proportion of drug treatment of hypertension among 45-64 year olds increased during 1972-81 from 3·5% to 14·6% for men and from 7·8% to 17·9% for women as reported by the Social Insurance Institution.[21 22] The better control of high blood pressure may be associated with the decrease in case fatality.

When causes of changes in incidence are considered the basic question is the change in prevalence and degree of coronary atherosclerosis.[23 24] In Finland the necropsy rate has been quite high during the past 30 years,[10] but there has been no systematic recording of the prevalence of coronary atherosclerosis. The effect of various factors on changes in incidence of ischaemic heart disease, however, remains open to debate as long as individual data are not available.

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Pulmonary haemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis

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Abstract

The incidence and characteristics of pulmonary haemorrhage in a series of 89 patients with systemic vasculitis were analysed. Pulmonary haemorrhage occurred in 32 of these patients and was associated with haemoptysis in all 32, alveolar shadowing in the chest radiograph in 28, and a significantly raised transfer coefficient in 30. Pulmonary haemorrhage usually resolved with treatment by immunosuppressive drugs but was the cause of death in 11 patients. In contrast with patients with antibasement membrane antibodies there was no correlation between pulmonary haemorrhage and cigarette smoking.

Pulmonary haemorrhage is a cause of serious morbidity in patients with systemic vasculitis.

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Introduction

The association of pulmonary haemorrhage with necrotising glomerulonephritis is usually called Goodpasture's syndrome. Many patients with Goodpasture's syndrome have autoantibodies to glomerular and alveolar basement membrane antigens[1] and the term is sometimes restricted to these. Nevertheless, glomerulonephritis and pulmonary haemorrhage coexist in other diseases, such as Wegener's granulomatosis,[2] microscopic polyarteritis,[3] systemic lupus erythematosus,[4] and, rarely, mixed essential cryoglobulinaemia, Henoch-Schönlein purpura, rheumatoid vasculitis, and mixed connective tissue disease.[5]

Descriptions of pulmonary haemorrhage and nephritis in patients without antiglomerular basement membrane antibody disease have generally been restricted to individual reports of severe, often fatal cases and the overall prevalence has not been documented reliably. This is partly because of the rarity of the underlying diseases and also because the diagnosis of pulmonary haemorrhage is usually circumstantial. For example, haemoptysis does not differentiate bleeding from the large airways, commonly found in Wegener's granulomatosis, and alveolar haemorrhage; haemoptysis may be trivial[6]; radiological features are not specific and may even be absent[7]; and traditional confirmatory investigations such as lung biopsy, bronchoscopy with lavage, or radioisotope techniques are cumbersome or invasive. The diagnosis has been simplified considerably by the observation that the diffusing capacity for carbon monoxide, especially

when corrected for alveolar volume—that is, the transfer coefficient—is a sensitive index of pulmonary haemorrhage,[8-10] and this has led to its use as the main adjunct to the chest radiograph in the diagnosis of pulmonary haemorrhage. In addition, serial measurements of transfer coefficient may be used to assess progress.

Since 1975 a detailed search for pulmonary haemorrhage, including routine use of transfer coefficient measurements, has been made in patients with severe nephritis presenting to the renal unit at Hammersmith Hospital. Elsewhere we have reported our experience of pulmonary haemorrhage in antiglomerular basement membrane antibody disease.[11 12] This paper documents the incidence and characteristics of pulmonary haemorrhage in patients with small vessel vasculitis.

Patients and methods

The study was based on the 89 patients referred to the renal unit at Hammersmith Hospital since 1975 and diagnosed as having systemic vasculitis due to Wegener's granulomatosis (53 patients) or microscopic polyarteritis (36 patients). The criteria used to diagnose Wegener's granulomatosis were as described[13 14] and differed only in detail from those of Fauci *et al*[15]; criteria for diagnosing microscopic polyarteritis were similar to those of Davson *et al*.[3] Generally, all patients had multisystem disease with severe renal impairment; 51 (57%) had plasma creatinine concentrations greater than 500 μmol/l (5·7 mg/100 ml) and 29 of these (33%) needed dialysis for renal failure during their presenting illness. Patients were treated with a standard regimen of cyclophosphamide, azathioprine, and prednisolone[16]; in addition, 46 patients underwent plasma exchange.

Routine investigations—Patients were assessed by standard clinical methods. Full blood counts and plasma urea and creatinine concentrations were measured at least three times a week. Radiographs of the chest were taken on admission and if abnormal were repeated about twice weekly. The obvious radiological feature of pulmonary haemorrhage is alveolar shadowing in the absence of pulmonary oedema or infection. We have described this and detailed the ancillary radiological features elsewhere.[7 10] The diffusing capacity for carbon monoxide was measured by the single breath technique[17] and corrected for the patient's lung volumes and haemoglobin concentration[18]: normal values have been established.[19] The transfer coefficient was considered to indicate pulmonary haemorrhage when 30% or more above the predicted normal for that patient or when serial measurements increased by more than 30% above a stable baseline.[9] The baseline was established from two or more concordant measurements taken on separate days in the absence of any signs of pulmonary haemorrhage. Whenever possible transfer coefficient was measured on the day of admission and, if abnormal, repeated every two or three days.

Pulmonary haemorrhage—The diagnosis of pulmonary haemorrhage is usually circumstantial and less weight can be placed on individual features in patients with systemic vasculitis than in antiglomerular basement membrane antibody disease. Consequently more stringent diagnostic criteria were used than before.[8 9 12] Pulmonary haemorrhage was considered "definite" if there was concurrence of haemoptysis and a raised transfer coefficient, with or without appropriate radiological signs; "suspected" when haemoptysis and characteristic radiological signs in the chest were present but transfer coefficient was not measured; and "considered" when the transfer coefficient was normal despite haemoptysis and a chest radiograph suggestive of alveolar capillary haemorrhage.

Results

Pulmonary haemorrhage occurred in 32 patients (table I). It was diagnosed as definite in 20 (63%), suspected in 10 (31%), and considered in 2 (6%). Table II shows the correlation of transfer coefficients with other features suggestive of haemorrhage. Necropsy confirmation of the diagnosis was available in five cases: fresh blood was found throughout the distal air spaces in three of these and haemosiderin laden macrophages in two. Presumably the latter finding indicated haemorrhage of much longer duration. The diagnosis was confirmed on transbronchial biopsy in two further patients.

Haemoptysis—All 32 patients with pulmonary haemorrhage had haemoptysis, which varied from blood streaked sputum to expectoration of frank blood. Haemoptysis started within one month of admission in most patients, but was sometimes present for much longer. Five patients with Wegener's granulomatosis and one with microscopic polyarteritis had haemoptysis without other evidence suggestive of pulmonary haemorrhage.

TABLE I—*Diagnosis of pulmonary haemorrhage in patients with Wegener's granulomatosis and microscopic polyarteritis. (Numbers in parentheses indicate patients with morphological confirmation of diagnosis)*

	Pulmonary haemorrhage			
	Definite	Suspected	Considered	Absent
Wegener's granulomatosis (n = 53)	13 (1)	7 (3)	2 (1)	31
Microscopic polyarteritis (n = 36)	7 (2)	3	0	26

TABLE II—*Correlation of transfer coefficient with other features suggestive of pulmonary haemorrhage. (Numbers in parentheses indicate patients in whom pulmonary haemorrhage was diagnosed)*

	Alveolar shadowing in chest radiograph	Transfer coefficient: Raised	Normal/low	Not done
Wegener's granulomatosis (n = 53)				
Patients with haemoptysis (n = 27)	Generalised	5 (5)	2 (2)	7 (6)†
	Limited	4 (4)	1*	1
	None	4 (4)	2	1
Patients with no haemoptysis (n = 26)	None	0	14	12
Microscopic polyarteritis (n = 36)				
Patients with haemoptysis (n = 11)	Generalised	4 (4)	0	3 (3)
	Limited	3 (3)	0	0
	None	0	1	0
Patients with no haemoptysis (n = 25)	Generalised	0	1†	1†
	None	0	17	6

*One patient with bronchopneumonia.
†One patient with pulmonary oedema.

Chest radiographs—Twelve of 36 patients with microscopic polyarteritis had alveolar shadowing in chest radiographs. Shadowing was generalised—that is, affecting most zones of both lungs—in nine cases and of more limited distribution in three. Ten of the 12 patients fulfilled the criteria for pulmonary haemorrhage, while two had pulmonary oedema which responded rapidly to removal of fluid by dialysis. Interpretation of the chest radiographs was more difficult in patients with Wegener's granulomatosis because of the coincidence of granulomas and alveolar haemorrhage. Alveolar shadowing was found in 20 of these patients, being generalised in 14 and of limited distribution in six. All but two of these patients had pulmonary haemorrhage. One of the remaining patients had pulmonary oedema, while bronchopneumonia was found at necropsy in the other. Four patients with Wegener's granulomatosis had definite pulmonary haemorrhage without alveolar shadowing in chest radiographs, a finding described in antiglomerular basement membrane antibody disease.[10]

Diffusing capacity for carbon monoxide—The transfer coefficient was measured sequentially in 29 patients. At presentation 17 had values at least 30% above the subsequently established baseline (fig 1). The maximum values in these patients were 30-178% greater than their baseline (mean 78 (SD 47)%). Sequential measurements in the 12 other patients showed no significant change in transfer coefficient throughout the clinical course; none of these had haemoptysis or radiological changes suggestive of pulmonary haemorrhage. Twenty seven patients had their transfer coefficients measured once only; five had pulmonary haemorrhage, 22 did not. In three of these patients the diagnosis was based on the concurrence of haemoptysis and a raised transfer coefficient (two also had the typical radiological changes). The remaining two patients had normal transfer coefficients despite haemoptysis accompanied by alveolar shadowing in chest radiographs. One of these died two days after measurement of a normal transfer coefficient and necropsy confirmed fresh pulmonary haemorrhage.

Haemoglobin concentration was a poorer guide to the presence of pulmonary disease than in antiglomerular basement membrane antibody disease. At presentation most patients were anaemic and the severity of anaemia did not discriminate between those with pulmonary haemorrhage (mean haemoglobin concentration 8·5 (SD 1·1) g/dl) and those without (mean concentration 9·5 (1·7) g/dl). The

haemoglobin concentration fell acutely by more than 2 g/dl over 24 hours in 10 patients with episodes of proved pulmonary haemorrhage.

Response to treatment—Signs of injury including those of pulmonary haemorrhage usually diminished within days of starting immunosuppressive treatment. In patients in whom sufficient measurements were made the transfer coefficient returned to normal between one and two weeks after starting treatment (fig 2); one patient improved before treatment was started. The return of the transfer coefficient to normal usually coincided with resolution of alveolar shadowing in the chest radiograph but radiological changes persisted for up to six weeks in four patients. Pulmonary haemorrhage recurred during the first two weeks of treatment in four patients.

Deaths—Eight of the 89 patients died of pulmonary haemorrhage; five of these had Wegener's granulomatosis and three microscopic polyarteritis. Two patients died within 24 hours of admission and the remaining six over the succeeding 14 days. Subsequently four patients with Wegener's granulomatosis had a recurrence of pulmonary haemorrhage, and it was responsible for the deaths of three. In total, therefore, 11 patients (12%) died of progressive respiratory failure due to intra-alveolar haemorrhage unresponsive to treatment.

Cigarette smoking—In contrast with antiglomerular basement membrane antibody disease[12] there was no correlation between cigarette smoking and pulmonary haemorrhage in patients with systemic vasculitis. A full smoking history was obtained from 82 patients. Of these, five of 30 patients (four with Wegener's granulomatosis, one with microscopic polyarteritis) with pulmonary haemorrhage were smokers at the time of presentation. Conversely, there were 12 smokers (three with Wegener's granulomatosis, nine with microscopic polyarteritis) among the 52 patients without pulmonary haemorrhage.

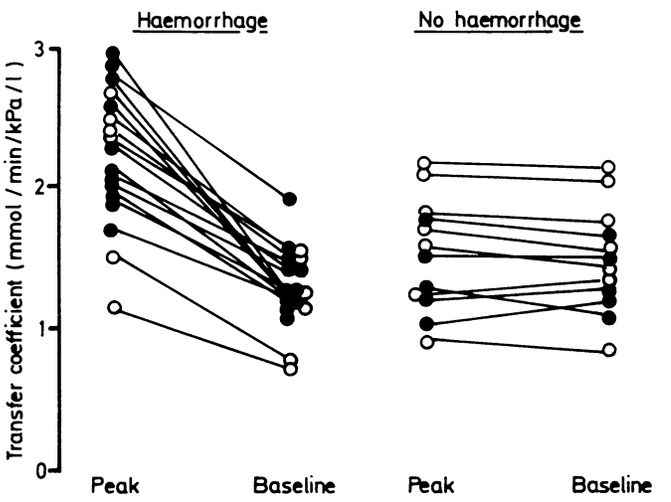

FIG 1—Absolute measurements of transfer coefficient at presentation and follow up in 17 patients with Wegener's granulomatosis (●) and microscopic polyarteritis (○). Patients categorised as those with and without pulmonary haemorrhage.

Conversion: SI to traditional units—Transfer coefficient: 1 mmol/min/kPa/l ≈ 3·0 ml/min/mm Hg/l.

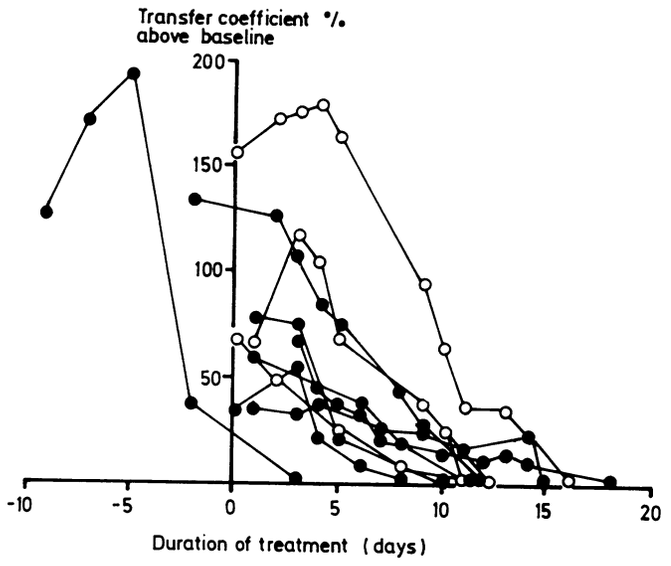

FIG 2—Response of pulmonary haemorrhage to treatment as shown by serial measurements of transfer coefficient in seven patients with Wegener's granulomatosis (●) and microscopic polyarteritis (○). Transfer coefficient expressed as percentage above baseline for that patient.

Discussion

Wegener's granulomatosis and microscopic polyarteritis are distinct forms of small vessel vasculitis of unknown aetiology but with many features in common. Often they present with prominent systemic symptoms and evidence of multisystem disease. Our study shows that pulmonary haemorrhage is not uncommon in patients with severe disease and is an important contributory factor to morbidity and mortality.

Our findings suggest that the incidence of pulmonary haemorrhage in Wegener's granulomatosis and microscopic polyarteritis is much higher than reported. Fauci *et al* found fresh pulmonary haemorrhage in only one of 85 patients with Wegener's granulomatosis[15] compared with 22 of 53 patients in our series. The three reasons most likely to account for these differences are (*a*) differences in the referral patterns of patients, (*b*) generally more severe disease in our patients, as shown by the incidence of renal failure, and (*c*) the more accurate diagnosis of pulmonary haemorrhage made feasible by routine measurement of the transfer coefficient.

A particular difficulty is that pulmonary haemorrhage cannot be diagnosed with confidence on the basis of a single clinical feature. Although the transfer coefficient is probably the most specific indicator of active pulmonary haemorrhage it has limitations. Firstly, a single transfer coefficient value within the predicted normal range does not exclude pulmonary haemorrhage, and changes in sequential values provide a more sensitive index. Secondly, carbon monoxide does not combine with denatured haemoglobin, so that increased uptake in lung haemorrhage depends on the presence of fresh blood in the lung periphery. Thus the transfer coefficient may return to normal within a few days of an episode of lung haemorrhage and results of measurements at this stage may be negative. Furthermore, carbon monoxide cannot enter unventilated spaces and will not detect fresh lung haemorrhage which has resulted in lobar consolidation.

This study documents the course of lung haemorrhage in Wegener's granulomatosis and microscopic polyarteritis. Usually haemorrhage follows the same course as other aspects of the disease, but may occasionally precede other symptoms by many months. The signs of pulmonary haemorrhage usually resolve shortly after treatment begins, but resolution may occur without treatment. Even so, 12% of our patients died of respiratory failure, most deaths occurring within the first 14 days of treatment and before maximal immunosuppression could be achieved. This emphasises how important it is to consider pulmonary haemorrhage in such patients and to start treatment early.

The combination of pulmonary haemorrhage and glomerulonephritis is strongly reminiscent of antiglomerular basement membrane antibody disease. Elsewhere we have emphasised the clinical differences between the small vessel vasculitides and antiglomerular basement membrane antibody disease and the differences in prognosis of the renal disease after treatment.[20] There are also differences in the manifestations of pulmonary haemorrhage. Pulmonary haemorrhage correlates closely with cigarette smoking in antiglomerular basement membrane antibody disease[12] but did not do so in the patients with Wegener's granulomatosis or microscopic polyarteritis reported here. The severity of pulmonary haemorrhage, as reflected by the increase in transfer coefficient and the fall in haemoglobin concentration, is greater in antiglomerular basement membrane antibody disease[8 10]; presumably, this is because of the different pathogenesis.

In summary our study has defined the characteristics of pulmonary haemorrhage in patients with small vessel vasculitis. The results emphasise the clinical usefulness of measuring the transfer coefficient in patients suspected of having pulmonary haemorrhage.

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Hyaluronate in bronchoalveolar lavage fluid: a new marker in sarcoidosis reflecting pulmonary disease

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Abstract

Hyaluronate (hyaluronic acid) was not detectable in bronchoalveolar lavage fluid from smoking or non-smoking healthy volunteers but was present in fluid from 23 patients with sarcoidosis; the mean concentration was 16 μg/l returned fluid (range ≤5-430) or, expressed in relation to the amount of albumin recovered, 0·22 μg/mg albumin (range ≤0·05-3·6). The serum hyaluronate concentrations in the patients with sarcoidosis were normal. There was a significant inverse correlation between vital lung capacity and hyaluronate concentrations in bronchoalveolar lavage fluid ($p < 0.001$), and patients with abnormal lung volumes had hyaluronate concentrations that were on average six times higher than those in patients with normal vital capacity. Duration of disease, pulmonary radiological findings, and markers for macrophage activation (angiotensin converting enzyme) and lymphocyte activation (β_2 microglobulin) were not correlated with bronchoalveolar lavage fluid hyaluronate.

It was concluded that in sarcoidosis release of hyaluronate into the airways is related to lung volume and therefore to the course of the disease. Increased synthesis of hyaluronate in lung parenchyma may reflect activation of fibroblasts, and measurements of hyaluronate may have clinical value for prognosis and treatment.

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Introduction

Fibrotic changes in the lungs may develop in a few patients with sarcoidosis. It is a clinical problem to distinguish at an early stage between those patients who have spontaneously resolving sarcoidosis and those who develop progressive pulmonary destruction. The search for markers to identify the population at risk has been an urgent task. Measurements of serum angiotensin converting enzyme activity,[1] lung scanning with gallium-67,[2] and bronchoalveolar lavage with analyses of lymphocyte subpopulations[3] and inflammatory markers such as β_2 microglobulin[4] have been the main approaches during recent years to assess the intensity of alveolitis in sarcoidosis. It has not, however, been ascertained whether the intensity of alveolitis can predict the risk of developing irreversible lung fibrosis.

Hyaluronate (hyaluronic acid) is a glycosaminoglycan and a connective tissue element present in lung parenchyma.[5] Its release into the culture medium of growing fibroblasts has been shown and its production is stimulated by various inflammatory stimuluses,[6-8] some of which may operate in sarcoidosis.