that few cases could remain unrecognised.

The classification of patients over many years as part of a prospective register may lead to inconsistencies. In some cases classification can change with time and the evolution of disease e.g. a patient regarded as mPA or limited WG in an earlier study may 'progress' to a classification of systemic WG at a later review. Application of criteria is subject to inter-observer variation as data interpretation can be subjective e.g. when determining whether a feature is caused by vasculitis or another pathology. The use of the CHCC definitions, which were not intended for classification, is likely to vary more than the ACR criteria. To maintain consistency and minimise these potential problems a single individual (RW) has been responsible for the final classification of cases since 1994. Classification of patients were however updated by case-note review of all patients (SL) and any disputed classifications were re-evaluated (RW).

Finally relevant information may be missing and impair classification, e.g. not all patients have biopsies or radiography (especially angiography) and case-notes may be incomplete.

Evaluation of the Sorensen diagnostic criteria

Of the 66 patients classified as WG by the Sorensen criteria, 59 cases could also be classified as WG by ACR and/or CHCC definitions but 7 'new' cases were also identified. However 7 cases previously classified as WG were excluded because of the presence of eosinophilia, despite strong clinical evidence for the diagnosis and the association of cANCA (Table 2.6). With the exception of one case none of these individuals could be

classified as CSS by other means. Eosinophilia has been reported to be associated with WG in the literature[55] and in our experience eosinophilia on tissue biopsy is a relatively common finding in WG although to a lesser extent than CSS (Figures 1.6-1.8, Chapter 1). It therefore seems inappropriate to use eosinophilia to exclude a diagnosis of WG without a clear guidance to the level of eosinophilia. (N.B. The final WG case excluded by the Sorensen criteria (No 17. Table 2.5) was initially classified as WG by a possible granulomatous infiltrate on biopsy but was later given a working diagnosis of mPA on review of histology).

As discussed use of current classification systems for systemic vasculitis is complicated by the fact that many individuals fulfil more than one set of criteria, especially WG (ACR) and mPA (CHCC). The Sorensen criteria may be of particular benefit in distinguishing between these diagnoses. The 7 'new' WG patients had previously failed to fulfil ACR criteria because they lacked biopsy evidence of disease and met only one of the ACR criteria. The introduction of cANCA into criteria therefore appears to be a useful tool, especially in distinguishing between mPA and WG when used in-patients with a clinical diagnosis of PSV. However the use of ANCA in distinguishing PSV from other disorders remains controversial.[70] In addition the use of surrogate markers for granulomatous inflammation remains subjective i.e. different observers give different results. The Sorensen criteria for mPA were restrictive, remain subjective, identify fewer patients than the use of CHCC definitions alone and seem to have few advantages over the application of these definitions. In conclusion with modification the Sorensen criteria for WG could provide a useful classification system although those for mPA seem to have little advantage. As they are presented they may have a role in distinguishing between a diagnosis of mPA and WG in individuals who fulfil more than one classification

Patient Characteristics

The mean age of patients in the Norfolk cohort is higher than other series for all diagnoses. A likely explanation is that referral to tertiary referral centres is biased towards younger patients whilst our unselected cohort includes a more representative cross-section of patients. However Norfolk has a slightly higher percentage of elderly people compared to other regions in Great Britain which may contribute towards some differences between centres (6.71% vs 6.4% over 75-years-old).[477]

The higher proportion of males compared to females in all diagnoses supports previous observations (Tables 1.3, 1.5, 1.7).

The prediagnostic period was slightly longer on average for WG patients than mPA and CSS patients. This is in keeping with a previous report by Schleiffler et al who described a mean period of 53 months (1-240) prediagnosis for WG and 9 months (1-40) for mPA. However the prediagnostic period was considerably shorter for both diagnoses in our cohort. The small number of cases in their study or an improving recognition of PSV may explain this over time (their cases were diagnosed between 1984 and 1993). A similar decrease in the length of the prediagnostic period has been seen in the Lubeck cohort which reported a duration of 1-16 years for WG in an early report compared to a mean of 7 months more recently.[121,478]

Clinical Features

WG

Although ENT involvement was a prominent feature of WG it was not quite as common either at presentation or during the course of disease as other published studies. The most likely explanation for this is a difference in referral patterns between our population based cohort and tertiary referral centres, e.g. there may be a bias towards the recognition and

referral of patients with 'classical' symptoms of WG in the latter report. Underreporting of ENT symptoms in case notes could potentially contribute to the relatively low proportion. A higher percentage (72.1%) of surviving WG patients, the majority of whom had been interviewed, had experienced ENT symptoms. Alternatively this higher proportion could reflect a better prognosis for WG with ENT involvement.

Lower respiratory tract involvement was similar for our cohort to others at presentation but lower than most for the course of disease. A similar proportion of our patients had renal disease (abnormal urinalysis and/or creatinine) at presentation (78.6%) and throughout disease course (85.7%) compared to other series and did not reproduce the findings of an initially low percentage found by Hoffman et al.[18] Ophthalmic, constitutional and cutaneous features were also in keeping with previous reports although there was a relatively high proportion of cutaneous features at presentation. Neurological features were relatively infrequent as expected and cardiovascular manifestations limited to one case of pericarditis. (See chapter 1,Tables 1.3,1.5,1.7 for details and references)

CSS

Clinical features were similar to previously reported series. All cases had respiratory disease defined by BVAS (Appendix 2). Unusually one patient had a documented fixed nodular lesion on CXR but as described previously also fulfilled classification criteria for WG. Fewer patients than expected had a history of rhinitis compared to other reports, which could again be explained by referral bias to tertiary centres. A higher proportion of patients had neurological involvement as expected and there was more renal disease than previously noted (35%). Gastrointestinal complications however were relatively infrequent (15%).

mPA

Clinical features were generally similar to those reported by Savage and Westman et al although fewer patients had renal involvement and respiratory disease was more common in our cohort.[36,50] By contrast the proportions of cutaneous, neurological, cardiovascular and abdominal features were lower than the French series.[51] The probable explanation for these differences is their exclusion of patients with ENT involvement because of the use of the CHCC definition. However the proportion of these clinical features remains relatively low for the 33 cases who were classified as mPA alone (cutaneous 24.2%, peripheral neuropathy 12.1%, central nervous system involvement 6.1%, cardiovascular disease 6.1% and abdominal features 9.1%). It is also interesting to note that 12.1% of these cases had nasal involvement and 9.1% had hearing impairment. These differences could be caused by a difference in disease between regions or patterns of referral but it is more likely that they reflect the subjective nature of the CHCC definitions and difficulty in applying them in a standardised manner.

There were no major differences in the pattern of disease for any classification in the NHA patients alone compared to the whole cohort.

The excess of cutaneous and mucocutaneous disease in the survivors maybe explained by reporting bias, many patients were interviewed so more detail may have been available than in case notes alone. The same may be true for nasal disease but as there was no significant difference in the percentage of hearing loss this may in fact be caused by a real discrepancy in ENT disease. The relative excess of gastrointestinal features in the non-survivors may indicate that this is a poor prognostic feature. Alternatively abdominal disease may be less severe and unrecognised in some surviving cases. Although gastrointestinal disease per se has not been reported to be a poor prognostic indicator in most series when severe complications, e.g. perforation occur mortality is very high (about

80%). In published series severity of renal disease and infiltrates on chest X-ray have been associated with increased mortality.[13,126]

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BVAS and VDI

The BVAS and VDI scores are likely to be an underestimate because they were calculated retrospectively. The mean BVAS1 were higher for WG than mPA and similar to figures reported by Brijker et al in their cohort of 32 ANCA positive SV patients. The median BVAS1 score at presentation in this series (also calculated retrospectively) was 21 for WG and 16 for mPA.[479] Similarly in its original evaluation the median BVAS score for WG during periods of disease activity was 19.5 (11-25) compared to 16 (10-29) in PAN.[91] In another study of outcome in WG the median BVAS was slightly higher at the start of treatment – 23(range 4-46).[127] These results suggest that our cohort is similar to previously described series in terms of initial disease activity for WG and mPA. However the median VDI was lower for both WG and mPA compared to the Brijker study (5 and 4 respectively compared to 2 and 1 in our study).[479] This is probably attributable to differences in information available in case-notes, features of permanent and on-going damage were in general documented less well than symptoms of the acute presentation and relapses. In particular fewer details of treatment side effects, e.g. cataracts were recorded than might have been expected. The limitations of retrospective note review mean that we cannot confidently compare VDI between series or comment upon their relationship to outcome. This highlights the need to keep a prospective record of both BVAS and VDI scores at each clinic attendance to facilitate such comparisons in the future.

Conclusion

Our PSV cohort is well defined and classification criteria have been applied in a standardised manner. However we have experienced similar limitations in classification to previous studies. The application of criteria remains subjective, particularly mPA (CHCC) and additional observers could dispute the classification of some individuals. We noted a considerable amount of 'overlap' between the diagnoses of mPA and WG. A classification system designed to distinguish these entities more clearly is needed to compare treatment response and prognostic factors between groups. The presence of PR3 ANCA and/or upper respiratory tract vasculitis seems a sensible approach to distinguishing between these diagnoses and reflects current clinical practice, making mPA a diagnosis of exclusion. Similarly some series of mPA patients have previously excluded all cases with ENT disease and the Sorensen et al suggested criteria based upon a similar rationale although we disagree with the exclusion of a diagnosis of WG by the presence of eosinophilia. However as mPA and WG may belong to a spectrum of disease caused by the same pathogenic mechanisms the attempt to distinguish separate entities may be of little value. Therefore the overlapping nature of disease must be remembered in interpreting results and in the analysis of potential environmental factors WG and mPA were investigated as a single disease group in addition to each individual disease.

Patient characteristics and disease activity in our cohort were similar to other series and differences noted, especially the higher mean age, may be due to referral bias affecting tertiary referral centre. The clinical features experienced in our population-based cohort are likely to be representative of the spectrum of disease. Alternatively there may be some difference in disease expression between regions because of environmental or genetic factors that affect disease expression. The relatively short prediagnostic periods compared to earlier reports probably reflect an improving recognition of PSV.

II. Mortality in the PSV cohort

Introduction

Mortality associated with PSV has improved considerably with the use of immunosuppressive treatment. Reports suggest that prognosis is worse for elderly patients, those with renal involvement, pulmonary infiltration on chest X-ray and a diagnosis of microscopic polyangiitis.[35,36,50,52,126]

We aimed to compare mortality between age and classification groups within our cohort of PSV patients and to obtain standardised mortality ratios (SMRs) compared to the denominator population.

Methods

All patients diagnosed with PSV and resident within the NHA between May 1988 and May 2000 were identified as previously described. Patients were classified according to the ACR criteria and CHCC definition for WG, the ACR and Lanham criteria for CSS and the CHCC definition for mPA.[41,42,43,60] In addition an individual with clinical evidence of WG but who did not fulfil criteria was included (detailed previously). Some cases fulfilled classification criteria for both WG and mPA. Where there was evidence of granulomatous inflammation of the upper or lower airways or cANCA/PR3, they were categorised as WG. Otherwise they were categorised as mPA.

For each year the number of incident and prevalent PSV cases and deaths were recorded. Details of age at diagnosis, sex, ANCA type, presence or absence of renal or respiratory disease (defined by the BVAS items, Appendix 2), cause of death and comorbidity which may have contributed towards death (e.g. pre-existing lung disease or ischaemic heart disease) was recorded.

The denominator population was taken to be the 1994 NHA population. Mortality figures (1994), subdivided by ward, for the whole Norfolk population were obtained by age band from the Norfolk City Council Demographic Unit. The area covered by the former NHA can be mapped by parishes (Map 6., Appendix 1.) which in turn make up the wards (Map 7, Appendix 1). Mortality figures for the NHA were therefore obtained by summing deaths per age group for the corresponding wards. Mortality was assumed to be stable over the ten-year period and the 1994 figures were applied for each year.

Analysis

Standardised Mortality Rates (SMR) were calculated for PSV patients diagnosed between January 1989 and December 1998 compared to the NHA population by Indirect Standardisation (Figure 2.2). A poisson distribution was assumed to obtain 95% confidence intervals (C.I.). Comparison was made between SMRs for cases greater or less than 65 years of age at diagnosis, men and women and between disease classifications by obtaining z values (Figure 2.3).

Kaplein Meyer Survival Plots were constructed for all patients identified between May 1988 to May 2000. Disease Classifications and age groups were compared using the log-rank test and the Cox proportional hazards model was used (by Dr L. Shepstone) to compare survival by disease type, sex, age, ANCA type, presence or absence of comorbidity and renal or respiratory involvement.

Figure 2.3 Indirect standardisation

$$\text{Standardised ratio } (s) = \frac{r_{STUDY}}{r_{REF}} = \frac{\sum_{i=1}^{I} n_i}{\sum_{i=1}^{I} \left(\frac{N_i m_i}{M_i} \right)}$$

r_{STUDY} = actual PSV death rate
r_{REF} = death rate expected if PSV mortality = NHA mortality
n = no. PSV deaths, N = no. PSV patients
m = no. NHA deaths, M = NHA population

Figure 2.4 Calculation of p-values

$$z = \frac{s_a - s_b}{\sqrt{[\text{var}(a) + \text{var}(b)]}}$$

s = Standardised mortality ratio, *var* = variance, a / b = groups compared

Results

97 NHA residents were diagnosed with PSV during the study period. Their classifications are given in Table 2.18. 15 patients (all diagnosed between 1989-1998) could be classified as both mPA and WG, 14 of these were allocated to the WG group on the basis of clinical features and/or presence of cANCA/PR3 (Table 2.5). 5 WG cases had disease limited to constitutional symptoms, ENT and cutaneous features. 31 deaths were observed: cause of death, duration of survival post-diagnosis and comorbidity are given in Table 2.19.

The SMR (95% C.I.) for PSV patients compared to the NHA population was 4.78 (2.98-6.59) and was higher for men than for women [5.94 (3.11-8.76) compared to 3.05(1.16-4.94)] although this difference was not significant (p=0.09). SMRs by disease and age groups are given in Table 2.20 There were no significant differences [S.M.R <65yrs 4.26 vs >65yrs 4.92, p=0.76; S.M.R. WG 4.61 vs mPA 4.99, p=0.85; S.M.R. WG 4.61 vs CSS 4.68, p=0.91; S.M.R. mPA 4.99 vs CSS 4.68, p=0.91]

Non-parametric survival plots for PSV and comparing age, sex and disease type are illustrated in figures 2.4-2.7. The mean survival was 51.5 months (1-144) for all PSV. There were no significant differences for males compared to females (LogRank 0.93) but survival was significantly less for the over 65 year-old age group compared to the under 65's and for mPA compared to other disease subtypes (Log-rank p=0.009 and p=0.07 respectively). 1-year and 5 year percentage survival by diagnosis are given in Table 2.21

Table 2.22 gives the Hazard ratios and 95% C.I. obtained by the Cox proportional hazards model comparing age, sex, diagnosis, pANCA vs cANCA, presence or absence of comorbidity and presence or absence of renal and respiratory involvement. The risk of mortality was significantly associated with increasing age with a highly significant increase in risk for those over 61 years old. There was no significant difference between males and females or diagnosis. However risk of mortality was highest for mPA, then CSS then WG. There was also no significant difference in survival between patients with or

without renal or respiratory involvement; cANCA and pANCA; or the presence or absence of comorbidity. Age adjusted hazard ratios did not significantly alter any of these findings.

Table 2.18 Diagnosis of PSV patients in the NHA

Time Period	May 1988 - May 2000	Jan. 1989 - Dec.1998
Diagnosis		
WG	50	47
mPA	28	26
CSS	19	17
Total	97	90

Table 2.19 Deaths of PSV cases May 1988 – May 2000

Diagnosis	Cause of death	Survival (months)	Comorbidity
Deaths associated with vasculitis (active disease or damage)			
WG	Active WG and pneumonia	2	Depression, HBP, IHD
	Disease progression	100	IDDM
	Small bowel perforation (WG)	3	Hypothyroidism
	Respiratory failure (WG)	32	Hyperlipidaemia
	Progression WG and CVA	1	-
	Unknown, recent relapse	23	-
	Sudden death, WG related	1	Fibrosing alveolitis
	Disease progression	57	Previous Ca Uterus
mPA	Active disease*	14	-
	General decline and deterioration in renal function	46	Dementia, HBP
	Cardiac arrest during haemodialysis	14	Previous Ca breast
	Active disease / chest infection #	2	-
	Sepsis / renal failure #	13	PVD, NIDDM
	Post operation for infected fistula*	68	HBP, IHD, MI Hyperlipidaemia
CSS	Disease progression*	4	-
	Exacerbation of CSS	7	-
Deaths potentially associated with immunosuppression			
WG	Pneumocystis carinii pneumonia	2	-
mPA	Septicaemia / bronchopneumonia	1	NIDDM, IHD
	Pneumonia	8	IHD, MI
	Streptococcal septicaemia	45	HBP
	Pneumonia / gram –ve septicaemia	61	LVF, PVD, Previous Ca rectum
	Pneumonia / Respiratory failure	28	Pulmonary fibrosis
	Carcinoma of the oesophagus	58	Depression
CSS	Ovarian Cancer (Prednisolone only)	59	-
Other causes of death			
WG	Pulmonary embolism	1	-
	Unknown, general deterioration	9	Osteoarthritis
mPA	Unknown (moved out of area)	84	-
	Unknown**	52	-
	Unknown**	61	Previous CVA
	Unknown * & **	3	Asthma
CSS	Suicide	3	Depression

* Death after December 1998; ** Disease stable at previous clinic appointment, died at home
Immunosuppression potentially contributory to death
–ve = negative; HBP = Hypertension; Ca = cancer; IHD= Ischaemic heart disease; MI=Myocardial infarction,; PVD = Peripheral vascular disease, IDDM= Insulin dependent diabetes mellitus; NIDDM= non-IDDM, CVA = cerebrovascular accident

Table 2.20 Standardised Mortality Ratios for PSV and subgroups

Group	S.M.R.	95% C.I.
Total PSV	4.78	2.98-6.59
<65 years	4.26	0.53-8.00
>65 years	4.92	2.86-6.98
Females	3.05	1.16-4.94
Males	5.94	3.11-8.76
WG	4.61	1.89-7.33
mPA	4.99	2.17-7.82
CSS	4.68	2.34-7.03

Table 2.21 Percentage 1 and 5-year survival in PSV

Diagnosis	Survival (%)		
	1 year	2 year	5 years
Total PSV	84.8	80.9	65.5
WG	85.5	83.4	75.9
mPA	82.7	71.4	45.1
CSS	83.2	80.8	68.1

Figure 2.4
Non-parametric survival plot for PSV(May 1988-May 2000)

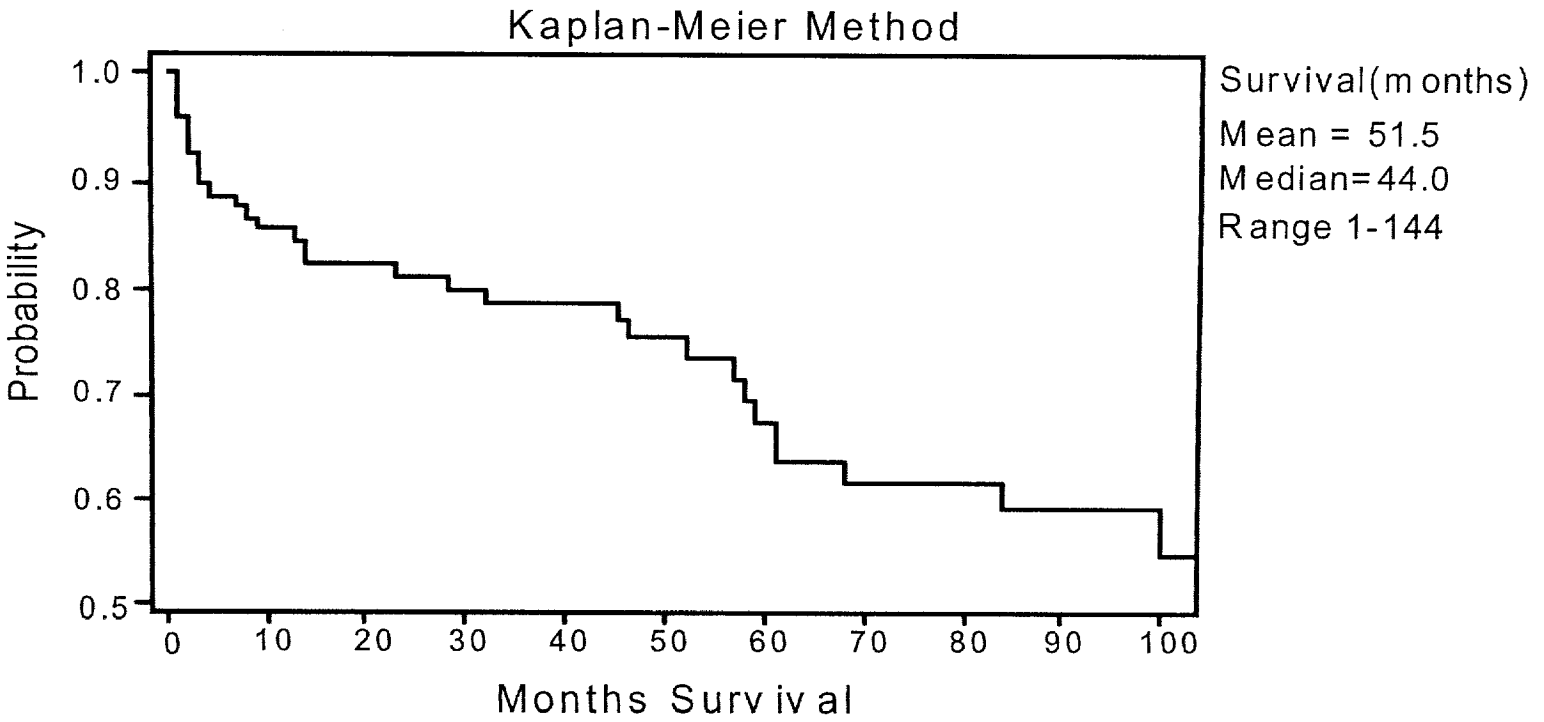


Figure 2.5 Non parametric Survival Plot Comparing Diseases

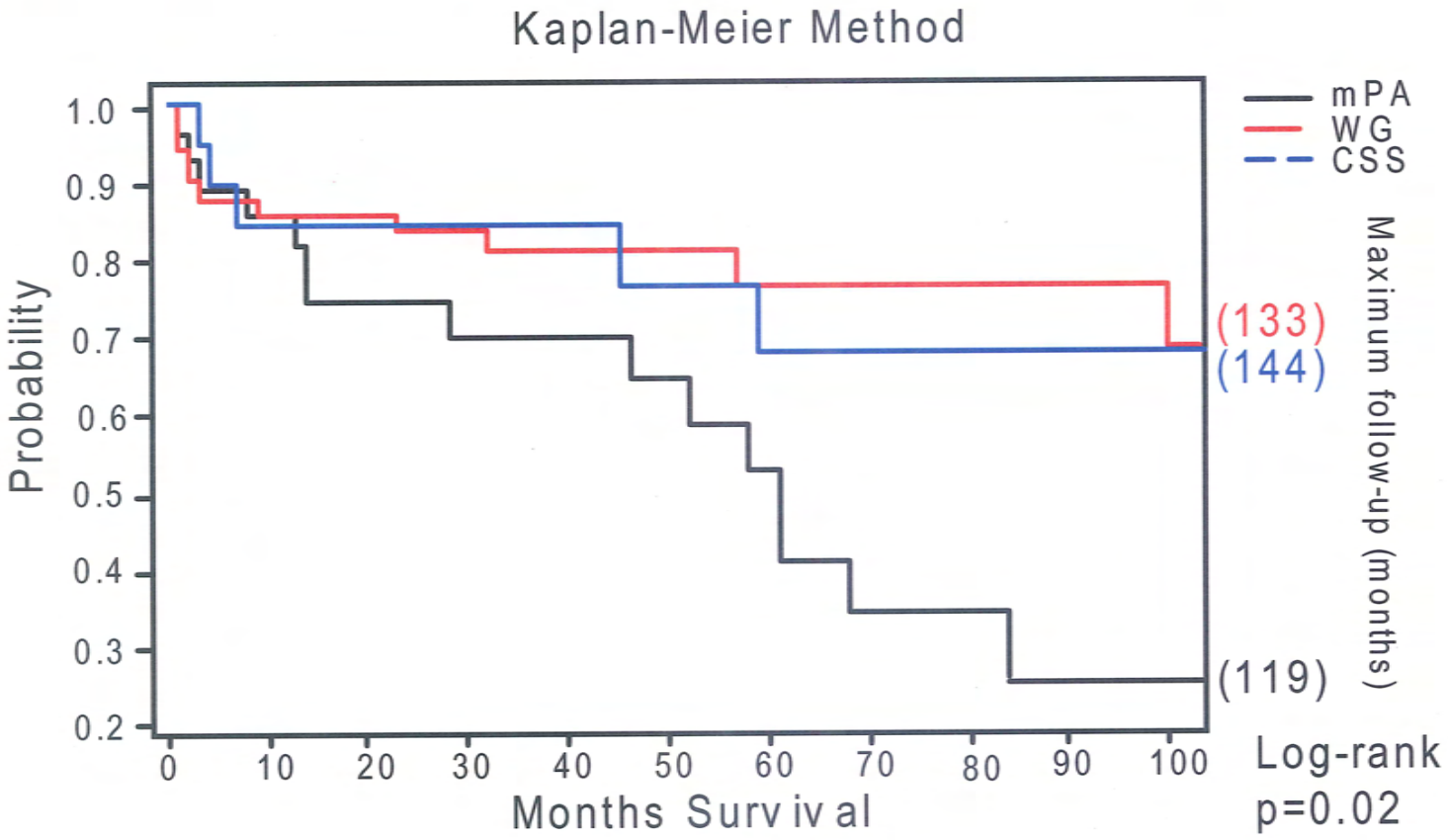


Figure 2.6
Non parametric Survival Plots Comparing Males and Females

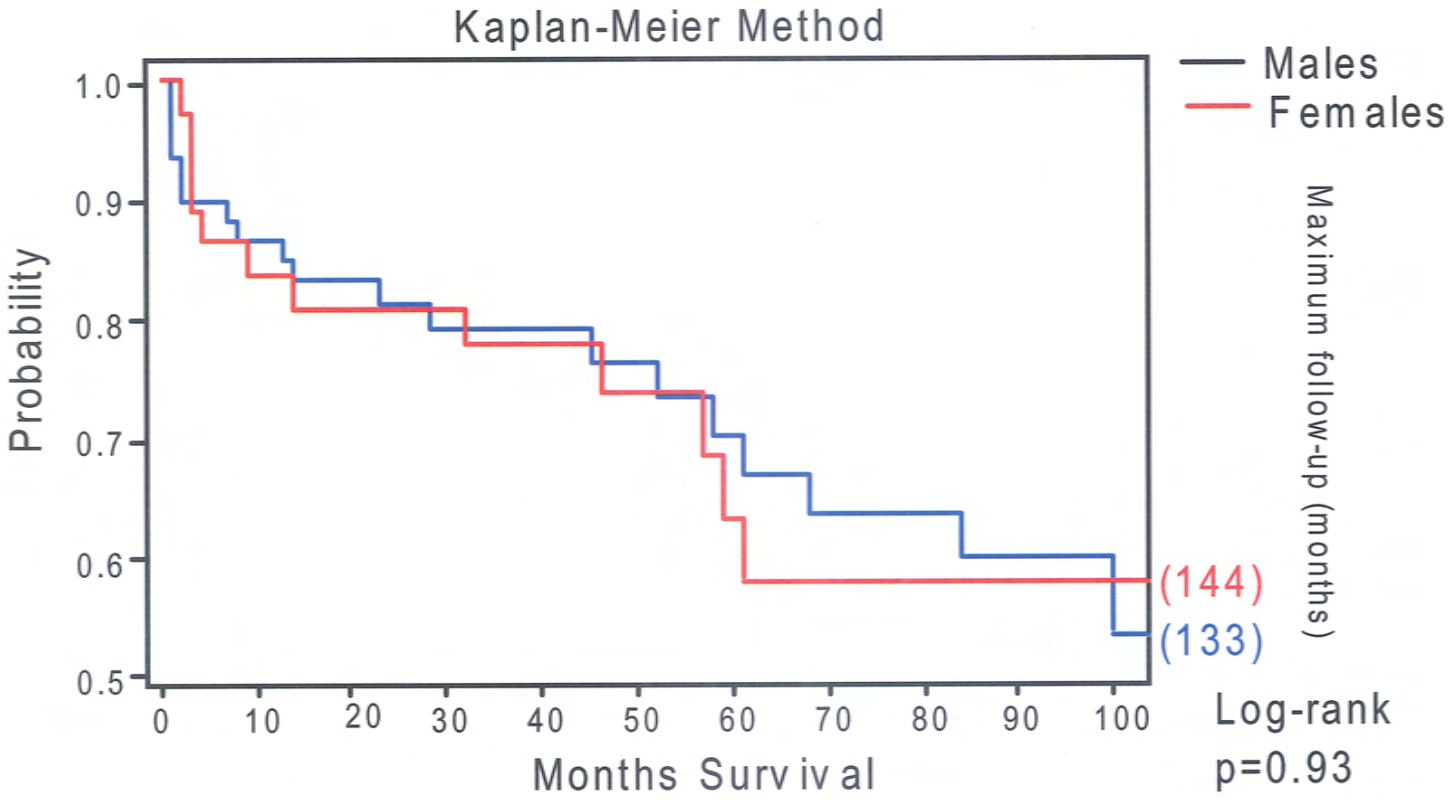


Figure 2.7 Non parametric Survival Plot Comparing Age-groups

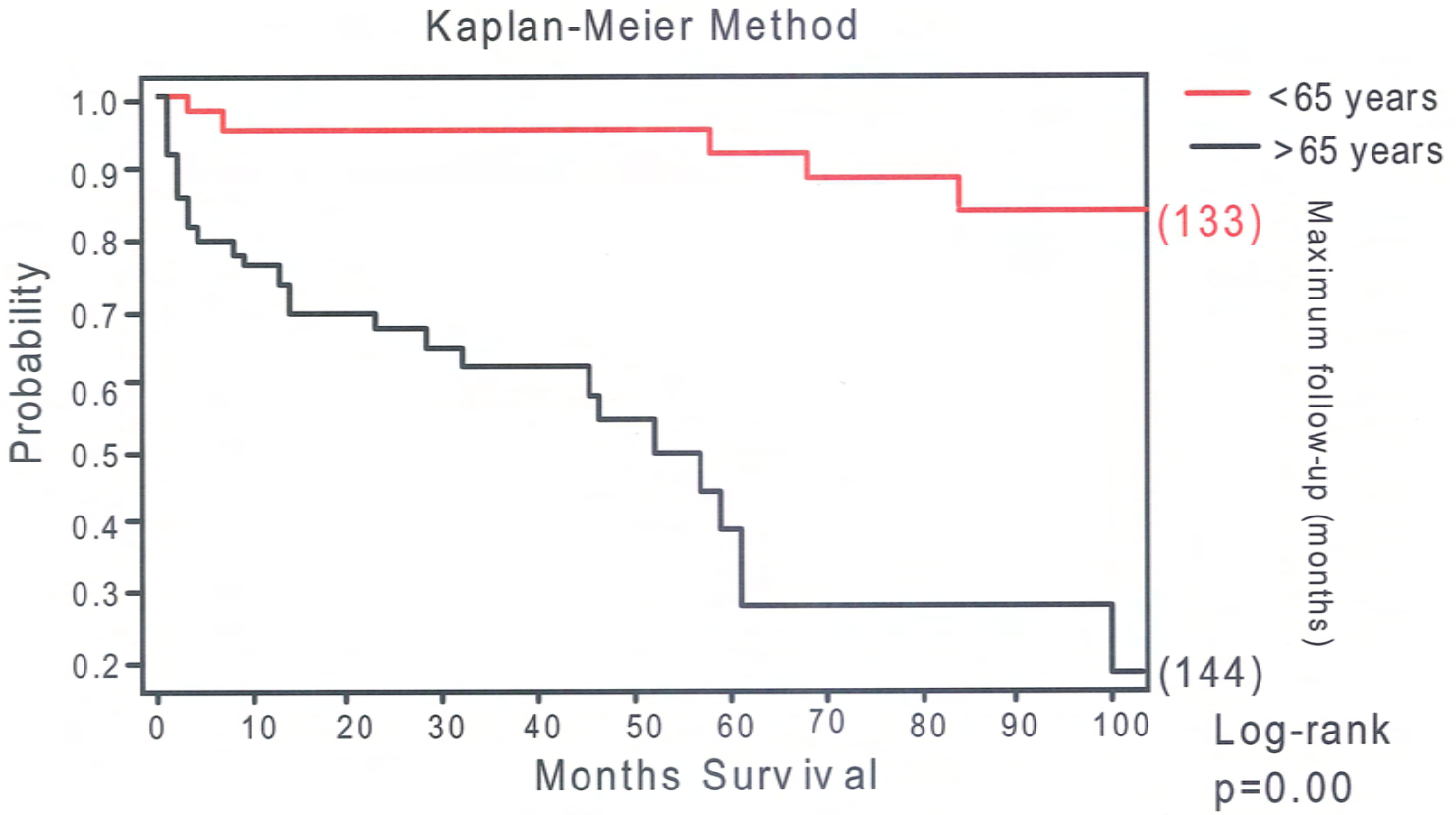


Table 2.22 Comparison of mortality between disease subgroups

Item		Hazard Ratio	Unadjusted 95% C.I.	p-value
Age (years)	<50	1.00	-	-
	50-60	1.70	0.30-9.64	0.540
	61-70	9.22	2.02-42.0	0.003
	>70	25.07	4.79-131.30	<0.001
Sex	Male	1.00	-	-
	Female	1.03	0.49-2.16	0.93
Diagnosis	CSS	1.00		
	mPA	2.52	0.89-7.15	0.077
	WG	0.87	0.28-2.74	0.812
	Ltd WG	1.05	0.27-4.00	0.948
ANCA	cANCA	1.00		
	pANCA	1.20	0.37-3.81	0.755
Comorbidity	Absent	1.00		
	Present	2.03	0.92-4.48	0.075
Renal Disease	Absent	1.0		
	Present	2.55	0.76-8.61	0.123
Respiratory Disease	Absent	1.0		
	Present	1.05	0.51-2.19	0.885

Discussion

Mortality in our cohort increased significantly with age. This reproduces previous findings and it has been suggested that disease may be more severe and resistant in the elderly compared to younger PSV patients.[35] However, there was no significant difference between SMRs for patients older and younger than 65-years. This suggests that the difference between age groups observed using Kaplein Meyer curves and Cox proportional hazards model reflects the expected difference in mortality between age groups in the population rather than a difference in disease severity. Comparison of BVAS1 at presentation between patients greater or less than 65-years of age showed no significant difference. There was no significant difference between surviving and deceased patients in scores of disease activity and damage (Table 2.17). The presence of comorbidity also did not contribute to mortality.

Mortality was higher for mPA compared to other diagnoses (HR- 2.52) and the ratio remained relatively high when adjusted for age [HR-1.92 (0.66-5.57)] so the difference cannot be explained wholly by a mean older age (Table 2.8). This supports previous reports of a worse outcome in mPA.[50] However early survival figures were similar for WG, mPA and CSS but percentage survival in mPA at 5 years was much less than other diagnoses (45.1%) which contrasts with previous reports.[36,50] Overall survival of PSV was slightly lower than many previously published figures. In particular 1 year survival in WG (85.5%) was less than recent estimates from other populations (e.g. Norway had 93% 1 year survival and Germany 99%).[34,127] In the latter case these figures were from a tertiary referral centre so referral bias may contribute to the difference, i.e. early deaths in the acute phase of illness may not be included and the case-mix may include patients fit to travel longer distances. Figures were however superior to those reported by Guilliven et al which probably relates to the high number of treatment side effects in their cohort, probably

related to the high dose steroids.[104] Although there have been few reports of survival in CSS, our figures were similar.[45]

We did not reproduce an association between renal disease and poor prognosis that has been previously reported[13,36] and found no association with pulmonary disease.
Although the difference was not significant the SMR was higher for men compared to women (5.94 vs 3.05). Previous reports have either found no difference in survival for males and females or have reported an excess in females.[18,126]

There was no association between ANCA type and mortality in our cohort although the retrospective analysis of ANCA results over a decade introduces potential problems because the type of assay used within the region has changed over time, e.g. immunofluorescence results were not available at the beginning of the period, i.e. if ANCA had been assessed using a standardised assay in all patients at the time of presentation we may have found a prognostic link.

Conclusion

In conclusion, age was significantly associated with mortality in PSV but this is probably due to the expected difference between age groups rather than a more severe disease course in the elderly as previously postulated. mPA seems to have a poorer late prognosis compared to other diagnoses but no other significant factors could be identified.

III. LONG-TERM TOXICITY OF CYCLOPHOSPHAMIDE REGIMENS

Introduction

Cyclophosphamide (CYC) therapy has transformed the prognosis of PSV from a severe illness, fatal in the majority of cases to a chronic remitting and relapsing disease.[12,18] Unfortunately it is associated with significant toxicity including haemorrhagic cystitis and increased risk of infection, bladder cancer and other malignancies.[93] Strategies to reduce the risk of toxicity whilst maintaining efficacy include the use of intermittent pulsed cyclophosphamide[107,112] and shorter courses of treatment, using alternative immunosuppressants (Azathioprine / Methotrexate) as maintenance therapy. In addition Mesna is used to reduce the risk of bladder toxicity and septrin is sometimes prescribed for the prophylaxis of pneumocystis carinii pneumonia. It has been suggested that high doses of steroids in treatment regimens may also contribute to the risk of infection.[104] The aim of this study was to retrospectively compare the toxicity associated with treatment regimens using pulsed IV CYC alone with earlier regimens using oral CYC in our PSV cohort. The study was retrospective and regimens described reflect clinical practice favoured by various hospital specialities over an eleven-year period.

Methods

All cases diagnosed with PSV between July 1988 and December 1999 were identified and classified as outlined in Chapter 2. Case notes were reviewed and patients were divided according to their treatment regimens. Three treatment regimens had been used during the study period as follows:

Regimen 1 – IV pulse CYC – 15 mg/kg (1g maximum) and IV methylprednisolone 1g, given with Mesna 400mg 2 hours prior to CYC and 2 and 6 hours post treatment. A reducing dose of daily oral prednisolone was also given.

Regimen 2 – Oral pulse CYC – 5 mg/kg and prednisolone 100mg on 3 consecutive days

In both regimen 1 and 2 the pulse interval was 2 weeks for remission induction (usually 6 pulses) then at 3, 4 and 6 weekly interval for maintenance up to one year.

Regimen 3- Continuous oral CYC – 2mg / kg / day with prednisolone in a reducing dose

The precise dose, interval and duration of treatment were tailored individually according to clinical response and white-cell count for all regimens. In some cases, especially with renal involvement, a pulse of IV methylprednisolone 1g was given on three consecutive days at the start of treatment. Subsequent maintenance treatment was with azathioprine (AZA) or methotrexate (MTX). Additional plasmapheresis and / or IVIG was administered in a minority of cases, where disease was aggressive and/or resistant to treatment. An H_2 antagonist was advised. Septrin prophylaxis was used in some cases but no strict protocol was applied.

The following information was recorded in each case: duration and cumulative dose of CYC; weight at onset of CYC treatment; duration and cumulative dose of prednisolone (where methylprednisolone had been given the dosage was converted to the equivalent prednisolone dose); the use of AZA or MTX for maintenance treatment; duration of follow-up prior to case-note review; deaths related to immunosuppression; episodes of infection requiring hospital admission; episodes of neutropenia (defined as $< 2x\ 10^9/l$) caused by CYC; haemorrhagic cystitis; malignancy, osteoporosis (diagnosed by DEXA scan, vertebral collapse on plain X-ray or bone-biopsy); and the prophylactic use of Mesna and Septrin. Comparison was made between patients who received regimen 1 only (Group 1) and those who had received either regimen 2 or 3 (Group 2). Group 2 included some patients who had initially received regimen 2 or 3 but later also received regimen 1. The rationale was to compare the toxicity of our latest protocol using pulsed IV CYC compared

to previously used regimens. Numbers were too small to compare the three regimens individually. Group characteristics were compared using the Mann-Whitney test and treatment side effects were compared using Fisher's exact test.

Results

121 individuals were diagnosed with PSV during the study period. 96 received cyclophosphamide, 30 of whom were in Group 1 and 76 in Group 2. (Group 2 contained 50 patients who received only continuous oral CYC, 4 pulse oral CYC alone, 4 both continuous and oral CYC and 17 oral and pulse IV CYC). There was no significance difference in the duration of follow-up between Group 1 and 2 but the age at diagnosis was higher in Group 2 compared to Group 1 ($p=0.048$). The cumulative dose of CYC received was significantly less in those who received IV CYC alone compared to Group 2 ($p=0.034$). However there was no significant difference between the mean duration of CYC treatment or the cumulative dose and duration of steroid therapy. Table 2.23 compares the age, follow-up duration, dose and duration of CYC and steroid treatment between the groups. Although significance was not reached there was a trend towards fewer deaths, malignancy, episodes of infection and neutropenia in Group 1 compared to Group 2 (Table 2.24). In Group 1, 18 received Mesna and 10 Septrin compared to 13 and 40 individuals respectively in Group 2. 8 deaths were thought to be related to CYC treatment (Table 2.25). Those who died were significantly older than survivors ($p=0.001$) and had received significantly less CYC than survivors ($p= 0.043$). However the duration of follow-up was significantly longer for survivors ($p=0.0004$). There was no significant difference in the steroid doses received ($p=0.12$). (Table 2.26). 7 malignancies were detected in patients receiving CYC within the study period. These are detailed in Table 2.27 and both CYC and steroid doses were similar to cases who did not develop malignancy ($p=0.27$ and $p=0.12$ respectively).

Table 2.23 Comparison of Treatment Groups

	Group 1	Group2	Mann Whitney	
No. cases	30	76	p	95% C.I.
Diagnosis Age (years)				
Range	32-90	33-87		
Median	59.5	66	**0.048**	0.001-11.03
Mean	60.1	64.9		
Follow up duration (months)				
Range	1-89	1-130		
Median	26	27.5	0.115	-2.01, 24.99
Mean	28.5	47.2		
CYC dose (g)				
Range	0.5-23.0	0.8-160.9		
Median	6.7	10.1	**0.034**	0.30, 7.55
Mean	7.69	20.54		
CYC duration (days)				
Range	1-583	1-2703		
Median	144.5	129.5	0.621	-40.1, 82.0
Mean	172.8	306.7		
Steroid dose (mg)				
Range	0-64000	240-43109		
Median	6800.5	6573.0	0.975	-2580.0, 2360.0
Mean	9557	9180		
Steroid duration (months)				
Range	1-74	1-123		
Median	19	22	0.291	-3.0, 14.0
Mean	21.1	32.0		
Weight at CYC onset (kg)				
Range	50-91*	42.2-102.2**		
Median	70.9*	67.6**	0.722	-5.20, 7.90
Mean	69.6*	68.9**		

* missing data in 6 cases; ** missing data in 7 cases

Table 2.24 Complications of Treatment

	Group 1	Group2	P*
Death	1	7	0.43
Cancer	0	7	0.19
Infection	4	21	0.20
Neutropenia	6	29	0.16
Osteoporosis	3	7	1.0
Haemorrhagic cystitis	0	1	-

* 2 tailed Fisher's exact test

Table 2.25 Comparison of survivors and deceased patients

	Survivors	Deceased	Mann Whitney	
No. cases	98	8	p	95% C.I.
CYC dose (g)				
Range	0.5-160.9	0.8-45.7		
Median	5.8	9.0	**0.043**	0.10, 6.10
Mean	10.8	19.6		
Steroid dose (mg)				
Range	300-75250	1095-45435		
Median	13948	8220	0.097	-465, 7068
Mean	16821	12217		
Duration of Follow-up (months)				
Range	1-130	1-100		
Median	36	15	**0.0004**	8.0, 33.0
Mean	50.0	23.5		

Table 2.26 Details of Cancer Cases

Cancer Type	Sex	Age	Cyclophosphamide			Months to Cancer	Other Rx
			method*	dose(g)	duration (days)		
Bladder	M	57	CO/PO/IV	160.9	974	124	AZA/ MTX
Bladder	M	59	PO	5.4	79	70	-
Bladder	M	57	PO / IV	28.3	298	1	AZA
Oesophageal	M	60	CO	33.6	224	48	AZA
Oesophageal	M	60	CO	4.9	39	1	AZA
Oesophageal	F	73	CO / IV	13.7	89	21	AZA
Seminoma	M	44	CO	5.4	54	22	AZA

M=Male; F=Female; Rx = Treatment; AZA=Azathioprine; MTX = Methotrexate
*CO = Continuous Oral; *PO = Pulse oral; *IV = Pulse Intravenous

Table 2.27 Details of CYC related deaths

Cause of death	Sex	Age	Cyclophosphamide			Other Treatment
			Method	dose (g)	duration (days)	
Septicaemia	M	73	CO	5.4	36	-
Septicaemia	M	75	CO	1.4	14	-
Septicaemia	M	86	CO	1.9	31	-
Septicaemia	M	69	CO	14.3	134	-
P.C.P.	M	67	CO	5.75	43	-
Pneumonia	M	81	CO	5.9	59	-
Pneumonia	M	80	CO	9.3	492	AZA
Pneumonia	M	82	IV	2.1	22	-

M – male; AZA=Azathioprine; PCP = Pneumocystis carinii
* CO = Continuous oral; *IV = Pulse IV

Discussion

The cumulative CYC dose was significantly lower in patients who had received only IV CYC compared to those who had been treated using other regimens. Because this is the most recent regimen a possible explanation that patients may not have been treated for as long as those in Group 2. However there was no significant difference between groups in terms of duration of treatment or follow-up and notably there was no significant difference in the weight of patients at the onset of CYC which would affect the dose of CYC received. (Table 2.23). Interestingly the mean cumulative dose of steroids received by Group 1 was in fact higher than Group 2 although significance was not reached. This may be explained by the high doses given as IV methylprednisolone pulses with each CYC pulse.

There appears to be a trend towards greater toxicity in Group 2 compared to Group 1 and although significance was not reached this suggests that reduced doses of CYC are associated with less toxicity. However patients in Group 2 were older than Group 1 which may influence results although there was no significant difference between the percentage of patients with comorbidity between groups (46.7 in Group 1 compared to 49.3% in Group 2). Guillevin and Haubitz et al described lower toxicity associated with IV CYC regimens[104,107] and our results suggest that remission regimens which give a lower cumulative dose of CYC (e.g. IV pulse therapy and the use of alternative maintenance treatment) reduce CYC-associated toxicity.

The Norwich protocol for CYC has recently been amended with the aim of reducing the period of CYC therapy to less than 6 months (minimum 3 months) where clinically possible and introducing either AZA or MTX as maintenance therapy according to patient characteristics. In addition the dose of IV Methylprednisolone has been reduced to 500mg with the first pulse of CYC and 250 mg with subsequent pulses. Patients continue to receive a reducing course of oral prednisolone. The study was however not designed to

evaluate the relative efficacy of treatment regimens. Prospective study of treatment regimens in PSV is essential to evaluate their relative efficacy and long-term follow-up is required to determine long-term outcome in terms of relapses, morbidity and survival.

CHAPTER 3

Descriptive Epidemiology of Primary Systemic Vasculitis in Norfolk

Chapter Overview

Introduction Until relatively recently lack of uniformity in the classification of PSV made epidemiological studies and comparison of results between centres difficult. The introduction of accepted classification criteria have allowed these studies to be undertaken. Norfolk is favourable for epidemiological study and this chapter reports the descriptive epidemiology of PSV over eleven years.

Methods In 1988 a prospective vasculitis register was established at the Norfolk and Norwich Hospital, the single central referral centre for the well-defined, relatively stable Norwich Health Authority (NHA) population. All cases of PSV between 1988 and 2000 were identified by this register and by searching the hospital histopathological and discharge records. All cases were classified according to the ACR classification criteria for WG, CSS and PAN, the Lanham criteria for CSS and CHCC definition for mPA. All cases of primary renal vasculitis including Henoch-Schonlein Purpura were identified. The annual incidence was obtained for PSV overall, WG, CSS, PAN, mPA and primary renal vasculitis. The age of onset of PSV was also investigated. Incidence figures were directly compared with other European regions using the same classification criteria and methods. The annual incidence of PSV, WG, CSS and mPA was compared between the rural and urban areas in the NHA defined by postcode. Seasonal and annual variation in disease was documented between January 1989 and December 1998.

Results The annual incidence for PSV was 20.7/million and primary renal vasculitis 18.0/million. WG was the most common diagnosis (annual incidence: 12.1/million/year) and the annual incidence for PAN, mPA and CSS was 11.2/million, 8.8/million and 3.3/million respectively. All diagnoses were more common in men than women. The annual incidence of PSV overall was highest in the 65-74 year-old age group. Peak annual incidence however occurred in an older age-group for women (>75 year-olds) and a younger group for CSS (55-64 year-olds). There was a non-significant trend towards

increasing incidence of PSV over the study period but no significant annual or seasonal variation in PSV. The incidence of PSV was similar in Lugo, Spain and Tromso, Norway and there was a trend towards an increasing incidence of WG with latitude and an excess of CSS in Norfolk. There was also a non-significant trend towards a higher incidence of CSS and WG in the rural Norfolk population compared to urban residents.

Conclusions The annual incidence of PSV was higher than earlier reports but similar to recent population-based figures and the peak age of onset of disease was higher than previously recognised. The incidence of PSV may be increasing with time, be higher in rural areas and vary between regions. This supports the hypothesis that environmental factors are important in the aetiology of PSV although genetic factors may also be important in the latter case. Results highlight the importance of including PSV in the differential diagnosis of multisystem disorders, the need for on-going prospective study of the epidemiology of PSV and suggest that investigation of the role of environmental factors in PSV is important.

I. Epidemiology of Primary Systemic Vasculitis in Norfolk 1989-1999

Introduction

Until relatively recently lack of uniformity in the classification of PSV made epidemiological studies and comparison of results between centres difficult. The development of recognised classification criteria by the American College of Rheumatologists (ACR) and definitions by the Chapel Hill Consensus Conference (CHCC) have allowed these studies to be undertaken.[42,83] Although the criteria are not perfect they allow direct comparison of PSV between centres. Norfolk is favourable for epidemiological study for the reasons set out in Chapter 2 and we published the first accurate incidence figures for PSV from a population-based cohort.[16] Most other studies have been based in tertiary referral centres with ill-defined denominator populations and the problems associated with referral bias. [36,57,129]

We have recently published a study of the epidemiology of PSV in Norfolk over a ten year period and reported the annual incidence of PSV within our cohort between 1988-1997 to be 19.8 / million / year (95% C.I.15.8-24.6).[128] Although significance was not reached there appeared to be a trend towards an increasing incidence of PSV with time and the mean age of our cohort was higher than in other studies. Appendix 3. contains a copy of the full published paper. Earlier reports from our centre have also suggested that there may be a peak onset of PSV in the winter and trough in the Autumn and data presented as an abstract suggested that there was an excess of CSS in the rural areas of our population compared to the built up areas. Conversely there were fewer WG patients in the urban areas. This chapter reports the annual incidence of PSV over an 11 year period 1989-1999, a six year study of primary renal vasculitis (1992-1997) in Norfolk and examines annual, seasonal and geographical variations in disease over ten years (1989-1998).

Epidemiology of PSV in Norfolk 1989-1999

Aims

The aims were to describe the annual incidence of PSV in the NHA over an 11 year period and re-examine the trend towards increasing annual incidence. Data from 1988 has been excluded because although we are relatively confident that the cohort is complete, there was an unusually low number of cases diagnosed in that year. This could be explained by initial underreporting to the register but this is hard to confirm or refute because the hospital coding index was less complete for 1988 than subsequent years. Exclusion of 1988 data therefore allows the trend towards increasing incidence to be re-examined with a reduced risk of bias.

Methods

All adults (>15 years) newly diagnosed with PSV at the Norfolk and Norwich Hospital between January 1989 and December 1999 were identified and classified as described in Chapter 2. Those registered with general practitioners who were formerly part of the Norwich Health Authority (NHA) and who fulfilled one of more of the following set of criteria were included WG (ACR 1990 or CHCC 1994), mPA (CHCC 1994), CSS (ACR 1990 or CHCC 1994), PAN(ACR 1990 or CHCC 1994).[41,42,60,84] The date and age at diagnosis were also recorded. Information about the denominator population was provided by the Norfolk Arthritis Register as a breakdown by age and sex of the patients registered with the 77 practices covered by the study population. At the mid-point of the study in 1994, the total adult NHA population (>15 years-old) was 413, 747 (men 199, 682; women 214, 065). The population is 99% Caucasian and relatively stable. Over the study period there has been a gradual increase in immigration into and migration out of Norfolk with a net increase in immigration peaking in 1997-1999. Between 1991-1998 the population of Norfolk grew by 4.1% compared to 2.6% for England and Wales which was

due to immigration rather than natural change (The population in 1998 was approximately 429, 000 compared to 413, 500 in 1992). The retirement population has shown the largest increase and the 20-29 year old labour force is the only group to show a small net loss. In 1998 around 20% of Norfolk's population was aged over 65 years-old compared to 16% in the whole of England and Wales.[480]

Age and sex specific incidence rates were calculated using the number of incident cases as the numerator and the NHA 1994 population as the denominator for all PSV cases. Similarly disease specific incidence was calculated for WG (ACR 1990), CSS (ACR 1990), mPA (CHCC) and PAN (ACR 1990).[41,42,60,84] Where a patient fulfilled criteria for more than one disease classification they were included in the calculation for each disease, 95% confidence intervals (C.I.) were calculated using the poisson distribution for the number of cases observed.

Results

166 patients were given a new diagnosis of PSV between May 1988 and June 2000. 127 patients had a diagnosis of PSV confirmed within the study period, as described in Chapter 2. Of these 96 were resident within the NHA, the remainder were excluded from the study. The mean age was 63.1 years (median 65 years, range 32-90 years). Table 3.1 gives the number of patients fulfilling classification criteria. 16 patients fulfilled both the ACR criteria for WG and CHCC definition of mPA (Table 2.4 gives details of these patients) and 29 fulfilled ACR criteria for both WG and PAN.

The overall annual incidence of PSV was 20.7 /million (95% C.I. 33.4-50.6). PSV was more common in men (26.0/million; 95% C.I. 19.7-33.6) than women (15.7 95% C.I. 11.1-21.7). There was a trend towards increasing annual incidence with time with an annual incidence in the first half of the study of 18.5/million/year (95% C.I. 13.3-25.0) compared to 22.9/million/year (95% C.I. 17.1-30.0) in the second half. Table 3.2 gives full details.

The age-specific incidence showed a clear increase with age (Figure 3.1) with a peak in the 65-74 year-old age group of 58.6/million/year (95% C.I. 40.6-81.9). In men the incidence peaked at 70.5 /million/ year (95% C.I. 44.2-106.8) in this age group but in women it peaked at 45.9/million/year (95% C.I. 19.8-90.5) in the over 75-year-olds. During the 11 year period the annual incidence was 12.1 (95% C.I. 9.1-15.7) for WG, 3.3 (95% C.I. 1.8-5.4) for CSS and 11.2 (95% C.I. 8.3-14.7) for PAN using the ACR criteria. The annual incidence for mPA was 8.8 (95% C.I. 6.3-12.0). No cases of PAN as defined by the CHCC definitions were observed. Comparison of the first half of the study with the second showed a trend towards an increase in all conditions (Table 3.3). All diagnoses were more common in men than women and increased with age (Figure 3.2).

Table 3.1
Number of patients fulfilling ACR classification criteria and CHCC definitions

Classification	Total	Criteria / Definitions fulfilled	
		ACR	CHCC
WG	55	55	14
mPA	40	-	40
CSS	15	15	4
PAN	51	51	0

N.B. Column 2 gives the total number of cases that could be classified as WG, mPA, PAN and CSS. Column 3-4 gives the number which could be classified using the ACR criteria and CHCC definitions. All cases that met the CHCC definitions also fulfilled the ACR criteria. There were 96 cases in total but 16 could be classified as both WG (ACR) and mPA (CHCC) and 49 cases classified as PAN also fulfilled criteria / definitions for WG and/or mPA.

Table 3.2
Annual incidence of Primary Systemic Vasculitis by time period and sex in the study population

	Male		Female		Total	
Time Period	**No.**	**A.I./million (95%CI)**	**No.**	**A.I./million (95% C.I.)**	**No.**	**A.I./million (95% C.I.)**
A. Jan 1989- Jun 1994	26	23.7 (15.5-34.7)	16	13.6 (7.8-22.1)	42	18.5 (13.3-25.0)
B. Jul 1994- Dec 1999	31	28.2 (19.2-40.1)	21	17.8 (11.0-27.3)	52	22.9 (17.1-30.0)
Total	57	26.0 (19.7-33.6)	37	15.7(11.1-21.7)	94	20.7 (33.4-50.6)

A.I. = Annual Incidence; Jan – January; Jun = June; Jul= July; Dec = December

Table 3.3 Annual Incidence of specific diagnoses by sex and time period

Classification	Period	No.	Male	No.	Female	No.	Total
• WG	A	13	11.8 (6.3-20.2)	10	8.5 (4.1-15.6)	23	10.1 (6.4-15.2)
	B	17	15.5 (9.0-24.8)	15	12.7 (7.1-21.0)	32	14.1 (9.6-19.9)
	Total	**30**	**13.7(9.2– 19.5)**	**25**	**10.6 (6.9-15.7)**	**55**	**12.1(9.1-15.7)**
• mPA	A	12	10.9 (5.7-19.1)	7	6.0 (2.4-12.3)	19	8.3 (5.0-13.0)
	B	14	12.8 (7.0-21.4)	7	6.0 (2.4-12.3)	21	9.2 (5.7-14.1)
	Total	**26**	**11.8 (7.7-17.3)**	**14**	**5.9 (3.3-10.0)**	**40**	**8.8 (6.3-12.0)**
• PAN	A	15	13.7 (7.6-22.5)	8	6.8 (2.9-13.4)	23	10.1 (6.4-15.2)
	B	15	13.7 (7.6-22.5)	13	11.0 (5.9-18.9)	28	12.3 (8.2-17.8)
	Total	**30**	**13.7 (9.2-19.5)**	**21**	**8.9 (5.5-13.6)**	**51**	**11.2 (8.3-14.7)**
• CSS	A	5	4.6 (1.5-10.6)	2	1.7 (0.2-6.1)	7	3.1 (1.2-6.3)
	B	4	3.6 (1.0-9.3)	4	3.4 (0.9-8.7)	8	3.5 (1.5-6.9)
	Total	**9**	**4.1 (1.9-7.8)**	**6**	**2.6 (0.9-5.6)**	**15**	**3.3 (1.8-5.4)**

A = January 1989-June 1994; B= July 1994-December 1999

Figure 3.1 Age specific incidence of PSV in the NHA, January 1989-December 1999

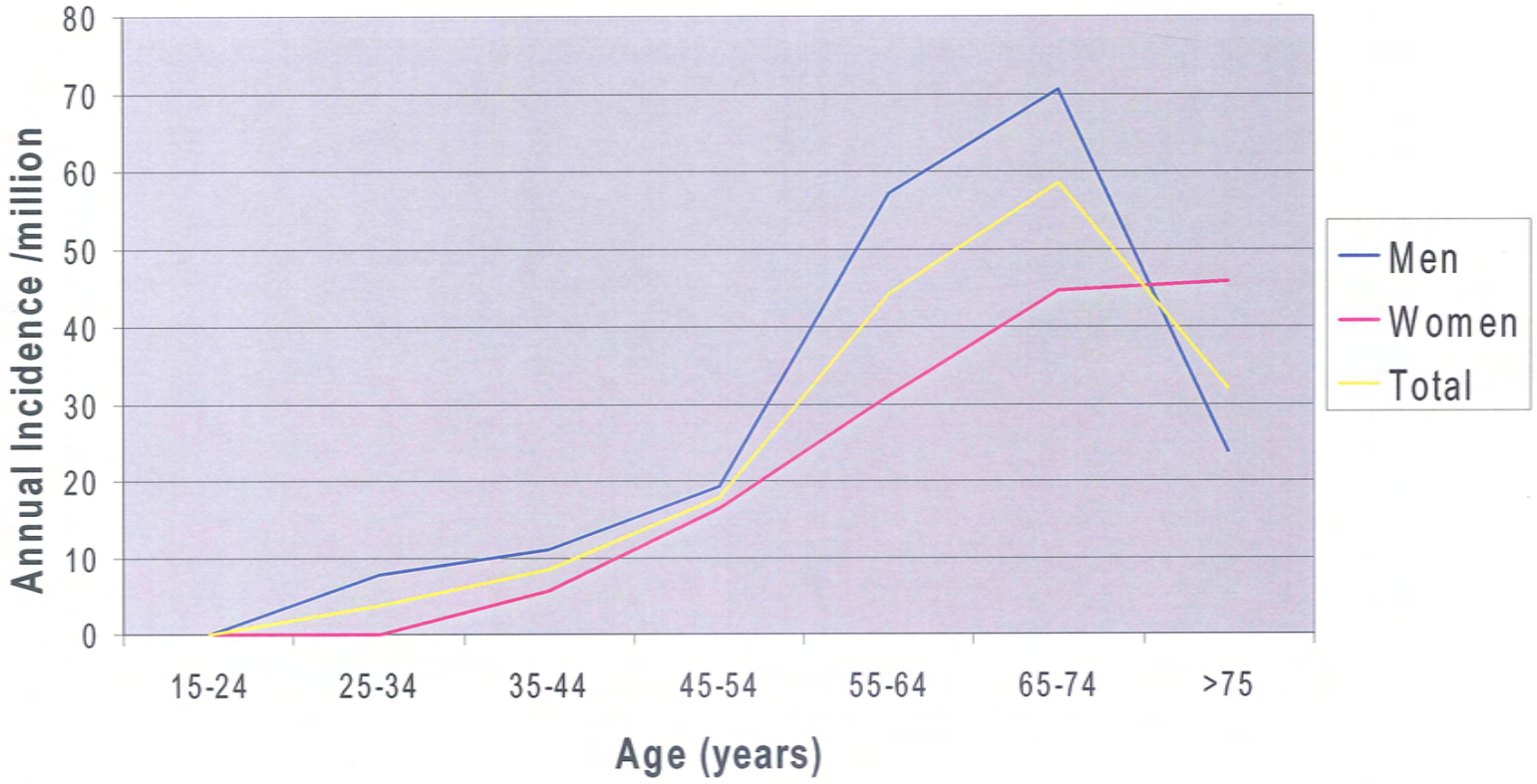
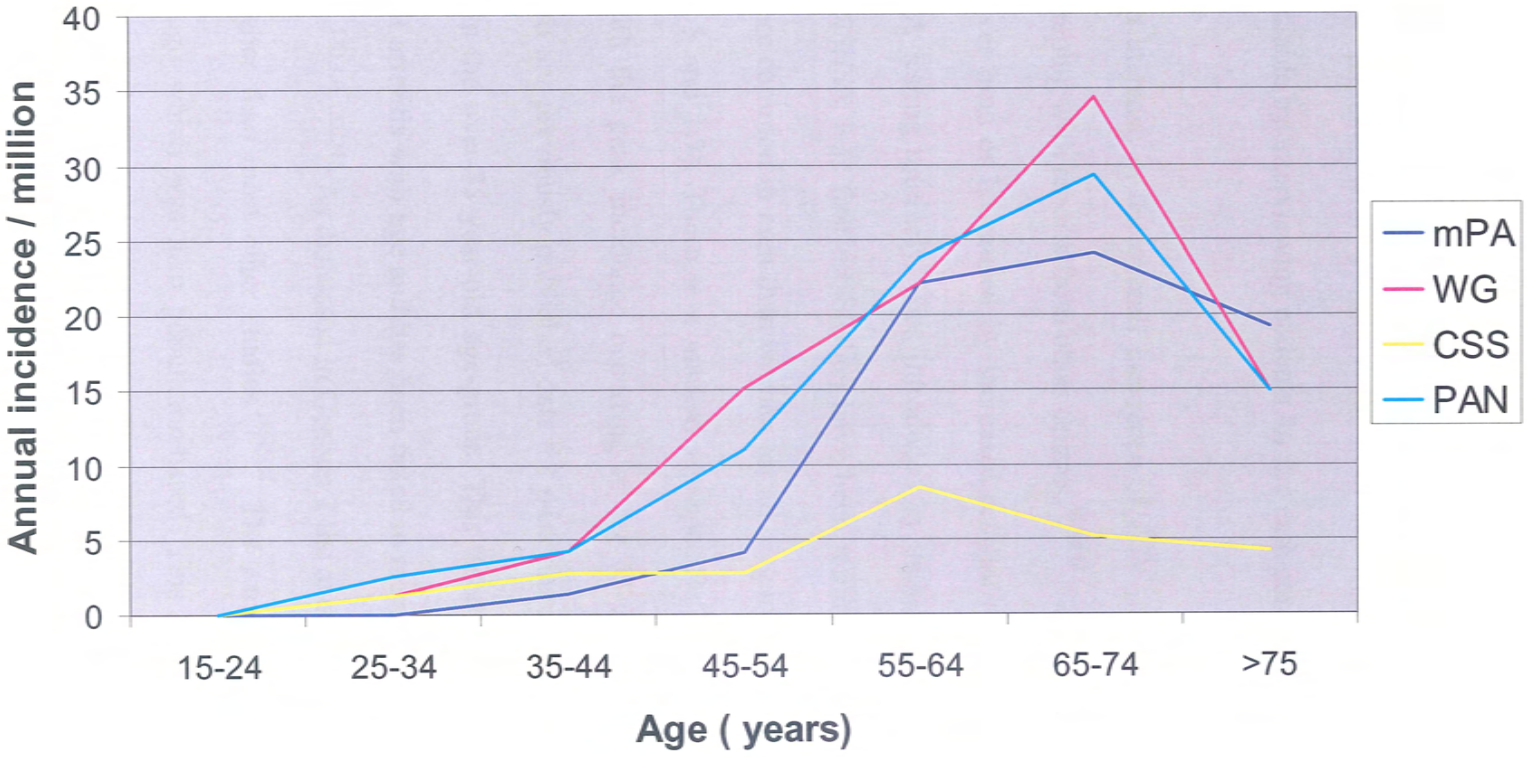


Figure 3.2 Age-specific incidence of WG, mPA, CSS and PAN in the NHA, January 1989-December 1999



Discussion

Values for the annual incidence of PSV in Norfolk over 11 years were similar to the ten-year study[128], although the annual incidence for PAN has increased from 8.0 /million (95% C.I. 5.5-11.2) to 11.2/million (95% C.I. 8.3-14.7). This increase is probably due to reclassification of all patients with a longer duration of follow-up and additional information made available by interviewing patients for the case-control study (Chapter 4).

The trend towards an increase in the overall incidence of PSV remained and was most marked for WG, in keeping with reports from other centres.[133,134] This may be due to a true increase in disease over time or be caused by increased recognition, especially with the introduction of ANCA testing routinely. Bias introduced by underestimating cases when the PSV register in Norfolk was first established have been minimised in this report. In addition PSV was more common in men than women for all diagnoses as reported in most series (Tables 1.3, 1.5 and 1.7). There is a marked age-specific increase in the annual incidence of PSV with the peak incidence occurring in the 65-74 year-old age group. However in contrast to our previously published data the peak annual incidence in women occurred even later, in the over-75 year-old age-group. This trend mirrors the increasing incidence of giant-cell arteritis with age and has been noted in more recent studies of PSV but not earlier reports.[130,131,132,245] As discussed in Chapter 2 the average age of our patients at presentation is higher than most other studies.[18,45,51] The exception is the study by Gonzalez-Gay for Lugo which was also population-based. This supports the idea that differences in the mean age of patients are caused by variation in referral patterns between secondary and tertiary referral centres with a potential bias towards the referral of 'fitter' and therefore younger patients in the latter case. However a higher average age of the population may also contribute to a limited extent because, as previously described, there is a slightly higher proportion of patients over 65 years-old compared to the rest of the

U.K. This observed peak of disease highlights the need to consider the diagnosis of PSV in the elderly who present with systemic disease when diagnosis is often especially difficult because of the presence of comorbidity. The peak incidence of CSS occurred in the 55-64 year-old age group which is ten years earlier than WG and mPA. This may reflect a difference in aetiology between these disorders. Potentially the effect of ageing upon cells may play a more important role in WG and mPA and an alternate trigger may be important in CSS.

Conclusion

Annual incidence figures obtained from a population based cohort in Norfolk are in general higher than those previously published but even so must be regarded as a minimum estimate. This may be due to better case identification or may indicate real variation in the incidence of disease between study regions which could reflect differences in important environmental factors. Results support a trend towards an increase in PSV (especially WG) with time, confirm a higher incidence in men compared to women and an increase in incidence with age.

II. Primary Renal Vasculitis in Norfolk 1992-1997

Introduction

Vasculitis is an important treatable cause of renal impairment that leads to significant morbidity and mortality. Little data is available on the incidence of renal vasculitis. Early reports are difficult to interpret due to confusing definitions and the absence of accepted criteria. In 1990 the ACR proposed criteria for individual diseases using clinical and histological features.[41,60,84,481] The CHCC in 1994 proposed definitions to take account of vessel size.[42] Using these criteria and definitions, epidemiological study has been possible and recent data suggests that these diseases are relatively rare, may be increasing with time and may occur more commonly in the elderly population than originally suspected. [133,146]

No study has considered the overall incidence of renal vasculitis using these criteria. Previous studies have considered individual disease subtypes e.g. WG or crescentic necrotizing glomerulonephritis (GN) and rapidly progressive GN.[36,57,133,149,150,151]

The aim of this study was to estimate the annual incidence in adults (>15 years old) resident in the NHA of PSV with renal involvement.

The annual incidence was obtained for those who fulfilled accepted classification criteria for WG, mPA, CSS, PAN and adult Henoch-Schonlein purpura (HSP). An overall annual incidence figure was also obtained for all patients with a primary renal vasculitis. (definition follows)

As the use of the classifications and definitions is continuing to evolve, detailed data of patients who fulfil more than one criteria is provided and ANCA data available is included to ensure that results may be reliably compared to future studies.

Methods

Definitions

For the purpose of this study we defined primary renal vasculitis as one of the following:

Either

1. A patient who fulfilled criteria for PSV and had either a renal biopsy appearance compatible with vasculitis where there was no other identifiable cause for these changes or renal impairment attributable to vasculitis.

or

2. A patient who did not fulfil classification criteria but had a renal biopsy highly suggestive of vasculitis with no other identifiable cause and who was treated clinically as having vasculitis.

Renal impairment was considered to be caused by vasculitis when an elevation of serum creatinine (above the laboratory normal range) coincided with a clinical flare of vasculitis and where there was no alternative identifiable cause.

The following disease classifications were used: WG (ACR 1990); PAN (ACR 1990); mPA (CHCC 1994); CSS (ACR 1990) and/or Lanham 1984; Henoch – Schonlein Purpura (HSP) - ACR (1990).[41,43,60,84,481]

Patients with secondary vasculitis due to an identifiable underlying disorder, for example rheumatoid arthritis, systemic lupus erythematosus or cryoglobulinaemia were excluded.

Patient Identification

Patients were identified using the prospective vasculitis register, renal biopsy records (Table 3.4) and the hospital coding index as described in Chapter 2. Between 1994 to 1997 records of patients who received plasmapheresis were available and were reviewed to identify any vasculitis patients too unwell to have a biopsy. No additional patients were identified in this way.

Case Note Review

Case notes of all patients identified were reviewed with respect to diagnosis, biopsy appearance and renal function. In each case the underlying diagnosis of the patient was established and those found to have vasculitis were classified as described. Some patients fulfilled criteria for more than one disease classification.

81 patients (61 resident in NHA) were classified as having PSV between 1992-97. 61 of these patients (47 in NHA) were already known to the vasculitis register. 15 patients not on the vasculitis register were found by renal biopsy review (9 in NHA) and a further 5 patients (all in NHA) were found on review of the hospital coding index.

9 patients (4 NHA) were identified who were felt to have primary renal vasculitis but did not fulfil classification criteria.(Table 3.5). 2 were already known to the register, 6 were found by renal biopsy review (3 NHA) and 1 by records review (NHA).

Data Analysis

Incidence figures were calculated for patients resident in the former NHA (>15 years-old). The annual incidence of renal vasculitis for each disease classification and the overall annual incidence of adult primary renal vasculitis was calculated using the adult population

of 413 747 (1994). The denominator population has previously been described. Where a patient fulfilled criteria for more than one disease classification they were included in the calculation for each disease. 95% confidence intervals were calculated using the poisson distribution for the number of cases observed.

Results

The classification of patients with PSV who attended the Norfolk and Norwich Hospital 1992-1997 is shown in Table 3.6 Each category is subdivided to show the sex ratio, residency in the NHA and renal involvement. 4 additional patients classified as CSS had renal impairment but this could be attributed to ovarian carcinoma, gentamicin administration, chronic renal failure due to both hypertension and insulin dependent diabetes mellitus and renal impairment in a critically ill patient within 24 hours of death rather than vasculitis per se. One patient diagnosed as mPA was found to have subacute bacterial endocarditis at post mortem and was therefore excluded. Renal impairment in all other cases could be attributed to vasculitis. One patient diagnosed with WG with renal impairment and a biopsy compatible with IgA nephropathy was included .

For the individual diseases the annual incidence for patients with renal involvement in each disease was as follows: WG 7.9 /million (95% C.I. 4.7- 12.5); mPA 7.5/million (95% C.I. 4.4-12.0); PAN 7.0 /million (95% C.I. 4.0- 11.4); HSP 3.1/million (95% C.I. 1.2 – 6.3); CSS 1.3/million (95% C.I. 0.3 – 3.9). Incidence by sex is shown in Table 4

In total 41 patients living in the NHA with renal vasculitis fulfilled at least one classification criteria for PSV. An additional 4 patients in the NHA failed to fulfil classification criteria but had clinical features of vasculitis, compatible renal biopsies and responded appropriately to treatment. An estimate for the annual incidence of primary renal vasculitis for our population was therefore 18.0/ million (95% C.I. 12.9-24.4).

The percentage of patients with renal involvement for each disease derived from all patients studied was as follows: mPA 92% (23/25); PAN 87% (20/23); WG 79% (26/33); HSP 64% (7/11); and CSS 20% (3/15). There was no significant difference in the percentage of male or female patients. Details of ANCA results for all patients is shown in Table 3.7.

Discussion

Our annual incidence figure for primary renal vasculitis, 18.0 /million/year is higher than previous European studies. In Leicester, England Andrews et al reviewed the incidence of mPA and WG between 1980 – 86.[133] Classification of WG used criteria similar to the ACR 1990 criteria and a diagnosis of mPA required clinical evidence of vasculitis in more than one organ system and histological evidence of small vessel vasculitis at least one site in the absence of specific respiratory or histological features of WG. There were 36 cases in their population of 1.3 million. All cases had renal involvement, 35 with focal segmental necrotizing GN and one with a scarred end stage kidney. The combined annual incidence for mPA and WG was 1.5/million.

In Lund, Sweden, Westman et al reported 56 cases of WG, fulfilling ACR criteria and 67 cases of mPA, using CHCC definitions, in their population of 1.2 million between 1971 and 1993.[36] All cases had renal involvement. The annual incidence for WG and mPA respectively was therefore 2.1/million and 2.5/million. The combined annual incidence for mPA and WG was 4.6/million.

31 patients in our population with renal vasculitis fulfilled classification criteria for WG and/or mPA. The annual incidence for renal involvement in WG and mPA combined in the NHA was 13.6/million (95% C.I. 9.3 –19.3) which is much higher than those reported by either the Leicester or Lund groups.

A survey of the Italian registry of renal biopsies in patients over 18 years of age revealed an annual incidence for 1993 of 1.6/million for necrotizing vasculitis and 1.3/million for HSP, lower than our figure for adult HSP of 3.1/million/year.[151]

Other studies have considered histological and laboratory definitions of renal vasculitis. Andrassy et al investigated the incidence of crescentic GN and rapidly progressive GN (RPGN) in Heidelberg, Germany between 1984 and 1989.[57] There were 33 cases of biopsy proven crescentic GN and 5 cases of RPGN on clinical definitions during the study period in their population of 930 000, giving a combined annual incidence of 7.0/million. This study included patients with SLE, Goodpastures and IgA nephropathy in addition to WG, HSP and mPA. In Huddinge, Sweden Pettersson et al found 71 new cases of pauci-immune necrotizing and crescentic GN between 1986 – 1992 in their adult population of 1.2million, giving a mean annual incidence of 8/million. It was noted that the annual incidence doubled from 6/million in 1986 to 12/million in 1992.[149] Both papers suggest that the incidence of renal vasculitis may be increasing. However, a ten year retrospective study 1986 to 1996 in Wessex, England found the annual incidence of biopsy proven rapidly progressive GN to be 3.5/million and this was stable throughout the period.[149] Although different definitions have been used the annual incidence we report is probably genuinely higher than that reported in the other studies, particularly as secondary vasculitis was included in some calculations and specifically excluded in ours.

One study does however find much higher incidence figures than our population. El-Reshaid et al studied renal disease associated with mPA and classical PAN using the CHCC definition in the Kuwaiti population.[145] The local population comprised of 60% heterogeneous expatriates so the remaining 40% of Kuwaiti nationals alone was used to determine incidence figures. An annual incidence of 45/million was found for mPA, classic PAN and patients with angiography compatible with PAN but who failed to fulfil criteria. The annual incidence was 65/million for males and 33/million/year for females.

Our annual incidence figure of 7.5/million for renal disease in mPA is much lower than that of the Kuwaiti study. No cases of classic PAN using CHCC definitions were seen in our population during the study period. Our incidence figure is likely to be a slight underestimate as some patients may have had only mild changes on their renal biopsy and would therefore not have been detected by renal biopsy review. Some patients may have also been missed if they had been too unwell to have a renal biopsy or if the biopsy was unsuccessful. However this difference in incidence would be slight and a large discrepancy in incidence remains between the two populations.

Conclusions

The overall annual incidence figure for primary renal vasculitis in Norfolk is 18.0/ million, 7.9/million for WG and 7.5/million for mPA which are all higher than previous European reports. These differences could reflect true variation between populations, be due to underestimation in previous studies or indicate that the incidence of renal vasculitis is increasing with time. The incidence of renal vasculitis in Norfolk is much lower than in Kuwait. Further study of different populations using comparable classification criteria will provide important information of the variation of these diseases in time and space and may lead to a greater understanding of their aetiology.

Table 3.4 Vasculitis on renal biopsy 1992 – 1997

Patients included		Patients Excluded	
Criteria fulfilled	**No. Patients**	**Diagnosis**	**No. Patients**
WG	14	Primary GN	44
mPA and PAN	8	SLE*	15
mPA	7	IgA nephropathy	3
HSP	5	HSP < 15 years old	2
CSS	3	Sarcoidosis	2
PAN	2	Bacterial endocarditis	2
WG and PAN	2	Systemic Rheumatoid	2
		FSGS†	2
		Malignancy/sepsis	1
		Cryoglobulinaemia	1
		Bechets	1
		MCTDψ	1
Total	**42**	**Total**	**76**

* Systemic Lupus Erythematosus † Focal Segmental Glomerular Sclerosis

ψ Mixed Connective Tissue Disease

Table 3.5 NHA patients with clinical primary renal vasculitis who did not fulfil classification criteria

	Renal Biopsy	Treatment	ANCA
1	Pauciimmune necrotizing GN with nuclear debris	IV cyclophosphamide and methylprednisolone	negative
2	Pauciimmune crescentic GN	IV methylprednisolone	pANCA
3	no biopsy, small kidneys	po cyclophosphamide and prednisolone	positive* 36%
4	Necrotizing crescentic GN	IV cyclophosphamide and methylprednisolone, plasmapheresis	positive* 68%

* early patients – 'crude' ANCA obtained using radioimmunoassay, normal<16%

Table 3.6 Primary systemic vasculitis 1992–1997

Criteria fulfilled	No. Patients		Renal Involvement	
	TOTAL (male)	NHA (male)	TOTAL (male)	NHA (male)
WG	21(13)	14(8)	14(9)	8(5)
WG and mPA	5(1)	4(1)	5(1)	4(1)
WG and PAN	7(4)	6(3)	7(4)	6(3)
mPA	7(4)	4(2)	7(4)	4(2)
mPA and PAN	12(6)	9(6)	10(6)	8(6)
PAN	3(0)	2(0)	2(0)	1(0)
mPA and HSP	1(1)	1(1)	1(1)	1(1)
PAN and HSP	1(1)	1(1)	1(1)	1(1)
HSP	9(7)	8(7)	5(4)	5(4)
CSS	15(9)	12(8)	3(2)	3(2)
TOTAL	81(46)	61(37)	55(32)	41(25)

Table 3.7. Annual incidence of renal vasculitis by classification in NHA 1992-1997

Disease Classification	Annual Incidence /million / year (95% C.I)		
	Total	Male	Female
Total Primary Renal Vasculitis	18.0 (12.9-24.4)	22.8 (14.7 – 33.6)	13.5 (7.8 – 22.1)
WG	7.9 (4.7 – 12.5)	8.2 (3.7-15.6)	7.6 (3.5 – 14.5)
mPA	7.5 (4.4-12.0)	9.1 (4.4 – 16.7)	5.9 (2.4 -12.3)
CSS	1.3 (0.3-3.9)	1.8 (0.2-6.6)	0.9 (0.02 - 4.7)
PAN	7.0 (4.0 – 11.4)	9.1 (4.4 – 16.7)	5.1 (1.9 – 11.1)
HSP	3.1 (1.2-6.3)	5.5 (2.0-11.9)	0.9 (0.02 - 4.7)

Table 3.8 Details of ANCA results

Criteria fulfilled	Negative or Unknown	Positive		
		Crude	pANCA / MPO	cANCA / PR3
WG	6	3	0	12
WG and mPA	0	2	1	2
WG and PAN	1	2	1	3
mPA	2	3	1	1
mPA and PAN	1	4	5	2
PAN	1	1	1	0
mPA and HSP	1	0	0	0
PAN and HSP	0	0	1	0
HSP	7	1	1	0
CSS	7	3	4	1

* In the earlier years of the study IIF and ELISA were not available. Percentage titres of more than 20% were regarded as a significant result.

III. Geographical Variation in Primary Systemic Vasculitis

i) Comparison of the Incidence of PSV Between Three European Regions

Geographical variation in disease may reflect differences in both genetic and environmental factors that contribute to disease. Anecdotal evidence suggests that WG is more common in northern Europe compared to the south whilst mPA is thought to show the opposite trend. The development of suitable classification criteria has allowed the formal comparison of the incidence of PSV between regions. Gonzalez-Gay et al have previously published data on the epidemiology of PSV in Lugo, Spain and more recently Koldingsnses has reported on the epidemiology of WG in Tromso, Norway.[134,143] We have attempted to directly compare the epidemiology of PSV between our three centres by harmonising methods of classification and calculation of incidence figures. Appendix 2 includes full details in the form of the published report comparing results from Lugo with Norwich and a letter and published abstract comparing all three regions.[483,484]

In summary the overall incidence and pattern of vasculitis was similar between the three regions but some interesting differences were noted. mPA was less common in Tromso compared to the other regions whilst WG was more common in Norwich and Norway. CSS had the highest incidence in Norwich. In all areas the incidence was greater in men than women and showed a similar age distribution, peaking in the 65 to 74-year-olds. Overall WG was the commonest diagnosis and 'classical' PAN (CHCC) the rarest.

Results support the idea that there are geographical differences in the incidence of WG and mPA. However it must be acknowledged that, as discussed previously, WG and mPA are difficult to distinguish and despite attempts to apply classification criteria in a unified manner there would certainly be some variation in their application between centres. Despite this, differences may reflect either a difference in genetic susceptibility to

vasculitis or variation in environmental factors responsible for either triggering disease or determining its precise expression.

ii) Comparison of the Incidence of PSV Between Urban and Rural Environments

Introduction

Earlier data from the NHA suggested that CSS was more common in the rural areas of Norfolk compared to the urban areas which may suggest that rural environmental factors such as pollens, pesticides or other chemicals may be important.[156] Conversely WG appeared to be more common in the urban areas suggesting that pollutants have a role to play. However results did not reach significance and the area of residence at the time of diagnosis was used rather than at the date of the first symptom of vasculitis (The Index Date) which is more relevant if considering precipitants of disease. Therefore I re-examined the hypothesis that CSS is more common in the rural population using a larger cohort of patients and more detailed methodology.

Methods

Patients diagnosed with PSV between January 1989 and December 1998 were identified and classified as previously described. The Index Date was established by case-note review and interview of survivors and the residential postcode at that time recorded. Patients were classified according to the ACR (1990) criteria for WG and CSS[41,60], Lanham criteria for CSS[43] and the CHCC definitions of mPA[42] were also applied. Urban residence was defined as residence within postal districts NR1-NR8 which is used by the Norwich City Council Department of Transportation and Planning to define the built-up area of Norwich. Population data for postal codes NR1-8 from 1994 was used to obtain the denominator

urban population (193755 individuals) and the denominator rural population (219992 individuals) was obtained by subtracting this from the total NHA population for 1994 (413747 individuals). 1994 was chosen because it is the midpoint of the study and the population was assumed to stay stable throughout the period. Annual incidence figures were obtained for total PSV and individual disease classifications (WG, mPA and CSS). In addition WG and mPA were examined together because a significant number of cases could be classified as both. 95% Confidence intervals (C.I.s) were calculated using the poisson distribution.

Results

96 cases of PSV were identified. 18 fulfilled criteria for CSS, 55 for WG and 39 for mPA. Of these 15 fulfilled criteria for both WG and mPA and 1 WG and CSS). In 2 cases the postcode at the Index date was not known (1 CSS, 1 WG/mPA overlap). They were therefore excluded from the study. Table 3.8 gives the number of cases and annual incidence for total PSV and individual diagnoses living in the rural and urban areas.

Table 3.9
Annual Incidence of PSV in Rural and Urban Areas of the NHA

Classification	No.	Urban		Rural	
		No. cases	A.I./million (95%C.I.)	No. cases	A.I./million (95% C.I.)
PSV	94*	33	15.5 (10.7 -21.7)	61	25.2(19.3-32.4)
WG	55	18	8.5 (5.0-13.4)	36	14.9 (10.4-20.6)
mPA	39	18	8.5 (5.0-13.4)	20	8.3 (5.1-12.8)
CSS	17*	3	1.4 (0.3-4.1)	14	5.8 (3.2-9.7)
WG/mPA	78*	30	14.1 (9.5-20.1)	48	19.9 (14.6-26.3)

* In 2 cases Postcode at the Index Date not known

Discussion

The annual incidence of PSV was higher in the rural NHA population compared to the urban population. As previously reported patients classified as have CSS lived more commonly in the rural areas compared to urban. However in contrast to previous results this was also true for those classified as WG. Similarly when WG and mPA were analysed together as a group the annual incidence was slightly higher for rural residents. Although confidence intervals overlapped between groups there is a trend towards a higher incidence of PSV, especially CSS in the rural population. Previous data from the United States also suggested that the prevalence of WG may be higher in non-urban counties but results were conflicting because one of the highest prevalence was noted in New York City.[153] A larger study would be necessary to confirm or refute this trend.

IV. Seasonal and Annual Variation in PSV in Norfolk 1989-1998

Introduction

The onset of PSV has been noted to vary with the seasons (mainly studies of WG). In several series there was an excess of cases occurring in the Winter and an earlier review from Norwich suggested a trend towards a Winter peak in WG and an Autumn trough.[16,112,130,137] Other studies have detected fluctuation in the incidence of PSV over many years. This may suggest an infectious trigger factor but findings are not consistent between studies (Table 1.25). Differences may be accounted for by the variation in populations studied and perhaps differences in the date used for the onset of PSV. To detect a seasonal aetiological factor responsible for triggering vasculitis it seems appropriate to define the date of the first symptom attributable to PSV rather than the date of diagnosis because sometimes the prediagnostic period is prolonged. (Table 2.9)

Aim

The aim was to identify seasonal and annual trends in the onset of PSV in the Norfolk population over 10 years (January 1989-December 1998) using the date of the first symptom attributable to PSV (The Index Date).

Methods

PSV cases diagnosed between January 1989 and July 2000 were identified as described in Chapter 2. Patients resident outside the NHA were excluded. The ACR (1990) criteria for WG and CSS[41,60], the Lanham criteria for CSS[43] and the CHCC definition for mPA[42] were applied to all patients. The month and year of the first symptom attributable to PSV (The Index Date) was estimated by case-note review and interview of all surviving patients. Where available, details were recorded of ANCA type by immunofluorescence and ELISA. Graphs were used to illustrate the number of new onset PSV by year (Jan 1989-

Dec 1999) and by month (Jan 1989-Dec 1998) for PSV as a whole, WG, mPA, CSS, cANCA/PR3 positive and pANCA/MPO positive patients. Seasons were defined as Winter (December–February), Spring (March-May), Summer (June-August) and Autumn (September-November) to allow direct comparison with previously published results. 1999 was excluded from the analysis of monthly and seasonal variation because some cases with an Index date within 1999 may not have been diagnosed prior to the study. The Poisson Distribution was used to compare annual fluctuation for each group and chi squared was used to compare seasonal variation. Details of annual general practice consultation rates for influenza and influenza like illness for the Central and Eastern regions (U.K.) and laboratory records for the Eastern region (U.K.) for positive mycoplasma and parvovirus serology made to the Communicable Disease Surveillance Centre (CDSC) between 1990 and 2000 were obtained from the Public Health Laboratory Services (PHLS), London. Details of positive chlamydia serology for the Eastern region between 1995-2000 was also noted. They were used to compare any peaks or troughs in the onset of vasculitis with peaks of infection.

Results

96 NHA residents were diagnosed and classified as having PSV between January 1989 and December 1999. 88 had an Index Date between January 1989 and December 1998. Figure 3.3 illustrates the number of PSV cases presenting in each year and those diagnosed each year. Using the Poisson distribution statistically significantly lower number of cases were diagnosed in 1995 ($p=0.0274$) but there were no significant peak in diagnosis. 1992, 1995 and 1997 had the highest numbers of patients with an onset of vasculitis but numbers were not significantly different from other years. Figure 3.4 -3.6 illustrate the annual rates of general practice consultations for influenza and influenza type illness and reports of mycoplasma, parvovirus and influenza serology. There does not appear to be an

association between the possible peaks and troughs in PSV compared with those of parvovirus, mycoplasma, influenza or chlamydia (data not shown).

Figure 3.7 illustrates the number of cases developing their first manifestation of PSV by year for each diagnosis. There appears to be a peak of WG in 1995 and CSS in 1997 but these were not significantly higher than expected. Both cANCA/PR3 and pANCA/MPO positive vasculitis reflect the apparent peak in 1995 (Figure 3.8). Figure 3.9 illustrates the onset of PSV by year according to the first symptom. There seems to be an excess of ENT symptoms in 1995 and respiratory symptoms in 1998. A high number of positive reports for parvovirus were recorded in 1998. However numbers of cases analysed are small for ANCA type and initial symptoms so these results may have occurred by chance and should be interpreted cautiously.

There appears to be a trend towards higher onset of PSV in the Winter months and fewer cases in the Summer, especially for WG and cANCA positive patients (Figure 3.10-3.12, Table 3.9) However this trend was not significant for total PSV or any of the subgroups using chi-squared (PSV, WG and CSS - $0.1< p <0.5$; mPA and cANCA - $0.05< p <0.1$; CSS $p>0.5$). Although numbers were small it is interesting to note the high number of cases with ENT symptoms as the first manifestation of disease in November, December and January relative to the Summer months (Figure 3.13-3.14).

Table 3.10 Seasonal Variation in PSV and subgroups (%)

	PSV	WG	mPA	CSS	cANCA	pANCA
WINTER	29.9	25.5	42.9	27.8	29	35
SPRING	25.3	23.5	17.1	38.9	19.4	30
SUMMER	17.2	15.7	17.1	16.7	9.7	15
AUTUMN	27.6	35.3	22.9	16.7	41.9	20

Figure 3.3 Comparison of the Annual Onset and Diagnosis of PSV in Norfolk

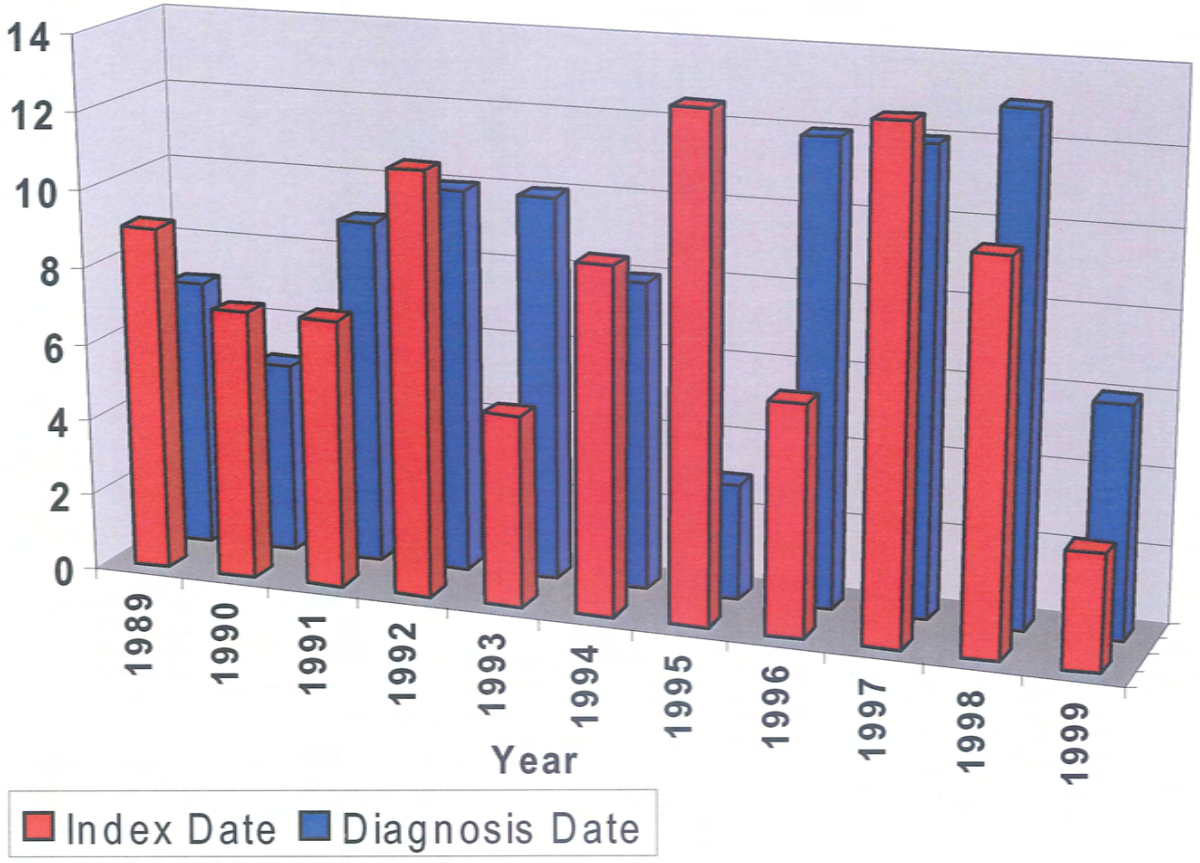


Figure 3.4 Rates of General Practice Consultations for Influenza for Central and Eastern Counties, UK (1991-2000)

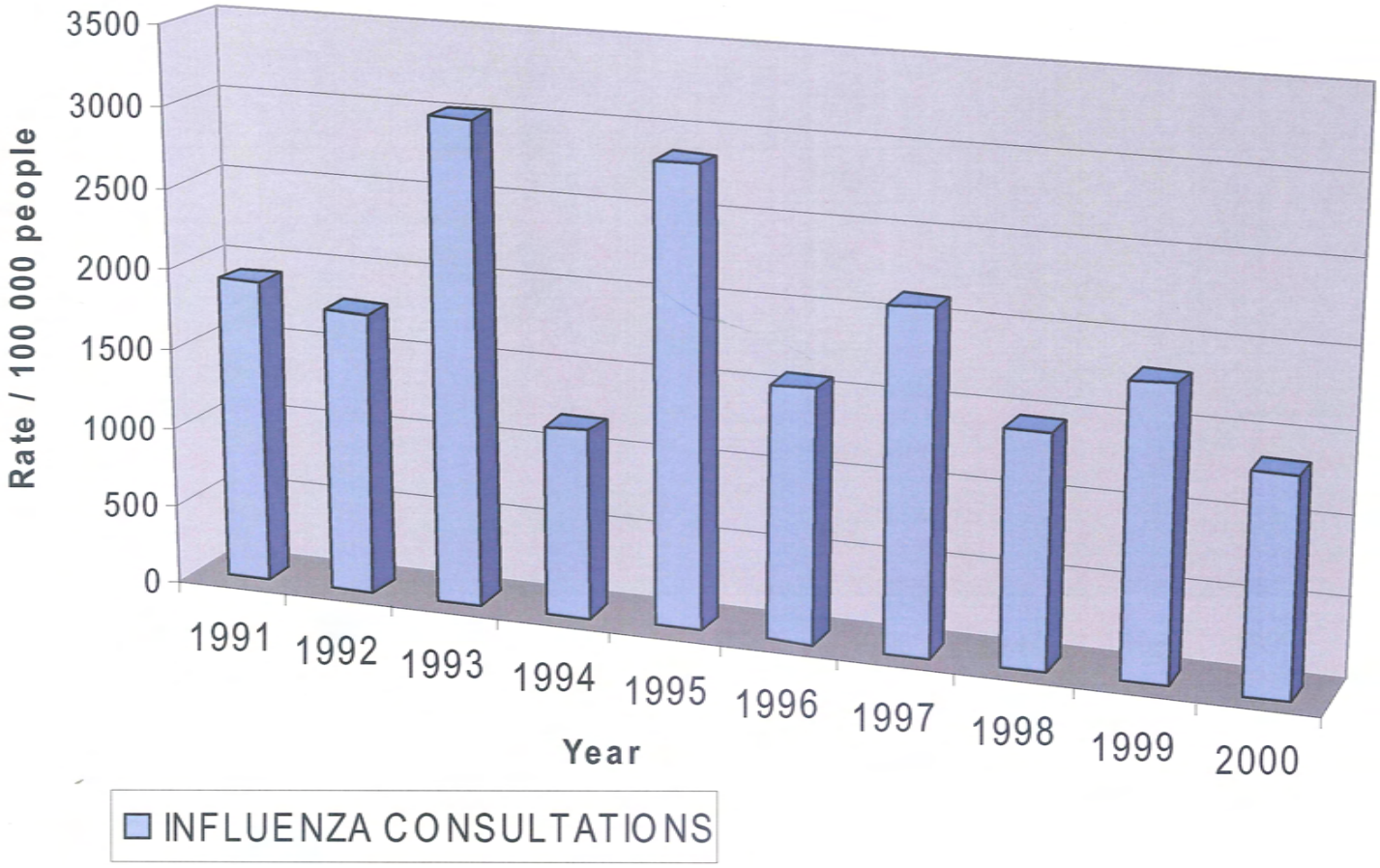


Figure 3.5 Laboratory reports of Influenza made to the CDSC from the Eastern Region, U.K. (1990-2000)

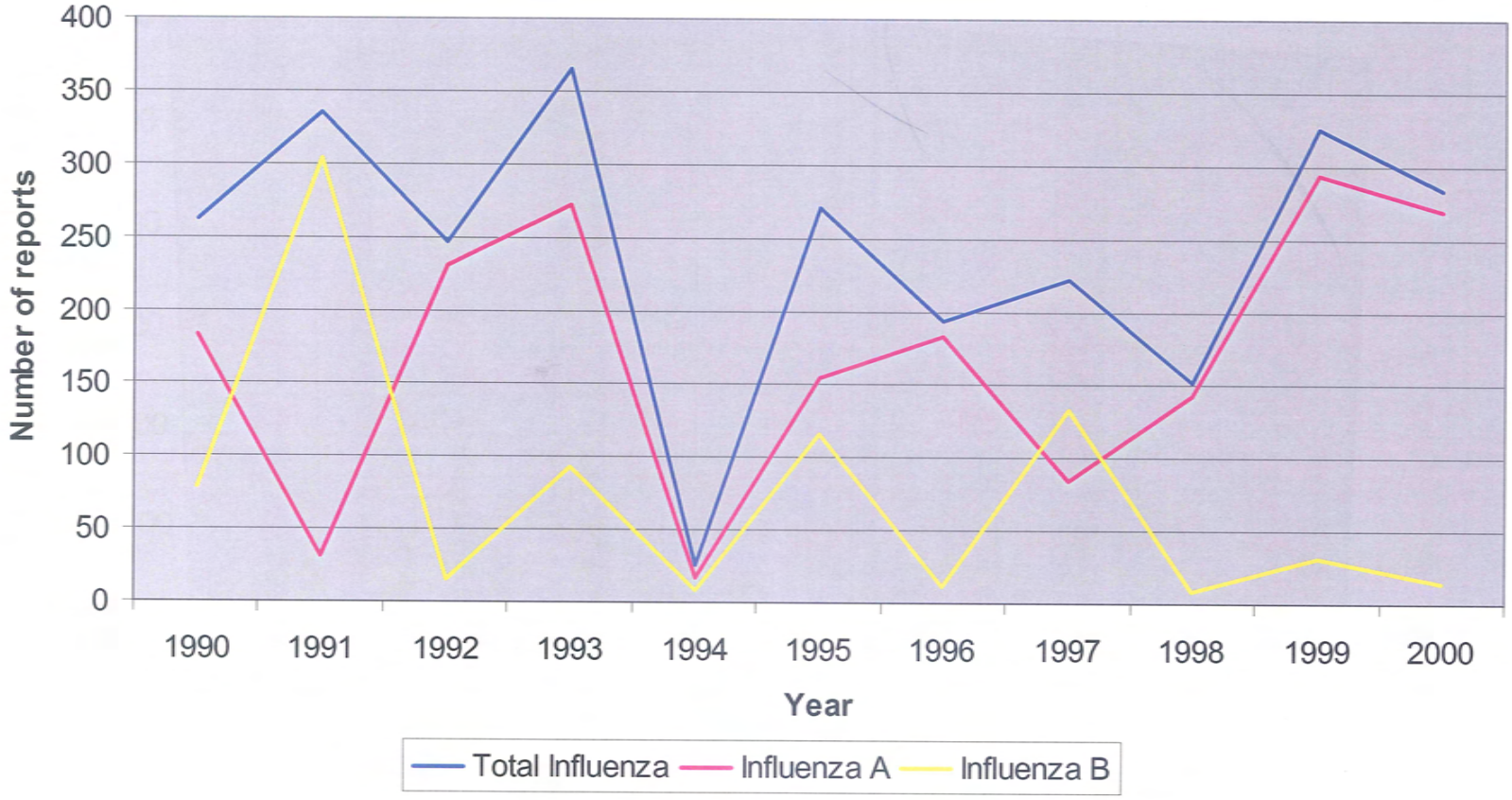


Figure 3.6 Laboratory reports of Mycoplasma and Parvovirus made to the CDSC from the Eastern Region, UK (1990-2000)

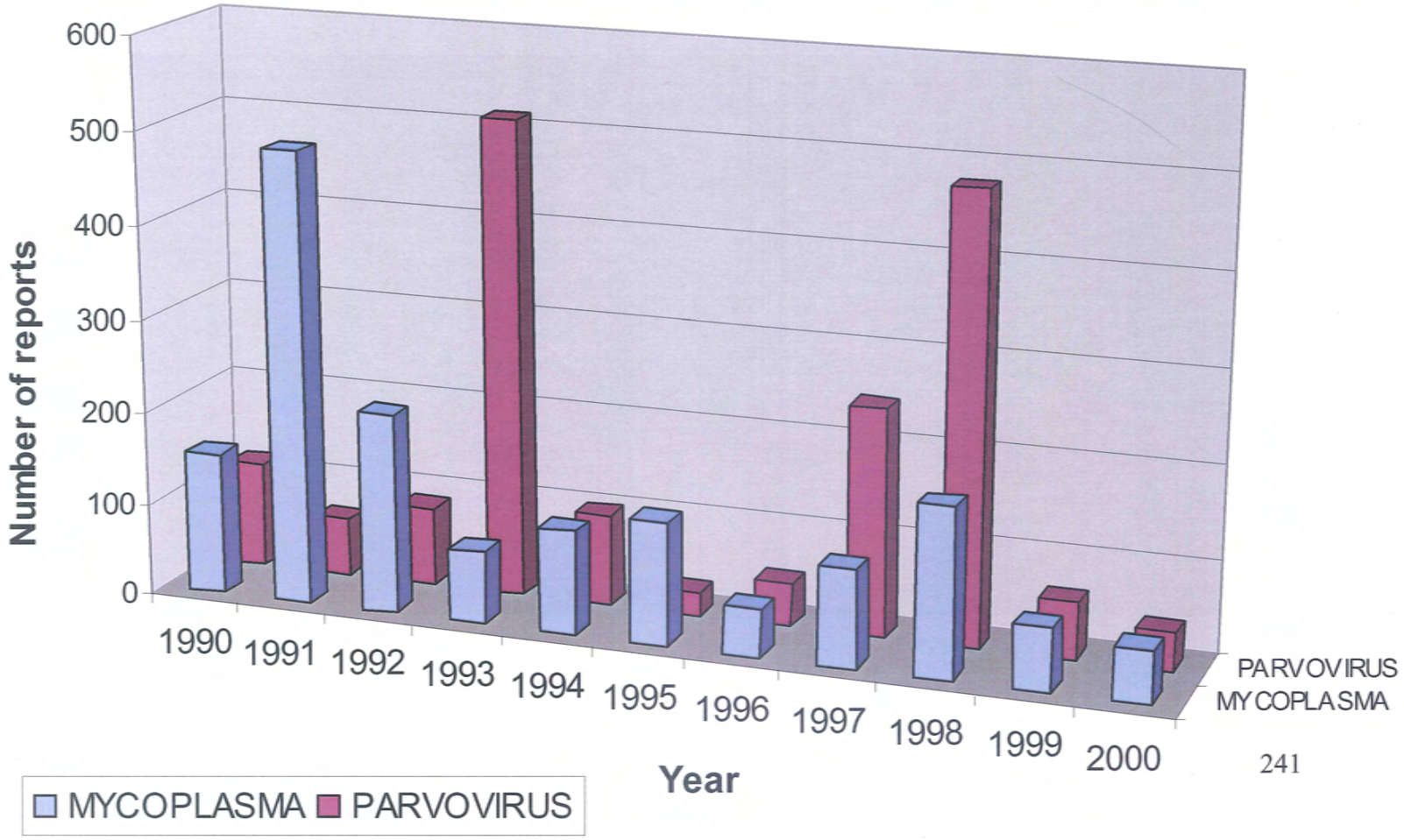


Figure 3.7 Onset of WG, mPA and CSS by Year

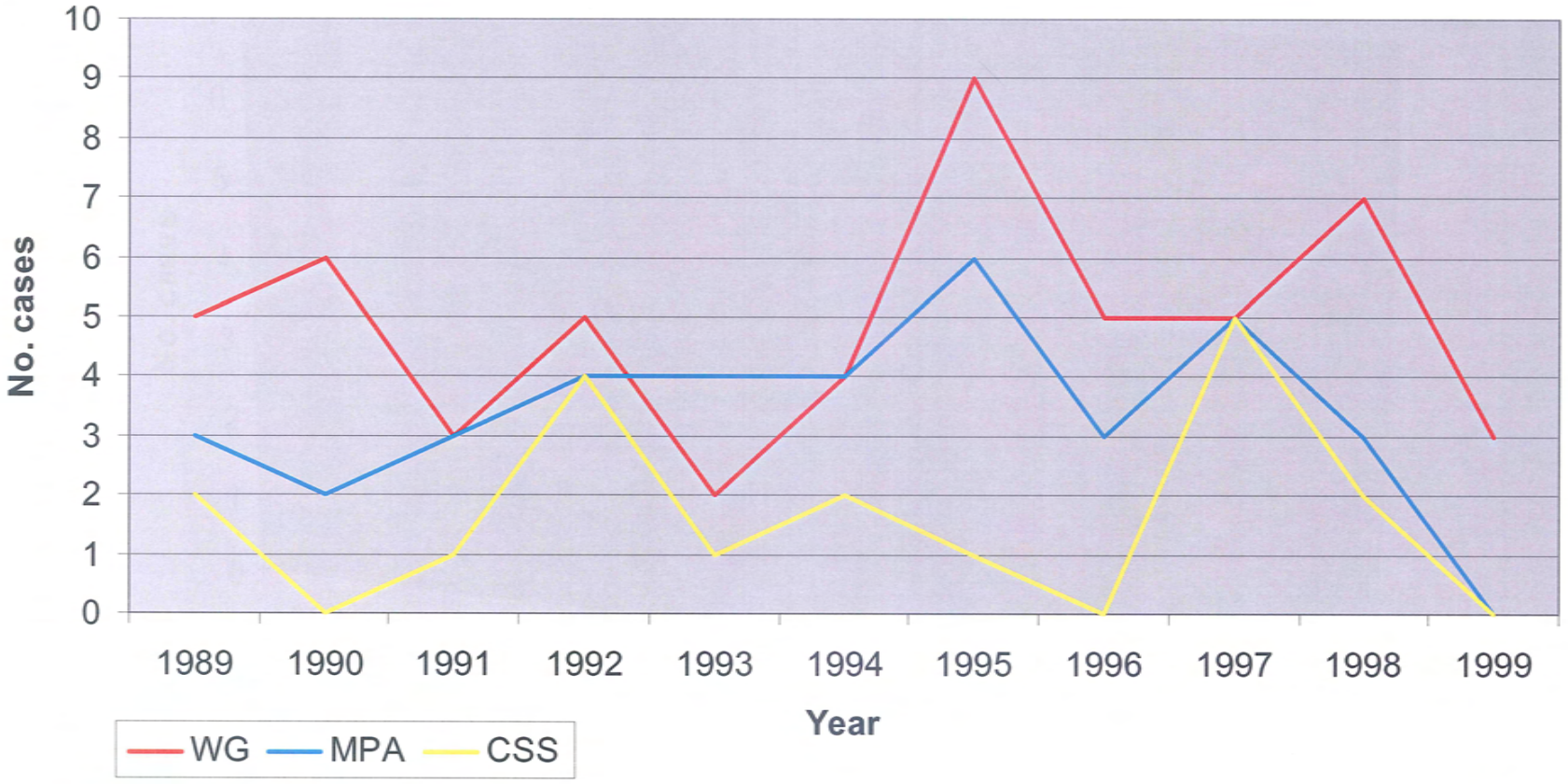


Figure 3.8
Onset of cANCA/PR3 and pANCA/MPO positive PSV by Year

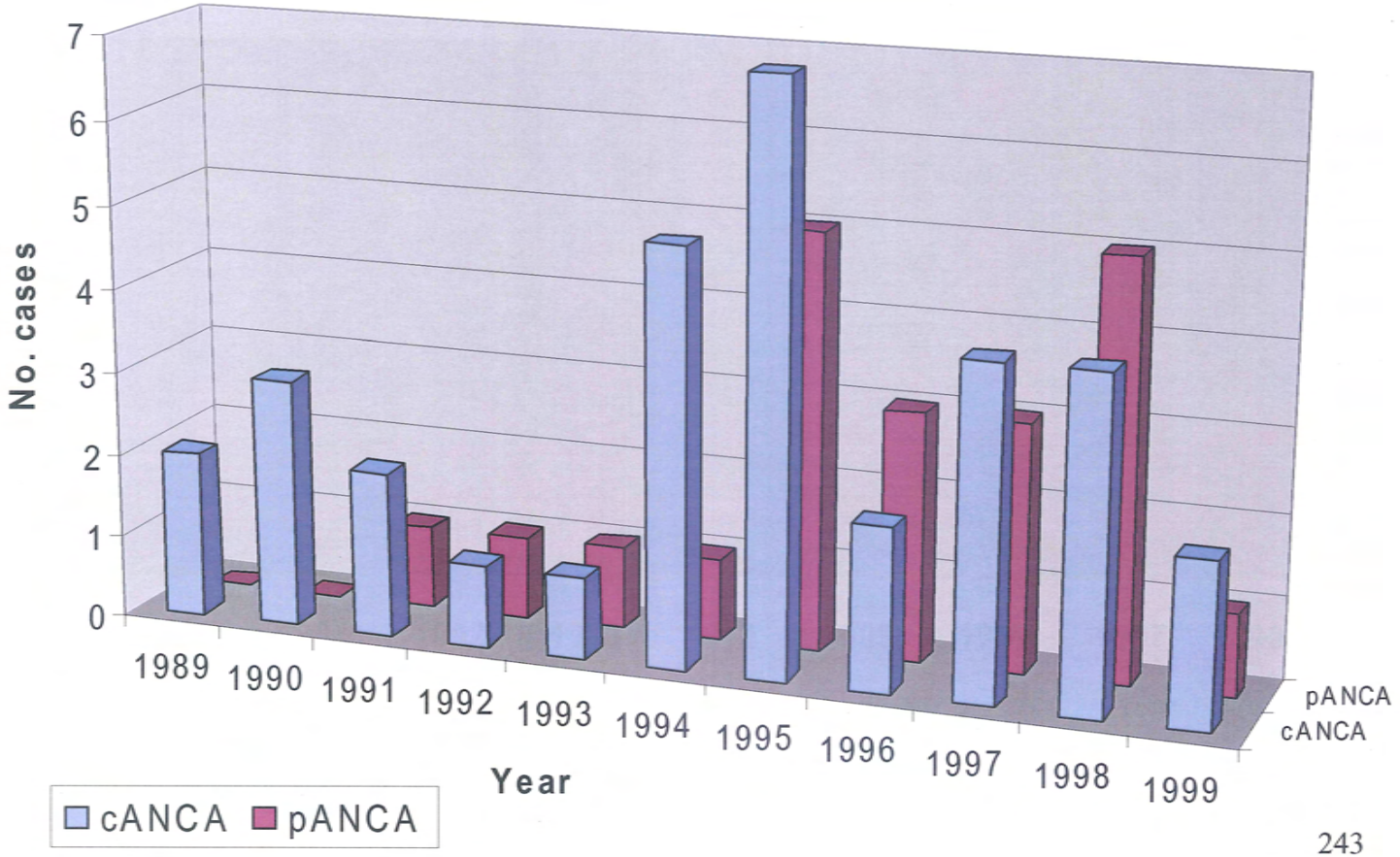


Figure 3.9 First Symptom of PSV by Year

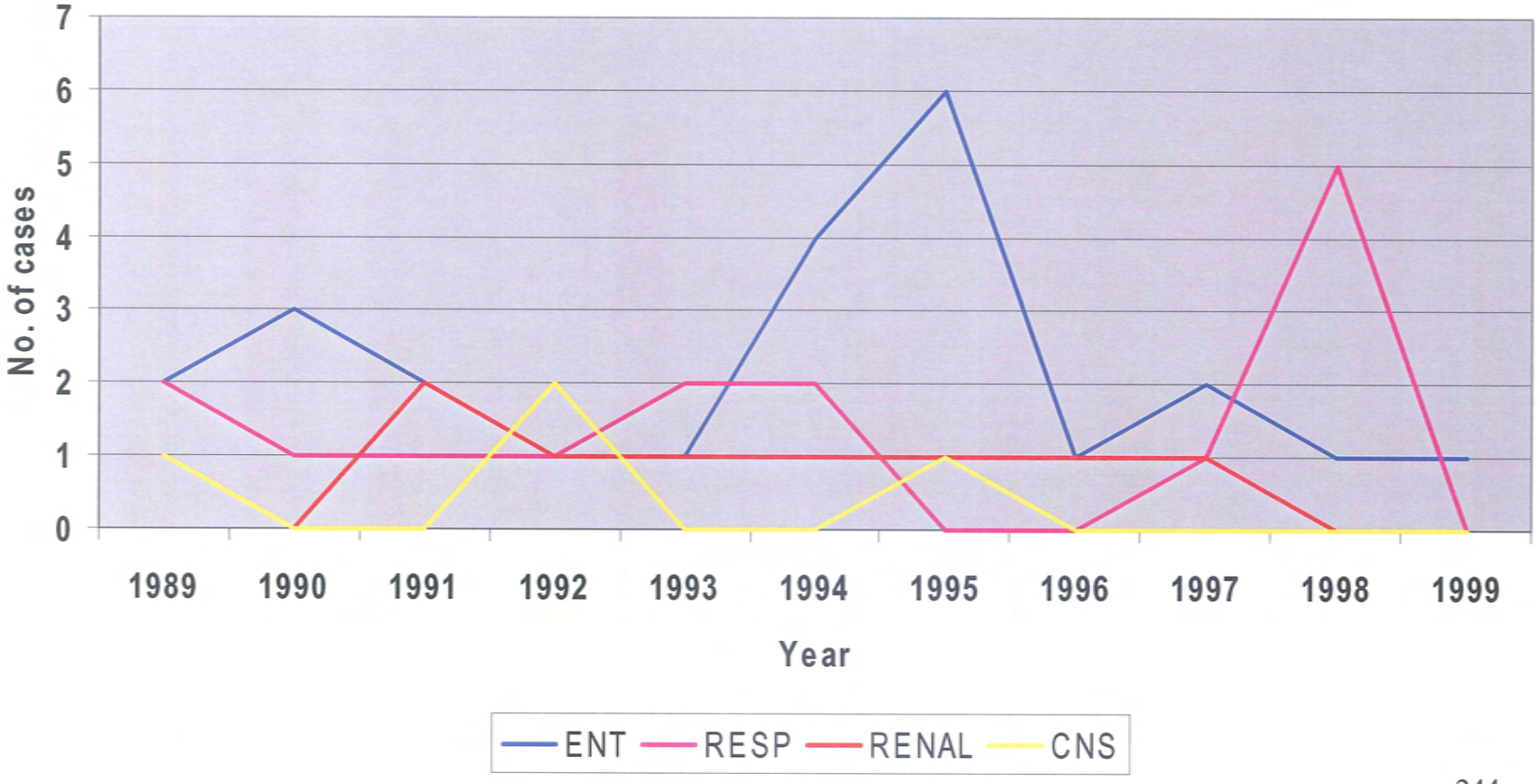


Figure 3.10 Onset of PSV by Month (January 1989 - December 1999)

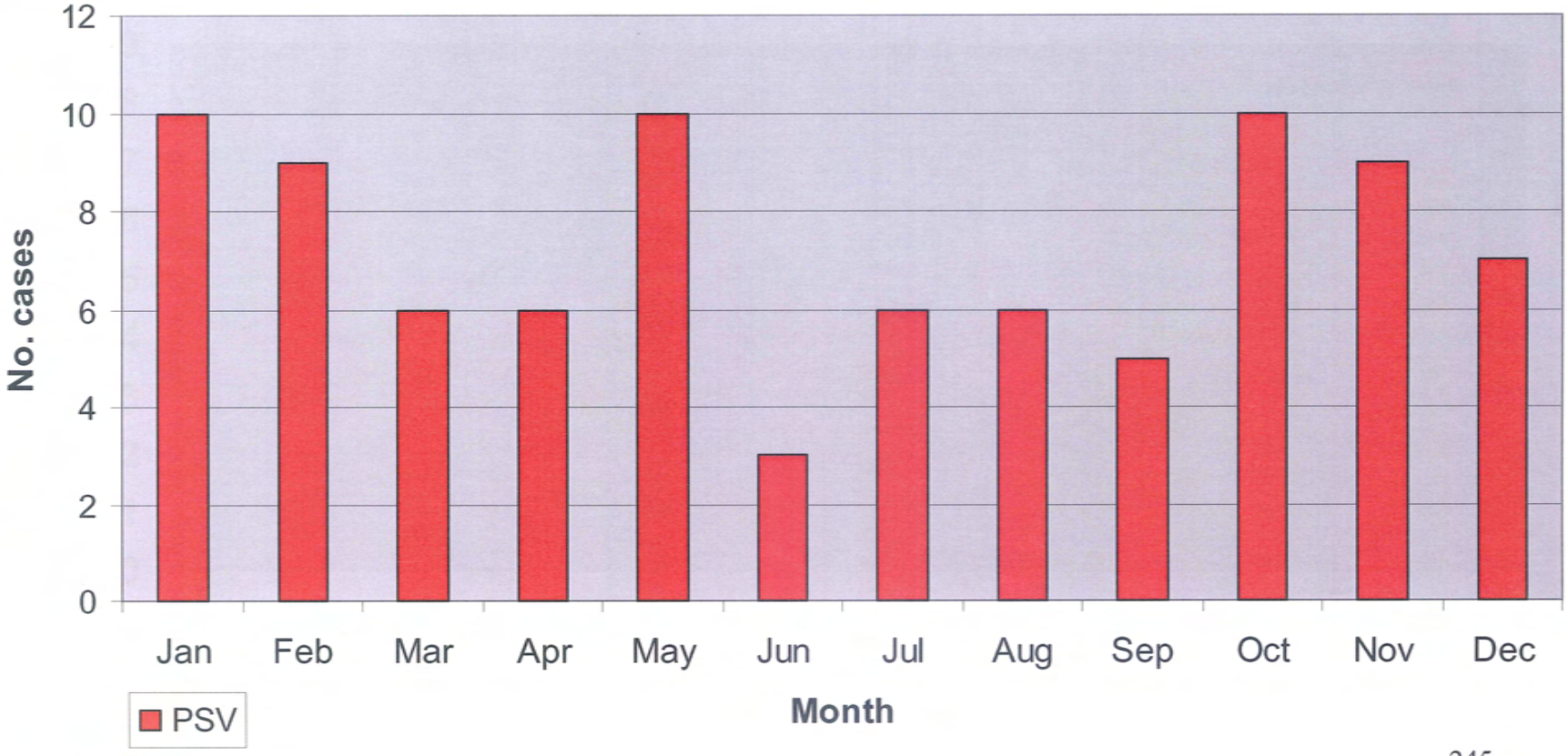


Figure 3.11 Disease Onset by Month in WG, mPA and CSS (January 1989-December 1999)

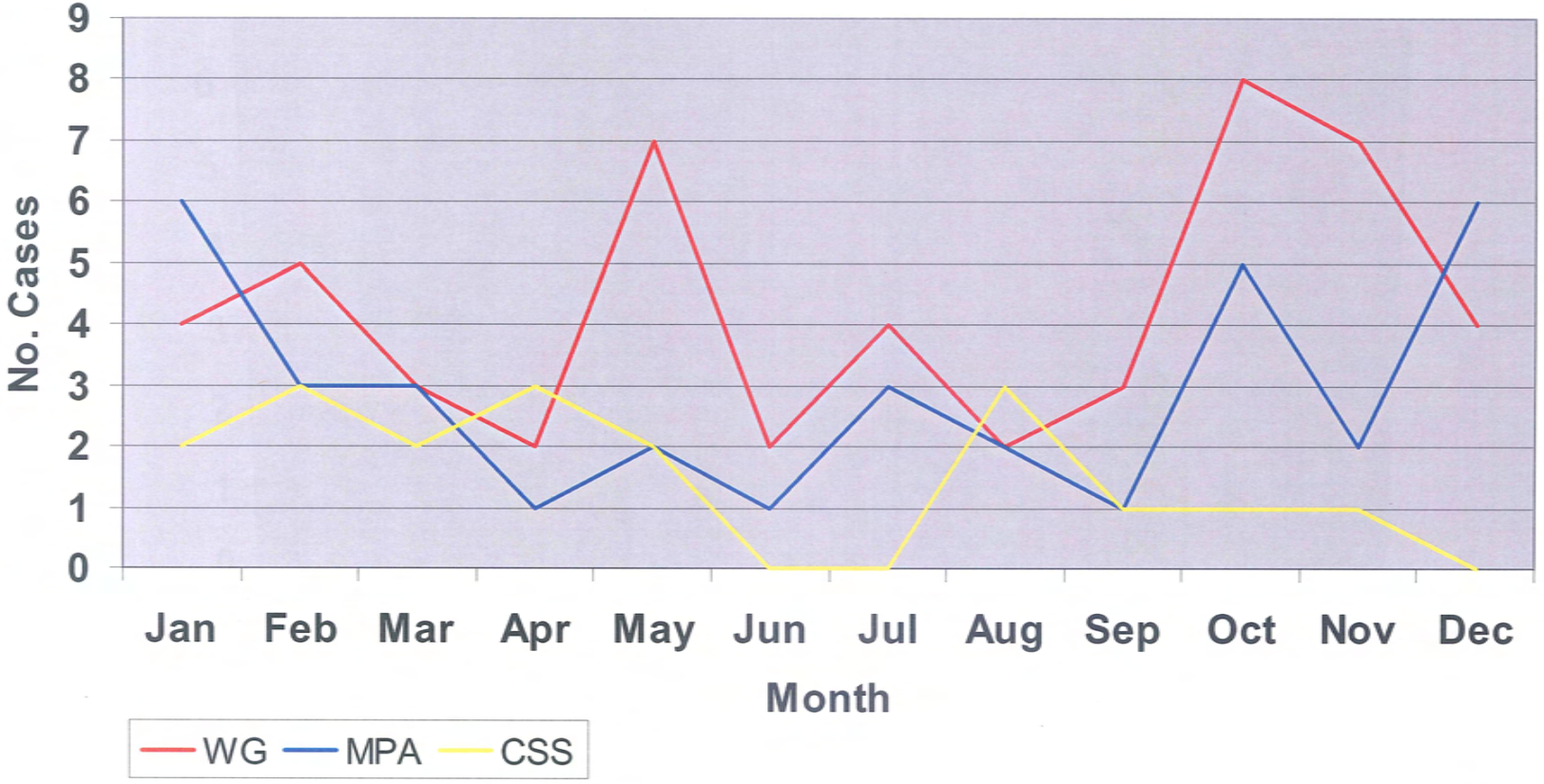


Figure 3.12 Comparison of disease onset by month between cANCA/PR3 and pANCA/MPO positive PSV cases (January 1989-December 1999)

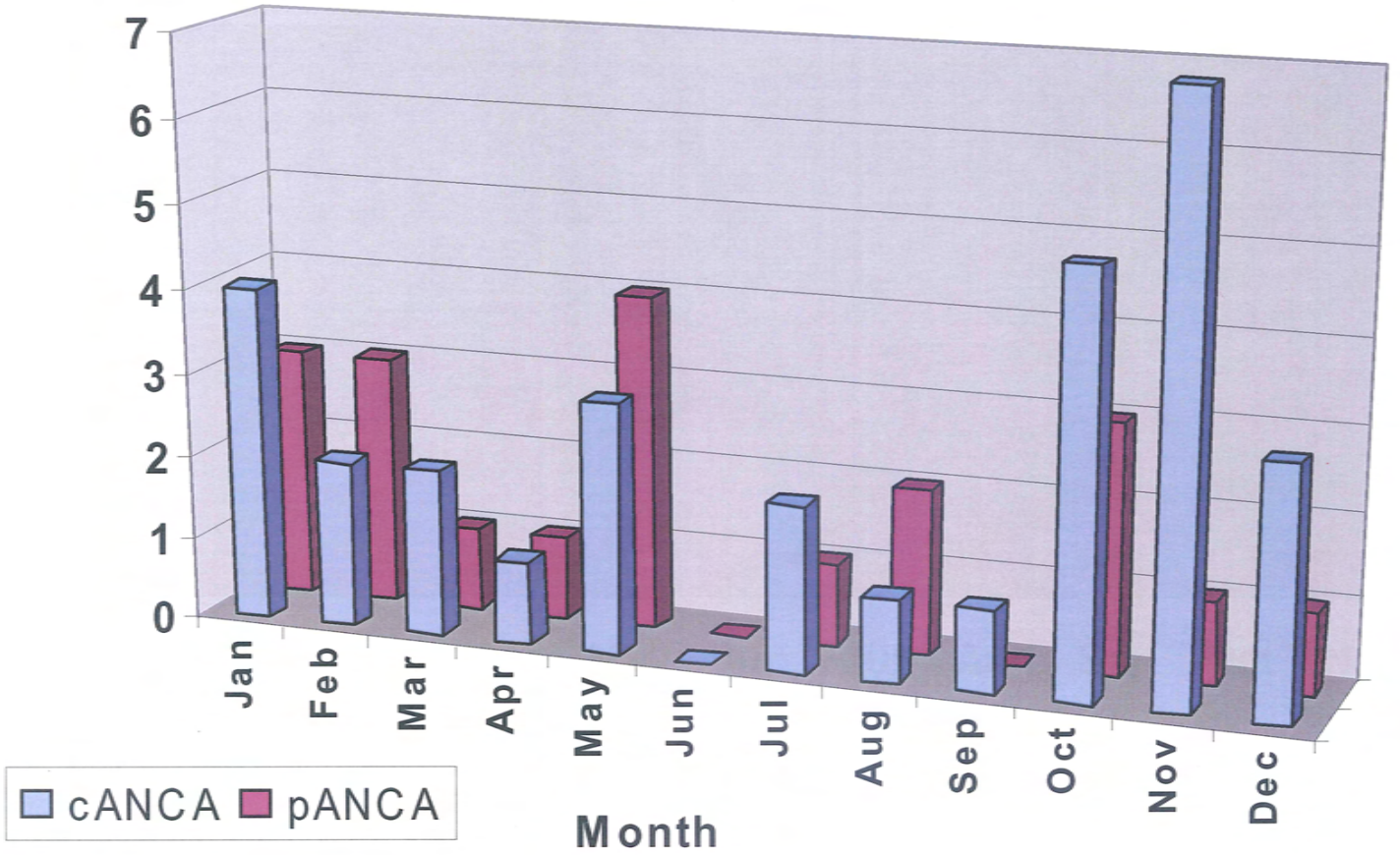


Figure 3.13 Comparison of First Symptom of PSV by Month (January 1989 - December 1999)

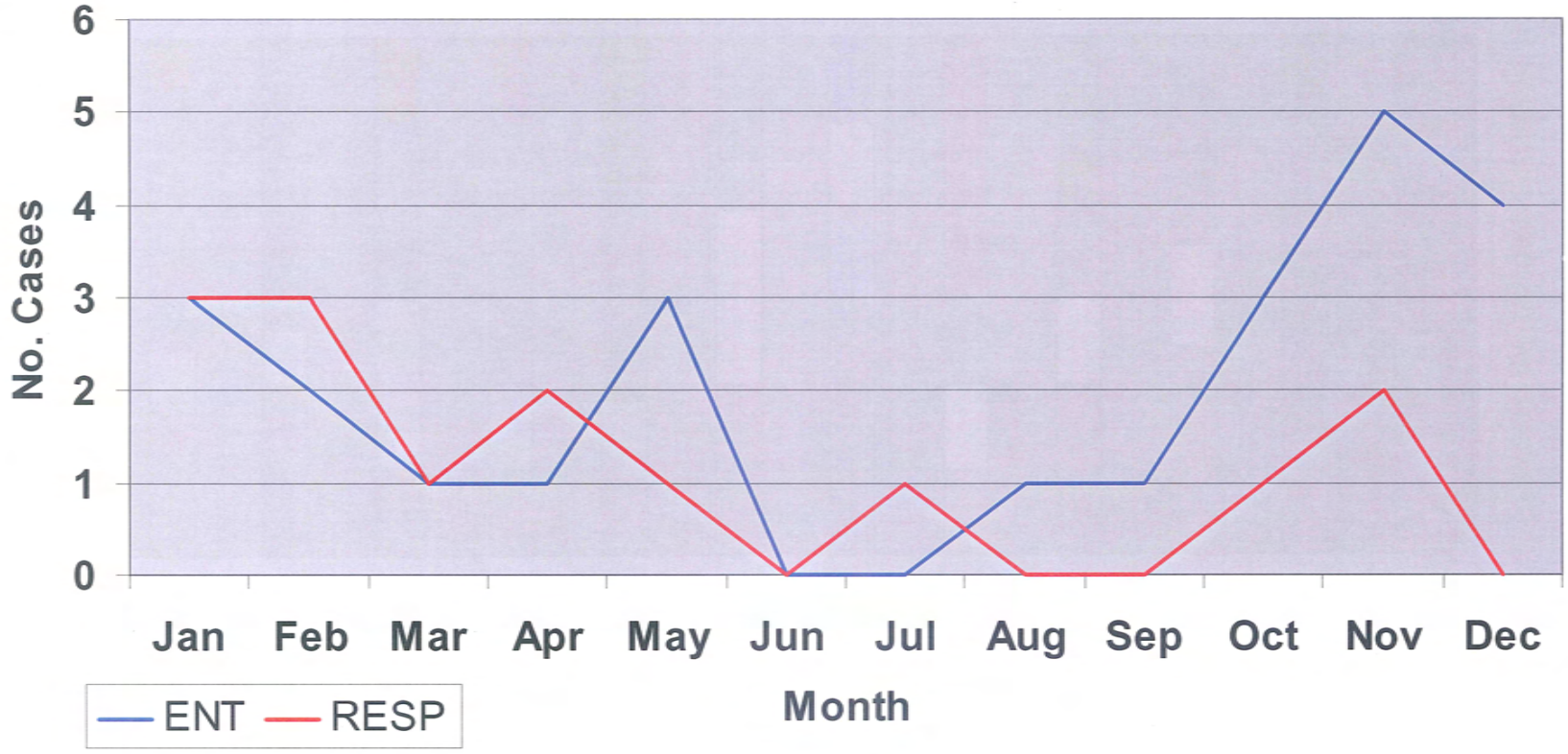
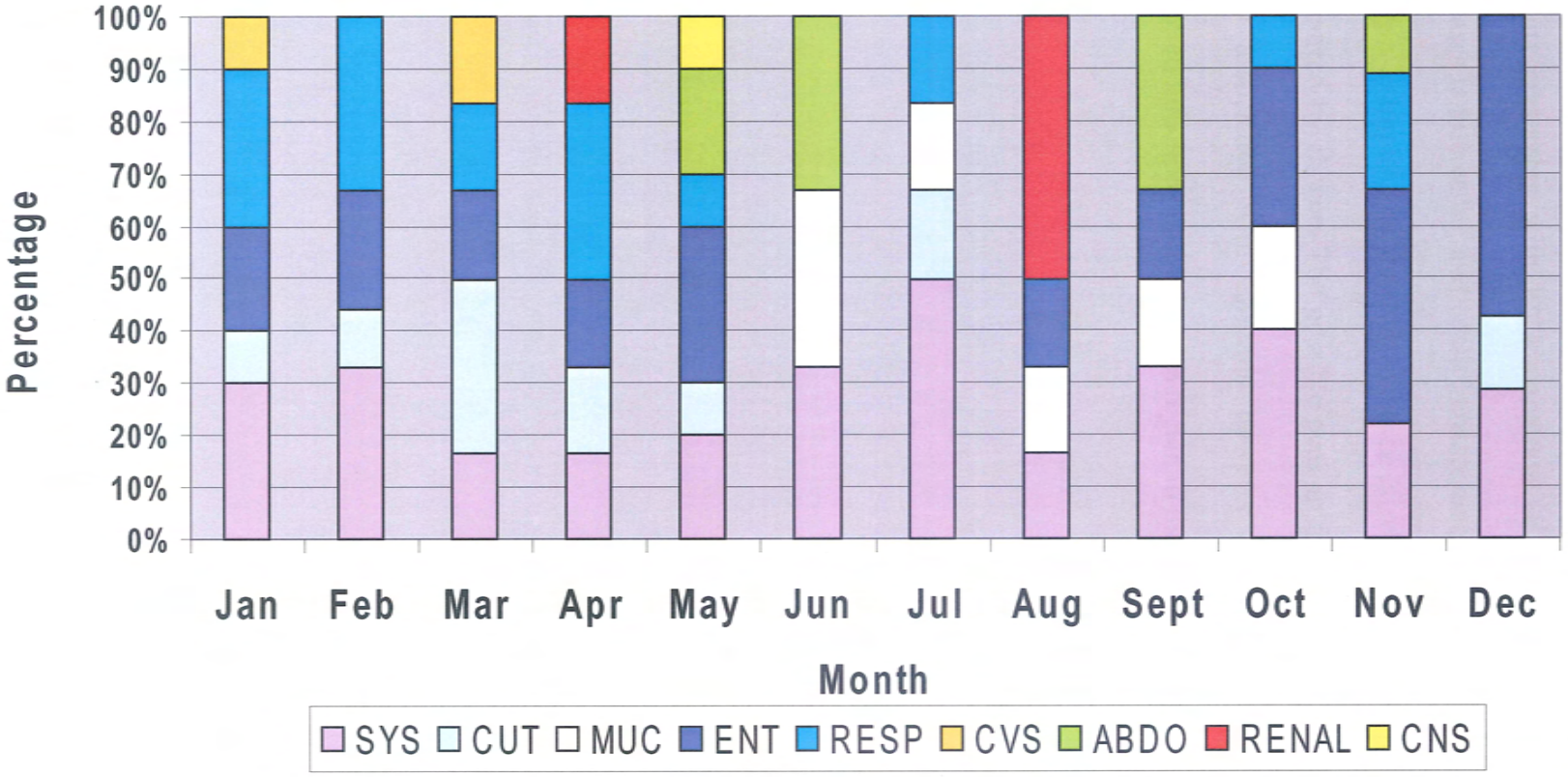


Figure 3.14 PSV symptom at onset by month (January 1989-December 1999)



Discussion

Although there appears to be a trend towards higher onset of disease in the Winter, in keeping with previous reports, this was not significant. The peak of cANCA positive disease and patients presenting with ENT symptoms in November with a dip in the Summer in both cases is interesting and could indicate an early winter infection. However in all three of these examples the number of cases is relatively small and results may therefore have occurred by chance. The possible peak in disease in 1995 and 1997 could also represent an association with infection however there were no corresponding outbreaks of suspected infections in the Eastern region in those years.

V. Conclusions

The annual incidence of PSV in the NHA was approximately 20/million/year which must be regarded as a minimum estimate. This is higher than previous reports and the peak age of onset of disease is higher than many other studies. These results are likely to be more representative of the natural distribution of PSV than earlier reports because the study was carried out in a well-defined population with comparatively little referral bias and similar findings have been noted in other population-based studies.[484] PSV is therefore more common and affects an older age group than previously recognised. Similarly the annual incidence of primary renal vasculitis, 18/million/year, was higher than previous European reports. This highlights the importance of considering a diagnosis of PSV in multisystem and renal disease, especially in the elderly.

An additional explanation for differences noted compared to earlier studies is that the incidence of PSV has actually increased in the intervening years. Although this is unlikely to be the whole explanation, our results support previous reports that the incidence of PSV (especially WG) is increasing with time. This may suggest that modern environmental factors, e.g. fuel emissions or an increase in allergy are important in the aetiopathogenesis of PSV. Alternatively incidence could fluctuate in peaks and troughs although we did not find significant fluctuation in Norfolk. Finally the increased recognition of disease and introduction of ANCA testing may also have contributed to the rise in annual incidence over time. The documented peak of PSV in the Winter in some studies and the cyclical fluctuation of disease in Sweden support the hypothesis of an infectious trigger.[112,130,137] Although there was a trend towards higher numbers of PSV in the Winter months in Norfolk this was not significant. Results from our cohort do not strongly support a seasonal or cyclical trigger. Prolonged documentation of the epidemiology of PSV is required to follow trends and monitor disease fluctuation.

There also appears to be differences in the incidence of PSV between regions which may reflect the effect of environmental and/or genetic factors. However variation between studies can be hard to interpret because of potential differences in the classification of PSV. Our comparison of three European regions with care to utilise the same techniques demonstrated an interesting increase in WG with latitude and a higher incidence of CSS in Norfolk which is worthy of further investigation although unavoidable bias in case ascertainment and classification may have contributed to the differences. Although non-significant, CSS and WG appear to be more common in individuals living in the rural areas of Norfolk compared to those living in built-up areas which indicates that risk factors within the rural environment are of particular importance.

Overall the descriptive epidemiology of PSV provides support for the hypothesis that environmental risk factors are important in the aetiology of PSV. To investigate this further a case-control study was designed with particular attention to rural risk factors including farming. (Chapter 4)

CHAPTER 4

Do Environmental Factors Play a Significant Role in the Aetiology of Primary Systemic Vasculitis? – A Case Control Study

CHAPTER OVERVIEW

Introduction The aetiology of PSV is unknown but a number of potential risk factors have been identified including infection, silica, solvents, metal fumes, allergy, vaccinations and rural residence. A case-control study was designed to investigate these and other factors with particular attention to the rural environment including farming.

Methods 75 PSV patients (from a prospective vasculitis register), 222 age/sex matched non-vasculitis hospital controls, 19 systemic rheumatoid vasculitis (SRV) and 34 age and sex matched asthma controls were interviewed using modified versions of two previously used questionnaires. Details included: social class, occupational and residential history, silica, smoking, pets, allergy, family history of atopy (FH) recent vaccinations, TB exposure, hepatitis, blood transfusions and detailed farm exposure in the year prior to symptom onset (Index Year). Jobs were coded using the Standard Occupational Classification 2000 and job-exposure matrices used to assess levels and duration of silica, solvent and metal exposure. Odds ratios (OR) and 95% confidence intervals (C. I.) were calculated by logistic regression. Total PSV and subgroups (WG, mPA, CSS, ANCA types, renal and respiratory disease) were compared to non-vasculitis controls. PSV and CSS were also compared to SRV and asthma controls respectively.

Results Significantly raised ORs were found for a number of factors including farm exposure in the Index Year in PSV, WG and mPA. Exposure to livestock, in particular direct contact, was significantly associated with PSV in contrast to crops. High occupational silica exposure in the Index Year gave significant ORs for PSV, WG and CSS and exposure during a working lifetime for mPA. Agricultural silica was significantly associated with PSV and WG in contrast to mPA. High occupational solvent exposure was also significantly associated with PSV, WG and cANCA. Increasing duration of occupational exposures was not associated with an increasing risk of PSV. Drug allergies, especially to antibiotics (predominantly penicillin) gave significant ORs for PSV, WG and

cANCA. As expected steroid withdrawal, asthma and rhinitis were significantly higher for CSS compared to non-vasculitis controls and PSV patients had fewer blood transfusions than SRV patients. No significant differences were found for age, sex, social class, urban / rural residence, pets, occupational metal exposure, specific occupational codes, other allergy types, FH of atopy, smoking, TB exposure, hepatitis or vaccinations.

Conclusions For the first time an association between farm exposures and PSV has been found. The association with livestock may suggest an infectious aetiology although other factors, e.g. pesticides, could also be important. Results support the reported association of PSV with occupational silica and solvent exposure and suggest that intensity of silica exposure is more important than its duration. A specific relationship between solvents and renal vasculitis was not found. The association with drug allergy, especially penicillin, may support a role for a Th2 predominant cytokine environment in the initiation of PSV but in the absence of an association with other allergies and atopy, alternative immunological mechanisms should also be considered. These findings make a further more detailed study of the association of PSV with farming and occupational factors desirable.

INTRODUCTION

The aetiology of primary systemic vasculitis (PSV) is unknown but potential risk factors described include infections, vaccinations, silica, solvents, metal fumes and rural residence (see Chapter 1). To investigate the influence of environmental factors on disease we designed a retrospective case-control study. The aim was to test the hypothesis that environmental factors play a significant role in the aetiology of primary systemic vasculitis (PSV). It was undertaken between February 1998 and August 2000 at the Norfolk and Norwich Hospital, the centre for the descriptive epidemiological studies reported in Chapter 3. For the reasons set out the hospital is favourable for epidemiological study as the single referral centre for the former Norwich Health Authority (NHA) which defines an area of 77 general practices. The study was made possible by the initiation of a prospective register of all vasculitis patients attending the hospital by Professor David Scott in 1988. The register has been maintained since then and benefits from virtually complete referral of cases from its catchment area. Good communication between hospital departments, primary care and adjacent health districts allows confidence in the completeness of referrals. The register had recently been updated as part of the study of the epidemiology of primary renal vasculitis (Chapter 2).

A retrospective case-control design was most appropriate to investigate the hypothesis as PSV is relatively rare. It allowed the study of multiple previously described and novel exposures. To recruit sufficient cases to obtain meaningful results in a realistic time-scale necessitated a retrospective approach. Methods and results are presented followed by a discussion of the study design, it's limitations, interpretation of results and conclusions.

II. METHODS

Estimation of sample size

Precise values for the prevalence of each factor investigated in our population were unknown. We estimated silica exposure in the Norfolk population to be 22%. A power calculation was carried out for 48 cases known to be available and 140 controls (3 per case). Assuming a power of 80% and a two-tailed alpha value of 5% this sample would give 80% power to detect an odds ratio of 3.

Case selection and definitions

All adult NHA residents (>15 years at the time of diagnosis) who had been diagnosed with PSV since February 1988 were invited to take part. Regular hospital attendees not resident within the NHA but who lived close to the NHA border were also recruited.

Each case was classified according to the 1990 American College of Rheumatology (ACR) classification criteria for Wegener's Granulomatosis (WG), polyarteritis nodosa (PAN) and Churg Strauss syndrome (CSS), the 1994 Chapel Hill Consensus Conference (CHCC) definition for microscopic polyangiitis (mPA) and the 1984 Lanham criteria for CSS.[41,42,43,60,84] Several individuals fulfilled definitions for both WG and mPA but for the purposes of the case control study were labelled as either WG or mPA as follows. Patients with ENT involvement, nodules or cavitation on chest-X ray or positive cANCA and / or PR3 were classified as WG. Remaining patients with predominantly renal vasculitis and no ENT symptoms were classified as mPA.

Patients with primary vasculitis who did not fulfil these criteria or who had secondary vasculitis (e.g. due to systemic lupus erythematosus or other connective tissue disease, infection, cryoglobulinaemia or malignancy) were excluded.

Controls

Non-vasculitis-controls

Three non-vasculitis controls per case were recruited from inpatients and outpatients of the orthopaedic and rheumatology directorate. Controls were identified by review of case notes of consecutive outpatient, day unit and ward attendees. Those matched for sex, age to within three years of cases and NHA residence were selected. They comprised patients attending the rheumatology outpatient clinics and day-unit and rheumatology and orthopaedic inpatients. The first 84 controls were matched to the age of cases at the time of the onset of symptoms. The subsequent 136 were matched to the case's age at the time of interview. Subjects were excluded if they had a personal history of the following: autoimmune disease including rheumatoid arthritis, thyroid disease, diabetes mellitus, vitiligo and pernicious anaemia; connective tissue disease including systemic lupus erythematosus, scleroderma, myositis, sjogren's syndrome and undifferentiated connective tissue disease; seronegative spondyloarthropathy and inflammatory bowel disease. In addition patients with dementia, mental handicap, cognitive impairment due to acute illness or medication and severely ill patients were excluded.

Disease Controls

Systemic Rheumatoid Vasculitis

Patients resident in the NHA who had been diagnosed with systemic rheumatoid vasculitis (SRV) since 1988 were chosen as separate disease controls for PSV patients to investigate whether distinct risk factors could be identified between primary and secondary vasculitis. 20 surviving patients were identified from the vasculitis register. 18 agreed to participate. They were unmatched due to the limitation in numbers available.

34 asthma controls, matched for age and sex, were selected as a control group for CSS patients to identify differences in exposure between patients with 'simple asthma' and asthma associated with CSS. Two per case were invited to participate by Dr Nick Innes (NI). They were selected as consecutive attendees at an asthma clinic at the Norfolk and Norwich Hospital.

PSV and SRV patients were invited to participate in the study either in person (by SL) at a clinic appointment or by letter and given a patient information sheet about the study. Non-vasculitis and asthma controls were approached in person at the time of their hospital visit (SL /NI). At the time of the interview they were given a further explanation where appropriate, the opportunity to ask questions and gave signed consent to complete the interview and / or to the drawing of whole blood for genetic studies and serum for storage in 1 ml aliquots for later study.

Ethics

Ethical approval was obtained from the Norwich District Ethics Committee (Reference number : 98/009) and the study registered with the Research and Development Office prior to recruitment (Registration number 98RH01).

Questionnaire

A structured questionnaire to measure factors of interest and potential confounders was designed to be administered by an interviewer. It was based on two questionnaires previously used in the investigation of the role of fumes and particulates in WG and allergy in all types of PSV.[135,287] They were adapted for the Norfolk population and to answer additional questions. (See Appendix 1 for the full questionnaires). A single interviewer

(SL) conducted interviews with all PSV patients, SRV patients and non-vasculitis controls. A second interviewer (N.I.) interviewed the asthma controls. N.I. was trained to interview in the same manner as SL by observation of interview technique. The questionnaire can be described as discrete sections although more than one section may be required to investigate a particular factor.

Section 1: PATIENT DETAILS AND ASSESSMENT OF INDEX DATE

The purpose was to record patient details, date of diagnosis (confirmed by case note review) and to establish the date of the first onset of symptoms caused by vasculitis (the Index Date). It was used with an adapted Birmingham Vasculitis Activity Score (BVAS) assessment form (Appendix 1.) to record dates and extent of organ system involvement. Case notes were also reviewed. (Chapter 2). This section, but not a BVAS form, was also completed by controls. All subsequent questions was directed towards the time prior to the Index Date for cases and the matched Index Date for controls. Cases were asked for their opinion of the cause of their illness prior to the interview.

Section 2: FAMILY AND SOCIAL CLASS

Some localities appear to have an excess of PSV compared to others, so exposure to a particular geographical environment may be important. The places of birth of the interviewee, their parents and grandparents were recorded to identify individuals with either a personal prolonged exposure to Norfolk or a history of generations residing in the area. Studies suggest that early exposures to infections and allergens may influence an individuals future immunological responses, especially allergy.[305,485] As PSV has been associated with allergy, an attempt was made to measure early exposures by recording the number of siblings (total and older) with whom the subject had lived as a child. Siblings who were remote to the subject were excluded (e.g. when separated by adoption or a large age difference). If a subject had lived in a children's home they were classed as having more that six siblings. The social class of study participants may be important, especially as a confounding factor in the investigation of occupational exposures. The occupations of

the participants father and partner were obtained to aid social class description for individuals with no previous employment.

Section 3. OCCUPATION

To investigate occupational environmental factors a full occupational history was taken including the title and duration of each employment and a brief description of the work. Although all jobs remembered were recorded only those of >3 months duration were used for analysis as short-term employment is more likely to be affected by recall bias. Subjects were asked to recall any unusual or significant exposures whilst at work and were prompted with examples such as chemical spills or leaks, dust and fumes. Direct questions were asked about exposure to grain dust, silica dust, commercial scouring powder and jobs with known silica exposure (farm worker, baker, brick and foundry worker, sandblaster, dental technician and mine / quarry worker). Where one of these jobs had been undertaken brief details were recorded. 'Farm worker' was defined as working on a farm after the age of 16. Exposure to farms as a child, for example bringing in the harvest were recorded separately.

Section 4. EXPOSURE TO CONSTRUCTION

This section covered exposures to construction and renovation to which the subject had been exposed for a period of at least four hours in close proximity (i.e. the same room as workmen) in the year prior to the index date (Index Year). Questions were asked about exposures both at work and home. Initially all subjects were asked specifically about each exposure listed (chimney cleaning, floor polishing, carpet cleaning, rooms plastered etc.) but this technique was modified as the extensive list caused a level of disinterest in the questionnaire. Instead subjects were asked to describe any building or construction, painting or decorating that was being carried out either at work or at home and the list was used as a guide. Everyone was asked specifically about painting, wallpapering, plastering, plumbing, heating and insulation. Specific types of materials or chemicals were not

identified. Barn exposure was included in this section as an adjunct to the construction and farming histories.

Section 5. HOBBIES

This section related to hobbies undertaken in the year prior to the Index Date. Associated exposures were sought and subjects prompted to identify chemicals, dusts, fumes, solvents or paints specifically. Exposure to fungus, moulds or damp either associated with the hobbies or otherwise within the time period was identified in the third question and a description of any gardening activities were recorded.

Section 6. RESIDENTIAL HISTORY.

A history of residence was obtained for at least ten years prior to the Index Date. The location, postcode, duration of residence, type of dwelling and heating (oil, electricity, wood, coal, other) were documented. Postcode was used to define whether the residential area at the Index Date was urban or rural (Chapter 3). The number of moves made within ten years was used to measure the effect of changes in living environment. A 'recent move' was defined as a move within 2 years of the Index Date. Participants were asked to give details of exposure to any major work or construction, for example extensive renovation, walls being demolished or extensions built for each dwelling.

Section 7. FARMING AND AGRICULTURAL EXPOSURE

Details of farming and agricultural exposures (defined as within 30 feet) in the Index Year were recorded. The manner of exposure (living on or by a farm, visiting a farm or working on a farm) and frequency of crop and livestock exposures were noted. Individuals were generally more certain about the type of livestock than crops they had been exposed to at the Index Date. Details of household pets and any illness they had suffered within the Index Year were also obtained.

Section 8 ALLERGY

A history of allergy (skin, drug, insect, plant and food) prior to the Index Date was recorded. Descriptions of symptoms ascribed to allergy were documented in each case and

a decision was made as to whether they were true allergic phenomena. Where doubt remained (e.g. the incident occurred in childhood) the episode was included as an allergy. The date of the first remembered episode and treatment was recorded. A history of allergic rhinitis (described as a runny, blocked nose recurring each year) and asthma including the use of inhalers was taken.

Section 9 OTHERS

Further details recorded included: personal contact or infection with tuberculosis (TB) including dates and relationship to the infected individual; hepatitis including type; and date and place of any blood transfusions received. The duration and quantity of cigarette or tobacco smoking and a family history of allergy or vasculitis in a close relative (defined as siblings, parents or children) were documented. Medication and vaccinations received and withdrawal from steroids within the six months preceding the Index Date were also recorded. All participants were asked to describe any significant incident or exposure that might be important but had not been covered by the questionnaire.

Section 10. RELAPSES

Cases who had experienced any six month period without any medication for vasculitis after diagnosis were asked about disease flares. The date and symptoms of the flare(s) and any exposures to chemicals, fumes, dust, smoke, plants, animals, fungus, moulds or infections were documented. All cases were again asked to give their opinion as to what might have caused their vasculitis after completing the interview.

MEASUREMENT OF CONFOUNDERS

There are no definite known risk factors in the aetiology of vasculitis (e.g. smoking and alcohol consumption) to consider as confounders. However several potential confounders were measured including social class, rural residence and smoking. In addition environmental exposures and items of interest, (e.g. silica and farming) may confound for each other. The fact that PSV is most common in males and the 65-74 year-old age group were adjusted for by matching controls.

Sub hypotheses for particular environmental factors were formulated and questionnaire data was used to investigate each individually. Minitab Release 13 software was used in analysis. For each item, data was tabulated and completeness verified. An initial chi squared test was performed to identify trends. Conditional binary logistic regression was used for each exposure independently and odds ratios (ORs) with 95% confidence intervals (C.I.s) were calculated. Stepwise multiple logistic regression was used to calculate adjusted ORs and C.I.s with potential confounders. Exposures significantly associated with PSV, age, sex, rural residence and social class were included in the model.

Interpretation of results

Multiple hypothesis testing is likely to give some spurious statistically significant results ($p<0.05$).[486,487] The plausibility of each hypothesis tested needs to be considered for each significant result because the chance of a detected association being false increases with reducing levels of plausibility. For example, using Baye's Theorem, there is a 22% chance of a result occurring spuriously when the prior chance of an effect being real is 1 in 2 compared to a 96% chance when they are 1 in 100.[488] The effect of a relatively small sample is to miss real effects rather than to find false ones so results that are close to the level of significance should not completely be discounted when considering further studies. However the most likely cause of any misleading significant results in this study are bias and confounding. These are discussed in context later.

In view of the unknown aetiology and pathogenesis of disease and potential differences between disease subtypes the cohort was investigated in several ways. All PSV patients were compared as a whole with both non-vasculitis and SRV controls. Individual disease types by classification (WG, mPA, CSS) may have different trigger factors and were analysed separately. Some patients fulfilled classification criteria for WG and mPA

therefore these diseases were also analysed together as a single group. CSS patients were specifically compared to asthma controls because asthma is inherent to the diagnosis. Differing factors could be responsible for triggering specific organ involvement in vasculitis e.g. an airborne stimulant may be responsible for respiratory disease whilst renal disease may be related to solvents, and PSV associated with different ANCA types could also have distinct aetiologies. Cases were therefore also divided by renal and respiratory involvement and ANCA specificity. Table 4.1 summarises cases and controls investigated. Items analysed and the section of the questionnaire from which the information was obtained are as follows.

Table 4.1 Groups which were compared by logistic regression

Cases	Controls
Total PSV (WG, mPA &CSS)	Non-vasculitis, SRV controls
WG	Non-vasculitis
mPA	Non-vasculitis
CSS	Non-vasculitis, asthma controls
WG & mPA together	Non-vasculitis
PSV with renal involvement*	Non-vasculitis
PSV without renal involvement	Non-vasculitis
PSV with respiratory involvement**	Non-vasculitis
PSV without respiratory involvement	Non-vasculitis
cANCA/PR3 positive PSV$^{\phi}$	Non-vasculitis
pANCA/MPO positive PSV$^{\Psi}$	Non-vasculitis

* haematuria, deranged electrolytes or biopsy appearances caused by vasculitis

** haemoptysis, persistent cough or dyspnoea or CXR changes caused by vasculitis

$^{\phi}$ PSV with positive ANCA test with cANCA specificity +/- PR3

$^{\Psi}$ PSV with positive ANCA test with pANCA specificity +/- MPO

DESCRIPTION AND DEFINITIONS OF ITEMS ANALYSED

1. AGE (Information from section 1 of the questionnaire)– Age at the Index date (or matched equivalent) was used to verify matching and for multiple logistic regression.

2. SOCIAL CLASS (section 2) – Occupations were coded using the Standard Occupational Classification (SOC) 2000.[489,490] Social class was based on the most recent full-time occupation prior to the Index Date. Where individuals had no previous occupation, social class was based on their partner or father's occupation. Occupations were converted to SOC 1990 codes and social class derived from the Office for National Statistics Occupational Support Service (OOSS) User guide 6.1, simplified list of social class based on occupation.[491] Non-manual workers were defined as social classes I, II and IIIN and manual workers as social classes IIIM, IV and V.[492]

3. URBAN OR RURAL RESIDENCE (section 6.) – Defined as the area of residence in the year prior to the Index Date. Urban was defined as postal district NR1-NR8 which define the built up area of Norwich for the NHA patients, NR30-31 for Great Yarmouth and Lowestoft, PE30 and PE34 for Kings Lynn and IP24 for Thetford residents. Rural was defined as all other postal districts. (Refer to Chapter 3. for further details)

4. NORFOLK HISTORY (section 2.)– The following were analysed

i) Birth in Norfolk

ii) Birth of parent or grandparent in Norfolk

iii) Either i) or ii)

5. OCCUPATIONAL EXPOSURES

5 (a) SILICA - The hypothesis that silica is important in the aetiology of PSV was investigated by comparison of the following factors:

i) **Occupational exposure to silica** - A job exposure matrix was constructed for high, intermediate and low silica exposure jobs (Table 4.2) using previously published tables of industries and tasks with high silica exposure.[161,166,201,493] Jobs ancillary to the building or construction industry such as carpenter, electrician and painter and decorator were classified as intermediate exposure. The following factors were analysed for both jobs in the Index Year and also throughout working life. (section 3.)

A - Any occupational silica exposure

B - High occupational exposure

C - Intermediate occupational exposure

D - Agricultural occupational exposure (i.e. grain dust)

E - Any occupational exposure except for agricultural

ii) **Duration of silica exposure** – Duration of occupational silica exposure was categorised to investigate the effect of duration of exposure on the risk of PSV.

iii) **Exposure to specific occupations** reported to be associated with PSV (section 6.)

- Coal worker (Coal miner or coal delivery services)
- Dental technician/ dentist
- Baker exposed to flour
- Commercial scouring powder use
- Brick / foundry worker
- Sandblaster
- Mine/ quarry worker

iv) **All exposures to silica dust** – Defined as exposure to crystalline silica dust either through hobbies or construction (sections 4 and 5) in the year prior to the Index Date and / or at any time in occupation (section 3)

v) **All exposures to grain dust** – Defined as exposure to grain dust associated with agricultural work or harvesting in the year prior to the Index Date (sections 5 and 7) and / or anytime during occupation or as a child during the harvest (section3)

vi) **Exposure to Construction** – Construction whether occupational or domestic is likely to be associated with silica exposure although many other potentially relevant exposures may also be encountered. It was specifically investigated as follows:

A - Working in the construction industry – (bricklaying, building, carpentry or allied professions) ever and in the Index Year (section 6).

B - Probable high peak exposure to silica - Defined as working in the construction industry or undertaking / being exposed to domestic renovation and building. (Sections 3,4.,5 and 6)

C - Exposure to Minor Construction in the Index Year at work or home – Personal participation or exposure to construction for 4 hours in the same room as workmen (Section 4.)

- All types
- Painting and decorating (painting or wallpapering)
- Plastering
- Plumbing, heating and insulation
- Floor polishing
- Carpet cleaning
- Chimney cleaning
- 'Do it yourself' as a hobby (section 5.)

Table 4.2 JOB-EXPOSURE MATRIX FOR SILICA

OCCUPATIONS WITH HIGH SILICA EXPOSURE

OCCUPATION	SPECIFIC TASK
Abrasives	Silicon carbide production; abrasive products fabrication
Agriculture	Mechanised ploughing, harvesting; sorting; cleaning; grading
Agricultural chemicals	Raw material crushing, handling
Asphalt and roofing felt	Filling and granule application
Automobile repair	Abrasive blasting
Boiler scaling	Clean ash and mineral deposits from coal fired boilers
Cement	Materials processing: clay, sand, limestone
Ceramics	Mixing, moulding, glaze or enamel spraying, finishing
Construction	Abrasive blasting; highway and tunnel construction; excavation/ earth moving; Masonry, concrete work, demolition
Foundries	Casting, shaking-out; abrasive blasting, felting; furnace installation and repair
Glass, fibreglass	Raw material processing (sand / quartz) ; refractory installation and repair
Iron, steel mills	Refractory preparation and furnace repair
Jewellery	Cutting, grinding, polishing, buffing (gems and stones)
Metal	Abrasive blasting (structural, machinery, transportation equipment)
Mining, milling	Most occupations and mines (ores, associated rock)
Paint	Raw materials handling (fillers)
Quarrying, milling	Stone, sand, gravel processing; stone cutting and abrasive blasting; slate work diatomite calcination
Rubber and plastics	Raw materials handling (fillers)
Shipbuilding, repair	Abrasive blasting
Silicon, ferro-silicon	Raw materials handling (sand)
Soaps, cosmetics	Abrasive soaps, scouring powders

INTERMEDIATE OR PROBABLE EXPOSURE

Dental material	Abrasive blasting, polishing
Occupations ancillary to construction trade	
	Carpenter
	Painter and Decorator
	Electrician
	Maintenance
	Boat-builder
Baker	
Sculptor	
Occupations / tasks related to those with high silica exposure	

LOW EXPOSURE

All other occupations

5 (b) SOLVENTS

A job exposure matrix was constructed for high, medium or indeterminate and low solvent exposure jobs (Table 4.3). A previously published matrix was adapted for this purpose.[203,227] The following factors were assessed for occupational solvent exposure ever and for exposure during the Index Year only.

A - Any occupational solvent exposure

B - High solvent exposure

C - Medium or indeterminate occupational exposure

5 (c) METALS – A simple job-exposure matrix was constructed (Table 4.4)[494]and information obtained (section 6.) analysed in the same manner as solvents.

6. EXPOSURE TO FARMING - Farming, agricultural and associated exposures were assessed using sections 3, 5 and 7. Items analysed are as follows:

i) **Ever Farm** – Defined as any exposure to farm / agriculture in the year prior to the Index Date and / or a history of any occupational exposure to farming (excluding work on farm as a child.)

ii) **Farm exposure (Index Year)** – Any exposure to crops and/or livestock within 30 feet (almost 10 metres) during the Index Year.

iii) **Crop exposure (Index Year)** – Exposure to crops within 30 feet in the 12 months preceding the Index Date.

iv) **Livestock exposure (Index Year)** - Exposure to livestock within 30 feet in the 12 months preceding the Index Date.

v) **Crop and livestock exposure (Index Year)** - Exposure to both Crops and livestock within 30 feet in the 12 months prior to the Index Date.

vi) **Category of livestock exposure** - The degree of livestock exposure was categorised as 'Direct', 'Close' and 'Distant'

vii) **Category of crop exposure** – The degree of crop exposure was categorised to 'High', 'Medium' and 'Low' exposure.

viii) **Type of farm exposure** - Individuals with contact to farms were divided into categories according to the cause of exposure.

- Living on or within 30 feet of a farm
- Working on a farm
- Visiting a farm.

The rationale was that the type of exposures might differ. Living adjacent to a farm may cause low levels of exposure compared to those working on a farm although both may be exposed for long periods. Individuals visiting a farm are likely to be exposed for a shorter duration although specific exposures may vary.

ix) **Frequency of Farming Exposure** – Frequency was divided into categories of 'Daily', 'Weekly' and 'Less Frequently' for both crops and livestock.

Table 4.3 JOB-EXPOSURE MATRIX FOR ORGANIC SOLVENTS

OCCUPATIONS WITH HIGH SOLVENT EXPOSURE

Compositors
Printing press operators
Printers
Printing workers
Aerographers and paint sprayers
Painters and decorators
Coach painters
Laundrers and dry cleaner

INTERMEDIATE AND UNCERTAIN EXPOSURE

Chemical process production workers
Turners
Machine setters and setter operators
Machine tool operators
Motor mechanics and auto engineers
Press workers and stampers
Carpenters and joiners
Workers in rubber
Workers in plastics
Other production process workers
Garage proprietors
Hairdressers
Armed forces
Inadequately described occupations

LOW EXPOSURE

All other occupations

Table 4.4 JOB / TASK-EXPOSURE MATRIX FOR METALS

HIGH METAL EXPOSURES

Aerospace / aircraft manufacture
Metal workers
- smelting, sintering, aluminium reduction, lead reclamation, galvanisation of steel, plating, refining, roasting, stainless steel production
- milling or grinding metals
- aircraft / aerospace manufacture
- automobile / heavy machinery manufacture
- lead battery manufacture

Metal mining
Welding

INTERMEDIATE METAL EXPOSURES

Boat building – Organotin paint protection for hulls
Building industry – including wood preservatives
Canning / can production
Catalysts
Cement production / use
Ceramics industry / pottery
Chemical industry
Coal boilers (fly-ash) exposure
Dentist / dental technician / nurse
Explosives / fireworks / munitions / matches manufacture
Fertilisers manufacture, farm and forestry workers
Furnace and flue maintenance
Glass manufacture
Grain fumigant use
Leather industry
Lithography
Nuclear industry
Oil refining
Opticals industry
Paint sprayer / painter and decorator / paint stripping
Pesticide manufacture
Photography
Pigments /inks / dyes
Plastics / PVC manufacture
Rodenticide handling
Rubber industry
Semiconductor / microelectronics / electronics industry
Soap manufacture
Soldering

LOW EXPOSURE

All other occupations

7. RESIDENTIAL HISTORY (Section 6.) The following were investigated.

i) **Type of Fuel** (gas, oil, electricity, coal, wood, solid fuel, other) was compared.

ii) **Recent move** - A history of moving to a new residence within two years of the Index Date.

iii) **Number of moves** within ten years of the Index Date were analysed as continuous and categorical data.

8. ALLERGY HISTORY

i) **Number of siblings (total and older)** were analysed as the following categories.

(section 2) 0 - None

1 - 1 sibling

2 - 2-3 siblings

3 - >4 siblings

ii) **Personal history of allergy** (section 8) Allergies occurring prior to the Index Date were compared between groups as follows:

A- Any type of Allergy

B - Skin Allergy

C - Drug Allergy (All drugs, antibiotic and penicillin)

D - Insect Allergy

E - Food allergy

F - Allergic rhinitis

G - Asthma

iii) **Family History of atopy or asthma in close relatives** (defined as parents, siblings and children. Grandchildren and grandparents were excluded.)

9. OTHERS (Section 9. unless stated otherwise)

a) **Pets** (section 7.) i) Owning or regular close contact with a pet during the Index Year

ii) Contact with an ill pet in the Index Year

b) **Blood Transfusion** - at any time prior to the Index Date.

c) **TB Exposure** - i) History of personal infection with TB

ii) Contact with an individual with TB

iii) Either i) or ii)

d) **Hepatitis** - A history of infectious hepatitis (A, B or C) at any time prior to the Index date. Other forms of hepatitis (e.g. drug induced) were excluded.

e) **Vaccinations** – A history of a vaccination in the year prior to Index Year

f) **Steroid withdrawal** – A history of withdrawal from a course of steroids within the Index Year

g) **Smoking History** i) A history of smoking ever

ii) Smoking in the Index Year

iii)Smoking expressed as 'Pack Years'(continuous & categorical)

h) **Gardening** (Section 5.) Participation within the Index Year

i) **Patients opinions** as to the cause of their illness

III. RESULTS

Characteristics of Cases

78 patients diagnosed with primary systemic vasculitis between May 1988 and May 2000 were invited to participate. 77 took part but 2 were excluded for not meeting disease classification criteria (i.e. 75 were used in analysis). 47 patients were classified as WG (1 limited to ENT symptoms alone), 16 CSS and 12 mPA. 19 SRV, 34 asthma and 228 non-vasculitis controls were recruited. 8 of the latter were excluded because an autoimmune or inflammatory condition was subsequently identified (4 thyroid disease, 1 insulin dependent diabetes, 1 probable connective tissue disease, 1 probable polymyalgia rheumatica, 1 ankylosing spondylitis) Tables 4.5 and 4.6 describe the classifications / definitions fulfilled by WG and CSS cases. All mPA cases fulfilled both the CHCC definition for mPA and the ACR classification for PAN. Table 4.7 describes the diagnoses of patients recruited as non-vasculitis controls. Table 4.8 and 4.9 give details of ANCA and renal and respiratory involvement for PSV cases.

Characteristics of Controls

All non-vasculitis controls were matched for sex. The first 86 were matched to the age of the case at the Index Date (and therefore asked to recall events in the year prior to interview) and the remaining 139 were matched to the age of the patient at the interview date (asked to recall the year prior to the matched Index Date). The change was made in an attempt to reduce recall bias between cases and controls. The second approach to interviewing controls was not initially possible because the Index Date for each case was not known prior to interview.

Response Rate

1 WG case, 2 SRV and 15 non-vasculitis controls did not participate giving a response rate of 98.7% for cases, 90.4% for SRV and 93.9% for non-vasculitis controls.

CLASSIFICATION CRITERIA FULFILLED BY PSV CASES

Table 4.5 Criteria / Definitions fulfilled by Wegener's patients

	Criteria Fulfilled	WG alone	WG & PAN	WG, PAN & mPA	Total
WG Criteria	ACR	13	14	12	39
	ACR & CHCC	2	5	0	7
	Other	0	1	0	1
	Total	**15**	**20**	**12**	**47**

Table 4.6 Criteria / Definitions fulfilled by CSS Patients

	Criteria Fulfilled	CSS alone	CSS & PAN	Total
CSS Criteria	ACR alone	1	3	4
	Lanham alone	1	3	4
	ACR & Lanham	4	3	7
	ACR & CHCC	0	1	1
	Total	**6**	**10**	**16**

Table 4.7

Main reason for hospital attendance in non-vasculitis controls.

Participants	
Rheumatological / Orthopaedic Diagnoses	
Hip replacement	51
Osteoarthritis (non-orthopaedic)	39
Fractures (except hip) , trauma and soft tissue injuries	32
Total knee replacement	24
Disc prolapse , mechanical back pain	20
Other orthopaedic procedures	20
Pagets disease	11
Osteomyelitis / septic joint	5
Gout	4
Tenosynovitis / R.S.I. *	3
Reflex Sympathetic Dystrophy	1
Vibration white finger	1
Subacromial impingement	1
Trochanteric bursitis	1
Non rheumatological / orthopaedic diagnoses	
Cellulitis	2
Urological procedures	2
Deep vein thrombosis	2
Haemarrhoids	1
Skin lesion excision	1
Metastatic prostate cancer	1
Total	220

Refusals	
Hip replacement	5
Knee replacement	3
Other orthopaedic procedures	2
Tenosynovitis	1
Disc decompression	1
Osteoarthritis	1
Subacromial bursitis	1
Gout	1
Total	15

* R.S.I. = 'Repetitive strain injury'

Table 4.8 ANCA status of PSV patients

Diagnosis / ANCA Type	WG	mPA	CSS	Total
cANCA (PR3 not tested /recorded)	17	3	0	20
PR3	10	0	0	10
pANCA (MPO not tested / recorded)	6	3	2	11
MPO	3	0	5	8
Positive ANCA (specificity not tested)	5	2	2	9
Negative	5	4	7	16
TOTAL	46*	12	16	74

* No recorded ANCA test in 1 WG patient

Table 4.9 Renal and Respiratory Involvement in PSV Patients

	Renal Involvement*		Respiratory Involvement**	
Diagnosis	Yes	No	Yes	No
WG	39	8	29	18
mPA	11	1	1	11
CSS	8	8	16	0
Total	58	17	45	30

* haematuria, deranged electrolytes or biopsy appearances caused by vasculitis

** haemoptysis, persistent cough or dyspnoea or CXR changes caused by vasculitis

Table 4.10 Percentage of cases and controls exposed to hypothesised aetiological factors (%)

Hypothesised Factor	PSV	Controls	SRV	Asthma
Occupational Exposures				
Silica - Ever	36.0	30.0	36.8	29.4
- During Index Year	17.3	8.2	*	11.8
Solvents - Ever	14.7	6.8	5.3	5.9
- During Index Year	9.3	2.3	*	*
Metals	20.0	23.2	21.1	20.6
Farming Exposures				
- Ever Farm	61.3	37.3	50.0	26.5
- During Index Year	33.3	13.7	16.7	11.8
- Livestock	21.3	7.3	5.6	8.8
- Crop	25.3	11.4	26.3	5.9
Allergy				
- All types	57.3	38.1	61.1	50.0
- Drug Allergy	34.3	13.4	13.8	21.2

* No patients were exposed to hypothesised factor

Table 4.10 gives the percentages of cases and controls exposed to the major aetiological factors investigated.

1 – 4. AGE, SOCIAL CLASS, AREA OF RESIDENCE, NORFOLK HISTORY

There were no significant differences between groups for age, manual / non-manual workers or area of residence (Tables 4.11-4.13) and no associations for personal or family history of birth in Norfolk.

Table 4.11 Age of study participants at Index Date (Years)

Diagnosis	Mean	Median	Range
PSV	60.16	61	17-89
- WG	58.87	59	17-89
- CSS	59.38	60.5	31-84
- mPA	66.25	67.5	42-76
Controls			
- Non-vasculitis	60.69	62	28-87
- Asthma	57.94	58	21-84
- SRV	55.84	56	22-74

Table 4.12 Social Class at the Index Date (%)

Social Class	I	II	IIIN	IIIM	IV	V	No. cases
PSV	1.4	21.6	27.0	31.1	17.6	1.4	74*
Controls							
- Non-vasculitis	3.7	22.6	18.4	25.3	23.5	6.5	217**
- SRV	0	10.5	31.6	15.8	36.8	5.3	19
- Asthma	0	23.5	23.5	23.5	20.6	8.8	34

* 1 case insufficient information ** 3 controls insufficient information

Table 4.13 Comparison of Urban / Rural residence at Index Date

	OR	95% C.I.
PSV vs Normal controls***	1.17	0.68-2.00
PSV vs SRV*	1.01	0.35-2.90
CSS vs asthma**	2.78	0.80-2.90

Insufficient information for * 1SRV, ** 2 asthma, *** 3 normal controls

5. OCCUPATIONAL EXPOSURES

5 (a) – SILICA

Table 4.14 gives details of occupations associated with silica exposure undertaken by participants. Working in an occupation with any silica exposure in the Index Year gave significantly raised ORs for PSV and CSS and the relationship with agricultural silica appears strongest. High silica exposure jobs were associated with PSV, WG and CSS. (Table 4.15) In contrast mPA was associated with silica exposure over a working lifetime and non-agricultural silica seemed more important. (Table 4.16)

pANCA but not cANCA gave significantly raised ORs for silica in the Index year (Table 4.17) but there were no striking differences for particular patterns of organ involvement. (Table 4.18)

There was no trend towards increased risk of PSV with duration of occupational silica exposure although there was a significant relationship with PSV for jobs of more than 480 months [OR (C.I.): 2.63(1.03-6.73)]. No subgroup showed an association with duration. Table 4.19 demonstrates the number of cases per group exposed to occupational silica and the mean, median and range of exposure duration.

A significant OR (95% C.I.) of 5.26 (1.14-24.20) was found for coal workers when mPA and WG were analysed together but there were no significant results for any other subgroup or job. Broader definitions of exposures to silica and grain dust (iv and v) were not significantly associated with PSV or any subgroups.

Table 4.14 OCCUPATIONS WITH SILICA EXPOSURE

HIGH SILICA EXPOSURE	No. people
Foundry / metal workers	3
Arable farm workers	26
Both farming and Construction (+Abrasive blasting in lotus manufacture)	7
Construction industry / Bricklayer/ Roofing	21
Road worker	2
Coal miner	4
Cement Industry worker	1
Abrasive blaster automobiles / maltings worker	1
Shipwright / shipyard worker	2
Terazzo floor polisher	1
	68

INTERMEDIATE OR PROBABLE SILICA EXPOSURE	
Dentist / Dental technician / Dental Nurse	5
Carpenter	4
Electrician	6
Property maintenance	1
Painter and decorator	6
Coal delivery	1
Land army	2
Baker	2
Fireman railways/ navy stoker	2
Sculptor	1
Transport of grain	1
Boatbuilder	7
Paint analyser	1
Poultry farm/grain	1
Industrial boiler servicing	1
Jeweller	1
	42

Table 4.15 OCCUPATIONAL SILICA EXPOSURE DURING INDEX YEAR – DISEASE SUBTYPES

Occupational Silica Exposure	PSV		WG		mPA		CSS	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
All Occupations	**2.35**	1.09-5.07	2.30	0.94-5.67	1.02	0.12-8.36	**3.74**	1.09-12.80
High silica exposure jobs*	**3.62**	1.41-9.31	**3.45**	1.16-10.25	2.04	0.24-17.57	**5.61**	1.34-23.46
Medium silica exposure jobs**	1.09	0.29-4.14	1.15	0.24-5.53	-	-	1.87	0.22-16.00
Agricultural silica#	**3.93**	1.02-15.06	3.77	0.81-17.49	-	-	**7.73**	1.30-45.91
Non-agricultural silica##	1.49	0.58-3.81	1.34	0.42-4.25	1.22	0.15-10.08	2.23	0.46-10.91

Information incomplete for: * 9 non-vasculitis controls, 1 WG and 1 CSS patient

** 9 non-vasculitis controls, 6 WG, 3 CSS, 1mPA

15 non-vasculitis controls, 4 WG, 1 CSS, 1 mPA

4 non-vasculitis controls, 3 WG, 2 CSS

Table 4.16 ANY OCCUPATIONAL EXPOSURE TO SILICA

Occupational Silica Exposure	PSV		mPA	
	OR	95% C.I.	OR	95% C.I.
All Occupations	1.31	0.72-2.28	**4.67**	1.36-16.04
High silica exposure jobs*	1.37	0.72-2.61	**4.58**	1.18-17.83
Medium silica exposure jobs**	1.20	0.52-2.76	**4.81**	1.01-22.85
Agricultural silica#	1.33	0.53-3.25	2.13	0.23-20.06
Non-agricultural silica##	0.90	0.43-1.89	**5.20**	1.33-20.33

Excluded due to incomplete information:

* 24 non-vasculitis controls, 4 WG, 2 CSS, 3 mPA

** 42 non-vasculitis controls, 9 WG, 4 CSS, 5 mPA

29 non-vasculitis controls, 6 WG, 3 CSS, 7 mPA

29 non-vasculitis controls, 7 WG, 3 CSS, 3 mPA

Table 4.17 OCCUPATIONAL EXPOSURE TO SILICA DURING THE INDEX YEAR – ANCA SUBTYPES

Occupational Silica Exposure	cANCA / PR3		pANCA / MPO	
	OR	95% C.I.	OR	95% C.I
All Occupations	1.73	0.54-5.50	**5.18**	1.76-15.26
High silica exposure jobs*	2.59	0.66-10.18	**8.63**	2.53-29.50
Medium silica exposure jobs**	0.86	0.11-7.09	1.73	0.20-14.69
Agricultural silica#	1.86	0.20-17.27	**7.18**	1.21-42.64
Non-agricultural silica##	0.99	0.22-4.58	**4.12**	1.20-14.21

Excluded due to incomplete information:

* 9 non-vasculitis controls, 1 cANCA, 1 pANCA

** 9 non-vasculitis controls, 3 cANCA, 5 pANCA

#15 non-vasculitis controls, 3 pANCA, 2 cANCA

4 non-vasculitis controls, 2 pANCA, 1 cANCA

Table 4.18 OCCUPATIONAL EXPOSURE TO SILICA IN THE INDEX YEAR – ORGAN INVOLVEMENT

Occupational Silica Exposure	Renal Involvement		No Renal Involvement		Respiratory Involvement		No Respiratory Involvement	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
All Occupations	2.06	0.87-4.87	**3.45**	1.02-11.70	**2.73**	1.14-6.54	1.80	0.56-5.73
High silica exposure jobs*	**3.21**	1.14-9.03	**5.18**	1.25-21.47	**3.64**	1.22-10.83	**3.59**	1.03-12.52
Medium silica exposure jobs**	0.92	0.19-4.38	1.73	0.20-14.69	1.82	0.47-7.04	-	-
Agricultural silica#	2.01	0.36-11.29	**10.77**	2.19-52.91	2.58	0.47-14.95	**6.03**	1.28-28.51
Non-agricultural silica##	1.61	0.59-4.35	1.03	0.13-8.42	2.12	0.77-5.80	0.54	0.07-4.23

Excluded due to incomplete information:

* 9 non-vasculitis controls, 2 renal disease, 1 non-renal, 3 respiratory

** 9 non-vasculitis controls, 7 renal, 3 non-renal, 6 respiratory, 4 non-respiratory

15 non-vasculitis controls, 6 renal, 5 respiratory, 1 non-respiratory

14 non-vasculitis controls, 2 renal, 3 non-renal, 2 respiratory, 3 non-respiratory

Table 4.19 Occupational silica exposure in cases and controls.

	Occupational silica exposure		Duration (months)		
Disease (No. of cases)	Ever	Index Year	Mean	Median	Range
PSV	27	13	284.4	228	12-648
WG (47)	13	5	324.9	372	36-648
mPA (12)	8	1	214.5	120	24-600
CSS (16)	6	2	290	312	12-576
Controls					
Non-vasculitis(219)	66*	18	277.4	288	3-720
SRV (19)	7*	3	84.0	54	12-252
Asthma (34)	10	0	171.6	174	24-336

* Information about duration incomplete in one case

5a (vi). CONSTRUCTION - Working in the construction trade was not significantly associated with any group but a high peak exposure to silica dust gave raised ORs for mPA and pANCA positive cases (Table 4.20). Exposure to minor construction of all types combined in the Index Year gave raised ORs (95% C.I.) for PSV compared to SRV [4.52 (1.37-14.91)] and CSS compared to asthma controls [7.46 (1.90-29.34)] but not PSV with non-vasculitis controls [1.35(0.80-2.28)] or any other subgroup. For specific exposures there were raised ORs for painting and wallpapering for CSS and PSV compared to disease controls [OR (95% C.I.) 9.60(1.67-55.29) and 5.99(1.29-27.81) respectively] but not non-vasculitis controls. Floor refinishing was significantly associated with PSV and WG [ORs (95% C.I.): 4.70(1.29-17.12) and 7.90(2.14-29.24)] in particular those with renal disease [5.09 (1.32-19.63] although C.I.s overlap. There were no other associations for any groups for chimney cleaning, carpet cleaning, plastering or DIY as a hobby.

5. (b) SOLVENTS

Table 4.21 describes the occupations with solvent exposure undertaken by cases and controls. A history of a job with high solvent exposure at any time was positively associated with PSV, WG and subgroups cANCA and renal involvement. ORs were higher for those working in these occupations during the Index Year (Table 4.22). There were no significant associations for jobs with intermediate solvent exposure or high and medium combined. There was no relationship between the duration of high solvent exposure with PSV or any subgroup (Table 4.23).

Table 4.20 Exposure to construction, renovation or building.

	Occupational Construction		High Peak Exposure to Silica Dust*	
	OR	95% C.I.	OR	95% C.I.
PSV	0.87	0.34-2.24	1.50	0.74-3.02
WG	0.44	0.10-1.97	1.32	0.56-3.10
mPA	3.33	0.83-13.32	**3.67**	1.01-13.31
CSS	0.67	0.08-5.31	0.92	0.20-4.24
cANCA	0.71	0.16-3.22	1.34	0.47-3.78
pANCA	1.88	0.50-6.99	**2.89**	1.04-8.40

*5 non-vasculitis controls, 1 mPA and 1 cANCA excluded due to incomplete information

Table 4.21 OCCUPATIONS WITH SOLVENT EXPOSURE

EXPOSURE TO HIGH SOLVENTS	No. people
Printer	8
Laundry worker	3
Aircraft fitter/aircraft fuel pumping	4
Painter and Decorator	9
Building and roofing	1
Factory work exposed to glues	1
Car repair/paint sprayer/paint factory	2
Paint analyser	1
Total	29

INTERMEDIATE AND UNCERTAIN EXPOSURE	
Forces	35
Illustrator/artist	3
Factory workers	22
Boat builder	6
Hairdresser	6
Health and safety consultant	1
Window cleaner	1
Building/Roofing	15
Cabinet/furniture maker	6
Electronics engineer	1
Carpenter	6
Engineer	7
Solvents used in cleaning	5
Plastics industry	7
Manufacturing chemist/laboratory technician	6
Leather industry	8
Car mechanic/salvage	4
Petrol pump attendant	2
Diesel fumes/ refrigerants	5
Paint delivery	1
Dye manufacture	1
Science teacher	1
Forestry worker	1
Total	149

Table 4.22 High Occupational Exposure to Solvents

	High Occupational Solvent Exposure			
	During Working Life		During Index Year	
	OR	95% C.I.	OR	95% C.I.
PSV	**2.35**	1.03-5.37	**4.43**	1.36-14.40
WG	**3.69**	1.54-8.85	**6.29**	1.83-21.59
mPA	1.24	0.15-10.28	3.91	0.42-36.39
CSS	-	-	-	-
cANCA	**3.42**	1.21-9.64	**4.78**	1.08-21.12
pANCA	0.75	0.09-6.08	2.39	0.26-21.57
Renal disease	**2.51**	1.04-6.07	**4.06**	1.13-14.53
No renal disease	1.82	0.38-8.72	**5.73**	1.03-32.06

N.B. No missing data

Table 4.23
Duration of Exposure to High Occupational Solvents (Months)

Diagnosis	Mean	Median	Range
PSV(11)	284.4	252	36-600
WG(10)	276.0	240	36-600
mPA(1)	-	-	360
CSS(0)	-	-	-
Controls			
Non-vasculitis(15)	313	312	9-522
Asthma(3)	96	144	24-120
SRV(1)	-	-	36

5. (c) METALS

There were no significant associations for occupational metal exposure (all exposures, high or intermediate) either throughout working life or within the Index Year. Table 4.23 describes jobs of individuals included. Intermediate exposures were analysed with and without farming occupations as these may represent only very minor metal exposures in the form of fertilisers or pesticides.

TABLE 4.24 OCCUPATIONAL EXPOSURE TO METALS

HIGH METAL EXPOSURES	No. people
Aluminium / Steel plant worker	7
Grinding metals/abrasive work	7
Iron moulder	1
Welding	7
Total	22

INTERMEDIATE METAL EXPOSURE	
Boatyard workers	6
Canning	2
Cement manufacture	1
Chemical processor/analytical chemist	4
Dentist / dental nurse / dental technician	5
Dye manufacture	1
Electrical wiring manufacture	1
Farm worker (possible fertiliser exposure)	35
Forestry worker	1
Gas fitter / heating engineer	1
Leather industry	6
Munitions factory	2
Other factory worker	1
Painter and Decorator/paint sprayer	8
Panel beating	2
Pest control	1
Plastics worker	4
Soldering	4
Total	107

6. FARMING EXPOSURES

PSV was significantly associated with farming exposures both during working life (Ever Farm) and within the Index year alone (Table 4.25). Figure 4.1 and 4.2 Illustrates the number of cases and controls exposed to crops and / or livestock within the Index Year. Individuals with 'Any farm exposure' are represented by A, B, C, D, E & F , ' Livestock exposure' by A & B, 'Crop exposure' by E & F and 'Livestock and crop exposure combined' by C & D. For each group ORs were obtained by comparison with H & G i.e. individuals who had no farm exposure in the Index Year but may have been exposed prior to that time.

PSV was significantly associated with exposure to livestock alone and livestock and crops combined (Table 4.26) although crops alone almost reached significance. Tables 4.27 and 4.28 describe livestock and crop exposures experienced by study participants. Direct and close contact to livestock showed a stronger association than distant contact for PSV, mPA and WG/mPA combined (Table 4.29). ORs were raised for all frequencies of livestock exposure but only reached significance for daily exposures in PSV and CSS. (Table 4.30)

High levels of crop exposure were not significantly associated with any group although intermediate levels of exposure gave increased ORs (95% C.I.) for PSV [2.87(1.39-5.93)], WG[(2.86(1.23-6.64)] and WG/mPA combined [2.99(1.38-6.49)]. Daily exposure to crops was also associated with PSV and WG (Table 4.31).

All modes of farm exposure (working on, living by or visiting) were associated with PSV. Table 4.32 gives details of ORs obtained by disease classification.

Significant associations were found for exposure to cows, sheep and chickens (Table 4.33) but it was not possible to identify a specific animal because most individuals were exposed

to more than one type. Multiple logistic regression for sheep, cows and chickens gave no significant results.

Both types of ANCA were associated with farm exposure within the Index year and throughout working life (Table 4.33). pANCA was associated with working on a farm [OR (95% C.I.): 6.69(1.53-29.26)] and both types with living by a farm [cANCA 4.33(1.49-12.60) ; pANCA 4.62(1.33-16.09)]. pANCA was also associated with daily crops and livestock [OR (95%C.I.): 3.40(1.01-11.46); 6.15(1.70-22.21) respectively] and also infrequently to crops and livestock [OR(95% C.I.):8.06(1.77-36.82); 11.28(1.72-74.03)] whilst cANCA was associated to daily livestock only [3.84(1.23-12.07)]. pANCA gave OR (95% C.I.) of 9.65(3.03-30.67) for exposure to cows and cANCA gave OR of 4.76 (1.08-21.02) and 6.58 (1.66-26.08) for sheep and chicken exposure respectively. However there were no significant differences in any case between ANCA types, between patients with differing patterns of organ involvement. (Table 4.35) or in comparisons with SRV and asthma control groups.

Figure 4.1
PSV Cases exposed to farming within the Index Year

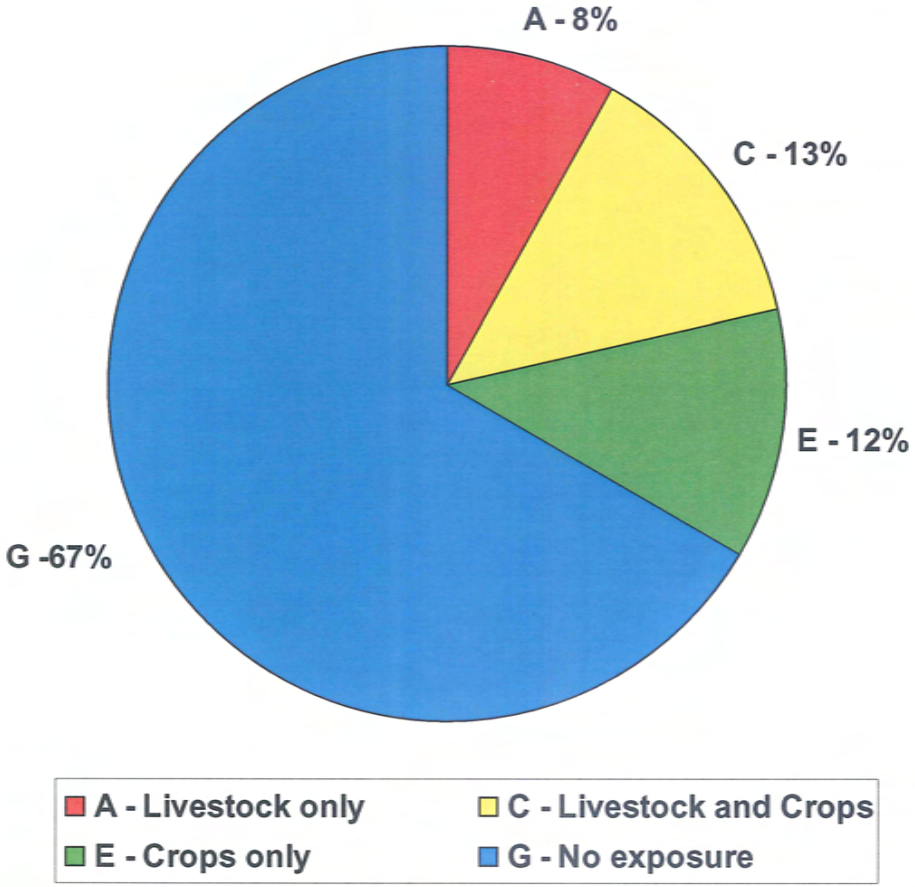


Figure 4.2
Non-vasculitis controls exposed to farming within the Index Year

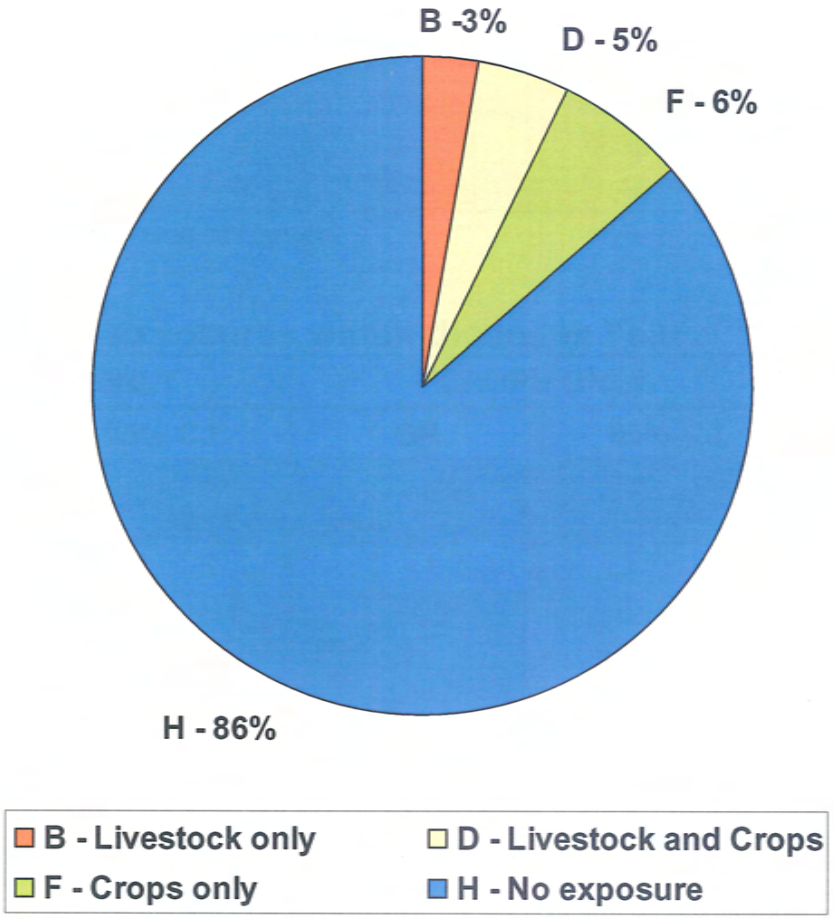


Table 4.25 Farming exposures in the Index Year and throughout working life

Group	FARM EXPOSURE EVER		FARM EXPOSURE IN INDEX YEAR	
	OR	95% C.I.	OR	95% C.I.
Total PSV	**2.67**	1.56-4.58	**3.15**	1.70-5.83
WG	**3.59**	1.83-7.03	**2.95**	1.43-6.09
CSS	1.01	0.35-2.88	2.10	0.64-6.94
mPA	3.37	0.98-11.53	**6.30**	1.91-20.82
WG/mPA	**3.54**	1.92-6.53	**3.48**	1.80-6.72

N.B. Incomplete information for 1 non-vasculitis control

Table 4.26 Specific farming exposures within the Index Year

Group	LIVESTOCK ONLY		CROPS ONLY		LIVESTOCK AND CROPS	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
Total PSV	**3.78**	1.17-12.22	2.43	0.99-5.94	**3.78**	1.49-9.58
WG	2.95	0.70-12.41	2.95	0.95-9.21	2.95	0.95-9.21
CSS	-	-	-	-	2.10	0.64-6.94
mPA	-	-	4.50	0.83-24.39	3.15	0.35-28.73
WG/mPA	**4.97**	1.52-16.25	**3.20**	1.29-7.92	**2.98**	1.02-8.70

N.B. Incomplete information for 1 non-vasculitis control

Table 4.27 Summary of Livestock Exposures in the Index Year

DIRECT LIVESTOCK EXPOSURE	No. exposed
Farm worker / small holding owner exposed daily to livestock	10
Intermittent exposure to family horse	3
Keeps own chickens	4
Occasional visits to commercial farm – directly handling animals	1
Raised Pheasants and visited farm 2-3 times / year	1
CLOSE LIVESTOCK EXPOSURE	
Visits farms in course of work not related to farming – e.g. insurance broker, farm secretary, water board technician	9
DISTANT LIVESTOCK EXPOSURE	
Livestock present in field within 30 feet of home	8

Table 4.28 Summary of crop exposures in the Index Year

HIGH CROP EXPOSURES	No. exposed
Farmer working daily with crops	6
Less frequent farming	3
MEDIUM CROP EXPOSURES	
Lives within 30 feet of crops	23
Visits farm	18

Table 4.29 Proximity of Livestock Exposure

	Direct		Close		Distant	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**3.60**	1.33-9.70	4.06	0.86-18.56	1.78	0.42-7.65
WG	2.45	0.71-8.51	4.91	0.96-25.13	0.98	0.11-8.15
mPA	**8.79**	1.99-38.82	-	-	3.89	0.42-36.22
CSS	3.77	0.73-19.45	3.86	0.76-19.63	1.50	0.28-7.94
mPA/WG	**3.55**	1.23-10.24	3.86	0.76-19.63	1.50	0.28-7.94

N.B. Information incomplete for 1 non-vasculitis control

Table 4.30 Frequency of Livestock Exposure

	Daily		Weekly		Less Frequent	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**3.08**	1.25-7.59	1.69	0.15-18.98	4.51	0.98-20.72
WG	2.84	0.99-8.13	-	-	3.47	0.56-21.45
mPA	2.05	0.24-17.66	11.28	0.93-136.24	7.52	0.71-79.59
CSS	**4.61**	1.13-18.77	-	-	5.64	0.54-58.36
mPA/WG	2.96	0.99-7.30	2.11	0.19-23.80	4.23	0.83-21.61

N.B. Information incomplete for 1 non-vasculitis control

Table 4.31 Frequency of Crop Exposure

	Daily		Weekly		Less Frequent	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**2.43**	1.09-5.41	1.48	0.27-8.25	2.42	0.63-9.27
WG	**2.62**	1.05-6.53	2.40	0.43-13.50	0.93	0.11-8.19
mPA	1.16	0.14-9.56	-	-	**8.61**	1.50-49.04
CSS	2.94	0.76-11.40	-	-	2.87	0.31-26.13
mPA/WG	2.30	0.96-5.50	1.89	0.34-10.61	2.30	0.53-9.93

Table 4.32 Type of Farm Exposure within the Index Year

	Living		Visiting		Working	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**3.9**	1.6-9.0	**3.5**	1.4-8.6	**4.5**	1.4-13.9
WG	**3.5**	1.3-9.5	2.7	0.9-8.3	**5.0**	1.4-17.3
mPA	4.6	0.9-24.3	**7.4**	1.7-32.8	4.6	0.5-43.0
CSS	**4.3**	1.1-17.7	3.2	0.6-16.0	2.9	0.3-36.2
mPA/WG	**3.7**	1.5-9.3	**3.6**	1.4-9.4	**4.9**	1.5-16.0

Table 4.33 Association of specific livestock with vasculitis

	COWS		SHEEP		CHICKENS	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**2.85**	1.11-7.31	3.06	0.86-10.87	**4.41**	1.35-14.33
WG	1.43	0.38-5.39	**3.98**	1.03-15.43	**3.98**	1.03-15.43
mPA	4.18	0.81-21.67	3.89	0.42-36.22	3.89	0.42-36.22
CSS	**6.97**	1.90-25.49	-	-	**6.11**	1.09-34.3
WG/mPA	1.94	0.63-5.90	**3.96**	1.11-14.18	**3.96**	1.11-14.18

Table 4.34 Farm Exposure and ANCA specificity of vasculitis

	cANCA / PR3	pANCA / MPO
	OR (95% C.I.)	OR (95% C.I.)
History of farm exposure	**4.63** (1.97-10.87)	**3.65** (1.33-9.96)
Index Year -		
All Exposures	**3.15** (1.34-7.38)	**5.67** (2.13-15.10)
Livestock Only	**6.30** (1.64-24.22)	**6.30** (1.13-35.26)
Crops Only	2.03 (0.54-7.65)	2.70 (0.54-13.54)
Livestock and Crops	2.84 (0.72- 11.16)	**9.45** (2.71-32.91)

Table 4.35 Farm exposure and organ involvement in vasculitis

	RENAL DISEASE		RESPIRATORY DISEASE	
	Present OR (95% C.I.)	Absent OR (95% C.I.)	Present OR (95% C.I.)	Absent OR (95% C.I.)
History of farm exposure	**2.75** (1.52-5.00)	2.40 (0.88-6.56)	**2.19** (1.15-4.17)	**3.74** (1.63-8.60)
Index Year -				
All Exposures	**3.07** (1.57-6.00)	**3.44** (1.18-9.99)	**2.48** (1.17-5.25)	**4.45** (1.93-10.23)
Livestock Only	3.23 (0.87-11.99)	**5.73** (1.03-31.73)	0.79 (0.09-6.71)	**7.40** (2.10-26.06)
Crops Only	2.42 (0.92-6.40)	2.45 (0.49-12.18)	1.02 (0.28-3.71)	**3.82** (1.34-10.91)
Livestock and Crops	**3.88** (1.44-10.45)	3.44 (0.67-17.63)	**5.08** (1.93-13.36)	0.75 (0.09-6.05)

RESIDENTIAL HISTORY

Types of heating fuel were analysed as gas, electric, oil, wood, coal solid fuel and combustibles combined. Table 4.36 illustrates fuel used by study participants. There were no significant associations for any category investigated in any group except for those without renal involvement who had raised ORs of 3.96 (95%C.I. 1.44-10.88) for combustibles (wood, coal, other solid fuel) but plausibility for the association is considered low so this is likely to be a spurious result.

There were no significant differences between any groups for the a recent move in residence or for either continuous or categorical increasing numbers of house moves in the ten years prior to the index date.

Table 4.36 Heating fuel used by study participants

Fuel Type	No. households with fuel type	No households with fuel as single source of heating
Gas	207	180
Oil	63	38
Electric	60	40
Wood	28	1
Coal	40	8
Solid Fuel	12	8
Combustion (all types)	66	28
Others (e.g. solar powered)	4	3

8. ALLERGY HISTORY

Significantly more PSV patients had a history of allergy compared to normal controls with raised ORs for WG and CSS but not for mPA. (Table 4.37) There were no significant differences between ANCA types, patterns of organ involvement or in comparison with disease controls.

Drug allergy but no other type of allergy (skin, insect, food or plant) showed a significant relationship with PSV, WG, WG/mPA and cANCA positive patients. (Table 4.38). Table 4.39 lists the specific drugs causing allergic reactions within the cohort. Antibiotic allergy specifically was associated with PSV, WG, CSS and cANCA whilst mPA was associated with other drug allergies.(Table 4.38) Penicillin was the predominant type of antibiotic allergy and was significantly associated with PSV, WG , CSS and cANCA specificity [ORs (95%C.I.) respectively: 4.27(1.78-10.27); 4.56(1.70-12.25); 4.66 (1.13-19.17) and 6.03(1.98-18.33)] in contrast to septrin [OR 95% C.I. for PSV: 1.31(0.31-12.83)]. Other antibiotics (mainly cephalosporins) were associated to PSV, WG and cANCA. [ORs (95% C.I.) respectively 6.53(1.51-28.28; 6.27(1.21-32.50 and 7.37 (1.15-47.21)].

As expected, CSS was also associated with allergic rhinitis [OR (95% C.I.) 4.09(1.30-12.86)] and asthma (all patients). pANCA positive patients had raised ORs for rhinitis and asthma [3.23 (1.06-9.82) and 10.15(3.65-28.19)] but this may be attributable to the CSS patients [ORs (95%C.I.) without CSS patients 0.82(0.10-6.67) and 2.26(0.46-11.09) respectively].

A family history of atopy or asthma was not found for any groups investigated.

Table 4.37 Allergy and Primary Systemic Vasculitis

	No Allergy	Allergy	OR	95% C.I.
PSV	32	43	**2.21**	1.30-3.77
WG	19	28	**2.43**	1.27-4.62
mPA	7	10	1.18	0.36-3.83
CSS	6	5	2.74	0.96-7.83
WG & mPA	26	33	**2.09**	1.17-3.74
cANCA	11	19	**2.84**	1.29-6.28
pANCA	9	10	1.83	0.71-4.69
renal	26	32	**2.03**	1.13-3.64
non-renal	6	11	**3.02**	1.08-8.47
respiratory	20	26	**2.14**	1.12-4.08
non-respiratory	12	17	**2.33**	1.06-5.13
PSV vs SRV	7	11	0.86	0.30-2.45
CSS vs asthma	17	17	1.77	0.52-6.00

N.B. Information incomplete for 3 non-vasculitis controls

Table 4.38 Association of Drug Allergies and Primary Systemic Vasculitis

	ALL DRUGS*		ANTIBIOTICS		OTHER DRUGS	
	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
PSV	**3.38**	1.81-6.29	**4.15**	1.99-8.65	2.61	0.89-7.69
WG	**3.46**	1.54-6.39	**4.42**	1.92-10.18	2.79	0.81-9.62
mPA	3.36	0.93-12.13	3.16	0.61-16.42	5.97	1.08-32.93
CSS	2.67	0.87-8.20	**4.02**	1.16-14.0	-	-
WG & mPA	**3.18**	1.64-6.15	**4.18**	1.90-9.22	**3.39**	1.14-10.09
cANCA	**4.17**	1.82-9.55	**5.85**	2.27-15.11	3.69	0.91-14.92
pANCA	2.11	0.71-6.26	2.37	0.62-9.07	1.49	0.18-12.63
renal	**2.78**	1.42-5.46	**4.07**	1.85-8.96	1.65	0.43-6.38
non-renal	**4.13**	1.47-11.65	**4.42**	1.25-15.62	**6.27**	1.47-26.80
respiratory	**3.24**	1.56-6.75	**4.79**	2.11-10.86	0.70	0.09-5.70
non-respiratory	**3.60**	1.51-8.56	**3.07**	1.01-9.30	**5.80**	1.76-19.18

*Incomplete information for 2 non-vasculitis, 1 SRV and 1 asthma controls, 1 WG, 1 mPA

Table 4.39 Drugs associated with allergic reactions

Antibiotics

Cephradine	1
Erythromycin	1
Kephlex	1
Klaricid	1
Neomycin	1
Oxytetracycline	1
Penicillin	31
Pethidine	1
Septrin	6
Trimethoprim	1
Unspecified	4

Other types of Drugs

Aspirin	6
Carbimazole	1
Codeine	3
Diclofenac	1
Evening Primrose Oil	1
HRT	1
Opiates	1
Paracetamol	1
Tetanus	1
Unspecified	2
Ventolin	1

9. OTHERS

a) **Pets** There were no significant associations of owning a pet except for p ANCA [OR (95%C.I.) 5.57(1.24-25.08)] or exposure to ill pets in any group. Analysis of pets together with direct livestock exposure also failed to show an association.

b) **Blood Transfusion** No groups showed an association with blood transfusions when compared to non-vasculitis controls but SRV patients were more likely to have had a transfusion than total PSV patients (p= 0.008) .However in six of the nine SRV patients who had received blood transfusions the indication was associated with their rheumatoid arthritis.

c) **TB exposure** PSV, sub classifications and ANCA types were not significantly associated with personal TB, contact with TB or the two combined. Patients without renal involvement showed an association to a personal history of TB [OR 8.15(2.17-30.66)] but not contact.

d) **Hepatitis** No group showed a significant association with infection related hepatitis .

e) **Vaccinations** There were no significant associations.

f) **Steroid Withdrawal** was associated with CSS [6.33(1.75-22.87)] but no other group investigated. This may be expected as all CSS patients had a diagnosis of asthma prior to their vasculitis and would therefore have been more likely to receive treatment with steroids than normal controls. Comparison of CSS with asthma controls did not reveal any difference.

g) Smoking History There were no significant associations for any group for a history of smoking ever or at the Index date. Furthermore there was no association with levels of smoking measured by 'Packyears' as either continuous or categorical data.

h) Gardening was significantly associated with PSV compared to SRV controls [OR (95% C.I.): 5.99(2.03-17.65)] and CSS to asthma controls [6.22(1.22-31.68)] but no other group. This could be attributable to the pre morbid state of the disease controls who may have been unable to carry out physical tasks.

i) Patients Opinions are listed in tables 4.40 and 4.41 Eight patients offered two explanations for an initial disease trigger.

Table 4.40
Patients suggestions for PSV triggers prior to questionnaire completion

- Accidents – Car accident
  Fell from a tree

- Change of environment – Moving to Norfolk
  Moving house (stress) / exposure to country areas
  Staying in rural Lincolnshire

- Drugs – Current medication
  Excessive antibiotics
  Oxytetracycline

- Infections – Influenza / other virus (4)
  Infection from bone marrow in lamb stews
  Exposure to spray from sewage contaminated waves in Majorca
  Swimming at Blackpool - ? bitten by leeches
  Post virus / infection caught swimming in the sea in Israel
  Infection many years previously in Malaya in the army
  Infection in milk (drinking 3-4 pints / day)
  Infection from food (went out for a meal prior to a relapse)

- Influenza / Pneumonia vaccination

- Occupational - Chemicals used in inseminating chickens
  Asbestos lagging pipes and working in shed 20 years earlier
  Printer (lead, methylethylketone, lithography, isopropylalcohol)
  Chemical spill
  Cleaning out deep fat fryers
  Working with wood from abroad
  Exposure to pigeon feathers from ventilation
  (working in dungeons as a tour guide)
  Building work, gluing down MDF boards

- Others – Ruptured duodenal ulcer
  Canal holiday – (got soaking wet and using ' superhuman strength to open a bridge)
  Converting a shower, exposed to Arbosyl
  Dust exposure from motorcross meetings / military lorries (2)
  Getting very cold (working as a Marie Curie nurse at night)
  Grass cuttings
  Hysterectomy (2)
  Menopause
  Swimming
  Vehicle fumes (2)
  Wearing tight shoes (rash)
  Working near power station

- No Suggestions (24)

- Stress (17)

Table 4.41 Extra Opinions after completion of the Questionnaire

- Brother used glues and sprays in model making and developed leukaemia
- Car spraying
- Depression
- Exposure to chemicals used to decorate goose eggs
- Exposure to dust
- Staying in Derbyshire in a field. No running water so had to boil it.
- Stress
- Working hard

CONFOUNDING FACTORS

Stepwise multiple logistic regression was carried out for the following significant aetiological factors: occupational silica exposure in the Index Year (total and high exposures); high occupational solvent exposure in the Index year and working lifetime; farming exposures ever and in the Index Year (all exposures, livestock and crops); drug and antibiotic allergies. ORs adjusted for rural residence, manual occupation and all other significant factors were obtained in each case (Table 4.42). ORs remained raised and significant for all items analysed except the following: history of a job with high silica exposure in WG; High occupational solvent exposure Ever in cANCA and in the Index Year with PSV; and drug allergy with mPA. Age and sex were not confounding for any aetiological factor. These results suggest that confounding by known factors did not greatly influence reported associations.

Table 4.42 Adjusted ORs for Significant Results

Item	Group	Simple OR	Adjusted OR
Any silica job Index*	PSV	2.35 (1.09-5.07)	**1.79 (0.77-4.16)**
	WG	2.30 (0.94-5.67)	1.91 (0.69-5.27)
	CSS	3.74 (1.09-12.80)	3.74 (1.09-12.80)
High silica job Index*	PSV	3.62 (1.41-9.31)	2.95 (1.03-8.41)
	WG	3.45 (1.16-10.25)	**2.54 (0.76-8.52)**
	CSS	5.61 (1.34-23.46)	5.61 (1.34-23.46)
High Solvent Job ever#	PSV	2.35 (1.03-5.37)	2.66 (1.08-6.59)
	WG	3.69 (1.54-8.85)	3.40 (1.30-8.93)
	cANCA	3.42 (1.21-9.64)	**3.26 (0.98-10.84)**
	Renal	2.51 (1.04-6.07)	2.75 (1.04-7.30)
High Solvent Index*	PSV	4.43 (1.36-14.40)	**3.37 (0.91-12.53)**
	WG	6.29 (1.83-21.59)	4.81 (1.17-19.84)
	cANCA	4.78 (1.08-21.12)	3.89 (1.60-9.47)
	Renal	4.06 (1.13-14.53)	2.44 (1.15-5.16)
Drug Allergy	PSV	3.38 (1.81-6.29)	3.59 (1.85-6.96)
	WG	3.46 (1.68-7.12)	3.99 (1.82-8.74)
	mPA	3.70(1.02-13.45)	**3.08 (0.80-11.85)**
Farm Ever	PSV	2.67(1.67-4.58)	2.19 (1.24-3.84)
	WG	3.59(1.83-7.03)	2.74 (1.32-5.70)
Farm Index	PSV	3.15(1.70-5.83)	2.30 (1.15-4.59)
	WG	2.95(1.43-6.09)	2.68 (1.23-5.83)
	CSS	6.30(1.91-20.82)	6.30 (1.91-20.82)
Allergy	PSV	2.21(1.30-3.77)	2.19 (1.23-3.89)
	WG	2.43(1.27-4.62)	2.77 (1.35-5.70)

* During the Index Year # During a working life-time

N.B. ORs adjusted for rural residence, manual occupations, any occupational silica exposure in the Index Year, high occupational silica exposure in the Index Year, high occupational solvent exposure ever or in the Index Year, total allergy, drug allergy, and farming exposures ever and in the Index year. (Age and Sex were not confounding for any item investigated.)

IV. CRITIQUE OF STUDY DESIGN

Case Selection

Referral and Selection Bias

We can be confident that virtually all incident cases of PSV in the denominator population after 1988 had been identified and included in the register (see Chapter 2.) The decision to recruit patients who regularly attended the hospital for PSV but lived marginally outside the NHA was made to increase the number of cases and therefore the power of the study. These cases may differ from those within the denominator population due to referral bias, e.g. more severe cases may be referred as the hospital is a known centre of expertise in vasculitis. In practice, patterns of referral are led by new health authority boundaries which are wider than the former NHA. Our knowledge of the local area suggests that environmental exposures are likely to be very similar for those living immediately outside the NHA. To reduce bias, matched controls living in approximately the same areas were selected. To identify any major effect of this bias patients and controls resident in the NHA were analysed separately for the reported associations (Table 4.43 gives details of age). The effect was to reduce associations for occupational silica and solvent exposure but to strengthen those for farming. Allergy ORs were virtually unchanged (Table 4.44).

Table 4.43 Age of NHA residents at the Index Date (Years)

Diagnosis	No.	Median	Mean	Range
PSV	71	61	60.10	17-89
WG	45	59	58.73	17-89
mPA	11	69	66.27	42-76
CSS	15	62	59.67	31-84
Non-vasculitis controls	204	62.5	60.89	28-87
Asthma	33	58	58.58	21-84
SRV	18	55	54.83	22-73

Item	Group	Total Cohort ORs (95% C.I.)	NHA Only ORs (95% C.I.)
Any silica job Index	PSV	2.35 (1.09-5.07)	**1.89 (0.85-4.24)**
	WG	2.30 (0.94-5.67)	1.90 (0.74-4.87)
	CSS	3.74 (1.09-12.80)	**2.58 (0.67-10.01)**
High silica job Index	PSV	3.62 (1.41-9.31)	2.76 (1.02-7.46)
	WG	3.45 (1.16-10.25)	**2.72 (0.86-8.57)**
	CSS	5.61 (1.34-23.46)	**3.44 (0.67-17.75)**
High Solvent Job ever	PSV	2.35 (1.03-5.37)	**2.07 (0.88-4.84)**
	WG	3.69 (1.54-8.85)	3.15 (1.28-7.75)
	cANCA	3.42 (1.21-9.64)	**2.63 (0.88-7.87)**
	Renal	2.51 (1.04-6.07)	**2.10 (0.84-5.24)**
High Solvent Index	PSV	4.43 (1.36-14.40)	3.67 (1.09-12.44)
	WG	6.29 (1.83-21.59)	4.97 (1.38-17.99)
	cANCA	4.78 (1.08-21.12)	**2.95 (0.54-15.95)**
	Renal	4.06 (1.13-14.53)	**3.06 (0.79-11.81)**
Farm Ever	PSV	2.67 (1.56-4.58)	2.86 (1.64-5.00)
	WG	3.59 (1.83-7.03)	3.89 (1.95-7.78)
	WG/mPA	3.54 (1.92-6.53)	4.03 (2.13-7.62)
	mPA	3.37 (0.98-11.53)	**4.68 (1.21-18.20)**
Farm Index	PSV	3.15 (1.70-5.83)	3.66 (1.78-6.53)
	WG	2.95 (1.43-6.09)	3.22 (1.51-6.86)
	WG/mPA	3.48 (1.80-6.72)	3.96 (1.99-7.87)
	mPA	6.30 (1.91-20.82)	8.54 (2.45-30.08)
Drug Allergy	PSV	3.38 (1.81-6.29)	3.51 (1.86-6.61)
	WG	3.46 (1.68-7.12)	3.53 (1.70-7.35)
	mPA	3.70 (1.02-13.45)	4.12 (1.09-15.52)
Antibiotic Allergy	PSV	4.15 (1.99-8.65)	4.16 (1.98-8.73)
	WG	4.42 (1.92-10.18)	4.36 (1.88-10.10)
	CSS	4.02 (1.16-14.00)	**3.39 (0.63-18.13)**

The change in significance of ORs may be due to variation in occupational factors between subjects living within and outside the NHA or may reflect a reduced ability to detect an association due to the smaller sample size.

The major selection bias was the exclusion of deceased patients who may differ from survivors in terms of disease severity or co-morbidity. Risk factors identified may

therefore be only relevant to survivors (although a number of enrolled cases have died since their interview) and different factors could be associated with patients who die. In total 76 cases were available to participate, only one declined. 27 patients had died prior to the start of the study (including a single individual who had moved away from the region since 1988). Therefore 72.8% of incident cases between 1988 and 2000 were included in the study. Causes of death are listed in Table 2.19 and those who died did not appear different to survivors in terms of clinical features (Table 2.16, Chapter 2). Relatives of deceased patients could be interviewed to reduce this bias but this was not done for the following reasons: recall bias and incomplete information is likely to be high for the associations detected (e.g. farming exposures), especially for patients whose disease was diagnosed several years ago; contacting relatives could cause distress and from an ethical point of view benefits gained may not outweigh this risk; in addition the confidentiality of the deceased individual could be breached. The notes of deceased cases were reviewed but information was incomplete and lacked many details of interest. Additional analysis was therefore not attempted.

Control Selection

Ideal controls would have been a random sample of the 'healthy' denominator population. Hospital controls were chosen due to time and resource constraints. However a geographically representative sample should be obtained as the majority of NHA residents requiring hospital treatment are referred to the Norfolk and Norwich Hospital as it is the single referral centre. Referral bias may have occurred, e.g. patients living closer to the hospital may be referred more frequently than those at a distance. This is more likely to be true for rheumatology outpatients than orthopaedic inpatients (e.g. patients with fractures). No significant difference was found between cases and controls for urban / rural residence suggesting that this type of referral bias was not was not extremely influential.

Bias may have been introduced by the controls' illnesses e.g. osteoarthritis patients are less likely to have manual jobs or participate in activities such as gardening than 'healthy' individuals. Controls who were unemployed through ill health at the Index Date were excluded from occupational analyses for the Index Year. In practice this only affected one SRV control.

Controls were selected consecutively according to age and sex of cases, but intermittently over a period of two years which may have introduced unknown bias (e.g. if interviewed in the winter months they may recall an influenza vaccination). Exclusion of controls 'inappropriate for interview' (e.g. through severity of illness or dementia) was subjective. This decision was made by personal observation and discussion with their nursing staff. Exclusion of inflammatory and autoimmune conditions may have led to some important associations being overlooked, for example anti-thyroid drugs, e.g. propylthiouracil, have been linked to ANCA positive vasculitis, particularly associated with MPO. We were unable to investigate this association as patients with thyroid disease were excluded. The literature suggests that PSV is more common in males and increases with age. Matching for age and sex adjusted for potential confounding.

Questionnaire

Observer bias Interviewers may have introduced bias as they were not blinded to the hypothesis. This was unavoidable and every attempt was made to interview each subject in the same manner. To improve reliability between the two interviewers (SL and NI). NI observed the interview technique of SL prior to interviewing the asthma controls. Reproducibility was assessed for SL by repeating the questionnaire for two cases approximately one year after their initial interview. This demonstrated that documentation had become more detailed over time. Answers to direct questions were the same but additional details were listed for occupations and hobbies.

Recall Bias Recall may have varied between subjects as some individuals were asked to remember details which occurred up to ten years prior to interview. Cases often seemed able to recall specific details more easily than controls, probably because they had been followed by an important event in their lives (disease onset). To minimise this difference an important event was identified within the matched Index Year for controls, e.g. a birthday, job or holiday. For each question subjects were reminded to think back to the particular year in question rather than recent events. Initially controls were matched to the age of the patient at the time of the Index Date and therefore had to recall only recent events. This technique was changed in an attempt to minimise bias introduced by recall and recent disability caused by the hospital control's current disease.

Analysis

Data interpretation can also introduce bias. The questionnaire contained both direct and open questions. Observer and non-response bias is likely to be minimised by direct questions. The relative importance of bias for each aetiological factor is discussed.

Assessment of the Index Date

Establishing the Index Date is important to identify exposures responsible for disease. The pathogenesis of disease is unknown so factors encountered within one year prior to symptom onset were investigated to identify acute trigger factors, so earlier risk factors could have been missed. The accuracy of the Index Date may vary between diagnoses. Index Dates are likely to be more accurate for WG where disease onset is usually well defined in WG compared to mPA which often has a prolonged period of general malaise and subclinical renal dysfunction prior to its recognition. In CSS the Index Date was chosen as the actual onset of systemic vasculitis. Environmental exposures linked to the atopic phase of disease may therefore have been overlooked.

Age, Social Class, Urban/Rural Residence and Norfolk history

Bias attributed to these factors was thought to be minimal. Cases and controls were successfully matched for age. Documentation of jobs allowed accurate categorisation of social class as 'manual' and 'non-manual'. Postcode definitions of 'built-up areas' used by Norfolk City Council were used to define urban and rural residence. Where individuals could not remember their postcode at the Index Date it was obtained using their address and a postcode map. Data was incomplete in only 6 controls. Norfolk history and sibling details were generally well remembered.

Occupational Exposures

Analysis of occupational data was limited by the detail of job descriptions obtained and job-exposure matrices employed. Job titles and industries were well documented and recall good but specific occupational tasks were not recorded in detail for many subjects (e.g. the specific task within a factory was not identified). Matrices used for silica and solvents were based upon previously published tables which had been formally evaluated by occupational hygienists but the matrix for metals was derived de novo. Assessment of silica and solvent exposures is therefore likely to be more accurate than metals. The use of job-exposure matrices by an inexperienced operator may be less accurate than the formal assessments of occupational hygienists. However the silica matrix used was previously employed in a study of silica and SLE. In that study similar coding of jobs were reached by an inexperienced investigator (C. Parks) compared to a panel of occupational hygienists (personal communication).[495,496] To minimise bias introduced when assessing the level of exposures in occupations, occupational data was tabulated anonymously prior to coding occupations and applying the job-exposure matrices.

In general occupations with a high risk of exposure to silica, solvents and metals were easy to identify and 'high-exposure' groups probably include few people who have not had high

exposures. In contrast it was difficult to identify cases who had not been exposed to silica, solvents or metals at all due to insufficient information. 'Intermediate' exposure groups are therefore likely to include some unexposed individuals and conversely the 'no exposure' groups will be underrepresented. ORs obtained for high exposure occupations are therefore likely to be most accurate.

Silica exposure was assessed using both open questions (occupational history) and direct questions. Significant relationships were associated with the former only. Analysis for specific types of silica (e.g. agricultural vs non-agricultural) were carried out on incomplete data sets as insufficient information was available to categorise all subjects. For example 15 non-vasculitis controls and 6 PSV patients were excluded from the analysis of agricultural silica exposure in the Index Year because their exposures were unknown (e.g. in farm labourers where particular task was not recorded). This may introduce unknown bias and results obtained are less robust than those for which a complete data set is available. Similar limitations in data are present for other occupational exposures.

Construction

Data obtained was inadequate to assess specific exposures associated with the building trade and construction but should have been sufficient to identify large trends, e.g. if an important exposure was related specifically to the building trade. Interpretation of results is therefore limited.

Farming Exposures

These exposures were assessed using direct questions and data was almost complete (missing information for 1 non-vasculitis control only). In general recall for type of animal was better than specific type of crop during the Index Year. Accuracy of results is therefore expected to be good.

Allergy History

Information was complete for all but 3 non-vasculitis controls for allergy overall and 4 controls and 2 PSV patients for drug allergy. The most likely bias is over-reporting as patients often misinterpret non-allergic reactions as allergies and the event may have occurred many years previously. Where there was uncertainty a reaction was included as an allergy. One might expect hospital controls to have received more medication prior to the Index Date than formerly healthy vasculitis patients and potentially to have experienced more drug allergies. This would tend to reduce ORs obtained. Reporting of a family history of atopy was limited by the subjects knowledge of their relatives.

Others

Assessment of the date of a vaccination was difficult but data was virtually complete for other factors and recall was especially good for residential details.

V. DISCUSSION

Silica

Occupational silica exposure was significantly associated with PSV. Recent exposures, in the Index Year, were associated with WG and CSS in contrast to exposures throughout working life in mPA. This difference could be explained by inaccuracy of the Index Date in mPA which can be difficult to define precisely, i.e. subclinical disease could have been unrecognised and silica exposure may have immediately preceded a true Index Date. These results and the lack of a trend for increasing risk of vasculitis with duration of exposure would then support a hypothesis that silica acts as an acute trigger of PSV by immune mechanisms, e.g. activating monocytes/ macrophages to produce cytokines and lysozymal enzymes and initiating inflammation. The report of MPO-ANCA angiitis within three years of the earthquake in Kobe could support this theory. However although silica dust was an important new exposure in Kobe, other factors during the same period could be implicated, e.g. an increase in infections caused by poor sanitation and survivors living in close proximity.[147]

The median time for mPA patients from the last silica exposure to the Index Date was 18 years (mean 23.5, range 0-56 years) and a delay in disease recognition of this duration is unlikely. Therefore silica may have a different role for WG and CSS compared to mPA i.e. it may act as an acute trigger in WG and CSS but as a non-specific adjunct promoting but not initiating disease in mPA. Alternatively the observed difference may be coincidental and the timing of silica exposure unimportant. Most studies report that the duration of silica exposure is less influential than it's intensity e.g. ORs for sandblasting, where peak exposures are high, are greater than for building trades.[169,182,183] Our questionnaire was not designed to assess levels of exposure so dose received could not be accurately estimated. As a secondary hypothesis, investigation of probable high peak silica exposure supported these reports with a weak association with mPA. Numbers of cases were too small to

comment on specific jobs such as sandblasting. The importance of exposure intensity may reflect a need for an overwhelming exposure to silica to initiate a perpetuating immune response whilst lower levels may be better tolerated resulting in the cycle of inflammation seen in PS. However it must be recognised that although risk did not increase with duration, in many reports of silica-related PSV the duration of exposure was substantial. In our study the median duration of exposure was 19 years (mean 23.7, range 1-54 years) and in Gregorini's study 28 years (mean 25.3, range 10-34 years).[201] Exposure duration was not reported by Nuyts or Hogan et al but the former estimated that the average exposure duration was >20 years and only 16% of cases in the latter were exposed to silica for less than two years prior to disease onset.[200,202] Similarly, many years may have elapsed between the last silica exposure and symptom onset (in our cohort mean =14.7 years, range 0-56 years).

The association of agricultural silica with WG and CSS in contrast to mPA has not previously been reported, perhaps because most studies have concentrated upon non-agricultural occupational cohorts. Potentially, disease expression could differ with the nature of silica exposure although plausible explanations for a difference in effect have not been noted in the literature. Unknown confounders could also be accountable. The stronger association of pANCA/MPO compared to cANCA/PR3 positive PSV is in keeping with the literature, as many reports concern MPO positive vasculitis.[147,198,199] However this result must not be over interpreted as there were only 19 pANCA/MPO positive patients and ANCA data was incomplete because its clinical use and laboratory technology have developed over the study period.

In conclusion, our results support published evidence that silica is associated with PSV and that the duration of exposure is not necessarily important. They also suggest a possible difference in the relationship of silica with mPA compared to WG and CSS, although the overlapping nature of WG and mPA classification must be remembered. It is very unlikely that silica is the sole factor in initiating PSV, especially as only a small proportion of PS

cases and silica-exposed individuals develop the disease. Evidence for a temporal association of silica exposure and vasculitis is lacking and a cumulative dose appears to be important (either through high intensity or prolonged exposures). It seems most likely that silica acts as an adjuvant to vasculitis, perpetuating or enhancing an immune response initiated by another factor. However results are limited by the design of the questionnaire, classification of mPA and WG and are confounded by other aetiological factors investigated. To further investigate the association an additional study is required using a questionnaire designed to measure levels of exposure by formal occupational hygiene assessment of specific tasks and to distinguish clearly between agricultural and non-agricultural exposures.

Solvents

The association of high occupational solvent exposure with PSV has previously been reported but not the particular association of WG rather than mPA.[202,213] This probably reflects the effect of disease classification or the limited number of mPA cases (12). The mean duration of exposure of our cases (23.7 years; range 3-50years) was similar to previous reports >20 years (Nuyts[202]) and mean 19-22 years; range 11-28 years (Steenland[227]). Therefore our results support an association of PSV with prolonged exposures to high levels of solvents but do not substantiate a specific link with renal vasculitis or the postulated association with pulmonary haemorrhage.[213] Hydrocarbons may therefore play a role in the aetiology of PSV apart from exacerbating renal dysfunction. A detailed assessment of occupational solvent exposure is warranted.

Metals

We failed to detect a significant relationship between occupational metal exposure and PSV which could be due either to a lack of association, small sample size or the methods of exposure assessment used. Previously, associations have been reported for metal fumes specifically[226] whereas we investigated a wider range of metal exposures, although pesticides and fertiliser exposures were not specifically sought. Therefore although no association was found, further focused investigation with occupational hygiene support and including agricultural exposures would be of interest as part of a wider study.

Farming

This study has detected an association of PSV with farming for the first time. Response to this part of the questionnaire was virtually complete and used direct questions. Results were not biased by the distribution of cases or controls living in the rural environment (Table 4.13). A previous study, from the National Institutes for Health (NIH), US using the same questionnaire failed to detect a significant association for WG.[135] The proportion of WG cases exposed to farms in the Index Year were similar for both studies (31.91% this study; 35.6% Duna et al) but more non-vasculitis controls were exposed in the NIH study (13.70% and 22.22% respectively). NIH cases and controls may have been drawn from differing denominator populations leading to bias e.g. cases may have been referred from a wider area than controls who were sequential age/sex matched patients attending a general medical clinic. Examining NHA participants alone in our study in fact strengthened the relationship between farming and all types of PSV, despite reducing the numbers of cases. (Table 4.43)

In addition patients with autoimmune disease were not specifically excluded from the NIH control group and factors important in the initiation of vasculitis and autoimmunity may be similar. The fact that 28.9% of their chronic inflammatory rheumatic disease controls and

27.8% of our SRV controls were exposed to farming in the Index Year may reflect a similar association to farming for these other inflammatory conditions. In addition Parks et al reported that 29% of a cohort of S.L.E. patients had been exposed to farming with increased risk for those who had worked on a farm for more than 20 hours per week [OR(95%C.I.) men: 3,9(1.0-15.8) and women 1.3(0.8-1.8)].[495] However exposures in SRV patients were not significantly different to non-vasculitis controls [OR 2.42 (95% C.I. 0.81-7.29)].

Prior to commencing the study we hypothesised that rural environmental factors were important in the aetiology of CSS in particular[156], however CSS was the only subgroup of PSV not significantly associated with farming. The relationship of PSV appears to be slightly stronger for livestock exposure than for crops. However the trend towards increased risk of vasculitis for direct contact to livestock compared to close or distant suggests that type of exposure is important. A plausible explanation is that an infectious agent may be important in the onset of vasculitis, in keeping with reports of a possible link of vasculitis syndromes with an infectious agent transmitted by pigs.[278,279] Alternatively other factors in the care of livestock and their surroundings may be responsible for the relationship, for example animal feed, antibiotics, disinfectants or cleaning agents.

Agricultural silica exposure may contribute to the association of farming with PSV but this is unlikely to have a strong influence as the significance of the relationships for farming were not affected by multiple regression, in contrast to silica.[Farming Index, OR 2.18(95% C.I. 1.10-4.32) and Agricultural Silica, OR 2.47(95% C.I. 0.60-10.17)].

The relationship of farming and PSV demands further, more detailed investigation with attention to specific exposures including types of livestock, chemical agents used in their care, tasks undertaken in farming occupations, crops, pesticides and fertilisers. The potential association of these exposures with other types of autoimmune and inflammatory rheumatological conditions favours a study encompassing a wider range of diseases (e.g. S.L.E.).

Allergy

An association of drug allergy with WG but not CSS has previously been reported by a group from St Thomas' Hospital, London using the same questionnaire[287], but otherwise results differ. They reported significant associations between WG and CSS and both a family history of atopy and other types of allergy, which we did not reproduce. These differences may be due to their smaller number of cases (20 WG and 8 CSS) or differences between cases or control groups. As a tertiary referral centre, their cases are likely to have more severe disease and to be younger than a population-based cohort such as ours and their cases and control groups were likely to have come from different base populations. Disease controls were selected from rheumatology patients with common complaints (osteoarthritis, gout, rheumatoid and seronegative arthritis), less likely to be referred from other centres for specialist advice than PSV cases and healthy controls from a commuting, population of hospital workers. Control groups may have introduced a positive bias towards the hypothesis that allergy is a risk factor for PSV because rheumatoid arthritis has been associated with a lower prevalence of atopy so the disease control group may have had lower-levels than might be expected.[291,293] However other controls such as seronegative spondyloarthropathies could have had the opposite effect[303] Hospital workers (normal controls) may underreport allergies compared to patients due to a better understanding of the term allergy. However the proportion of controls reported to have allergy was similar to the Norfolk controls (35-38% vs 38.1%) so these explanations are unlikely to wholly explain the differences.

The association with atopy reported by the St Thomas' study supports the hypothesis that a Th2 cytokine environment (type-1 hypersensitivity) may play a role in the initiation of vasculitis. Drug allergy however is heterogeneous and may be caused by all types of hypersensitivity reactions.[328] Therefore the association of PSV with drug allergy does not

necessarily correspond to an association of an atopic, Th2 cytokine environment but could reflect previous type 2 hypersensitivity with antibody formation or type 3 hypersensitivity with immune complex deposition. However beta lactam allergy (penicillins) has been associated with a Th2 environment even in clinically non-atopic individuals[498] so the significant association found for antibiotics and penicillin specifically could still support the hypothesis although one might expect significant associations for other types of allergy too. It is especially surprising that we did not find any significant relationships of allergy with CSS despite asthma being part of classification criteria. This might be explained by sample size. In summary the specific association of drug allergy may support a role for a Th2 cytokine environment in the initiation of PSV but in the absence of an association with other allergies and atopy other immunological mechanisms should also be considered. Alternatively other explanations for the association of drug allergies e.g. allergy to antibiotics may be a marker for previous exposure to infection which could render the individual more susceptible to PSV.

Others

In contrast to previous reports, we did not find an association between recent vaccination and PSV. This may be explained by bias introduced by the timing of interviews and recall. Alternatively the period of association sought (6 months) may have been too short.

Medication taken by cases and controls was not assessed because drugs previously associated with PSV will be underrepresented in controls because of the exclusion of patients with autoimmune disease. Individual hobbies were not analysed due to a paucity of plausible mechanisms for an association and the reliability between subjects of reporting specific exposures such as solvent exposure is likely to be low.

VI Conclusions

In conclusion, we have found a plausible, significant association between farming and PSV for the first time. A possible explanation is that exposure to an infectious agent transmitted by livestock is responsible for triggering disease, which is supported by reports in the literature. However numerous other aetiological factors could also be implicated (e.g. pesticides or herbicides)

A relationship between drug allergy, especially penicillin, has also been established but, in contrast to published reports, not for other types of allergy and atopy. This may support a role for a Th2 cytokine environment providing a suitable milieu for the initiation of vasculitis but alternative immunological mechanisms could also be responsible or drug allergy may act as a marker for another risk factor, e.g. infection. The reported association of PSV with occupational silica and solvent exposure is also supported by this study. The possibility of variation in disease expression between agricultural or other silica types and a differing mechanism of action between PSV subtypes is raised.

The associations discovered are certainly of sufficient strength and importance to warrant further investigation and a strategy for this is discussed in the final conclusions.

CHAPTER 5

Final Conclusions and Future Plans

CONCLUSIONS

The primary systemic vasculitides, WG, mPA and CSS, are an interesting group of disorders characterised by inflammation and necrosis of small and medium blood vessels. Although relatively rare (annual incidence approximately 20 / million in our unselected population) PSV is an important area for research.

Historically they were almost universally fatal but have been transformed into chronic relapsing and remitting illnesses by the introduction of cyclophosphamide and, more recently, other immunosuppressive therapy.[12,18] However despite modern treatment, mortality from these disorders remains substantial.[18,104] Amongst our cohort of PSV patients in Norfolk the Standardised Mortality Ratio (SMR) was 4.78 (2.98-6.59) compared to the normal population and was similar regardless of age at diagnosis. In keeping with previous studies hazard ratios for mortality were significantly higher for mPA.

Side-effects of both the disease and treatment are also considerable. Affected individuals experience significant morbidity in terms of periods of active inflammation, permanent damage caused by vasculitis and treatment side-effects including malignancy.[18,36,93] The mean number of organ systems affected for all PSV amongst our patients was 4.3 (range 1-8) with a mean VDI (representing permanent damage caused by disease) of 2.3 (0-9), which although less than earlier studies is likely to be an underestimate of damage because of the retrospective nature of the survey. Amongst 96 individuals who received cyclophosphamide 57 experienced treatment related complications including 8 deaths and 7 malignancies. This is similar to other centres although some have noted much higher complication rates, particularly for infection including pneumocystis carinii.[104] Patients may also experience significant psychological problems (see Appendix 3) and social

consequences including loss of independence, disruption of interpersonal relationships and unemployment.[498,499]

In addition PSV is a burden to health care services. During periods of active disease, especially at first presentation, patients often require prolonged hospital treatment which may include intensive care, haemodialysis and plasmapheresis. Patients usually require life-long surveillance at the hospital and prolonged immunosuppression, which requires monitoring. During the course of their illness patients often have recurrent hospital admissions directly and indirectly related to vasculitis and require considerable support from both primary and secondary care.[500]

Although the aetiology of PSV is unknown it is generally thought to be multifactorial with one or more environmental factor triggering disease in a genetically susceptible individual. Review of the literature highlights a number of environmental factors that may be important in the aetiology of PSV. It also supports a genetic contribution to disease with reports of familial cases and the association of genetic polymorphisms with subtypes of PSV e.g. α-1 antitrypsin phenotypes and cANCA positive disease.[427,428,429,430,431,432,433,434,468,469,470,471]

The main environmental factors reported to be associated with systemic vasculitis are exposure to silica and solvents, especially in studies of occupation; inhaled fumes and particulates including metal fumes; infections including hepatitis B and C, parvovirus B19 and chlamydia; allergy; drugs e.g. propylthiouracil and hydralazine; and vaccinations.[73,135,213,227,242,287,357,358,359] Seasonal fluctuation of PSV has been described which may suggest an infectious aetiology.[130,134,135,136,137] Although there were no significant annual or seasonal fluctuations in PSV in Norfolk there was a trend towards a

higher number of cases occurring in the winter months. The incidence of PSV may also be increasing with time. To assess these trends further study is required over a prolonged period. In addition geographical variation in the incidence of PSV has been noted including the increase in WG with latitude and a non-significant excess of CSS and WG in rural areas of Norfolk compared to the built-up areas. These findings support a role for environmental factors in the aetiology of PSV.

The case-control study of environmental factors supported an association between occupational exposures to high levels of silica and solvents. In keeping with the literature there was no increasing risk of PSV with duration of exposure to either silica or solvents. Exposure to occupational silica was associated with all diagnoses of vasculitis but only WG gave significantly raised ORs for solvent exposures. Another interesting difference was that silica was associated with pANCA positive vasculitis whilst solvent exposure was associated with cANCA. Although data was less robust, exposure to 'agricultural' silica (i.e. grain dust) was associated with WG and CSS whilst mPA gave significantly raised OR's for 'non-agricultural' silica. This may suggest a different role for silica between WG or CSS and mPA.

The most striking finding, however, was the association of PSV with farming which has not previously been reported. It has not been possible to identify any particular exposure responsible for triggering vasculitis but certainly suggests that further investigation of potential risk factors associated with farming is important. Data suggests that exposure to livestock may be particularly important, with a trend towards higher ORs for individuals directly involved with handling animals compared to those who did not have direct contact. This may suggest an infectious aetiology although direct contact is not necessary to spread infection which may, for example, be airborne. Several reports have linked other types of

vasculitis with animal infections. A paramyxovirus has been demonstrated to pass from pigs to farmers causing a systemic illness characterised by vasculitis.[278] Pig handlers may have a higher risk of Behcets disease and viral infections causing SV are transmissible between species.[279,285] However many other factors associated with farming could also trigger vasculitis: e.g. cleaning fluids, disinfectants, sheep dip and other chemicals, foodstuffs including grain, antibiotics and medications. A study using the same questions at the N.I.H., United States failed to find an association with farming but did find a link with pesticides and herbicides.[135] Farming did show a weak association with S.L.E. in a study primarily concerning silica exposures. Their data concerning livestock exposure has not been published.[495]

It is important to investigate these environmental factors further because identification of an agent important in triggering disease could help understand the pathogenesis of disease and potentially improve therapy. Identification of a specific risk factor could help with primary prevention or to reduce relapses in established disease by avoidance of the substance.

The contribution of environmental and genetic factors to the aetiology of PSV is complex and investigation of these factors complicated. The study was designed with the aim of casting a wide net to highlight areas of potential importance. It has succeeded in identifying some exciting areas for further investigation and an outline of plans for future studies follows.

FUTURE PLANS

Introduction

The case-control study suggests a significant association between PSV with farming, occupational silica and solvent exposure and raised some interesting questions which were beyond the scope of the study design. In the first instance it will be important to repeat the study in at least one different population to ascertain whether the findings are valid. If the results are confirmed a further study should be designed. The aim of a future study is to address these questions.

Aims and Objectives

To answer the questions:

- Which factors are responsible for the relationship of PSV and farming?
- Is the risk of PSV related to the dose of silica and solvent exposures?
- Is the risk of silica and solvent exposure related to ANCA type?
- Does the risk of PSV differ for 'agricultural silica' compared to 'non-agricultural silica'?

Methods

Questionnaire design

Initially information will be obtained about potentially important farming exposures by a review of the literature about veterinary infections, farming methods and rural environmental health issues. Advice will be sought from relevant veterinary and farming authorities and if appropriate observation of procedures will be arranged. Direct questions will be designed to ascertain a detailed history of exposures e.g. including types of herbicides / pesticides used.

Formal occupational hygiene support will be sought to design questions with sufficient detail to assess the dose of silica and solvents. Particular care will be taken to identify silica exposure in the form of grain dust and 'non-agricultural' forms of silica. Non-occupational exposures of both will also be included.

Questions for potential confounding factors including social class, smoking, age and will be included in the same manner as the previous questionnaire. Additional questions will be added to make the subject of interest less transparent and interviewers will be blinded to the hypothesis to reduce observer bias. The questionnaire will be piloted for reliability and reproducibility.

Cases

To allow a sufficiently detailed history and to reduce recall bias ideally only incident PSV cases will be recruited. To recruit sufficient numbers in a realistic time-scale this implies that a multi-centre study will be necessary. It also may be interesting to recruit patients with other connective tissue diseases e.g. S.L.E. and scleroderma for whom similar exposures have been reported but this is beyond the scope of this thesis.

Controls

Community rather than hospital-based controls should be recruited. Controls could be identified by primary care practices or neighbourhood controls could be selected. They should be matched for age and sex. Controls with autoimmune disorders may could also be considered.

Sample Size

Once participating centres are identified the number of cases available for recruitment in

the planned time-period will be estimated. A power calculation will be carried out to estimate the number of controls required.

Serology

Blood will be drawn from all consenting participants during active vasculitis. ANCA type will be assessed using the methods agreed by the European Standardisation Work group. This will allow accurate analysis of the association of factors of interest and ANCA type which has been limited in the current study by its retrospective nature and the evolution of ANCA testing over the study period.

Serum obtained during the acute phase of illness will also be stored pending future analysis e.g. for a newly identified virus.

Ethical Considerations

Ethical approval will be obtained from all participating centres and a consent form designed for participation in the study and to allow access to relevant medical records and laboratory data.

Data Analysis

Multiple logistic regression will be used to obtain ORs and 95% C.I. for factors of interest adjusted for potential confounding factors.

Job-exposure and hobby-exposure matrices will be designed to carefully assess levels of exposure to silica and solvents. Information obtained from the occupational history should be sufficiently detailed to allow scoring of exposures by task and duration of exposure. Data will be coded to reduce bias during analysis.

Additional Plans

Investigation of Genetic Polymorphisms

Whole blood will also be obtained from consenting participants and DNA extracted to expand the number of samples obtained from participants in the present study. Studies of the HLA associations and relevant genetic polymorphisms (discussed in the literature review) with individual disease subtypes and ANCA types are planned compared to population controls.

Descriptive Epidemiology

Study of the descriptive epidemiology in the NHA will continue. This will help answer the question 'Is the incidence of Primary Systemic Vasculitis increasing with time?'. Additionally periodic fluctuations of PSV both annually and with the seasons can be observed over a longer period. In addition the hypothesised association of CSS with rural residence can be revisited when a sufficient number of cases have been recruited.

Assessment of the Impact of PSV on the Health Service

The cohort of PSV patients described in this thesis could be studied to estimate the cost of PSV to the National Health Service. An initial study of the use of health services would be required to include inpatient and outpatient care. Both primary and secondary care would be considered including consultations, procedures, drug therapy and monitoring. A full cost of illness study could then be planned including direct and indirect costs to the patient.

FINAL CONCLUSION

This thesis has described the clinical characteristics and epidemiology of a well-defined population-based cohort of PSV patients. A case-control study of the role of environmental factors in PSV demonstrated a significant association with farming for the first time. Associations were also demonstrated for drug allergies and occupational exposure to silica and solvents. In conclusion, environmental factors do seem to play a significant role in the aetiology of Primary Systemic Vasculitis but further study is required to establish the exact nature of the association. Results obtained are an important guide to planning another step towards understanding the aetiology of these complex disorders.

CHAPTER 6

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APPENDIX 1

Maps of the Norwich Health Authority

1. Population density by parish in the Norwich Health Authority (1983) – From NHA District Review 1984 . Interim Reports

p. 370-371

2. Location of General Practice Surgeries (1988) –
From Norfolk Family Practitioner Committee for Primary Care Annual Report, 1988-89

p. 372-73

3. Local Government Districts (North Norfolk, Breckland, Broadland and South Norfolk) incorporated in the Norwich Health Authority (1981)–
From Norwich Health Authority – A profile 1981

p.374-375

4. Administrative Areas and local Authority boundaries in Norfolk –
From Norfolk Family Practitioner Committee for Primary Care Annual Report 1988-89

p.376-77

5. Hospital Services within the Norwich Health Authority (1981) –
From Norwich Health Authority – A profile, 1981

p. 378-379

6. Civil parishes within the county of Norfolk and Norwich Health Authority-
From Demographic Information Note 5/00; Mid-1999 small area estimates for Norfolk parishes, urban wards, county electoral divisions and built-up areas

p.380-82

7. Wards within Norfolk and the Norwich Health Authority 1991 –
From Demographic Information Note 5/99; Mid-1998 small area estimates for Norfolk wards and other areas of interest.

p.383-384

Pamphlets 1-5 available from the main library, University of East Anglia

Pamphlets 6-7 available from Norfolk City Council planning and transportation demographic unit, Tel. (01603) 222 143

N.B. Permission to reprint these maps has been obtained from the Norfolk City Council planning and transportation demographic unit.

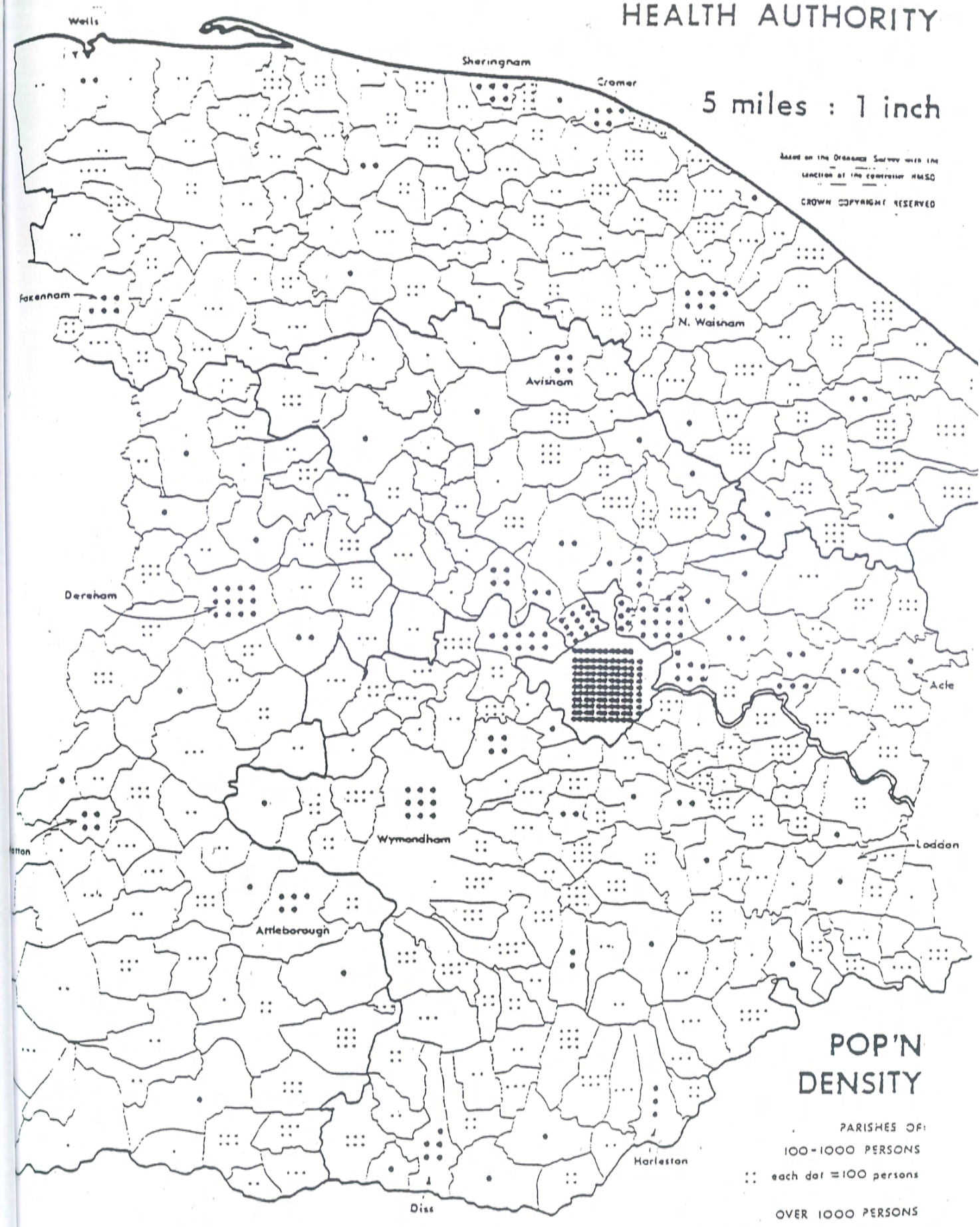
MAP 1

Population density by parish in the Norwich Health Authority (1983)

– From NHA District Review 1984, Interim Reports

NORWICH

HEALTH AUTHORITY



MAP 2.

Location of General Practice Surgeries (1988)

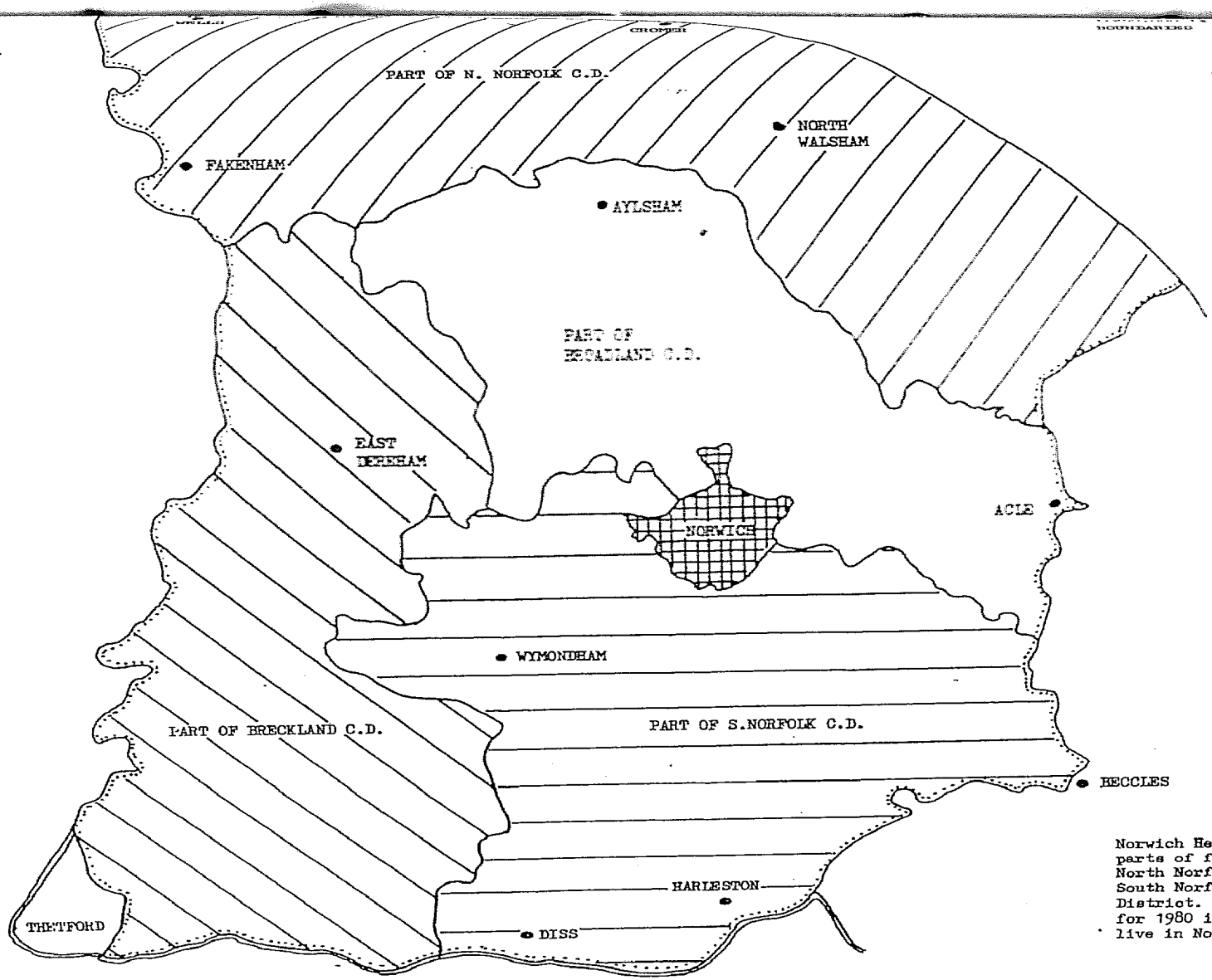
-From Norfolk Family Practitioner Committee for Primary Care Annual Report, 1988-89

LOCATION OF GENERAL MEDICAL SERVICES

MAP 3

Local Government Districts incorporated in the Norwich Health Authority (1981)

- From Norwich Health Authority – A profile 1981

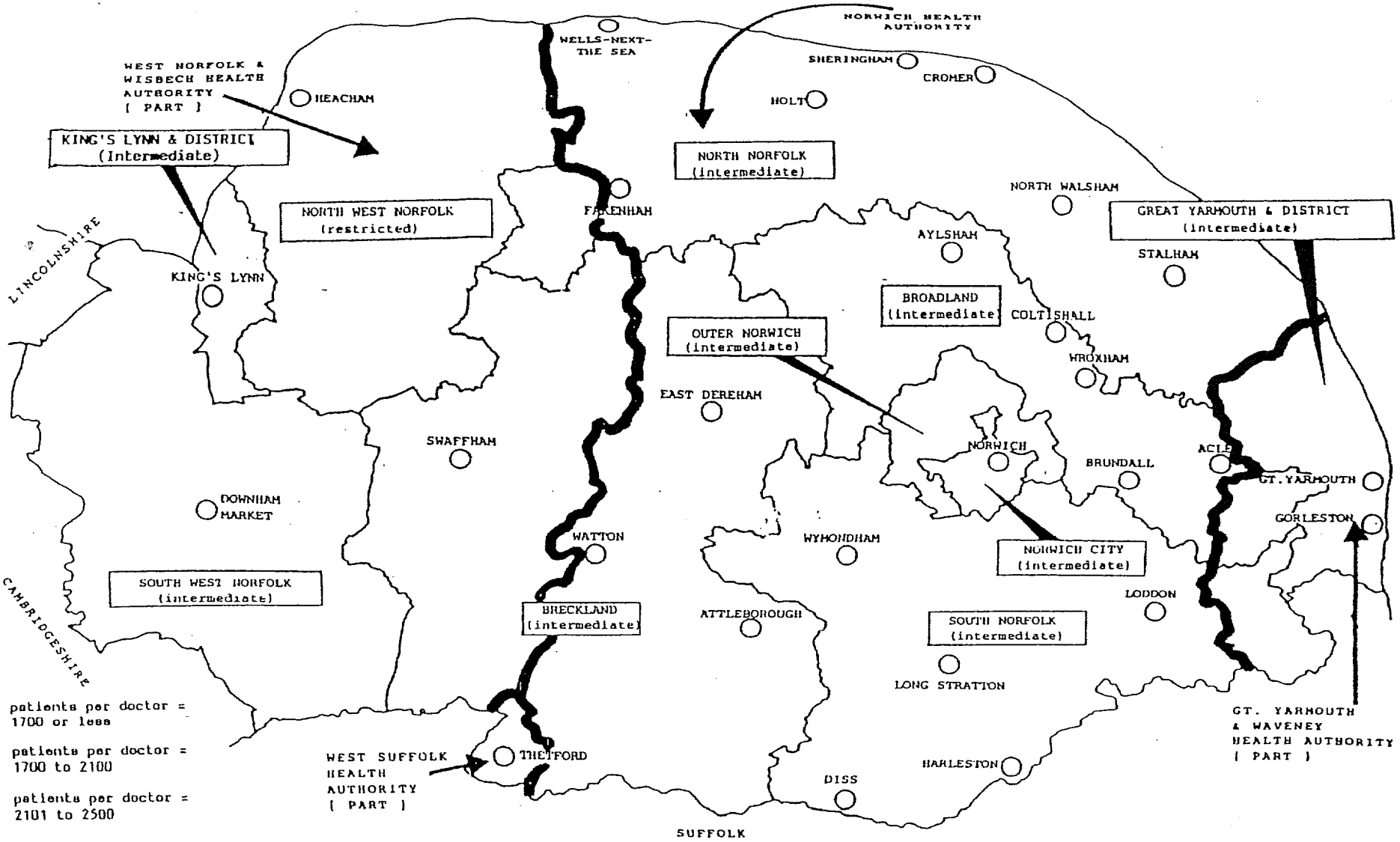


Norwich Health Authority incorporates parts of four Local Government Districts, North Norfolk, Breckland, Broadland and South Norfolk; and the whole of Norwich District. The total population estimate for 1980 is 441,800. Approximately 27% live in Norwich.

MAP 4.

Administrative Areas and local Authority boundaries in Norfolk

- From Norfolk Family Practitioner Committee for Primary Care Annual Report 1988-89



RESTRICTED AREA : patients per doctor = 1700 or less

INTERMEDIATE AREA : patients per doctor = 1700 to 2100

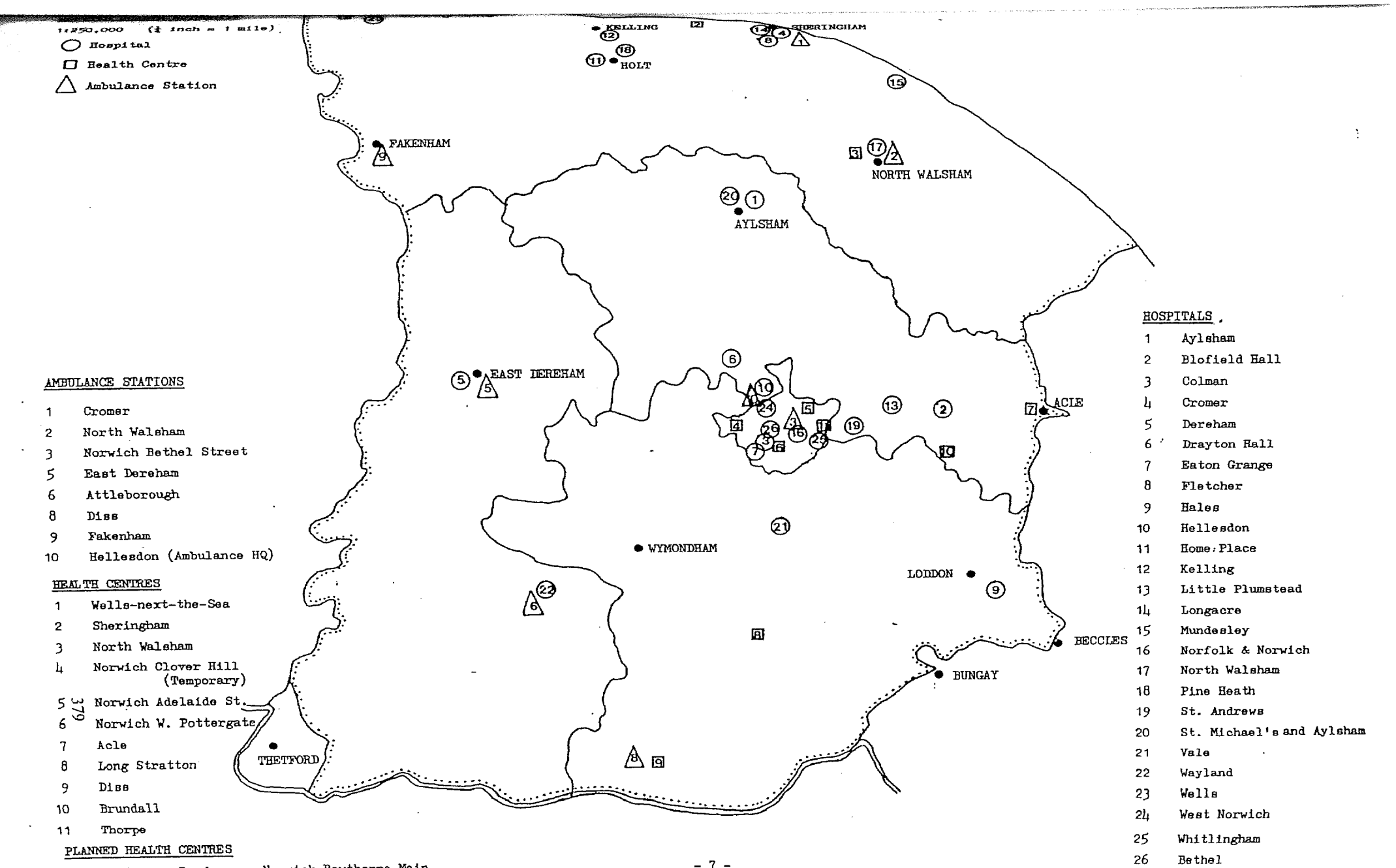
OPEN AREA : patients per doctor = 2101 to 2500

Since the Committee reviewed its MPC areas these are largely coterminous with local authority boundaries and have similar titles. Exceptions to this are outer Norwich which impinges upon Broadland and South Norfolk District Councils and King's Lynn and West Norfolk District Council which is covered by North West and South West Norfolk and King's Lynn and District MPC areas. The FPC's administrative area is the county of Norfolk.

MAP 5.

Hospital Services within the Norwich Health Authority (1981)

-From Norwich Health Authority – A profile, 1981



AMBULANCE STATIONS

1 Cromer
2 North Walsham
3 Norwich Bethel Street
5 East Dereham
6 Attleborough
8 Diss
9 Fakenham
10 Hellesdon (Ambulance HQ)

HEALTH CENTRES

1 Wells-next-the-Sea
2 Sheringham
3 North Walsham
4 Norwich Clover Hill (Temporary)
5 Norwich Adelaide St.
6 Norwich W. Pottergate
7 Acle
8 Long Stratton
9 Diss
10 Brundall
11 Thorpe

PLANNED HEALTH CENTRES

Norwich Lawson Road
Wymondham
Norwich Bowthorpe Main
Colman Road

HOSPITALS

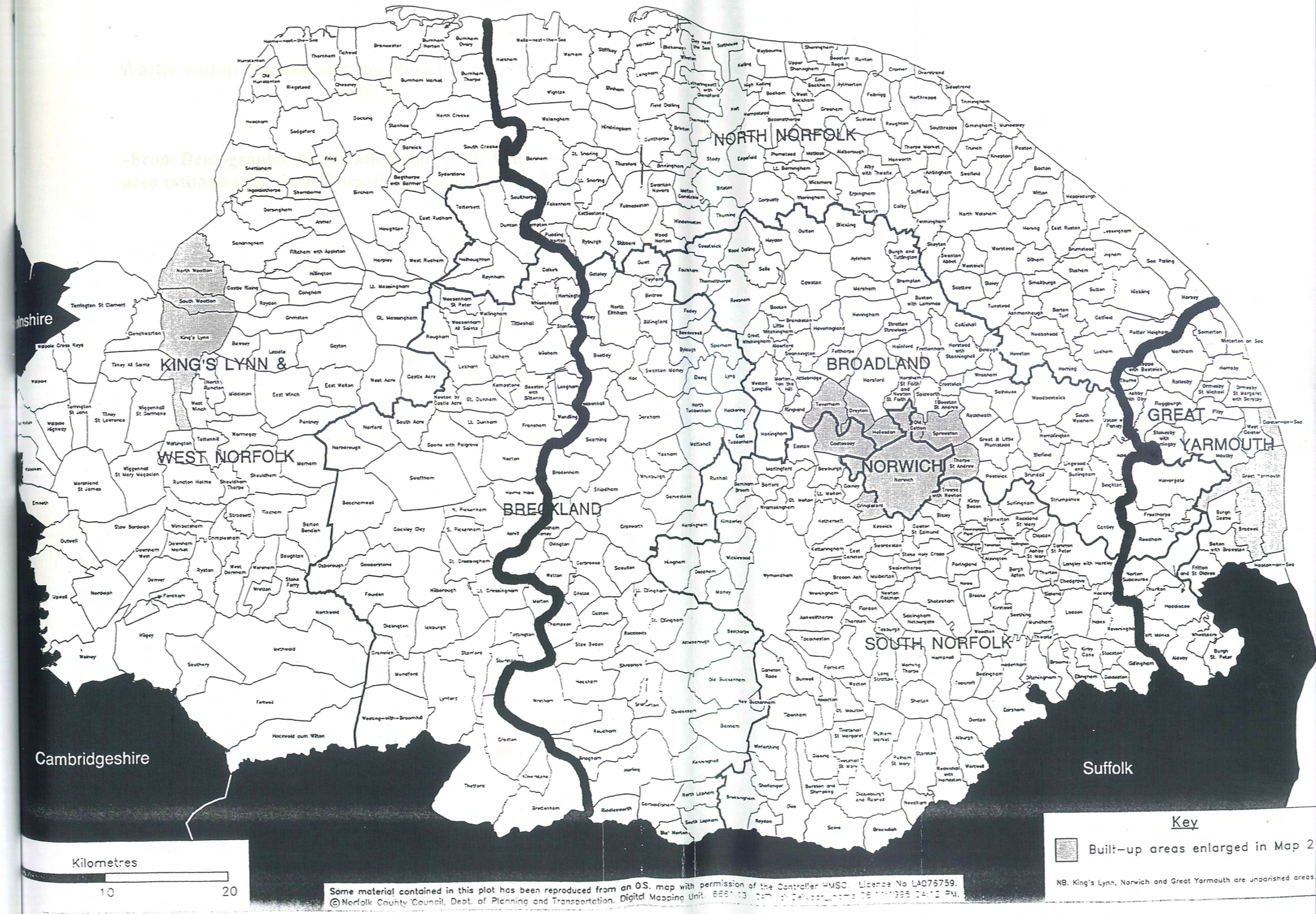
1 Aylsham
2 Blofield Hall
3 Colman
4 Cromer
5 Dereham
6 Drayton Hall
7 Eaton Grange
8 Fletcher
9 Hales
10 Hellesdon
11 Home Place
12 Kelling
13 Little Plumstead
14 Longacre
15 Mundesley
16 Norfolk & Norwich
17 North Walsham
18 Pine Heath
19 St. Andrews
20 St. Michael's and Aylsham
21 Vale
22 Wayland
23 Wells
24 West Norwich
25 Whitlingham
26 Bethel

MAP 6.

Civil parishes within the county of Norfolk and Norwich Health Authority

From Demographic Information Note 5/00; Mid-1999 small area estimates for Norfolk parishes, urban wards, county electoral divisions and built-up areas

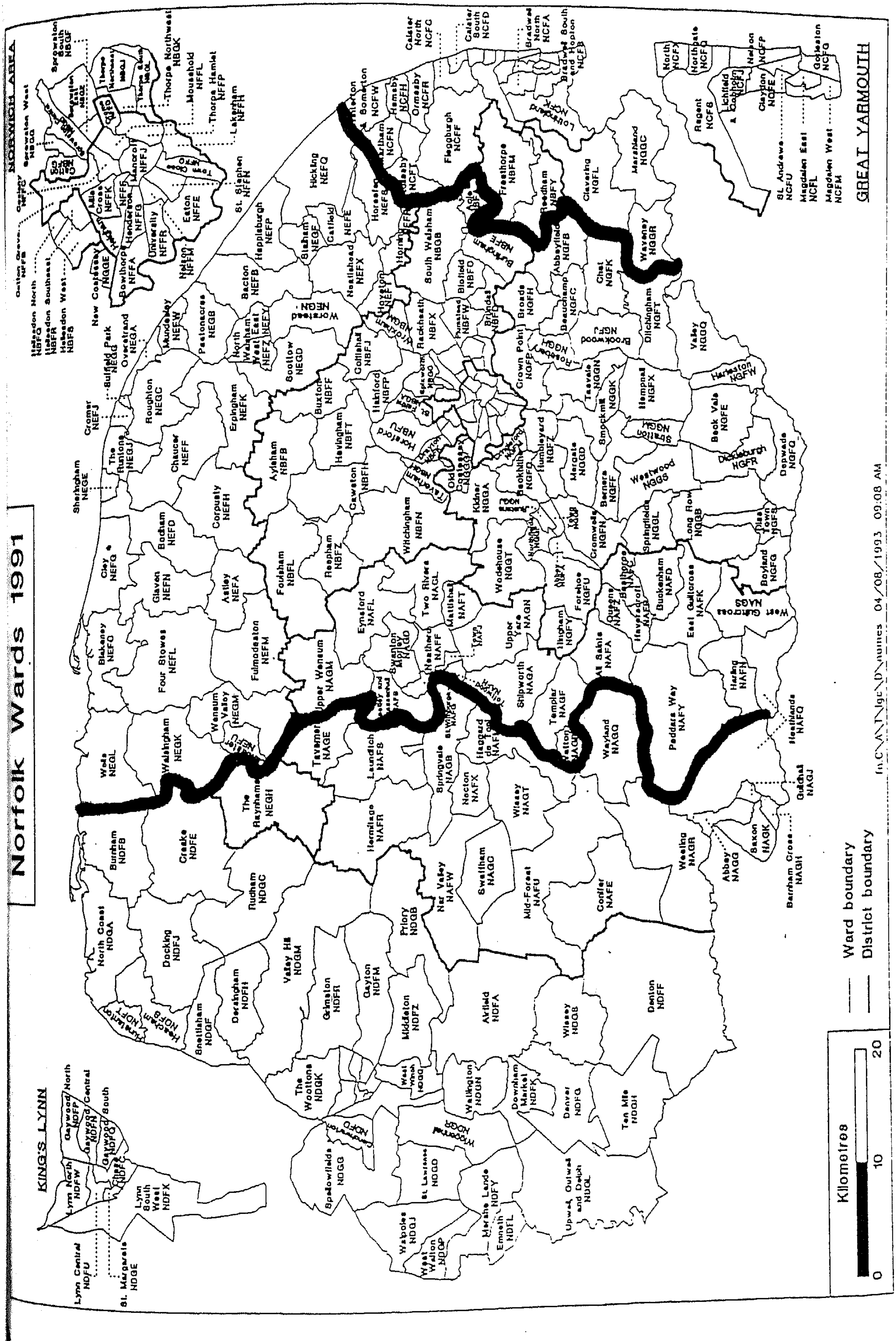
Civil parishes within the county of Norfolk



MAP 7.

Wards within Norfolk and the Norwich Health Authority 1991

-From Demographic Information Note 5/99; Mid-1998 small area estimates for Norfolk wards and other areas of interest.


Norfolk Wards 1991
NORWICH AREA
GREAT YARMOUTH
KING'S LYNN
Ward boundary
District boundary
Kilometres
0
10
20

APPENDIX 2.

Questionnaires / Assessment Forms

1. Questionnaire for the Study of the Etiology of Wegener's Granulomatosis

p. 386-396

Duna GF, Cotch MF, Galperin C, Hoffman GS, Wegener's Granulomatosis; role of environmental exposures, Clin. Exp. R heumatol, 16(6): 669-74

2. Allergies in Systemic Vasculitis

p. 397-398

Cuadrado MJ, D'Cruz D, Lloyd M, Mujic F, Khamashta MA, Hughes GRV, Allergic disorders in systemic vasculitis: A case -controlled study, British Journal of Rheumatology, 1994. 33: 749-753

3. Do Environmental Factors play a Significant role in the Aetiology of Primary Systemic Vasculitis?- A case control study

Section 1------**p. 399-400**
Section 2------**p. 401**
Section 3------**p. 402**
Section 4------**p. 403**
Section 5------**p. 404**
Section 6------**p. 405**
Section 7------**p. 406**
Section 8------**p. 407-409**
Section 9------**p. 410-411**
Section 10----**p. 412**

4. Birmingham Vasculitis Activity Score Assessment Form

Luqmani RA, Bacon PA, Jayne D, Westman K, de Groot K, Rasmussen N, Development of a European consensus on disease activity assessment in primary systemic vasculitides **p. 413-414**

5. Birmingham Vasculitis Damage Index Assessment Form

Luqmani RA, Exley AR, Kitas GD, Bacon PA, Disease assessment and management of the vasculitides, Baillieres C lin Rheumatology, 1997. 11: 423-446 **p. 415-416**

N.B. Permission has been requested to reproduce these documents

QUESTIONNAIRE FOR STUDY OF THE ETIOLOGY OF WEGENER'S GRANULOMATOSIS

10/90

NAME:_____ INITIALS OF INTERVIEWER:_____

DATE:_____ TIME STARTED:_____ TIME FINISHED:_____

CLINICAL PRECURSORS

When were you born? __/__/__

When were you diagnosed with Wegener's Granulomatosis? __/__/__

Think about the time before you were told that you had Wegener's.

[READ THE NEXT PHRASE BEFORE READING EVERY CONDITION BELOW]:

Before you were actually diagnosed with Wegener's, did you ever have...

	Y or N	Month/Year first had
-An unexplained fever > 100° F. that lasted more than 2 weeks?	____	_____
-Any pain, swelling or redness in or around your eye that lasted more than 2 weeks?	____	_____
IF YES, Did you consult a physician?		__Y __N
Did it occur more than once?		__Y __N
-A sore or an injury to your skin or mouth that failed to heal within 2 months?	____	_____
-An infection or allergy in your nose or sinuses that lasted more than 2 months?	____	_____
IF YES, Were your symptoms bad enough to make you change your daily activities?		__Y __N
Did you consult a physician at that time?		__Y __N

Before you were actually diagnosed with Wegener's, did you ever have...

-Sudden nosebleeds that weren't the result of a blow or any physical irritation? ____ _____

IF YES, Did you consult a physician? __Y __N

Did it occur at least 6 times over a 2 week period? __Y __N

-A persistent cough lasting more than 2 months? ____ _____

IF YES, Were you a smoker at that time? __Y __N

IF YES, Was there a change in the quality of the cough or of any phlegm? __Y __N

IF YES, Did you cough up blood? __Y __N

-Any muscle or joint pain in more than two separate areas of your body which lasted more than 2 months? ____ _____

-An ear pain or discharge? ____ _____

IF YES, Did you consult a physician? __Y __N

Have you had this more than once? __Y __N

Summary

Of these conditions, it seems that_____ was the first sign or symptom that could be associated with Wegener's. Do you think this is accurate?

Yes___ No___ IF NO,

Which do you think was the first sign?

_____

_____

_____

Index Date: _____ (TO BE ESTIMATED BY INTERVIEWER)

How old were you at the time of [**INDEX DATE**]?:_____

Most of the following questions I'm going to ask you about now will focus on a time just before [**INDEX DATE**], when you were [AGE at that time]. Please try to recall the events surrounding that time period.

OCCUPATION

Now I'd like to make a list of all the jobs you have held before [**INDEX DATE**]. This should include any time that you've spent in the military.

[IF THE PATIENT WAS OVER 25 YEARS OLD AT THE TIME OF [**INDEX DATE**], OBTAIN INFORMATION ABOUT ALL THE JOBS THEY HAD THAT LASTED AT LEAST 6 MONTHS. IF SHE/HE WAS 25 YEARS OLD OR YOUNGER AT THE TIME OF [**INDEX DATE**], OBTAIN INFORMATION ABOUT ANY JOBS THEY HAD THAT LASTED FOR AT LEAST 3 MONTHS.]

Let's begin with the job you had on [**INDEX DATE**] and work backwards in time from there.

Years Worked	Type of Work OCCUPATION	Most important activity or major responsibility	Type of INDUSTRY
__/__-__/__			
__/__-__/__			
__/__-__/__			
__/__-__/__			
__/__-__/__			
__/__-__/__			
__/__-__/__			

Do you remember any unusual or significant exposures which you experienced while at work? IF YES, please elaborate.

FOR PEOPLE WHO WORK PRIMARILY INSIDE

Now think about the room or rooms where you worked in the 1 year before [**INDEX DATE**]. Do you remember working in a room for more than 4 hours where workmen were performing any major construction, remodeling, installation or other work?

Specifically, was/were	Y/N	IF YES, [DESCRIBE THE UNUSUAL]
a chimney cleaned	___	_____
floors refinished	___	_____
carpets cleaned or shampooed	___	_____
rooms plastered	___	_____
wallcovering removed/applied	___	_____
rooms painted	___	_____
pesticide/insecticide applied	___	_____
chemical spill or leak	___	_____

Was there extensive work done on:

a plumbing system	___	_____
a heating/AC system	___	_____
installing insulation	___	_____

Other renovation(s) performed: _____
(e.g. whole room added)

_____

AVOCATION

Now I'd like to ask you some questions about your hobbies. Can you tell me about any hobbies at which you regularly spent time doing before [**INDEX DATE**]. Also, tell me how much time you spent at each hobby (hours spent per week or month), and the date when you began pursuing each hobby.

HOBBY	TIME SPENT/MONTH	DATE BEGAN HOBBY

Thinking about the hobbies you just mentioned, were you ever regularly exposed to any chemical, fume, dust or smoke that you could have inhaled in the one year before [** INDEX DATE **]?

Yes ____ No ____

IF YES, Substance	Hobby	Dates of Exposure

As part of these hobbies, did you have any significant exposure to fungus, mold (yeast), or other germs or plants, animals or any other living matter in the one year before [** INDEX DATE **]?

Yes ____ No ____

IF YES, Substance	Hobby	Dates of Exposure

In the 1 year before [**INDEX DATE**], did you garden or do any type of yardwork (including digging, mowing, and/or raking)?

Yes____ No ____ [IF NO, go to next page]

IF YES, How much time did you spend doing yardwork and what activities were involved?

_____

_____

_____

RESIDENCE HISTORY

Now I'd like to ask you about the places you've lived for at least 6 months in the 2 year period before [**INDEX DATE**]. Let's begin with the place where you lived in [**INDEX DATE**] and work backwards in time from there.

For each:

1. What was the name of each city/town where you lived?
2. What were the years that you lived there?
3. What type of dwelling was it? (e.g apartment, single family home, etc)
4. What kind of fuel was used to heat the dwelling?

Name (city/state)	Years	Type of dwelling (1-4)	fuel (a-g)

Type of dwelling:

1 - Apartment (3 or more households in the building)
2 - Detached, single family home or duplex (1 or 2 households)
3 - Dormitory
4 - Barracks

Type of heating:

a-gas b-oil c-electricity d-woodburning e-kerosene f-coal g-other

Was there any major construction going on in this dwelling or dwellings?
IF YES, please describe:

Dwelling: _____ Which room or rooms: _____

Type of construction: _____

_____

Did you participate in the construction? _____

Dwelling: _____ Which room or rooms: _____

Type of construction: _____

_____

Did you participate in the construction? _____

FARM EXPOSURE

Now I'd like to ask you some questions about any time that you've spent on farms. In the 1 year before [**INDEX DATE**], did you live on or visit any farm?

Yes___ No___ [IF NO, GO TO NEXT PAGE]

IF YES,

How much time in the 1 year prior to [**INDEX DATE**] did you spend on a farm? ____ Days ____ Weeks ____ Months

In which season did you live on or visit a farm?
Summer ____ Fall ____ Winter ____ Spring ____

When you were on a farm, did you spend any time within 30 feet of any crops?
Yes___ No___

IF YES, When you were on the farm how often were you within 30 feet of the following?

		Daily	Weekly	Monthly	Less often
Crops	Corn ___	____	____	____	_____
	Wheat___	____	____	____	_____
	Soybeans____	____	____	____	_____
	Oats___	____	____	____	_____
	Hay____	____	____	____	_____
	Alfalfa____	____	____	____	_____
	Cotton___	____	____	____	_____
	Other_____	____	____	____	_____

Oil seed rape
Linseed oil

When you were on a farm, did you spend any time within 30 feet of any lifestock? Yes___ No___

IF YES, When you were on the farm how often were you within 30 feet of the following?

		Daily	Weekly	Monthly	Less often
Livestock	Cows____	____	____	____	_____
	Pigs____	____	____	____	_____
	Horses____	____	____	____	_____
	Sheep____	____	____	____	_____
	Goats____	____	____	____	_____
	Chickens____	____	____	____	_____
	Other_____	____	____	____	_____

PERSONAL CONTACTS

Do you know of anyone who has Wegener's granulomatosis?

Yes _____ No _____ Don't Know _____ Refused _____

IF YES, Does this person live within 30 miles of your home?

Yes _____ No _____ Don't Know _____ Refused _____

Is this person a relative, a friend or neither?

Relative _____ Friend _____ Neither _____

If this person is a relative,

What relation is this person to you? _____

Does this relative live in the same house with you?
Yes____No____

If this person is a friend,

Where do you know this person from?
School _____
Work _____
Neighborhood _____
Other (specify) _____

If neither friend nor relative,

Where do you know this person from?
School _____
Work _____
Neighborhood _____
Doctor's office _____
Other (specify) _____

Have you had direct personal contact with this person; that is, have you actually seen, talked to, or come within 30 feet of this person?
Yes___ No___

FOR ALL THOSE WHO KNOW ANOTHER PERSON WITH WEGENER'S:
In the 1 year before [index manifestation, date of diagnosis, or designated year], on average, how many days per month or days per year did you have direct personal contact (see above for definition) with this person?

_____ days per month OR _____ days per year

Now I would like to ask you some questions related to the time AFTER you were diagnosed with Wegener's. Since your diagnosis, have you ever had any 6 month periods where you were off all drugs for treatment of Wegeners?

Yes ___ No ___ [IF NO, STOP]

IF YES, After having been off all drugs for at least 6 months, did you then ever have another episode ("flare-up") of Wegener's?

Yes ____ No ____ [IF NO, STOP]

IF YES, Can you tell me how many such episodes of sickness you have had and when they occurred.

DATE	Symptoms
_____	_____
_____	_____
_____	_____

In the 6 months BEFORE an episode of sickness, do you remember any significant or unusual exposure to any chemicals, fumes, dust, smoke, plants, animals, fungus, molds or germs?

Yes _____ No _____

IF YES, Date	Substance	Circumstances of exposure
_____	_____	_____
_____	_____	_____
_____	_____	_____

In your opinion, what do you think caused you to have another episode of Wegener's?

_____

_____

_____

_____

NAME: _____

DATE: _____

Now I would like to ask you some questions related to the time AFTER you were diagnosed with Wegener's. Since your diagnosis, have you ever had any 6 month periods where you were off all drugs for treatment of Wegeners?

Yes ___ No ___ [IF NO, STOP]

IF YES, After having been off all drugs for at least 6 months, did you then ever have another episode ("flare-up") of Wegener's?

Yes ____ No ____ [IF NO, STOP]

IF YES, Can you tell me how many such episodes of sickness you have had and when they occurred.

DATE	Symptoms
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

In the 6 months BEFORE an episode of sickness, do you remember any significant or unusual exposure to any chemicals, fumes, dust, smoke, plants, animals, fungus, molds or germs?

Yes _____ No _____

IF YES,

Date	Substance	Circumstances of exposure
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

In your opinion, what do you think caused you to have another episode of Wegener's?

_____

_____

_____

_____

In YOUR opinion, no matter how silly it may sound, what do you think could have caused you to get WEGENER's?

Allergies in Systemic Vasculitis

Name: **Ethnic Origin:** **Sex:**

Date of Birth: **City of Residence:**

Diagnosis: **Age of onset:** **Month of onset:**

ALLERGY HISTORY

1. **Skin reactions** directly related to skin contact with:

Metals
Soap
Creams
Other products

Urticaria
Erythemato-vesicular
Other

Date:
Duration:
Treatment:

2. **Allergic rhinitis** (Recurrent seasonal symptoms for more than one year)

Rhinohorrea
Nasal obstruction

Date:
Duration:
Treatment:

3. Extrinsic asthma

Recurrent wheezing
Nasal obstruction
Shortness of breath
Nocturnal cough

Date of onset:
Duration:
Treatment

4. Drug Allergy

Urticaria
Angioedema
Anaphylaxis

Drug(s):

Date:
Duration:
Treatment:

5. Insect allergy (unusual reactions to insect bites)

Urticarial rash (> 24 hours)
Extensive Local Erythema (> 24 hours)

Insect(s):

Date:
Duration:
Treatment:

6. Plant allergy

Skin reactions
Asthma
Rhinitis

Oil seed rape flowers
Other plant allergies

Date:
Duration:
Treatment:

7. Food allergy

Urticaria
Angioedema
Anaphylaxis

Food:

Date:
Duration:
Treatment:

8. Personal TB history

TB
Contact with affected individuals

Date:
Duration:
Treatment:

9. Smoking history

Smoker?
When did you start smoking?
Cigs/day
Do you still smoke?
If not Date of cessation:

10. Family history of allergies

Any close relative with allergies, asthma or atopy?:

Specify allergy:

11. Other factors

Vaccination within six months prior to disease onset?
Desensitisation programme?
Recent discontinuation of steroid therapy prior to disease onset?
Administration of immunoglobulins eg. antitetanus, Hepatitis globulins etc.

SECTION 1

QUESTIONNAIRE FOR STUDY OF THE AETIOLOGY OF VASCULITIS

NAME:_____ INITIALS OF INTERVIEWER:_____

DATE: _____ TIME STARTED:_____ TIME FINISHED:_____

CLINICAL PRECURSORS

When were you born? ____/____/____

Have you ever been diagnosed with vasculitis Y ☐ N ☐

If so when were you diagnosed with vasculitis? ____/____/____

In the time before you were told that you had vasculitis (or in the last 6 months if you do not have vasculitis) did you ever have...

	Y	N	Month/Year first had
- An unexplained fever > 100° F (38°C) that lasted more than 2 weeks?	☐	☐	☐☐
-Any pain, swelling or redness in or around your eye that lasted more than 2 weeks?	☐	☐	☐☐
IF YES Did you consultant a doctor	☐	☐	
Did it occur more than once?	☐	☐	
-A sore or an injury to your skin or mouth that failed to heal within 2 months?	☐	☐	☐☐
-An infection or allergy in your nose or sinuses that lasted more than 2 months?	☐	☐	☐☐
IF YES Were your symptoms bad enough to make you change your daily activities?	☐	☐	
Did you consult a doctor at that time?	☐	☐	

Before you were actually diagnosed with vasculitis (or in the last 6 months if you do not have vasculitis), did you ever have...

		Y	N	Month/year first had
-Sudden nosebleeds that weren't the result of a blow or any physical irritation?		☐	☐	☐☐
IF YES	Did you consultant a doctor?	☐	☐	
	Did it occur at least 6 times over a 2 week period?	☐	☐	
-A persistent cough lasting more than 2 months?		☐	☐	☐☐
IF YES	Were you a smoker at that time?	☐	☐	
IF YES	Was there a change in the cough or phlegm?	☐	☐	
IF YES	Did you cough up blood?	☐	☐	
-Any muscle or joint pain in more than two separate areas of your body which lasted more than 2 months?		☐	☐	☐☐
-An ear pain or discharge from your ear?		☐	☐	☐☐
IF YES	Did you consultant a doctor?	☐	☐	
	Have you had this more than once?	☐	☐	

For those with vasculitis

What do you think was the first sign or symptom that could be associated with vasculitis?

_____

When was this first sign or symptom? _____

What do you think caused this to happen?

_____

_____

Index Date: _____ (TO BE ESTIMATED BY INTERVIEWER)

How old were you at the time of [** INDEX DATE**]? _____

Most of the following questions I'm going to ask you about now will focus on a time just before [**INDEX DATE**], when you were (AGE at that time]. Please try to recall the events surrounding that time period.

SECTION 2.

FAMILY AND SOCIAL CLASS

Where were you born? _____

Were your parents born in Norfolk ? Y ☐ N ☐

Were your grandparents born in Norfolk? Y ☐ N ☐

How many brothers or sisters do you have? _____

How many are older than you? _____

What was your father's occupation? _____

Have you got a partner? Yes ☐ No ☐

What is your partner's occupation? _____

SECTION 3.

OCCUPATION

Now I'd like to make a list of all the jobs you have held before [**INDEX DATE**] (or date of interview if you don't have vasculitis). This should include any time that you've spent in the military.

[IF THE PATIENT WAS OVER 25 YEARS OLD AT THE TIME OF [**INDEX DATE**], OBTAIN INFORMATION ABOUT ALL THE JOBS THEY HAD THAT LASTED AT LEAST 6 MONTHS. IF SHE/HE WAS 25 YEARS OLD OR YOUNGER AT THE TIME OF [**INDEX DATE**], OBTAIN INFORMATION ABOUT ANY JOBS THEY HAD THAT LASTED FOR AT LEAST 3 MONTHS.]

Let's begin with the job you had on [**INDEX DATE**] and work backwards in time from there.

Years Worked	Type of work Occupation	Most important activity or major responsibiity	Type of INDUSTRY	Where
__/__-__/__				
__/__-__/__				
__/__-__/__				
__/__-__/__				
__/__-__/__				

Do you remember any unusual or significant exposures (eg.dust or chemicals) which you experienced while at work? IF YES, what were they?

_____

_____

Specifically, have you ever been exposed to any of the following: Notes

Grain dust	YES ☐	NO ☐
Silicon dust	YES ☐	NO ☐
Commercial scouring powder	YES ☐	NO ☐

Specifically, have you ever worked as a:

Farm worker	YES ☐	NO ☐
Baker	YES ☐	NO ☐
Brick and foundry worker	YES ☐	NO ☐
Sand blaster	YES ☐	NO ☐
Dental technician	YES ☐	NO ☐
Miner/quarry worker	YES ☐	NO ☐

Which mine or quarry? _____

SECTION 4

FOR PEOPLE WHO WORK PRIMARILY INSIDE

Now think about the room or rooms where you worked in the 1 year before [**INDEX DATE**] (or in the past year if you do not suffer with vasculitis).

Do you remember working in a room for more than 4 hours where workmen were performing any major construction, remodelling, installation or other work?

Y ☐ N ☐

Specifically, was/were	Y	N	IF YES, [Describe the unusual]
a chimney cleaned	☐	☐	_____
floors refinished	☐	☐	_____
carpets cleaned or shampooed	☐	☐	_____
rooms plastered	☐	☐	_____
wallcovering removed/applied	☐	☐	_____
rooms painted	☐	☐	_____
pesticide/insecticide applied	☐	☐	_____
chemical spill or leak	☐	☐	_____

Was there extensive work done on:

a plumbing system	☐	☐	_____
a heating/AC system	☐	☐	_____
installing insulation	☐	☐	_____

Other renovation(s) performed: _____
(e.g. whole room added)

Have you ever lived/worked in a barn? Yes ☐ No ☐

SECTION 5.

HOBBIES

Now I'd like to ask you some questions about your hobbies. Can you tell me about any hobbies at which you regularly spent time doing before [**INDEX DATE**] / prior to interview. Also, tell me how much time you spent at each hobby (hours spent per week or month), and the date when you began pursing each hobby.

HOBBY	TIME SPENT/MONTH	DATE BEGAN HOBBY

Thinking about the hobbies you just mentioned, were you ever regularly exposed to any chemical, fume, dust or smoke that you could have inhaled in the one year before [**INDEX DATE**]?

Yes ☐ No ☐ IF YES,

Substance	Hobby	Dates of Exposure

As part of these hobbies or other activites, did you have any significant exposure to fungus, mould (yeast), or other germs or plants, animals or any other living matter in the one year before [** INDEX DATE**]?

Yes ☐ No ☐ IF YES,

Substance	Hobby	Dates of Exposure

In the 1 year before [**INDEX DATE**], did you work in the garden (including digging, mowing, and/or raking)?

Yes ☐ No ☐ [IF NO, go to next page]

IF YES How much time did you spend gardening and what activities were involved?

SECTION 6.

RESIDENCE HISTORY

Now I'd like to ask you about the places you've lived for at least 6 months in the 2 year period before [**INDEX DATE**]. Let's begin with the place where you lived in [**INDEX DATE**] and work backwards in time from there.

For each:
1. What was the name of each city/town where you lived?
2. What were the years that you lived there?
3. What type of dwelling was it? (e.g. flat/home etc)
4. What kind of fuel was used to heat the dwelling?

Name (village/town/county)	Years	Type of dwelling (1-5)	Fuel(s) (a-g)	Does it have a garden?

Type of dwelling:
1 = Flat, no garden ☐
2 = Flat, with garden ☐
3 = House, no garden ☐
4 = House, with garden ☐
5 = Other ☐

Do you have central heating? Yes ☐ No ☐

What type? ☐ a = gas b = oil c = electricity d = wood burning e = coal f = other

Do you use other types of fuel? Which type ? ☐

Was there any major construction going on in this dwelling or dwellings?

IF YES, please describe:

Dwelling: _____ Which room or rooms: _____

Type of construction: _____

_____

Did you participate in the construction? _____

Dwelling: _____ Which room or rooms: _____

Type of construction: _____

Did you participate in the construction? _____

SECTION 7.

FARM EXPOSURE

Now I'd like to as you some questions about any time that you've spent on farms. In the 1 year before [**INDEX DATE**], did you (a) live on a farm (b) visit any farm (c) work on a farm (d) none of these ☐

IF YES, How much time in the 1 year prior to [**INDEX DATE**] did you spend on a farm?

_____ days _____weeks _____ months

In which season did you live on or visit a farm?

Summer ☐ Autumn ☐ Winter ☐ Spring ☐

When you were on a farm, did you spend any time within 30 feet of any crops?

Yes ☐ No ☐

IF YES, when you were on the farm how often were you within 30 feet of the following?

		Daily	Weekly	Monthly	Less often
CROPS:	Wheat	☐	☐	☐	☐
	Barley	☐	☐	☐	☐
	Oats	☐	☐	☐	☐
	Hay	☐	☐	☐	☐
	Sugarbeet	☐	☐	☐	☐
	Oil seed rape	☐	☐	☐	☐
	Linseed oil	☐	☐	☐	☐
	Other	☐	☐	☐	☐

When you were on a farm, did you spend any time within 30 feet of any livestock?

Yes ☐ No ☐

IF YES When you were on the farm how often were you within 30 feet of the following?

		Daily	Weekly	Monthly	Less often
LIVESTOCK:	Cows	☐	☐	☐	☐
	Pigs	☐	☐	☐	☐
	Horses	☐	☐	☐	☐
	Sheep	☐	☐	☐	☐
	Goats	☐	☐	☐	☐
	Chickens	☐	☐	☐	☐
	Other	☐	☐	☐	☐

Did you have any pets in the year prior to the [Index Date]? YES ☐ NO ☐

If YES were any of them ill?_____ What was the illness_____

SECTION 8.

ALLERGIC HISTORY

1. Skin reactions

Have you ever noticed a skin rash after contact with any of the following?

	YES	NO
Metals	☐	☐
Soap	☐	☐
Creams	☐	☐
Other products	☐	☐

If YES, please give:

Date: _____

Duration: _____

Treatment: _____

2. Allergic rhinitis

Have you ever had the following symptoms that recur each year?

	YES	NO
Rhinohorrea (runny nose)	☐	☐
Nasal obstruction	☐	☐

If YES, please give:

Date: _____

Duration: _____

Treatment: _____

3. Asthma

Do you suffer with the following symptoms?

	YES	NO
Recurrent wheezing	☐	☐
Nasal obstruction	☐	☐
Shortness of breath	☐	☐
Is your sleep disturbed by night time cough, wheeze or shortness of breath ?	☐	☐

If YES, please give Date: _____

Duration: _____

Treatment: _____

Have you ever been prescribed inhalers? YES ☐ NO ☐

If YES, what sort? _____

4. Drug Allergy

Have you ever been 'allergic' to any medication? YES ☐ NO ☐

Which medication? _____

Please give: Date: _____

Duration: _____

Treatment: _____

Please describe the symptoms: _____

_____

5. Insect allergy (unusual reactions to insect bites)

Have you had any reactions to an insect bite or sting?

	YES	NO
(a) generalised rash	☐	☐
(b) localised rash	☐	☐
(c) anaphylaxis (facial swelling & wheezing)	☐	☐

Which insect? _____

Please give: Date: _____

Duration: _____

Treatment: _____

6. Plant allergy

Are you allergic to any plants? YES ☐ NO ☐

If YES, which plants? _____

What happens?

Skin reactions ☐
Asthma ☐
Rhinitis (runny nose, itchy eyes) ☐

When did this occur? Date: _____

Duration: _____

Treatment: _____

Food allergy

Are you allergic to any food? YES ☐ NO ☐

If YES, which food? _____

What happens?
- Urticaria (weals/hives) ☐
- Angiodema (swollen lips & mouth) ☐
- Anaphylaxis (swelling & wheezing) ☐

When did this occur?
- Date: _____
- Duration _____
- Treatment: _____

SECTION 9.

. Personal TB history

Have you ever had TB? YES ☐ NO ☐

If YES, Date: _____

Duration: _____

Treatment: _____

Have you had contact with affected individuals? YES ☐ NO ☐

If YES, when? _____

9. Have you ever had hepatitis? YES ☐ NO ☐

Which sort? _____

10. Have you ever had a blood transfusion? YES ☐ NO ☐

IF SO, when _____ and where _____

11. Smoking history

Have you ever smoked? YES ☐ NO ☐
When did you start smoking? _____
How many cigarettes per day _____
Do you still smoke? YES ☐ NO ☐
If not, when did you give up? _____

10. Family history of allergies

Do you have any close relatives with allergies, asthma or atopy? YES ☐ NO ☐
(ie. brother, sister, parents, children)

Specify allergy: _____

11. Other factors

Have you a close relative diagnosed with vasculitis? YES ☐ NO ☐

What medication were you taking in the 6 months prior to [INDEX DATE]/last 6 months

_____

_____

Did you have a vaccination within six months of [INDEX DATE] /this interview?

YES ☐ NO ☐

Which ones? _____

Had you recently stopped steroid therapy prior to [INDEX DATE]/ this interview?

YES ☐ NO ☐

What sort, inhaled/oral steroids? _____

SECTION 10.

Now I would like to as you some questions related to the time AFTER you were diagnosed with vasculitis. Since your diagnosis, have you ever had any 6 month periods where you were off all drugs for treatment of vasculitis?

Yes ☐ No ☐ [IF NO, STOP]

IF YES After having been off all drugs for at least 6 months, did you then ever have another episode ("flare-up") of vasculitis?

Yes ☐ No ☐ [IF NO, STOP]

IF YES Can you tell me how many such episodes of sickness you have had and when they occurred.

DATE	SYMPTOMS
_____	_____
_____	_____
_____	_____

In the 6 months BEFORE an episode of sickness, do you remember any significant or unusual exposure to any chemicals, fumes, dust, smoke, plants, animals, fungus, moulds or germs?

Yes ☐ No ☐

IF YES

DATE	SUBSTANCE	CIRCUMSTANCES OF EXPOSURE
_____	_____	_____
_____	_____	_____
_____	_____	_____

In your opinion, what do you think caused you to have another episode of vasculitis?

_____

_____

FOR ALL PATIENTS

In YOUR opinion, no matter how silly it may sound, what do you think could have caused you to get VASCULITIS?

_____

_____

ppendix 1 New BVAS form for EUVAS studies

VASCULITIS ACTIVITY SCORE

○ Tick box **only** if abnormality is **newly present** since last assessment or **worse** in the last **few weeks** (use the Vasculitis Damage Index, VDI to score items of damage)
□ Tick box **only** if abnormality is due to **active** (but not new or worse) vasculitis
◊ Tick box if more information (specialist opinion/tests) is requested
@ oral/axillary temperatures; rectal temperatures are 0.5°C higher

DEMOGRAPHY
Trial Number
Visit Date / /
Investigator

	PERSISTENT	NEW/WORSE
1. GENERAL	□ (none)	
malaise	□	○
myalgia	□	○
arthralgia/arthritis	□	○
headache	□	○
fever (< 38.5°C) @	□	○
fever (≥ 38.5°C) @	□	○
wt loss (≥ 2kg)	□	○
2. CUTANEOUS	□ (none)	
infarct	□	○
purpura	□	○
other skin vasculitis	□	○
ulcer	□	○
gangrene	□	○
multiple digit gangrene	□	○
3. MUCOUS MEMBRANES/EYES	□ (none)	
mouth ulcers	□	○
genital ulcers	□	○
significant proptosis	□	○
red eye- conjunctivitis	□	○
red eye- epi/scleritis	□	○
blurred vision	□	○
sudden visual loss	□	○
ophthalmic opinion	◊	
no active vasculitis	□	
uveitis	□	
retinal exudates	□	
retinal haemorrhage	□	
ENT	□ (none)	
Nasal obstruction		
Bloody nasal discharge	□	○
Nasal crusting	□	○
Sinus involvement	□	○
Hearing loss	□	○
Hoarseness/stridor	□	○
ENT opinion	◊	
No active vasculitis	□	
Granulomatous sinusitis	□	
Conductive hearing loss	□	
Sensorineural hearing loss	□	
Significant Subglottic inflammation	□	
4. CHEST	□ (none)	
Persistent cough	□	○
Dyspnoea or wheeze	□	○
Haemoptysis/haemorrhage	□	○
Chest radiology performed	◊	
No active vasculitis	□	○

	PERSISTENT	NEW/WORSE
5. CHEST continued		
nodules or cavities		□
pleural effusion/pleurisy		□
infiltrate		□
massive haemoptysis or alveolar harmorrhage	□	○
respiratory failure	□	○
6. CARDIOVASCULAR	□ (none)	
bruits	□	○
new loss of pulses	□	○
new loss of pulses with threatened loss of limb	□	○
aortic incompetence	□	○
pericardial pain/rub	□	○
ischaemic cardiac pain	□	○
congestive cardiac failure	□	○
cardiology opinion/tests		◊
no active vasculitis		□
pericarditis		□
myocardial infarct/angina		□
cardiomyopathy		□
7. ABDOMINAL	□ (none)	
severe abdominal pain	□	○
bloody diarrhoea	□	○
surgical opinion/tests		◊
no active vasculitis		□
gut perforation/infarct		□
acute pancreatitus		□
8. RENAL	□ (none)	
hypertension (diastol>95)	□	○
proteinuria (>1+/>0.2g/24h)	□	○
haematuria (>1+/>10rbc/ml)	□	○
creatinine 125-249 umol/l		○
creatinine 250-499 umol/l		○
creatinine >500 umol/l		○
rise in creatinine >30% or fall in creatinine clearance>25%		○
9. NERVOUS SYSTEM	□ (none)	
organic confusion/dementia	□	
seizures(not hypertensive)	□	○
stroke	□	○
cord lesion	□	○
sensory peripheral neuropathy	□	○
cranial nerve palsy	□	○
motor mononeuritis multiplex	□	○
10. OTHER	□	○

ppendix 2. GLOSSARY for BVAS

NERAL RULE: disease features are scored only when they are due to active vasculitis, after exclusion of other obvious causes (e.g. infection, hypertension, etc.). If the feature has curred afresh or represents a recent deterioration of status since last visit, it is scored in the NEW/WORSE boxes. It is essential to apply these principles to each item below. Scores have en weighted according to the severity which each symptom or sign is thought to represent. Tick box (Persistent) if the abnormality indicates the presence of active (but not new or worse) sculitis. For some features, further information (from specialist opinion or further tests) is required if abnormality is newly present or worse. Remember that in most instances, you will be e to complete the whole record when you see the patient. However, on occasions, you may require further information before entering some items. We would suggest that you leave se items blank, and once the information is available, please remember to take the time to fill in the information. For example, if the patient has new onset of stridor, you would usually an ENT colleague to investigate this further to determine whether or not it is due to active Wegener's granulomatosis.

RIVATION of BVAS.1 (new/worse) BVAS.2 (persistent) scores. The data from the score sheet will be used to derive indices of disease activity as follows:

AS.1 - This represents a score of new/worse disease activity attributable to vasculitis

AS.2 - This represents a score of disease activity due to persisting or grumbling disease, which is neither new nor worse, compared to the previous assessment..

ores are calculated using the values given to each item as shown; each section has a maximum score, corresponding to the total value for BVAS (new/worse) and BVAS (persistent).

Item	Definition	BVAS persistent	BVAS new/worse
1. General	**Maximum scores**	**2**	**3**
Malaise	a general feeling of tiredness, illness & discomfort.	1	1
Myalgia	pain in the muscles	1	1
ralgia or arthritis	pain in the joints or joint inflammation;	1	1
Headache	new, unaccustomed & persistent	1	1
Fever <38.5	Documented oral/axillary temperature elevation. Rectal temperatures are 0.5 C higher	1	1
Fever >=38.5	documented oral/axillary temperature elevation. Rectal temperatures are 0.5 C higher	2	2
Weight Loss	At least 2kg loss of body weight (not fluid) having occurred since last assessment or in the 4 weeks not as a consequence of dieting	2	2

2. Cutaneous	**Maximum scores**	**3**	**6**
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Petechiae (small red spots), palpable purpura, or ecchymoses (large plaques) in skin or oozing (in the absence of trauma) in the mucous membranes.	1	2
her skin vasculitis	e.g., livedo reticularis, nodules etc.	2	2
Ulcer	Open sore in a skin surface.	1	4
Gangrene	Extensive tissue necrosis (e.g. digit)	1	6
Multiple digit gangrene	Extensive tissue necrosis occurring in more than one digit or limb.	2	6

3. Mucous membranes/eyes	**Maximum score**	**3**	**6**
Mouth ulcers	Ulcers localised in the mouth. Exclude other causes, such as drugs, Crohn's disease, pemphigus etc.	1	1
Genital ulcers	Ulcers localised in the genitalia or perineum.	1	1
ificant proptosis	Protrusion of the eyeball due to significant amounts of inflammatory in the orbit. This may be associated with diplopia due to infiltration of extra-ocular muscles.	2	4
Red eye conjunctivitis	Inflammation of the conjuctivae (exclude infectious causes); (specialist opinion not usually required).	1	1
Red eye (Epi)scleritis	Inflammation of the sclerae (specialist opinion not usually required).	1	2
Blurred vision	Significant impairment of vision.	2	3
dden visual loss	Sudden loss of vision requiring ophthalmological assessment.		6
thalmic opinion	To diagnose & score retinal exudates, haemorrhages, uveitis & reason for sudden visual loss. This data must be entered on score sheets subsequently.		
Uveitis*	Inflammation of the uvea (iris, ciliary body, choroid) confirmed by ophthalmologist.		6
tinal exudates*	Any area of soft retinal exudates (exclude hard exudates) seen on ophthalmoscopic examination.		6
Retinal haemorrhages*	Any area of retinal haemorrhage seen on ophthalmoscopic examination.		6

4. ENT	**Maximum scores**	**3**	**6**
sal obstruction	A history of nasal blockage	1	2
Bloody nasal discharge	Blood stained secretions from the nose, irrespective of severity, or frequency & severity of previously occurring bleeding since last visit.	2	4
Nasal crusting	Discharge of large serous or serosanguinous crusts from either nostril.	2	4
nus involvement	Tenderness or pain over paranasal sinuses or X-ray evidence of sinusitis. If nasal bridge collapse is observed, this may be recorded separately (in 10. Other)	1	2
Hearing loss	Significant new hearing loss requiring specialist opinion.		3
oarseness/stridor	Increasing hoarseness & inspiratory stridor.		5
ENT opinion	To ascribe otitis media, deafness, or diagnose subglottic involvement due to vasculitis. This data can be entered on score sheets subsequently.		
Granulomatous sinusitis*	Characteristic appearance on nasal examination		4
nductive hearing loss*	Any hearing loss due to middle ear involvement preferably confirmed by audiometry.		3
Sensorineural hearing loss*	Deafness attributable to auditory nerve or cochlear damage.		6
Significant subglottic inflammation*	Inspiratory stridor with significant narrowing of subglottic space confirmed by further examination (usually by an ENT specialist) or by radiological assessment		6

5. Chest	**Maximum scores**	**3**	**6**
Persistent cough	Cough for more than 2 weeks (other causes for the cough having been excluded eg infection)	1	2
pnoea or wheeze	Shortness of breath or audible wheeze on exercise, by history &/or clinical examination.	1	2
Haemoptysis/ haemorrhage	Production of blood stained sputum. Other causes (e.g. infection, cancer) should be excluded.	1	3
Chest radiology performed	A chest radiograph should be performed if there are significant signs or symptoms to suggest chest disease or in the presence of a generalised flare – to determine the following three:		
dules or cavities*	New lesions, detected by CXR.		3
Pleural ffusion/pleurisy*	Pleural pain &/or friction rub on clinical assessment or new onset of radiologically confirmed pleural effusion. Other causes (e.g. infection, cancer) should be excluded.		4
Infiltrate	By CXR, CT scan.		4
sive haemoptysis/	major pulmonary bleeding, with shifting pulmonary		6
Alveolar haemorrhage	infiltrates & usually associated with signs of shock; other causes of bleeding should be excluded.		
Respiratory failure	dyspnoea which is sufficiently severe as to require artificial ventilation; arterial blood gases should be performed to confirm the presence of hypoxaemia & or hypercapnia.	3	6

6. Cardiovascular	**Maximum scores**	**3**	**6**
Bruits	Murmurs detected by auscultation of large arteries, e.g. carotid, subclavian.	1	2
New loss of pulses	Any vessel, detected clinically without threatened loss of limb.		4
New loss of pulses with threatened loss of limb	Any vessel, detected clinically with threatened loss of limb.		4
Aortic incompetence	Significant aortic valve regurgitation, detected clinically or echocardiographically.	2	4
Pericardial pain/rub	Pericardial pain &/or friction rub on clinical assessment.	2	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain. Consider the possibility of more common causes (eg atherosclerosis)	2	4
Congestive cardiac failure	By history or clinical examination	2	4
Cardiology opinion or tests	specialist opinion/tests are usually required to determine the following features		
Pericarditis*	Pericardial pain &/or friction rub on clinical assessment.		4
Myocardial infarction/angina*	Typical history of cardiac pain.		6
Cardiomyopathy*	Heart failure by history or clinical examination		6

7. Abdominal	**Maximum scores**	**4**	**9**
Severe abdominal pain	Of recent onset & attributed to vasculitis.	2	3
Bloody diarrhoea	of recent onset, not due to known inflammatory bowel disease, etc.	2	3
Surgical opinion/tests	specialist opinion/tests required to determine the cause of abdominal pain or diarrhoea if they are of recent onset or worse since last visit.		
Gut perforation/infarction*	typical pain & peritonism includes gall bladder or appendix. Confirmed by X-ray or at surgery.		9
Acute pancreatitis*	typical history & clinical examination findings of acute abdominal pain & tenderness with guarding. Confirmed by elevated serum amylase & a surgical opinion		9

8. Renal	**Maximum scores**	**6**	**12**
Hypertension	Diastolic BP>95, accelerated or not, with or without retinal changes.	1	4
Proteinuria	>1+ on urinalysis; >0.2g/24 hours. Infection should be excluded.	2	4
Haematuria	>1+ on urinalysis; >10 rbc/ml, or red cell casts seen on urine microscopy. Infection should be excluded.	3	6
Creatinine 125-249	Serum creatinine values 125-249 umol/l at first assessment only.	2	4
Creatinine 250-499	Serum creatinine values 250-499 umol/l at first assessment only.	3	6
Creatinine >=500	Serum creatinine values 500 umol/l or greater at first assessment only.	4	8
Rise in creatinine > 30% or creatinine clearance fall > 25%	Significant deterioration in renal function attributable to active vasculitis.		6

9. Nervous system	**Maximum scores**	**6**	**9**
Organic confusion/Dementia	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Paroxysmal electrical discharges in the brain & producing characteristic physical changes including tonic & clonic movements & certain behavioural changes.	3	9
Stroke	Cerebrovascular accident resulting in focal neurological signs such as paresis, weakness, etc. A stroke due to other causes (eg atherosclerosis) should be considered & appropriate neurological advice is recommended	3	9
Cord lesion	Transverse myelitis with lower extremity weakness or sensory loss (usually with a detectable sensory level) with loss of sphincter control (rectal & urinary bladder).	3	9
Sensory Peripheral neuropathy	Sensory neuropathy resulting in glove &/or stoking distribution of sensory loss. Other causes should be excluded (e.g. idiopathic, metabolic, vitamin deficiencies, infectious, toxic, hereditary).	3	6
Cranial nerve palsy	Isolated acute cranial nerve palsy, excluding sensorineural hearing loss, or optic nerve lesion secondary to retro-orbital mass.	3	6
Motor mononeuritis multiplex	Simultaneous neuritis of many peripheral nerves, only scored if motor involvement. Other causes should be excluded (diabetes, sarcoidosis, carcinoma, amyloidosis).	3	9

10. Other	**Significant features attributable to active vasculitis not listed above.**		
	Total maximum score	**33**	**63**

VASCULITIS DAMAGE INDEX

Tick box (O) if damage has been present for at least 3 months unless otherwise stated.
Damage occurring since the onset of vasculitis and which may be attributable to the effects of disease, therapy or any other cause and which does not have to be present (it is not a score of active vasculitis, which should be assessed on the Vasculitis Activity Score sheet (BVAS).)

Vasculitis Damage Index (VDI): This is a score of damage due to non-healing scars. Please note that damage does not have to be currently present. This is a cumulative assessment of organ dysfunction, damage or scarring. Damage is ascertained by clinical assessment and can either remain stable or deteriorate with time.

* Subsequent events must have developed more than 3 months after initial events

Adverse drug reactions (ADR)
Although many of the features of VDI may reflect drug related damage, there is a quite separate ADR form for any types of ADR, which must be completed separately. Please ensure that you carefully record a detailed description of the ADR

MUSCULOSKELETAL		VDI
None	O	
Significant atrophy or weakness		O
Deforming or erosive arthritis		O
Osteoporosis + fracture/vertebral collapse		O
Avascular necrosis		O
Osteomyelitis		O
SKIN/MUCOUS MEMBRANES		
None	O	
Alopecia		O
Cutaneous ulcers		O
Mouth ulcers		O
OCULAR		
None	O	
Any cataract		O
Retinal change/optic atrophy		O
Visual impairment/diplopia		O
Blindness in one eye		O
Blindness in other eye		O*
Orbital wall destruction (X ray/CT/MRI)		O
ENT		
None	O	
Hearing loss		O
Nasal blockage/chronic nasal discharge/crusting		O
Nasal bridge collapse/septal perforation		O
Chronic sinusitis/radiological evidence of bone destruction		O
Subglottal stenosis		
without surgical intervention		O
with surgical intervention		O
PULMONARY		
None	O	
Pulmonary hypertension		O
Pulmonary fibrosis/cavity		O
Pulmonary infarction		O
Pleural fibrosis		O
Chronic asthma		O
Significant chronic breathlessness		O
Impaired pulmonary function tests		O

VDI

DEMOGRAPHY
Trial Number
Visit Date / /
Investigator

CARDIOVASCULAR		VDI
None	O	
Angina or coronary artery bypass		O
Myocardial infarction		O
Subsequent myocardial infarction		O*
Cardiomyopathy		O
Valvular disease		O
Pericarditis >3 months or pericardiectomy		O
Hypertension (diastolic BP >95) or requiring anti-hypertensive drugs		O
PERIPHERAL VASCULAR DISEASE		
None	O	
Absent peripheral pulses in one/more limbs		O
Subsequent fresh loss of peripheral pulses		O*
Major vessel stenosis		O
Claudication > 3 months		O
Minor tissue loss		O
Major tissue loss		O
Subsequent major tissue loss		O*
Complicated venous thrombosis		O
GASTROINTESTINAL		
None	O	
Gut infarction or resection		O
Mesenteric insufficiency or pancreatitis		O
Chronic peritonitis		O
Oesophageal stricture OR upper gastrointestinal tract surgery		O
RENAL		
None	O	
Estimated or measured GFR <50%		O
Proteinuria 24hr >0.5g		O
End stage renal disease (on renal replacement therapy)		O
NEUROPSYCHIATRIC		
None	O	
Cognitive impairment OR major psychosis		O
Seizures requiring therapy		O
Cerebrovascular accident		O
Subsequent cerebrovascular accident		O*
Cranial nerve lesion (excludes sensorineural deafness and optic nerve lesions)		O
Peripheral motor or sensory neuropathy		O
Transverse myelitis		O
OTHER DAMAGE/DRUG REACTION		
None	O	
PREMATURE GONADAL FAILURE		O
MARROW FAILURE		O
DIABETES		O
CHRONIC CHEMICAL CYSTITIS		O
MALIGNANCY		O
OTHER FEATURES		O

Are there any scars or consequences of the patient's disease that you wish to record freehand below?

VASCULITIS DAMAGE INDEX

Tick box (O) if damage has been present for at least 3 months unless otherwise stated.
Damage occurring since the onset of vasculitis and which may be attributable to the effects of disease, therapy or any other cause and which does not have to be present (it is not a score of active vasculitis, which should be assessed on the Vasculitis Activity Score sheet (BVAS).)

Vasculitis Damage Index (VDI): This is a score of damage due to non-healing scars. Please note that damage does not have to be currently present. This is a cumulative assessment of organ dysfunction, damage or scarring. Damage is ascertained by clinical assessment and can either remain stable or deteriorate with time.
* Subsequent events must have developed more than 3 months after initial events
Adverse drug reactions (ADR)
Although many of the features of VDI may reflect drug related damage, there is a quite separate ADR form for any types of ADR, which must be completed separately. Please ensure that you carefully record a detailed description of the ADR

MUSCULOSKELETAL	VDI
None	[0]
Significant atrophy or weakness	[1]
Deforming or erosive arthritis	[1]
Osteoporosis + fracture/vertebral collapse	[1]
Avascular necrosis	[1]
Osteomyelitis	[1]
SKIN/MUCOUS MEMBRANES	
None	[0]
Alopecia	[1]
Cutaneous ulcers	[1]
Mouth ulcers	[1]
OCULAR	
None	[0]
Any cataract	[1]
Retinal change/optic atrophy	[1]
Visual impairment/diplopia	[1]
Blindness in one eye	[1]
Blindness in other eye	[1]
Orbital wall destruction (X ray/CT/MRI)	[1]
ENT	
None	[0]
Hearing loss	[1]
Nasal blockage/chronic nasal discharge/crusting	[1]
Nasal bridge collapse/septal perforation	[1]
Chronic sinusitis/radiological evidence of bone destruction	[1]
Subglottal stenosis	
without surgical intervention	[1]
with surgical intervention	[1]
PULMONARY	
None	[0]
Pulmonary hypertension	[1]
Pulmonary fibrosis/cavity	[1]
Pulmonary infarction	[1]
Pleural fibrosis	[1]
Chronic asthma	[1]
Significant chronic breathlessness	[1]
Impaired pulmonary function tests	[1]

VDI -Weighted scores

DEMOGRAPHY
Trial Number
Visit Date / /
Investigator

CARDIOVASCULAR	VDI
None	[0]
Angina or coronary artery bypass	[1]
Myocardial infarction	[1]
Subsequent myocardial infarction	[1]
Cardiomyopathy	[1]
Valvular disease	[1]
Pericarditis >3 months or pericardiectomy	[1]
Hypertension (diastolic BP >95) or requiring anti-hypertensive drugs	[1]
PERIPHERAL VASCULAR DISEASE	
None	[0]
Absent peripheral pulses in one/more limbs	[1]
Subsequent fresh loss of peripheral pulses	[1]
Major vessel stenosis	[1]
Claudication > 3 months	[1]
Minor tissue loss	[1]
Major tissue loss	[1]
Subsequent major tissue loss	[1]
Complicated venous thrombosis	[1]
GASTROINTESTINAL	
None	[0]
Gut infarction or resection	[1]
Mesenteric insufficiency or pancreatitis	[1]
Chronic peritonitis	[1]
Oesophageal stricture OR upper gastrointestinal tract surgery	[1]
RENAL	
None	[0]
Estimated or measured GFR <50%	[1]
Proteinuria 24hr >0.5g	[1]
End stage renal disease (on renal replacement therapy)	[1]
NEUROPSYCHIATRIC	
None	[0]
Cognitive impairment OR major psychosis	[1]
Seizures requiring therapy	[1]
Cerebrovascular accident	[1]
Subsequent cerebrovascular accident	[1]
Cranial nerve lesion (excludes sensorineural deafness and optic nerve lesions)	[1]
Peripheral motor or sensory neuropathy	[1]
Transverse myelitis	[1]
OTHER DAMAGE/DRUG REACTION	
None	[0]
PREMATURE GONADAL FAILURE	[1]
MARROW FAILURE	[1]
DIABETES	[1]
CHRONIC CHEMICAL CYSTITIS	[1]
MALIGNANCY	[1]
OTHER FEATURES	[1]

Are there any scars or consequences of the patient's disease that you wish to record freehand below?

APPENDIX 3

Associated Publications

1. Lane S.E, Scott DGI, Heaton A, Watts RA; Primary renal vasculitis in Norfolk – increasing incidence or increasing recognition?; Nephrol. Dial. Transplant. 2000; 15 : 23-27 **p. 418-422**

2. Watts RA, Lane SE, Bentham G, Scott DGI; Epidemiology of Systemic Vasculitis : A ten Year Study in the United Kingdom; Arthritis & Rheumatism 2000; 43; 2 : 414-419 **p.423-428**

3. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DGI; Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe; Ann Rheum Dis 2001; 60 : 170-172 **p.429-431**

4. Watts RA, Koldingsnes W, Nossent H, Gonzalez-Gay MA, Garcia-Porrua C, Lane S, Bentham G, Scott DGI; Geoepidemiology of systemic vasculitis in three European Regions; Rheumatology; 2001; 40 (Abstract suppl. 1): 123 (350) **p.432**

5. Watts RA, Koldingsnes W, Nossent H, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DGI; Epidemiology of vasculitis in Europe; Annals of Rheum Dis – In Press **p.433-435**

6. Koutantji M, Harrold E, Lane SE, Pearce S, Watts RA, Scott DGI, An Investigation of Quality of Life, pain , disability and disease status in Primary Systemic Vasculitis; Rheumatology, 2000, 39 (Abstract suppl. 1) : 153 (289) **p.436**

7. Koutantji M, Harrold E, Lane SE, Pearce S, Watts RA, Scott DGI, The relationship between coping strategies, illness perceptions and psychological adjustment in patients with primary systemic vasculitis; Rheumatology, 2000, 39 (Aabstract suppl. 1) : 180 (341) **p.437**

N.B. Permission to reprint these publications has been requested.

Nephrol Dial Transplant (2000) 15: 23–27

Nephrology
Dialysis
Transplantation

Original Article

Primary renal vasculitis in Norfolk—increasing incidence or increasing recognition?

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Abstract

Background. The incidence of renal vasculitis has previously been estimated using histological definitions or only a single clinical diagnosis, e.g. Wegener's Granulomatosis (WG). Our hospital is the single referral centre for the former Norwich Health Authority (NHA) which encompasses a stable, homogenous, well-defined and studied population. We estimated the overall incidence of primary renal vasculitis and the incidence within individual clinical disease classifications.

Methods. All cases of primary renal vasculitis diagnosed within the NHA over 66 months (1992–1997) were identified by review of renal biopsies, the Norfolk Vasculitis Register, hospital discharge summaries and plasmapheresis records. Patients were classified using the 1990 American College of Rheumatology criteria for Polyarteritis Nodosa (PAN), Churg Strauss Syndrome (CSS) and Henoch–Schonlein Purpura; the Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis (mPA) and the Lanham criteria for CSS. Incidence figures were calculated using the NHA adult population of 413747 (1994). Ninety-five per cent confidence intervals (C.I.) were calculated using the poisson distribution.

Results. The overall annual incidence for primary renal vasculitis was 18/million (C.I. 12.9–24.4). The annual incidence of renal involvement of individual diseases was as follows: WG 7.9/million (95% C.I. 4.7–12.5); mPA 7.5/million (95% C.I. 4.4–12.0); PAN 7.0/million (95% C.I. 4.0–11.4); HSP 3.1/million (95% C.I. 1.1–6.3); CSS 1.3/million (95% C.I. 0.3–3.9).

Conclusions. The annual incidence for primary renal vasculitis overall and the individual subtypes in Norfolk is much higher than previous European estimates. This may reflect an increasing incidence in primary renal vasculitis with time or underestimation in previous studies. However the incidence of renal vasculitis in our population is markedly lower than reported in Kuwait. There may therefore be true variation in incidence between populations which could have implications for the aetiology of primary vasculitis.

Keywords: classification; epidemiology; pauci-immune glomerulonephritis; vasculitis

Introduction

Vasculitis is an important treatable cause of renal impairment that leads to significant morbidity and mortality. Little data is available on the incidence of renal vasculitis. Early reports are difficult to interpret due to confusing definitions and the absence of accepted criteria. In 1990 the American College of Rheumatology (ACR) proposed criteria for individual diseases using clinical and histological features [1–4]. The Chapel Hill Consensus Conference (CHCC) in 1994 proposed definitions to take account of vessel size [5]. Using these criteria and definitions, epidemiological study has been possible and recent data suggests that these diseases are relatively rare, may be increasing with time, and may occur more commonly in the elderly population than originally suspected [6,7].

No study has considered the overall incidence of renal vasculitis using these criteria. Previous studies have considered individual disease subtypes e.g. Wegener's Granulomatosis (WG) or crescentic necrotizing glomerulonephritis (GN) and rapidly progressive GN (RPGN) [6,8–12].

The area covered by the former Norwich Health Authority (NHA), an administrative grouping of 77 primary care practices, has been used successfully to study the epidemiology of primary systemic vasculitis and rheumatoid arthritis [13,14]. It is suitable for epidemiological study because it has a stable, well-defined adult population of about 415000, served by a single district general hospital which provides a renal service to the NHA and also surrounding areas. There is little referral out of district and these patients can be identified because of good communication between hospital specialities, adjacent health districts and primary care. A prospective register of all patients dia-

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gnosed with vasculitis at the central hospital was established in 1988.

The aim of this study was to estimate the annual incidence in adults (>15 years old) resident in the NHA of clinical primary systemic vasculitis with renal involvement.

The annual incidence was obtained in those who fulfilled accepted classification criteria for each of the following: WG; Microscopic polyangiitis (mPA); Churg Strauss syndrome (CSS); Polyarteritis Nodosa (PAN); and adult Henoch–Schonlein purpura (HSP). In addition an overall annual incidence figure was obtained for all patients with a primary renal vasculitis (definition follows).

As the use of the classifications and definitions is continuing to evolve, detailed data of patients who fulfil more than one criteria is provided and ANCA data available is included to ensure that results may be reliably compared to future studies.

Methods

Definitions

For the purpose of this study we defined primary renal vasculitis as one of the following.

(i) A patient who fulfilled criteria for one of the primary systemic vasculitides and had either a renal biopsy appearance compatible with vasculitis where there was no other identifiable cause for these changes or renal impairment attributable to vasculitis;

(ii) A patient who did not fulfil classification criteria but had a renal biopsy highly suggestive of vasculitis with no other identifiable cause and who was treated clinically as having vasculitis.

Renal impairment was considered to be caused by vasculitis when an elevation of serum creatinine (above the laboratory normal range) coincided with a clinical flare of vasculitis and where there was no alternative identifiable cause.

The following disease classifications were used:

Wegener's Granulomatosis (WG)	ACR (1990) criteria [1]
Polyarteritis Nodosa (PAN)	ACR (1990) criteria [2]
Microscopic polyangiitis (mPA)	CHCC (1994) definition [5]
Churg Strauss Syndrome (CSS)	ACR (1990) [3] and/or Lanham 1984 [15]
Henoch-Schonlein Purpura (HSP)	ACR (1990) criteria [4].

Patients with secondary vasculitis due to an identifiable underlying disorder, for example rheumatoid arthritis, systemic lupus erythematosus or cryoglobulinaemia, were excluded.

Patient identification

Patients with primary systemic vasculitis were identified in the following ways to ensure that as far as possible no cases were missed.

(i) Records of all renal biopsies performed at the Norfolk and Norwich Hospital over 66 months (1992–1997) were reviewed and those with appearances suggestive of vasculitis were evaluated. Although necrotizing GN with or without crescent formation or arteritis is the classical appearance of vasculitis on biopsy, various biopsy appearances can occur. Therefore biopsies were included for review where there was evidence of focal segmental proliferative GN, necrosis, crescents, mesangial proliferation, a pauci-immune appearance on immunofluorescence, arteritis or granuloma formation. Any biopsy that was reported as suspicious of vasculitis was also included for further assessment. Biopsies after January 1995 were readily identifiable through the pathology computerized records. Prior to this date patients who had had a renal biopsy were identified from ultrasound records, then biopsy results obtained through pathology computerized records or by case note review. Table 1 illustrates the diagnoses of patients included and excluded from the study by biopsy review.

(ii) The prospective Vasculitis Register was used to identify patients known to have primary vasculitis diagnosed during the study period [7].

(iii) Hospital records of patients' discharge summaries were searched for any patients coded as having a renal biopsy or a diagnosis of a primary or renal vasculitis.

(iv) Between 1994 and 1997 records of patients who received plasmapheresis were available and were reviewed to identify any vasculitis patients too unwell to have a biopsy. No additional patients were identified in this way.

Case note review

The case notes of all patients identified were reviewed with respect to diagnosis, biopsy appearance and renal function. In each case the underlying diagnosis of the patient was established and those found to have vasculitis were classified as above using a form adapted from the Birmingham Vasculitis Activity Score form [16]. Some patients fulfilled criteria for more than one disease classification.

Eighty one patients (61 resident in NHA) were classified as having a primary systemic vasculitis between 1992 and 1997 following case note review. Sixty one of these patients (47 in NHA) were already known to the vasculitis register. Fifteen patients not on the vasculitis register were found by renal biopsy review (nine in NHA) and a further five patients (all in NHA) were found on review of hospital discharge letters.

Table 1. Vasculitis on renal biopsy 1992–1997

Patients included		Patients excluded	
Criteria fulfilled	No. Patients	Diagnosis	No. Patients
WG	12	Primary GN	44
mPA	8	SLE[a]	15
mPA and PAN	5	IgA nephropathy	3
HSP	5	HSP < 15 years old	2
mPA and WG	4	Sarcoidosis	2
CSS	3	Bacterial endocarditis	2
PAN	2	Systemic Rheumatoid	2
WG and PAN	2	FSGS[b]	2
		Malignancy/sepsis	1
		Cryoglobulinaemia	1
		Bechets	1
		MCTD[c]	1
Total	41	Total	76

[a]Systemic Lupus Erythematosus; [b]Focal Segmental Glomerular Sclerosis; [c]Mixed Connective Tissue Disease.

Nine patients (four in NHA) were identified who were felt to have primary renal vasculitis but did not fulfil classification criteria (Table 2). Two were already known to the register, six were found by renal biopsy review (three in NHA) and one by records review (NHA).

Data analysis

Incidence figures were calculated for patients resident in the former NHA. Residency in the NHA was established according to the location of the patient's general practitioner at the time of diagnosis. We used the NHA although it is no longer in existence as this population has been studied by the Norfolk Arthritis Register and well-established population details are available [13]. All patients resident in the former NHA continue to be referred to our single District General Hospital.

The annual incidence of renal vasculitis for each disease classification and the overall annual incidence of adult primary renal vasculitis was calculated using the adult population of 413 747 (1994). This was the population of patients over the age of 15 registered with the 77 general practitioners that comprised the former NHA. The adult population in 1994 consisted of 199 682 males and 214 056 females. The population was 99% caucasian and split between urban and rural areas. Where a patient fulfilled criteria for more than one disease classification they were included in the calculation for each disease. Ninety-five per cent confidence intervals (C.I.) were calculated using the poisson distribution for the number of cases observed.

Results

The classification of patients with primary systemic vasculitis who attended the Norfolk and Norwich Hospital 1992–1997 is shown in Table 3. Each category is subdivided to show the sex ratio, residency in the NHA and renal involvement. Four additional patients classified as CSS had renal impairment but this could be attributed to ovarian carcinoma, gentamicin administration, chronic renal failure due to both hypertension and insulin dependent diabetes mellitus, and renal impairment in a critically ill patient within 24 h of death rather than vasculitis *per se*. One patient diagnosed as mPA was found to have subacute bacterial endocarditis at post-mortem and was therefore excluded. Renal impairment in all other cases could be attributed to vasculitis. One patient diagnosed with WG with renal impairment and a biopsy compatible with IgA nephropathy was included.

For the individual diseases the annual incidence for patients with renal involvement in each disease was as follows: WG 7.9/million (95% C.I. 4.7–12.5); mPA 7.5/million (95% C.I. 4.4–12.0); PAN 7.0/million (95% C.I. 4.0–11.4); HSP 3.1/million (95% C.I. 1.2–6.3); CSS 1.3/million (95% C.I. 0.3–3.9). Incidence by sex is shown in Table 4.

Table 3. Primary systemic vasculitis 1992–1997

Criteria fulfilled	No. patients		Renal involvement	
	Total (male)	NHA (male)	Total (male)	NHA (male)
WG	21(13)	14(8)	14(9)	8(5)
WG and Mpa	5(1)	4(1)	5(1)	4(1)
WG and PAN	7(4)	6(3)	7(4)	6(3)
Mpa	7(4)	4(2)	7(4)	4(2)
Mpa and PAN	12(6)	9(6)	10(6)	8(6)
PAN	3(0)	2(0)	2(0)	1(0)
Mpa and HSP	1(1)	1(1)	1(1)	1(1)
PAN and HSP	1(1)	1(1)	1(1)	1(1)
HSP	9(7)	8(7)	5(4)	5(4)
CSS	15(9)	12(8)	3(2)	3(2)
Total	81(46)	61(37)	55(32)	41(25)

In total 41 patients living in the NHA with renal vasculitis fulfilled at least one classification criteria for primary systemic vasculitis. An additional four patients in the NHA failed to fulfil classification criteria but had clinical features of vasculitis, compatible renal biopsies and responded appropriately to treatment. An estimate for the annual incidence of primary renal vasculitis for our population was therefore 18.0/million (95% C.I. 12.9–24.4).

The percentage of patients with renal involvement for each disease derived from all patients studied was as follows: mPA 92% (23/25); PAN 87% (20/23); WG 79% (26/33); HSP 64% (7/11); and CSS 20% (3/15). There was no significant difference in the percentage of male or female patients. Details of ANCA results for all patients is shown in Table 5.

Discussion

Our annual incidence figure for primary renal vasculitis, 18.0/million/year is higher than previous European studies. In Leicester, England, Andrews *et al.* reviewed the incidence of mPA and WG between 1980–1986 [6]. Classification of WG used criteria similar to the ACR 1990 criteria and a diagnosis of mPA required clinical evidence of vasculitis in more than one organ system and histological evidence of small vessel vascul-

Table 2. NHA patients with clinical primary renal vasculitis who failed to fulfil criteria

	Renal biopsy	Treatment	ANCA
1	Pauciimmune necrotizing GN with nuclear debris	I.v. cyclophosphamide and methylprednisolone	Negative
2	Pauciimmune crescentic GN	I.v. methylprednisolone	pANCA
3	No biopsy, small kidneys	P.o. cyclophosphamide and prednisolone	Positive 36%
4	Necrotizing crescentic GN	I.v. cyclophosphamide and methylprednisolone, plasmapheresis	Positive 68%

Table 4. Annual incidence of renal vasculitis by classification in NHA 1992–1997

Disease Classification	Annual incidence/million/year (95% C.I.)		
	Total	Male	Female
WG	7.9 (4.7–12.5)	8.2 (3.7–15.6)	7.6 (3.5–14.5)
mPA	7.5 (4.4–12.0)	9.1 (4.4–16.7)	5.9 (2.4–12.3)
PAN	7.0 (4.0–11.4)	9.1 (4.4–16.7)	5.1 (1.9–11.1)
HSP	3.1 (1.2–6.3)	5.5 (2.0–11.9)	0.9 (0.02–4.7)
CSS	1.3 (0.3–3.9)	1.8 (0.2–6.6)	0.9 (0.02–4.7)
Total primary renal vasculitis	18.0 (12.9–24.4)	22.8 (14.7–33.6)	13.5 (7.8–22.1)

Table 5. Details of ANCA results

Criteria fulfilled	Negative/unknown	Positive		
		Crude	pANCA /MPO	cANCA /PR3
WG	6	3	0	12
WG and Mpa	0	2	1	2
WG and PAN	1	2	1	3
Mpa	2	3	1	1
Mpa and PAN	1	4	5	2
PAN	1	1	1	0
Mpa and HSP	1	0	0	0
PAN and HSP	0	0	1	0
HSP	7	1	1	0
CSS	7	3	4	1

itis at least one site in the absence of specific respiratory or histological features of WG. There were 36 cases in their population of 1.3 million. All cases had renal involvement, 35 with focal segmental necrotizing GN and one with a scarred end-stage kidney. The combined annual incidence for mPA and WG was 1.5/million.

In Lund, Sweden, Westman *et al.* reported 56 cases of WG, fulfilling ACR criteria and 67 cases of mPA, using CHCC definitions, in their population of 1.2 million between 1971 and 1993 [8]. All cases had renal involvement. The annual incidence for WG and mPA respectively was therefore 2.1/million and 2.5/million. The combined annual incidence for mPA and WG was 4.6/million.

Thirty one patients in our population with renal vasculitis fulfilled classification criteria for WG and/or mPA. The annual incidence for renal involvement in WG and mPA combined in the NHA was 13.6/million (95% C.I. 9.3–19.3) which is much higher than those reported by either the Leicester or Lund groups.

A survey of the Italian Registry of Renal Biopsies in patients over 18 years of age revealed an annual incidence for 1993 of 1.6/million for necrotizing vasculitis and 1.3/million for HSP, lower than our figure for adult HSP of 3.1/million/year [9].

Other studies have considered histological and laboratory definitions of renal vasculitis. Andrassy *et al.* investigated the incidence of crescentic GN and RPGN in Heidelberg, Germany, between 1984 and 1989 [10]. There were 33 cases of biopsy proven crescentic GN and five cases of RPGN on clinical definitions during the study period in their population of 930 000, giving a combined annual incidence of 7.0/million. This study included patients with SLE, Goodpastures and IgA nephropathy in addition to WG, HSP and mPA. In Huddinge, Sweden, Pettersson *et al.* found 71 new cases of pauci-immune necrotizing and crescentic GN between 1986 and 1992 in their adult population of 1.2 million, giving a mean annual incidence of 8/million. It was noted that the annual incidence doubled from 6/million in 1986 to 12/million in 1992 [11]. Both papers suggest that the incidence of renal vasculitis may be increasing. Conversely a 10-year retrospective study from 1986 to 1996 in Wessex, England, found the annual incidence of biopsy proven RPGN to be 3.5/million and this was stable throughout the period [12]. Although different definitions have been used, the annual incidence we report is probably genuinely higher than that reported in the other studies, particularly as secondary vasculitis was included in some calculations and specifically excluded in ours.

One study does however find much higher incidence figures than our population. El-Reshaid *et al.* studied renal disease associated with mPA and classical PAN using the CHCC definition in the Kuwaiti population [17]. The local population comprised of 60% heterogeneous expatriates so the remaining 40% of Kuwaiti nationals alone was used to determine incidence figures. An annual incidence of 45/million was found for mPA, classic PAN and patients with angiography compatible with PAN but who failed to fulfil criteria. The annual incidence was 65/million for males and 33/million/year for females.

Our annual incidence figure of 7.5/million for renal disease in mPA is much lower than that of the Kuwaiti study. It is interesting to note that there were no cases of classic PAN using CHCC definitions in our population during the study period. Our incidence figure is likely to be a slight underestimate as some patients may have had only mild changes on their renal biopsy and would therefore not have been detected by renal biopsy review. Some patients may have also been missed if they had been too unwell to have a renal biopsy or if the biopsy was unsuccessful. However this difference in incidence would be slight and a large discrepancy in incidence remains between the two populations.

Conclusions

The overall annual incidence figure for primary renal vasculitis in Norfolk is 18.0/million, 7.9/million for WG and 7.5/million for mPA which are all higher than previous European reports. These differences could reflect true variation between populations, be due to underestimation in previous studies or indicate that the incidence of renal vasculitis is increasing with time.

The incidence of renal vasculitis in Norfolk is much lower than in Kuwait. Further study of different populations using comparable classification criteria will provide important information of the variation of these diseases in time and space and may lead to a greater understanding of their aetiology.

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EPIDEMIOLOGY OF SYSTEMIC VASCULITIS

A Ten-Year Study in the United Kingdom

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Objective. To describe the epidemiology of the primary systemic vasculitides (PSV; Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, polyarteritis nodosa) in a well-defined population over a 10-year period.

Methods. An inception cohort of patients from the Norwich Health Authority (NHA) who were >15 years of age and had PSV first diagnosed between January 1, 1988 and December 31, 1997 was collected. Incidence rates were adjusted for age and sex to the 1992 population. The prevalence of PSV in this cohort was estimated on December 31, 1997. Patients were classified according to the American College of Rheumatology 1990 vasculitis criteria and the Chapel Hill Consensus definitions.

Results. Eighty-two NHA residents fulfilled the inclusion criteria. There were 47 men and 35 women, with a mean age of 62.9 years (median 65.0 years). The overall annual incidence of PSV among NHA residents was 19.8/million (95% confidence interval [95% CI] 15.8–24.6). The point prevalence on December 31, 1997 was 144.5/million (95% CI 110.4–185.3). PSV was more common in males (23.5/million; 95% CI 17.3–31.3) than females (16.4/million; 95% CI 11.4–22.8). The age- and sex-specific incidence showed a clear increase with age, with an overall peak in the 65–74 year age group (60.1/million).

Conclusion. In our study population, the annual incidence of PSV is slowly increasing with time and the incidence is greatest in the elderly.

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The primary systemic vasculitides (PSV)—Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), and Churg-Strauss syndrome (CSS)—are a group of rare conditions characterized by inflammation and necrosis of blood vessel walls. The etiology of these conditions is unknown, but geographic, environmental, and genetic factors are important. Until recently, there were relatively few accurate descriptive epidemiologic data available. The development of generally recognized classification criteria by the American College of Rheumatology (ACR) in 1990 (1–3) and definitions by the Chapel Hill Consensus Conference (CHCC) in 1994 (4) has enabled epidemiologic studies to be performed.

Classification of patients with PSV can be difficult. The ACR criteria were developed by studying patients with well-defined types of vasculitis, and the criteria have a high sensitivity and specificity for WG, PAN, and CSS (1–3). The criteria were less sensitive and specific for some other types of vasculitis, in particular, hypersensitivity vasculitis and Henoch-Schönlein purpura. The sensitivity and specificity are less good when the criteria are used to classify patients with less well-defined vasculitis (5). The CHCC definitions were not intended to be used to classify patients. The ACR criteria and the CHCC definitions identify different patients (6,7). However, the ACR criteria included patients with PAN but not MPA. MPA was included by the CHCC, and since no other definitions/classification criteria exist for this condition, we have used both the ACR criteria and the CHCC definitions in the present study.

The first estimate of the annual incidence of systemic vasculitis came from Bath/Bristol (United Kingdom) in the 1970s. That study estimated the overall annual incidence to be 10/million (8). Studies reported since then have suggested that there is an increasing incidence of WG (9). Andrews et al (10) reported that

the incidence of WG and MPA was increasing in Leicester (UK), particularly following the introduction of assays for antineutrophil cytoplasmic antibodies (ANCA). The reasons for such an increase are not clear but include better case definition and increased physician awareness.

Previous studies of both the clinical and epidemiologic features of vasculitis have often come from tertiary referral centers and have the associated problems of referral bias, selection bias (e.g., patients who have had renal biopsies), and uncertainty of denominator population. These studies have often been of relatively short duration (<5 years), and it is therefore difficult to assess whether there has been a genuine increase in incidence.

Since 1988, we have maintained a prospective register of patients with systemic vasculitis who attend our institution, which serves a stable and ethnically homogenous population of ~500,000. The population is well defined and is therefore suitable for epidemiologic and clinical studies (11). This provides a good environment in which to study the epidemiology of vasculitis over a prolonged period of time. In the present study, we present data relating to epidemiologic trends with respect to time, sex, and age over a 10-year period.

PATIENTS AND METHODS

The study was hospital based in the former Norwich Health Authority (NHA), Norfolk, UK. The NHA provided administrative services to a group of general medical practices covering a population of 413,500. Patients were included in the study if they were registered with one of these practices. Despite the abolition of the NHA, details of the denominator population registered with these practices could be obtained from the successor organization, the East Norfolk Health Authority.

The study area covers a relatively isolated coastal region in the east of England, with a single referral hospital located centrally. In the UK, patients are referred by their family practitioners for secondary care to the nearest district hospital.

Patients attending as outpatients and those hospitalized with a new clinical diagnosis of systemic vasculitis between January 1, 1988 and December 31, 1997 were prospectively recorded and those registered with a general practitioner in the NHA identified. Detailed demographic data were recorded prospectively. The complete case records of all patients identified with systemic vasculitis were reviewed. In addition, the computerized records of the histopathology department were searched for patients with a histologic diagnosis of systemic vasculitis on tissue biopsy (renal and skin), and the case records were reviewed. Renal biopsy records were reviewed. The hospital discharge diagnostic index was also searched for patients with a discharge diagnosis of PSV (using International Classification of Diseases, Ninth Revision, Clinical Modification codes).

Patients with a documented episode of systemic vasculitis prior to 1988 were excluded, as were patients with giant cell arteritis (GCA), Takayasu arteritis, Henoch-Schönlein purpura, cutaneous leukocytoclastic angiitis, and vasculitis secondary to connective tissue disease or rheumatoid arthritis.

The ACR criteria for PAN (1), WG (2), and CSS (3) were used to classify all patients. The CHCC definitions (4) were applied to all patients. In addition, the Hammersmith criteria for CSS were used (12). A physician not directly involved in patient care (RAW) confirmed the diagnosis of vasculitis and classified the patients. Patients without histologic evidence of granuloma or clinical evidence of upper respiratory tract involvement were considered to have MPA rather than WG, using the CHCC definitions.

The denominator population was provided by the East Norfolk Health Authority as a breakdown by age and sex of the patients registered with the 77 general practices covering the study population. At the midpoint of the study in 1992, the total adult (>15 years) population registered with these general practices was 413,500 (men 200,000; women 213,500). There has since been a slight increase in the population: in 1997 the total adult population was 429,000 (207,000 men). The population includes a slightly higher number of patients who are ≥65 years old (21.5%) compared with the national average for England and Wales (17.8%).

Age- and sex-specific incidence rates were calculated using the number of incident cases as the numerator and the population as the denominator. Incidence rates were compared during the first (from 1988 to 1992) and second (from 1993 to 1997) quinquennia. To estimate whether there were any peaks and troughs in incidence, rates were calculated using a 3-year centered moving average. Prevalence was calculated as a point prevalence on December 31, 1997, using the number of NHA residents who fulfilled the criteria on that date as the numerator and the population as the denominator. A total 10-year period prevalence was also calculated. For purposes of calculating disease-specific incidence, the following criteria were used: PAN ACR (1), WG ACR (2), CSS ACR (3), and MPA CHCC (4).

The population is 98% caucasoid, and one-third of the population lives within 5 km of the city center.

To calculate 95% confidence intervals (95% CI) it was

Table 1. Number of patients with primary systemic vasculitis classified according to ACR criteria, CHCC definitions, and Hammersmith criteria*

	ACR	CHCC	Hammersmith
Wegener's granulomatosis	40	19	–
Microscopic polyangiitis	–	33	–
Polyarteritis nodosa	33	–	–
Churg-Strauss syndrome	11	3	14

* A total of 82 patients were evaluated. Two fulfilled American College of Rheumatology (ACR) criteria (1–3) for both Wegener's granulomatosis and polyarteritis nodosa. Twenty-seven patients did not fulfill the Chapel Hill Consensus Conference (CHCC) definitions (4). The Hammersmith criteria (12) were for Churg-Strauss syndrome only.

Table 2. Annual incidence of primary systemic vasculitis, by time period and sex, in the study population*

Year	Men		Women		Total	
	No. of Patients	Rate	No. of Patients	Rate	No. of Patients	Rate
1988–1992	20	20.0 (12.2–30.9)	14	13.1 (7.2–22.0)	34	16.5 (11.4–23.0)
1993–1997	27	26.1 (17.2–38.0)	21	18.9 (11.7–28.9)	48	22.4 (16.5–30.0)
Total	47	23.5 (11.2–31.3)	35	16.4 (11.4–22.8)	82	19.8 (15.8–24.6)

* Values are the incidence, expressed per million (95% confidence interval).

assumed that the number of cases followed the Poisson distribution.

RESULTS

A total of 140 patients with a new diagnosis of primary systemic vasculitis were identified during the period January 1, 1988 through December 31, 1997. Of these, 105 patients with PSV were registered with general practices in the NHA. The other 35 patients were not resident in the catchment area nor were they registered with a general practice in the NHA and were therefore excluded. Twenty-one patients who were originally diagnosed before 1988 or after 1997 were excluded. Two patients were unclassifiable.

The remaining 82 patients (47 men) were included in this study. Their mean age was 62.9 years (median 65.0 years). The ACR classification criteria (1-3), CHCC definitions (4), and the Hammersmith definition for CSS (12) were applied to all 82 patients, and the number of individuals fulfilling these criteria definitions is given in Table 1. Two patients fulfilled 2 sets of ACR criteria (WG and PAN). Twenty-seven patients fulfilled ACR criteria but not CHCC definitions. There was biopsy evidence of vasculitis in 77% of the patients.

The overall annual incidence of PSV was 19.8 million (95% CI 15.8–24.6). PSV was more common in males (23.5/million; 95% CI 17.3–31.3) than females (16.4/million; 95% CI 11.4–22.8), but this difference was not statistically significant. There was a trend toward an increase in annual incidence. The incidence in the first quinquennium (1988–1992) was 16.5/million (95% CI 11.4–23.0) and in the second (1993–1998), 22.4/million (95% CI 16.5–30.0) (Table 2). The age-specific incidence showed a clear increase with age (Figure 1), with a peak in the 65–74-year-old age group of 60.1/million (95% CI 40.8–85.3). This was observed among both males and females. In men, the incidence peaked at

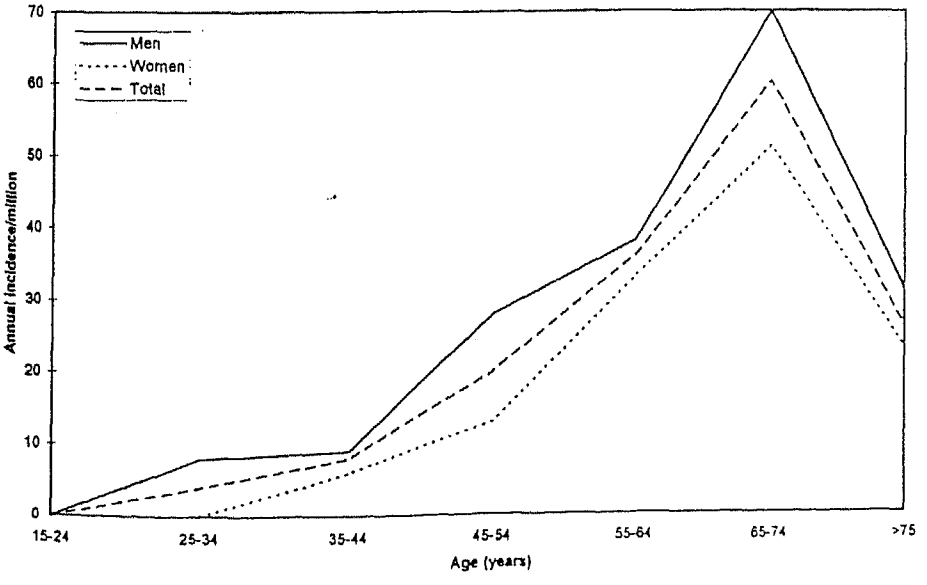

Figure 1. Age-specific incidence of primary systemic vasculitis in the Norwich Health Authority, January 1, 1988 through December 31, 1997.

Table 3. Annual incidence of Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa, and microscopic polyangiitis, by time period, in the study population*

Year	Wegener's granulomatosis		Churg-Strauss syndrome		Microscopic polyangiitis		Polyarteritis nodosa	
	No. of Patients	Rate	No. of Patients	Rate	No. of Patients	Rate	No. of Patients	Rate
1988–1992	18	8.7 (5.2–13.8)	3	1.5 (0.3–4.3)	14	6.8 (3.7–11.4)	14	6.8 (3.7–11.4)
1993–1997	22	10.3 (6.4–15.5)	8	3.7 (1.6–7.4)	19	8.9 (5.3–13.8)	19	8.9 (5.3–13.8)
Total	40	9.7 (7.1–13.5)	11	2.7 (1.3–4.8)	33	8.0 (5.5–11.2)	33	8.0 (5.5–11.2)

*Values are the incidence, expressed per million (95% confidence intervals). Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa classified by American College of Rheumatology criteria (1–3); microscopic polyangiitis defined by Chapel Hill Consensus Conference definition (4).

70.8/million (95% CI 41.2–113.2) and in women at 50.8/million (95% CI 28.0–85.3).

The point prevalence on December 31, 1997 was 144.5/million (95% CI 110.4–185.3) with a 10-year period prevalence of 221.4 (95% CI 179.2–270.2).

The annual incidence of WG during the 10-year period was 9.7/million (95% CI 7.1–13.5) using the ACR criteria. The annual incidence of CSS was 2.7/million (95% CI 1.3–4.8) using the ACR criteria and 3.4/million (95% CI 1.9–5.6) using the Hammersmith definition. The CHCC definitions were used to identify patients with MPA; the annual incidence was 8.0/million (5.5–11.2), which was identical to that seen for PAN using the ACR criteria. No cases of PAN as defined by the CHCC were observed.

Comparison of the first quinquennium with the second showed a trend toward an increase in all conditions studied (Table 3). All conditions were more common in men than women. The age-specific incidence increased with age for all groups until age 65–74 (Figure 2). The point prevalence of WG on December 31, 1997 was 62.9/million (95% CI 41.5–91.6) with a 10-year prevalence of 106.4/million (95% CI 77.3–142.8).

DISCUSSION

This study extends our previous report on the incidence of vasculitis in a stable population and is the first to provide data from a cohort of patients collected prospectively over a 10-year period. There was a trend toward an increase in overall incidence during this period. However, we cannot be certain that this was not

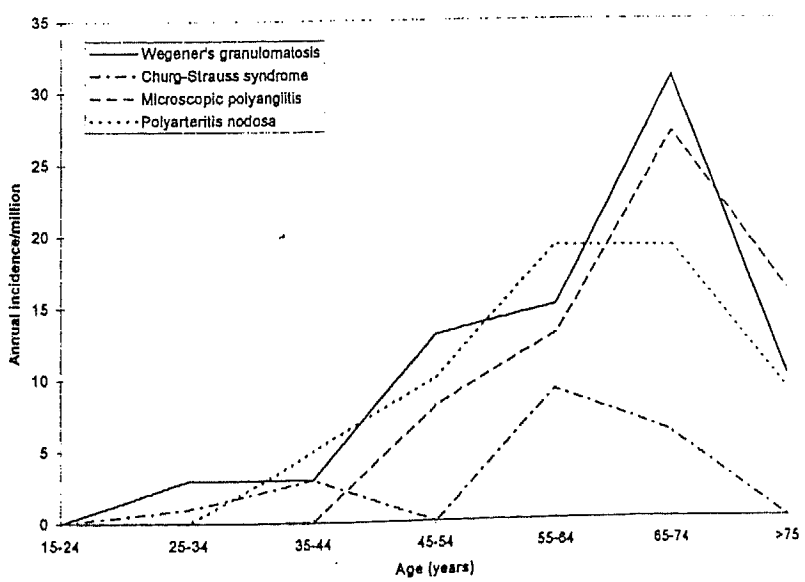

Figure 2. Age-specific incidence of Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and polyarteritis nodosa in the Norwich Health Authority, January 1, 1988 through December 31, 1997.

attributable to better case ascertainment later in the study, since the histopathology records and clinical discharge records were more complete after 1990. Previous studies have suggested that the incidence of WG is increasing, but whether this was due to better case recognition after the introduction of ANCA testing is uncertain (10). A triennial rolling analysis (results not shown) did not reveal any peaks and troughs in incidence such as that reported in GCA, with a 5–7-year interval between peaks (13,14), or that recently reported by Tidman et al (15) in a 25-year hospital-based retrospective study of small vessel vasculitis. Our study duration is not long enough to determine whether there is a regular pattern in the incidence of PSV, with peaks and troughs, or a continual slow increase in the incidence.

Our data show the incidence of PSV to be higher than that reported in other studies, and this may reflect better case identification. We have attempted to identify all cases at our institution, using several sources for case identification; however, as with any study of this type, the estimates represent a minimum incidence. For this study, we reclassified all patients in our database and extended our search for patients to the records of renal biopsies and reviewed the histopathology database for all renal biopsy records. This has resulted in our identifying more patients, in particular, more patients with MPA, than we previously reported (16).

We have confirmed previous studies suggesting that PSV is more common in men than women. The study population is 98% white, and thus other racial and ethnic groups are not included, and the results are only generalizable to the UK white population.

The most striking observation was a marked age-specific increase in annual incidence. This is similar to that seen in GCA, which has a peak incidence in the population older than age 80 years (13). Tidman et al (15) also noted a peak in incidence at 55–64 years of age.

The median age of the patients in our series was 65 years, which is higher than most previous series from tertiary referral centers (12,17). Elderly patients with PSV may not be accurately diagnosed and may not be so readily referred to tertiary referral centers as younger, "fitter" patients, resulting in a bias toward younger patients in series from tertiary referral centers. Our population had a slightly higher proportion of people over age 65 years than the rest of England and Wales. This might partly explain the relatively high median age of our population, but it does not account for the age-specific increase in incidence that we observed. We have previously reported that our patients do not differ in clinical features from those seen in tertiary referral centers (9). The incidence of CSS possibly peaked a decade earlier than the other conditions, and this might reflect the possibly different etiology of CSS compared with WG and MPA, which share a number of clinical features and could therefore be considered to have a similar etiology. It is important to consider the diagnosis in elderly patients presenting with a systemic illness.

As we and others have previously noted (6,7,16), the CHCC definitions are more restrictive than the ACR criteria. Application of the CHCC definitions is, however, subjective, since there are no explanations attached to the components of the definition. We recognize that the CHCC definitions were not intended to be used in this manner, but there are no other accepted definitions or criteria for MPA. Our application of the CHCC definition for WG probably underestimated the number of patients who fulfilled this definition, because we required biopsy evidence of granulomata. It should be noted that 2 patients fulfilled 2 ACR criteria, while 27 patients were not considered to have fulfilled CHCC definitions. These were mainly patients meeting the ACR criteria for WG. Microscopic polyangiitis is not included in the ACR vasculitis criteria. We therefore used both methods to identify patients. Incidence rates were calculated using the ACR criteria for WG, PAN, and CSS and the CHCC definition for MPA. For all conditions, there was an excess of males over females, together with an increasing age-specific incidence.

The estimated point prevalence of WG at ~63/million is higher than previous estimates. The 5-year prevalence in the United States in 1986–1990 was estimated to be 26.0/million and in New York 30.0/million (18). In Germany in 1994, the prevalence of WG alone was estimated to be 51.2/million in the north of the country and 42.3/million in the south (19). This value provides an estimate of the disease burden due to PSV in the population at any one time. These patients are likely to be relatively heavy users of secondary care facilities because of the severity of initial disease and the requirement for long-term monitoring of an at-present incurable, relapsing condition. The prevalence is likely to increase as the mortality declines due to better therapy.

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Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe

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Abstract

Objective—The aetiopathogenesis of the primary systemic vasculitides (PSV) is unknown but includes both environmental and genetic factors. The development of classification criteria/definitions for PSV allows comparison of the epidemiology between different regions.

Methods—The same methods and the American College of Rheumatology (1990) criteria or Chapel Hill definitions were used to compare the epidemiology of Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and polyarteritis nodosa in Norwich (east England population 413 500) and Lugo (northwest Spain population 204 100). Patients with PSV were identified between 1 January 1988 and 31 December 1998.

Results—Overall, the incidence of PSV in adults was almost equal in Norwich (18.9/million) and Spain (18.3/million). The incidence of Wegener's granulomatosis in Norwich (10.6/million) was greater than in Spain (4.9/million). There was a marked age-specific increase in incidence in Norwich with a peak age 65–74 years (52.9/million), but a virtually equal age distribution between ages 45 and 74 in Lugo (34.1/million). There was no significant increase with time in either population, or evidence of cyclical changes in incidence.

Conclusion—These data support the suggestion that environmental factors may be important in the pathogenesis of PSV.

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The primary systemic vasculitides (PSV—Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA), polyarteritis nodosa (PAN)) are a group of rare conditions characterised by inflammation and necrosis of blood vessel walls. The aetiopathogenesis of these conditions is poorly understood, but environmental and genetic factors are important. Clues to environmental factors can be obtained by comparing the incidence in different regions of the world, looking for clusters both in time and space and for associations with infectious disease. Pointers towards a genetic component come from studies of the human leucocyte antigen (HLA) type of patients, familial occurrence, and differences in incidence in various ethnic groups. The recent development of agreed classification criteria and definitions enables comparison of studies from different groups. Anecdotal evidence suggests that WG is more common in northern Europe, whereas MPA is believed to show the opposite trend. We previously reported data on the epidemiology of PSV in our two populations[5 6] using different methods. This study aimed at comparing directly the incidence of PSV over an 11 year period in two different regions of Europe using the same methods and classification criteria.

Patients and methods

The study was hospital based in two regions of Europe—Norwich Health Authority (NHA) Norfolk, UK (latitude 52°N), and Hospital Xeral-Calde, Lugo, Spain (43°N). The NHA provided administrative services to a group of general practices covering a population of 413 500. Patients were included if they were registered with one of these practices. Hospital services were provided by a single institution—Norfolk and Norwich Hospital. In Lugo the Hospital Xeral-Calde is the only referral centre for a population of almost 250 000 people and serves a defined population. The studies were both performed between 1 January 1988 and 31 December 1998. Patients with vasculitis diagnosed before or after the study period were excluded.

CLASSIFICATION CRITERIA

The American College of Rheumatology (ACR) criteria for PAN,[1] WG,[2] and CSS[3] were used to classify all patients. The Chapel Hill Consensus Conference (CHCC) definitions were applied to all patients.[4] Patients who failed to fulfil any of these criteria were not included, nor were patients with other types of vasculitis.

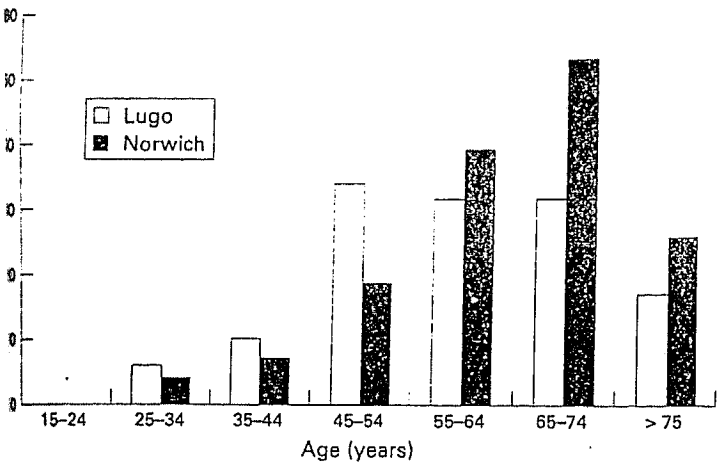
DENOMINATOR POPULATION

In 1992 the adult (>15 years) population in Norwich was 413 500 (men 200 000, women 213 500). The population has now increased and in 1997 was 429 000 (men 207 000) owing to slight net immigration. The population turnover is about 3–4% each year. The population includes a higher number of patients who are aged >65 years old (21.5%) compared with the national average for England and Wales (17.8%). The population is 98% Caucasoid, and one third live within 5 km of the city centre. The adult population of Lugo in 1992 was 204 100 (men 99 900, women 104 200). The population fell by 6000 between 1980 and 2000. There is little immigration or emigration. The population contains 21.3% aged

Table 1 *Incidence of primary systemic vasculitis in Norwich and Lugo.*

	No	Norwich annual incidence/ million (95% CI)	No	Lugo annual incidence/ million (95% CI)
Wegener's granulomatosis	48	10.6 (7.8 to14.0)	11	4.9 (2.4 to8.8)
Male	25	11.4 (7.4 to16.8)	4	3.6 (1.0 to9.3)
Female	23	9.8 (6.2 to14.7)	7	6.1 (2.4 to12.6)
Churg-Strauss syndrome	14	3.1 (1.7 to5.2)	2	0.9 (0.1 to3.2)
Male	9	4.1 (1.9 to7.7)	1	0.9 (0.0 to5.1)
Female	5	2.1 (0.7 to5.0)	1	0.9 (0.0 to4.9)
Microscopic polyangiitis	38	8.4 (5.9 to11.5)	26	11.6 (7.6 to17.0)
Male	25	11.4 (7.4 to16.8)	15	13.7 (7.6 to22.5)
Female	13	5.5 (2.9 to9.5)	11	9.6 (4.8 to17.2)
Polyarteritis nodosa	44	9.7 (7.0 to13.0)	14	6.2 (3.4 to10.5)
Male	27	12.3 (8.1 to17.8)	7	6.4 (2.5 to13.1)
Female	17	7.2 (4.2 to11.6)	7	6.1 (2.4 to12.6)
All	86	18.9 (15.1to23.4)	41	18.3 (13.1to24.8)
Male	52	23.7 (17.6to34.1)	21	19.1 (11.8to29.2)
Female	34	14.5 (10.1to20.2)	20	17.4 (10.6to27.0)

ACR criteria were used for Wegener's granulomatosis, Churg-Strauss syndrome, and polyarteritis nodosa, the CHCC definition was used for microscopic polyangiitis.
Number of patients in each category is the number who fulfilled the criteria/definition. The number of patients in each group was Norwich 86 and Lugo 41. Some patients fulfilled two sets of criteria–typically the ACR criteria for polyarteritis nodosa and the CHCC definition for microscopic polyangiitis. In Norwich 24 patients and in Lugo 12 patients fulfilled both the ACR criteria for polyarteritis nodosa and the CHCC definition for microscopic polyangiitis.



1 *Age-specific incidence of primary vasculitis in Norwich and Lugo, Spain.*

years of age. The population is Caucasoid of Celtic origin and 21% live within the city.

STATISTICAL ANALYSIS

Age-specific and sex-specific incidence rates were calculated using the number of incident cases as the numerator and the population as the denominator. Incidence rates were compared for the periods 1988–92 and 1993–98. To investigate whether there were any cyclical peaks a rolling three year centred average was calculated. 95% Confidence intervals (95% CI) were calculated assuming that the number of observed cases followed the Poisson distribution.

Results

A total of 127 patients presented with new onset PSV (86 Norwich, 41 Lugo) in the two populations over an 11 year period. The overall annual incidence of PSV in adults was 18.9/million in Norwich and 18.3/million in Lugo (table 1). There was a greater incidence of WG in Norwich (10.6/million) than in Lugo (4.9/million), whereas MPA was more common in Lugo (table 1). The incidence of PAN and CSS was higher in Norwich. There was no significant change in incidence between 1988–92 and 1993–98 in either Norwich (15.5/million (95% CI 10.6 to 21.9) and 21.0/million (95% CI 15.6 to 27.4)) or Lugo (18.6/million (95% CI 11.2 to 29.1) and 18.0/million (95% CI 11.3 to 27.2). A rolling triennial average did not disclose any cyclical changes in incidence. In Norwich, there was an age-specific increase in incidence peaking in the 65–74 year group; the age distribution was much flatter in Lugo with an almost equal incidence between ages 45 and 74 (fig 1). In Norwich the peak incidence was 52.9/million (35.6 to 75.5), and in Lugo 34.1/million (16.3 to 62.8). The incidence was greater in men than women for all groups except for Wegener's granulomatosis in Lugo, where there was female preponderance (table 1).

Discussion

We have previously reported the epidemiology of vasculitis in Norwich and Lugo[5 6] using different methods. In this study we harmonised our methods and therefore could compare directly the incidence of PSV in our two populations. In both centres a single referral centre provides secondary care to its local population and this population can be easily identified. Referrals to outside hospitals are rare because both populations are relatively geographically isolated. Patients with PSV are sufficiently ill to be referred for secondary care and are therefore not managed in the community, by either general practitioners or private physicians. The data provide minimum estimates of the incidence of PSV in our communities. No significant change (although there was an upward trend) in incidence occurred during our study, suggesting that there were no major changes in the completeness of our data collection or referral patterns.

The overall incidence of PSV was similar in Norwich and Lugo, but there were trends towards differences in incidence for each condition. There was a greater incidence of WG in Norwich and MPA in Lugo. This supports the idea (suggested anecdotally by doctors interested in vasculitis) that WG is more common in the north, whereas MPA is more common in the south of Europe. CSS and PAN were both more common in Norwich. These differences reflect, we believe, genuine variations in incidence between populations rather than differences in classification or patient selection. By applying the same classification criteria/definitions to a defined population it is possible to identify differences in incidence between populations. For the reasons mentioned above we believe that our figures represent a population based incidence, but as with any epidemiology study we cannot be absolutely confident that we identified all patients.

The latitudinal trends in incidence for WG and MPA are supported by other studies. Koldingsnes from Tromso in North Norway reported a higher annual incidence of WG (15.0/million) than we did from the UK.[7] In the south MPA is particularly common in Kuwait, with an annual incidence of 24/million.[8] Methodological differences make it difficult to compare these populations directly with ours.

The aetiopathogenesis of PSV is unknown, but genetic and environmental factors are likely to be important. MPA and WG can sometimes be difficult to distinguish clinically and it has been suggested that they have a common pathogenesis. These data, however, point towards a difference in the pathogenesis of WG compared with MPA.

The age and sex distribution of the populations of Norwich and Lugo are broadly similar. Both populations are mainly Caucasoid, but there is a significant component of Celtic ancestry in Lugo. The HLA make up of the Lugo population differs from that found in other Mediterranean areas and has a similar proportion of HLA-DRB1 alleles to that in the UK population.[9] No clear HLA association has been shown with any type of PSV,[10] suggesting that environmental factors may be more important than genetic factors. There was a trend towards an increase in incidence in Norwich but not Lugo, suggesting that any environmental factors were probably unchanged during the period of the study. We were unable to find any evidence for cyclical changes in incidence as recently suggested in a retrospective hospital based study from Sweden.[11] In the 1980s it was suggested that there was an increase in incidence of WG. This does not seem to have continued and was probably due to the introduction of routine antineutrophil cytoplasmic antibody testing and greater awareness of doctors.[12]

Further studies conducted in other parts of the world may yield interesting clues to the pathogenesis of these so far enigmatic diseases, and permit dissection of the interplay between genes and environment.

Dr Lane is supported by the Arthritis Research Campaign. We are grateful to the physicians of both hospitals for referring patients to us.

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autoimmune disease or positive anti-nuclear antibodies and hypergammaglobulinaemia. Ideally, histological confirmation should be obtained. The pancreatic abnormality appears to be very responsive to treatment of the underlying condition.

349. Case Series: The musculoskeletal manifestations of Fabry's disease

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Fabry's disease is an X Linked recessive storage disorder caused by an inborn error of glycosphingolipid metabolism. Deficient activity of the enzyme alpha-galactosidase A leads to an accumulation of sphingolipids in blood vessels, ganglion cells and multiple organs.

Affected males typically present in their teenage years with burning pains in the extremities (acroparaesthesias) and angiokeratomas. Premature death occurs in the fourth and fifth decade due to ischaemic heart disease, cerebrovascular disease and renal failure.

Documented musculoskeletal manifestations of Fabry's disease are acroparaesthesias, erythromelalgia, osteonecrosis and an arthropathy of the DIP (distal interphalangeal) joints.

Reduced levels of alpha-galactosidase A activity in plasma, leukocytes and skin fibroblasts confirms the diagnosis.

Carbamazepine is used for pain relief. Patients with fascular complications are anticoagulated. Dialysis and renal transplantation may be required. Trials in enzyme replacement therapy are underway.

Three cases of Fabry's disease are presented. All three had raised inflammatory markers. One had a small joint polyarthralgia made worse by exercise and a purpuric rash. Another had early morning stiffness, large joint effusions and an arthralgia affecting his DIP joints. The final case had painful feet on exertion and a palmar rash.

An initial misdiagnosis of juvenile idiopathic arthritis was made in each case. Once the correct diagnosis was established carbamazepine was started with good effect. It is important to realise that metabolic disorders can masquerade as rheumatic conditions. A delay in diagnosis can results in inappropriate use of disease modifying drugs and suboptimal pain relief.

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Vasculitis

350. Geoepidemiology of systemic vasculitis in three European regions

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The epidemiology of systemic vasculitis (SV) has until recently been poorly documented. Development of accepted criteria and definitions by the ACR and Chapel Hill Consensus Conference (CHCC) now permits comparison of data from different areas. We have reported that Wegener's granulomatosis (WG) is more common in Norwich (UK) than Lugo (Spain)[1]. Our aim was to extend our study comparing the epidemiology of WG, microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), Churg Strauss syndrome (CSS) to include a population in the far north of Europe.

Adult patients with a new diagnosis of SV were prospectively identified in Tromsø, North Norway (population 371,000; latitude 70°N), Norwich (population 420,000; latitude 52°N), and Lugo, North West Spain (population 241,000; latitude 43°N) between 1988–98. WG, PAN and CSS were classified using the ACR (1990) criteria and MPA, the CHCC definition. 95% confidence intervals (95% CI) were calculated using the Poisson distribution for the observed number of cases.

The results are given in the table, n = number of patients fulfilling each criterion. 18 Tromsø patients, 24 Norwich patients and 12 Lugo patients fulfilled more than one set of classification criteria.

	Tromsø		Norwich		Lugo	
	n	/million (95% CI)	n	/million 95% CI)	n	/million (95% CI)
WG	43	10.5 (7.6–14.2)	48	10.6 (7.8–14.0)	11	4.9 (2.4–8.8)
CSS	2	0.5 (0.06–1.8)	14	3.1 (1.7–5.2)	2	0.9 (0.1–3.2)
MPA	11	2.7 (1.3–4.8)	38	8.4 (5.9–11.5)	26	11.6 (7.6–17.0)
PAN	18	4.4 (2.6–7.0)	44	9.7 (7.0–13.0)	14	6.2 (3.4–10.5)
Total	56	13.7 (10.3–17.8)	86	18.9 (15.1–23.4)	41	18.3 (13.1–24.8)

In all areas and all disease categories the incidence was greater in men than women and peaked age 65–74 years. We conclude that the overall incidence and pattern of vasculitis in terms of age and sex distribution is similar in the three areas studied. MPA is more common and WG less common in Southern Europe, whilst CSS appears to be more common in Norwich. This study points to importance of environmental and/or genetic factors in the pathogenesis of vasculitis.

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351. Drug allergy is associated with primary systemic vasculitis (PSV)

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Background: Allergy has been associated with PSV[1] (Wegener's Granulomatosis (WG) and Churg Strauss syndrome (CSS)) and is one of the classification criteria for CSS. This is supported by reports of raised IgE levels and Th2 predominant cytokine profiles in CSS and active WG. We examined the evidence for allergy in a case-control study.

Methods: Detailed histories (events prior to symptom onset) including a validated questionnaire[1] were taken from 75 adult PSV patients, 222 age/sex matched non-disease hospital controls, 19 systemic rheumatoid vasculitis and 34 age/sex matched asthma controls. Details included: type (Skin, drug, insect, plant, food), date and cause of allergy; allergic rhinitis; asthma; family history of allergies/asthma; vaccination or steroid withdrawal in the preceding 6 months; smoking history; TB exposure; hepatitis and blood transfusion. Odds ratios (OR) and 95% confidence intervals (C.I.) were calculated by conditional logistic regression. Total PSV and 7 subgroups (47 WG, 16 CSS, 12 microscopic polyangiitis–mPA, 30 cANCA/PR3 positive, 19 pANCA/MPO positive) are compared to non-disease controls. PSV and CSS were also compared to disease controls.

Results: ORs (95% C.I.) were significantly raised in PSV for combined allergy [2.21(1.30–3.77)], drug allergy [3.38(1.81–6.29)] and asthma [4.96(2.49–9.88)] but not other allergy types or rhinitis. Significant ORs (95% C.I.) were found for drug allergy in WG [3.46

Epidemiology of vasculitis in Europe

Sir,

We have recently compared the annual incidence of primary systemic vasculitis (PSV) in two different regions of Europe (Norwich, UK (latitude 52°N) and Lugo, Spain (latitude 43°N) (1). Wegener's granulomatosis (WG) was more common in Norwich (10.6/million) than Spain (4.9/million), although the overall incidence of PSV was similar. This supports the idea that environmental factors might be important in the aetiopathogenesis of PSV. To extend our observations we have now studied the incidence of PSV in northern Europe (Tromsø, Norway (latitude 70°N). The methodology was the same as used in the previous study (1). All new patients presenting with PSV between 1 January 1988 and 31 December 1998 were identified in the three centres. Wegener's granulomatosis , Churg Strauss syndrome (CSS), polyarteritis nodosa (PAN) were classified using the ACR (1990) criteria (2-4) and microscopic polyangiitis (MPA) and classical PAN the Chapel Hill consensus definition (5). Incidence figures were calculated using the Poisson distribution for the observed number of cases.

The results are shown in the Table. The overall incidence and pattern of vasculitis was similar in the three regions, there were however some differences. Microscopic polyangiitis was less common in Tromsø compared with the other two regions, whilst there was a trend for Wegener's granulomatosis to be more common in the North. Churg Strauss syndrome was more common in Norwich than in the other two regions. In all areas and all disease categories the incidence was greater in men than women and showed a peak incidence at age 65-74 years. Overall WG is the most common type of PSV and classical PAN the rarest.

These results support the notion suggested by physicians interested in vasculitis that there are geographical differences in the incidence of WG,MPA and CSS, in particular there is an iverse relationship in the incidence of WG and MPA. In clinical practice MPA and WG can be difficult to distinguish. It is possible that despite our best attempts to harmonise the application of classification criteria/definitions there were still differences in approach. The reasons for the apparent excess of CSS in Norwich is unclear but could reflect local environmental factors. The aetiopathogenesis of PSV is unknown, both genetic and environmental factors are likely to be important. The clinically observed differences between MPA and WG may reflect interaction of varying trigger factors on a heterogeneous genetic background. It should therefore not be assumed that the same triggers are operating in all regions of Europe.

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Table 1 Annual incidence of primary systemic vasculitis in three regions of Europe.

	Criteria/ definition	Tromsø n	Tromsø /million (95% CI)	Norwich n	Norwich /million(95% CI)	Lugo n	Lugo /million (95% CI)
WG	ACR	43	10.5 (7.6-14.2)	48	10.6 (7.8-14.0)	11	4.9 (2.4-8.8)
CSS	ACR	2	0.5 (0.06-1.8)	14	3.1 (1.7-5.2)	2	0.9 (0.1-3.2)
MPA	CHCC	11	2.7 (1.3-4.8)	38	8.4 (5.9-11.5)	26	11.6 (7.6-17.0)
PAN	ACR	18	4.4 (2.6-7.0)	44	9.7 (7.0-13.0)	14	6.2 (3.4-10.5)
PAN	CHCC	2	0.5 (0.06-1.8)	0	0.0 (0.0-0.8)	2	0.9 (0.1-3.2)
TOTAL		56	13.7 (10.3-17.8)	86	18.9 (15.1-23.4)	41	18.3 (13.1-24.8)

Total represents the number of patients seen in each centre
n= number of patients fulfilling each criteria in each centre, 18 Tromsø patients, 24 Norwich patients and 12 Lugo patients fulfilled more than one set of classification criteria

AN INVESTIGATION OF QUALITY OF LIFE, PAIN, DISABILITY AND DISEASE STATUS IN PRIMARY SYSTEMIC VASCULITIS 288

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Background & purpose: Recent developments in the management of systemic vasculitis have resulted in an improved rate of survival. However, it is often associated with long term morbidity and significant restrictions in quality of life (QOL). Preliminary data on measures such as SF-36 have suggested a significant impact on the physical and mental component scores in selected patients from tertiary referral centres. In this study we examined the relationship between QOL scores using the SF-36 and physical characteristics of vasculitis in an unselected group of patients with primary systemic vasculitis (PSV) attending a general district hospital.

Methods: Sixty-two patients with PSV (Wegener's Granulomatosis n=31, Microscopic Polyangiitis n=9, Churg Strauss Syndrome n=11) resident in the former Norwich Health District (on the Norwich Vasculitis Register) were contacted. Self-report questionnaires were returned by 51 patients and data on disease related variables were collected from interview and hospital notes using modified versions of the Birmingham Vasculity Activity Score (BVAS) and the Vaculitis Damage Index (VDI). Scores on disability (HAQ), pain, fatigue, symptom severity and sleep (101 point Visual Analogue Scales) were also obtained. The SF-36 was used to assess certain aspects of patients' QOL and the HAD to assess depression and anxiety levels. The data were analysed using t-tests and correlations as appropriate.

Results: There were no significant correlations between BVAS or VDI scores with any of the SF-36 subscales or with the other self-report disease related measures, except for VDI with the SF-36 Pain score (Pearson $r = -.31$, $p < 0.05$). There were significant positive correlations between the HAQ scores and: pain, symptom severity, problems of fatigue and sleep, and with all SF-36 measures except for role reduced due to emotional problems or to physical problems. SF-36 scores in this patient cohort appear to be lower than those obtained from patients attending a tertiary referral centre (Herlyn et al, 1998) and lower than those in a normal population (of similar age). Patients with pain when compared to those without pain had significantly impaired scores in all aspects of QOL (SF-36) except for mental health. They also scored significantly higher on scores of depression, symptoms of fatigue, problems with sleep, and perceived symptom severity (associated p levels ranged from $p < 0.001$ to $p = 0.04$). The 2 groups did not differ on age, duration of illness, BVAS or VDI Scores.

Conclusions: Clinical markers serve as indicators of physical status of vasculitis. However, self-reported pain or disability scores, scores on depression, the SF-36, and self-report measures of disease symptoms are significant indicators of the impact of vasculitis on the patient's life and need to be taken into account in overall management.

THE RELATIONSHIP BETWEEN COPING STRATEGIES, ILLNESS PERCEPTIONS AND PSYCHOLOGICAL ADJUSTMENT IN PATIENTS WITH PRIMARY SYSTEMIC VASCULITIS

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Background & purpose: Recent developments in treatment have resulted in patients with primary systemic vasculitis (PSV) having an improved survival. However, this is often associated with relapses and chronic morbidity, which can have a variety of psychological effects, as is seen in other chronic diseases. The aim of this study was to explore in detail psychological adjustment in patients with PSV using specific psychological instruments. We investigated the relationships between: a) use of specific coping strategies, mood and disease related variables, and b) patient perceptions of illness and mood.

Methods: Sixty-two patients with PSV resident in the former Norwich Health District were contacted. Self-report questionnaires were returned by 51 patients and data on disease related variables were collected from interviews and hospital notes using a modified version of the Birmingham Vasculitis Activity Scores (BVAS) and the Vasculitis Damage Index (VDI). The self-report questionnaires assessed disability (HAQ), pain (101 point Visual Analogue Scale), depression and anxiety (Hospital Anxiety and Depression Questionnaire), coping strategies (Ways of Coping Questionnaire, WOC) and patients' perceptions of their illness (Illness Perception Questionnaire). Multiple linear regression analyses were used to predict depression and anxiety scores from degree of use of specific coping strategies, BVAS, VDI, and pain scores. Correlations were computed for illness perception scores and mood.

Results: Overall the most significant predictor of depression was the degree of use of self-control (WOC) followed by pain severity and planful problem solving (WOC) ($R^2 = 0.48$, $F(3,33) = 9.22$, $p < 0.001$). There was a negative correlation between planful problem solving and depression scores. The most significant predictor of anxiety was pain severity followed by use of self-control and escape-avoidance (WOC) ($R^2 = 0.59$, $F(3,32) = 13.81$, $p < 0.001$). There was a strong positive correlation between pain severity and disability scores (HAQ) (Pearson $r = 0.5$, $p < 0.001$). Anxiety levels were significantly correlated with number of disease symptoms reported by the patients (Pearson $r = 0.48$, $p < 0.01$) and perceived consequences of the illness (Pearson $r = -0.53$, $p < 0.01$). Perceptions of low control over the illness were associated with high anxiety scores (Pearson $r = 0.50$, $p = 0.01$). Patient reports on the consequences of their illness were correlated to depression scores (Pearson $r = -0.53$, $p < 0.05$) with severe perceived consequences associated with higher depression scores.

Conclusions: Depression and anxiety levels in PSV are significantly related to pain severity, use of specific coping strategies, and patients' illness perceptions but not to disease activity or severity scores as measured by modified versions of BVAS and VDI. Future interventions aimed at facilitating psychological adjustment to PSV need to address these factors.

APPENDIX 4. GLOSSARY

α- 1AT - Alpha 1 anti-trypsin

AASV - ANCA associated small vessel vasculitis

ACR - American College of Rheumatology

AI - Annual Incidence

ANA - Antinuclear antibodies

ANCA - Anti-neutrophil cytoplasmic antibody

APC - Antigen presenting cell

ARDS - Adult respiratory distress syndrome

AZA - Azathioprine

BCG - Bacille Calmette Guerin

BP - Blood pressure

BPI - Bactericidal/permeability-increasing protein

BUN - Blood urea nitrogen

BVAS – Birmingham Vasculitis Activity Score

cANCA - classic ANCA

Ca - Carcinoma

C.I. - Confidence Interval

C3 - complement 3

CCF - Cleveland Clinic Foundation

CHCC - Chapel Hill Consensus Conference

CMV - Cytomegalovirus

CNS - Central nervous system

cPAN - Classical PAN

CRP - c-reactive protein

CSS - Churg Strauss Syndrome

CVA - Cerebrovascular accident

CVS - Cardiovascular system

CXR - Chest X-ray

CYC - Cyclophosphamide

CYCAZAREM - ECSYSVASTRIAL comparing CYC with AZA as maintenance therapy in PSV

CYCLOPS - ECSYSVASTRIAL study comparing continuous with pulse oral CYC

DGIS - Professor D.G.I. Scott

DH - District general hospital

DNA - deoxyribonucleic acid

ECSYSVASTRIAL – European Union Study Group of Therapeutic Trials for PSV

ELISA - Enzyme linked immunosorbant assay

ELK system - De Remee classification of WG (Ear, lower respiratory tract, kidney)

ENT - Ear, nose and throat

ESR - Erythrocyte sedimentation rate

ESRD - End-stage renal disease

ESRF - End-stage renal failure

ESW - European Standardisation Workshop (for ANCA)

F - Female

FcγR - Fc gamma receptor

FH - Family history

F/U - Follow up

FSH - Follicular stimulating hormone

FSPGN - Focal segmental necrotizing GN

GCA - Giant cell arteritis

G.I.T. - Gastrointestinal tract

GN - Glomerulonephritis

HBP - Hypertension

HBsAg - Hepatitis B surface antigen

HBV - Hepatitis B serology

HC - Hydrocarbon

HCV - Hepatitis C virus

HD - Haemodialysis

HIV - Human immunodeficiency virus

HLA - Human leucocyte antigens

HSP - Henoch-Schonlein purpura

HR - Hazard ratio

ICAM - Adhesion molecule of the IgG superfamily group

ICD - Cross Index of Diseases for hospital discharge coding

IDDM - Insulin dependent diabetes mellitus

IFN - Interferon

Ig	- Immunoglobulin
IHD	- Ischaemic heart disease
IIF	- Immunofluorescence
IL	- Interleukin
Index Date	– The date of the first symptom attributed to vasculitis
Index Year	– The year prior to the first symptom attributed to vasculitis
IV	- Intravenous
IVIG	- Intravenous immunoglobulin
LCV	- Leukocytoclastic vasculitis
LF	- Lactoferrin
LFA 1	- Adhesion molecule of the integrin group
M	- Male
Mac 1	- Adhesion molecule of the integrin group
MDS	- Myelodysplastic syndrome
MEPEX	- ECSYSVASTRIAL evaluating plasmapheresis and high dose IV methylprednisolone in resistant PSV
MI	- Myocardial infarction
MP	- Methylprednisolone
mPA	– Microscopic polyangiitis
MPO	– Myeloperoxidase
MRI	- Magnetic resonance imaging
MTX	- Methotrexate
MUPIBAC	- ECSYSVASTRIAL study of nasal mupirocin to prevent relapse in WG
NAG	- beta- N-acetylglucosaminidase
NCGN	- Necrotising crescentic glomerulonephritis
NHA	– Norwich Health Authority
NI	– Dr N. Innes
NIDDM	- Non-insulin dependent diabetes mellitus
NIH	- National Institutes of health
NK cell	- Natural killer cell
No.	– Number
NOAR	- Norfolk arthritis register
ONS	– Office of National Statistics
OOSS	– Office for National Statistics Occupational Support Service
OR	– Odds ratio

pANCA	- perinuclear ANCA
PAN	– Polyarteritis nodosa
PCP	- Pneumocystis carinii
PCR	- Polymer chain reaction
PECAM	- Platelet endothelial cell adhesion molecule
PHA	- Phytohaemoglutanin
PMN	- Polymorphonuclear cell
PNS	- Peripheral nervous system
PR3	- Proteinase 3
Pred	- Prednisolone
PS	- Pulmonary Silicosis
PSV	- Primary Systemic Vasculitis
PTU	- Propylthiouracil
RA	- Rheumatoid arthritis
RAST	- Radioallergosorbent test
RPGN	- Rapidly progressive glomerulonephritis
RR	- Relative risk
RW	- Dr Richard Watts
Rx	- Treatment
SEM	- Standard error of the mean
SIR	- Standardised incidence ratio
SL	– Dr S. Lane
SLE	- Systemic lupus erythematosus
SMR	- Standardised mortality rate
SNVDI	- Systemic necrotizing vasculitis damage index
SOC	– Standard Occupational Classification
SOLUTION	- ECSYSVASTRIAL study of antithymocyte globulin in refractory PSV
SRV	– Systemic Rheumatoid Vasculitis
SV	- Systemic vasculitis
SVV	- Small vessel vasculitis
TA	- Takayasu arteritis
TAP	- Transporter associated with antigen presentation
TB	- Tuberculosis
TCR	- T-cell receptor
Th-cell	- T- helper cell

TGF	- Transforming growth factor β
TNF	- Tumour necrosis factor
TR	- Tertiary referral centre
T/S	- Trimethoprim / sulphamethazole
URTI	- Upper respiratory tract infection
VDI	– Birmingham Vasculitis Damage Index
VITAL	- Vasculitis integrated assessment log
UK	- United Kingdom
US / USA	- United States of America
VCAM	- Adhesion molecule of the IgG superfamily group
VLA 4	- Adhesion molecule of the integrin group
WG	– Wegener's Granulomatosis