Thorax 1997;**52**:38–44

British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management

I D A Johnston, R J Prescott, J C Chalmers, R M Rudd for the Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society

Abstract

***Background* – Mortality due to cryptogenic fibrosing alveolitis (CFA) is increasing, particularly in the elderly. Optimum management remains uncertain and previous studies of the disease have largely been from specialist centres. A national study was carried out of the presentation and initial management of CFA in the UK.**

***Methods* – All respiratory physicians in England, Scotland and Wales were invited to enter patients with newly diagnosed CFA over a two year period. CFA was diagnosed on histological grounds or according to clinical criteria which included the absence of a defined connective tissue disorder or pneumoconiosis. Participating physicians (n = 150) completed a questionnaire at patient entry and at all subsequent follow up visits and death.**

***Results* – A total of 588 patients (373 men, 63%) were studied of whom 441 (75%) were referrals from primary care. Their mean (SD) age was 67.4 (10.0) years and median duration of symptoms at presentation was 9.0 months. Clubbing was more common in men (203/373; 54%) than in women (86/215; 40%); 209 patients (36%) were graded as severely breathless at presentation. A history of dust exposure (organic or inorganic) was present in 274 patients (47%) of whom 87 had had some exposure to asbestos. Subjects exposed to dust were more likely to have smoked and had slightly higher mean lung volumes, but were otherwise indistinguishable from those not exposed in terms of clinical presentation, management, and outcome. Transbronchial biopsy specimens were taken in 164 patients (28%) and open lung biopsy specimens in 73 (12%), but 60% had no histological diagnostic procedure. Biopsy procedures were more likely to be performed in younger patients, those with better lung function, and those with a history of asbestos exposure. At presentation a decision not to initiate specific treatment was made in 284 cases (48%). The decision to initiate treatment was made predominantly on symptomatic grounds. Two years after the close of entry to the study 266 patients (45%) had died.**

***Conclusions* – CFA is predominantly a disease of elderly patients and has a poor prognosis. Physicians generally considered CFA to be a clinical diagnosis and did not initiate treatment in up to half of patients at presentation.**

(*Thorax* 1997;**52**:38–44)

Keywords: cryptogenic fibrosing alveolitis, presentation, treatment, British Thoracic Society.

University Hospital, Nottingham NG7 2UH, UK
I D A Johnston

London Chest Hospital, London E2 9JX, UK
R M Rudd

Medical Statistics Unit and Department of Public Health Sciences, University of Edinburgh, Edinburgh EH8 9AG, UK
R J Prescott
J C Chalmers

Correspondence to:
Dr I D A Johnston.

Received 3 May 1995
Returned to authors
3 October 1995
Revised version received
24 July 1996
Accepted for publication
24 July 1996

In England and Wales mortality due to cryptogenic fibrosing alveolitis (CFA, also known as idiopathic pulmonary fibrosis) doubled between 1979 and 1988[1] and continues to increase in the UK, Australia, and Canada.[2] The increase in mortality in the elderly is particularly striking and the median age at diagnosis has been most recently reported as being in the seventh decade.[3 4] This compares with earlier reports of the disease presenting in the fifth or sixth decade.[5–7] There are indications that the disease is frequently diagnosed on clinical grounds[3] despite previous recommendations that histological data should be obtained.[8 9] Reports from specialist centres are unlikely to reflect the whole spectrum of the disease, concentrating on a younger, possibly more severely affected, group of patients. Moreover, the last major review of the clinical presentation of CFA concerned a population of patients diagnosed at least 20–40 years ago.[6]

Against this background the Research Committee of the British Thoracic Society (BTS) initiated a national study of the current presentation, management, and natural history of the disease. Apart from carefully defined diagnostic criteria, this is an observational study with no attempt to influence the usual practice of participating physicians. We present here the methods of the study, clinical features at presentation, and initial management of patients in this, the largest ever study of patients with CFA.

Methods

PATIENTS

In mid 1990 all respiratory physicians in England, Scotland, and Wales were invited to participate in a study designed by the Research Committee of the BTS. Participating physicians were requested to enter prospectively into the study all patients for whom a new diagnosis of CFA was made from 1 December 1990 to 30 November 1992. Patients entered

were then to be followed until death or until November 1996, whichever was the earlier. This paper deals with data collected up until November 1994.

DIAGNOSIS OF CFA

A diagnosis of CFA was accepted if a patient had either (1) bilateral interstitial chest radiographic shadowing with bilateral basal inspiratory crackles and lung function parameters compatible with CFA – that is, a restrictive and/or gas transfer defect, or (2) histological evidence of CFA. In addition a diagnosis of CFA required the patient to have no evidence of a defined connective tissue disorder, allergic alveolitis, sarcoidosis, or bronchiectasis and, in the opinion of the participating physician, to have no occupational exposures which would be accepted as a sufficient basis for a diagnosis of pneumoconiosis for the purposes of state compensation (as performed in the UK by a Medical Boarding Centre).

QUESTIONNAIRE

All participating physicians completed a request for data about the unit(s) in which they worked, how close the unit was to a thoracic surgical unit, and how often a thoracic surgeon visited. At entry the physician completed a questionnaire for each patient containing the following features: demographic details, source of referral, degree of certainty of diagnosis, other diagnoses being considered, symptoms (including breathlessness, cough, chronic bronchitis, arthritis, arthralgia), gradual or acute onset (for example, flu-like illness) of symptoms, exercise grade on five point scale, presence of clubbing; structured occupational, smoking and past medical histories; results of full blood count, erythrocyte sedimentation rate, rheumatoid factor, antinuclear factor, avian precipitins, chest radiographic appearances (to be categorised as one of five predominant patterns – normal, fine nodules/short linear, ground glass, patchy/confluent, or honeycomb), and results of lung function tests (performed according to the standards of each participating laboratory); whether invasive diagnostic tests had been or were about to be performed and the complications from and the rationale for such tests; the initial management plan together with the physician's stated reasons for observation or treatment. This questionnaire was piloted in two centres for acceptability of use. Physicians were asked to complete the questionnaire with the patient at the time of diagnosis.

On receipt of the patient entry questionnaire each physician was sent a dedicated set of forms to record and return information on clinical status, investigations, lung function, and management at each follow up visit. Physicians were requested to see patients at least every three months. Ten days before the patient's visit physicians received a written reminder and, if necessary, a further reminder 10 days after the date of the intended visit.

At death physicians were asked to complete a further questionnaire giving details on the certificated cause of death, presence of lung cancer, and the perceived contribution that CFA had made to the death.

DATA ANALYSIS

Data were entered onto PCs in both centres using D-Base 4. Information on lung function was provided as raw data by physicians, together with height, and converted to percentage predicted values using the European Community for Steel and Coal equations.[10] Missing or discrepant data were checked where possible by direct enquiry to the physician or by obtaining the patient records. Statistical analysis was performed using SPSS 4.0. Ethical approval for the study was obtained from the Nottingham University Hospital medical ethical committee.

Results

Of 415 physicians contacted, 330 agreed to participate in the study. Patients were eventually entered by 150 physicians of whom 49 entered five or more patients. In total, 611 patients were entered but at November 1994 23 had been withdrawn, either because alternative diagnoses had emerged (n = 18) or because of administrative reasons (duplication of entries or diagnosis outside study period, n = 5). Data analysis is confined to the remaining 588 patients.

The mean (SD) age was 67.4 (10.0) years (67.0 years for men and 68.2 years for women, p = NS) and the male:female ratio was 1.7:1 with 373 (63.4%) being men and 577 (98%) white. Four hundred and forty one patients (75%) were referred direct from primary care, 18% were referred by colleagues within the same hospital (18%) and 7% from other hospitals. A total of 374 (64%) patients were seen in a district general hospital, 115 (20%) in a teaching hospital, and 99 (17%) in a regional/specialist centre with no significant differences between the mean ages at presentation in these hospitals.

CLINICAL FEATURES, OCCUPATIONAL HISTORY

The clinical features at presentation are shown in table 1. Arthritis/arthralgia was significantly more common in women and clubbing was more common in men. In 452 patients (76.9%) the disease began gradually and, overall,

Table 1 Clinical features at presentation

	Men (n=373)	*Women (n=215)*	*Total*
Breathlessness	324 (86.9)	197 (91.6)	521 (88.6)
Cough	272 (72.9)	166 (77.2)	438 (74.5)
MRC chronic bronchitis	76 (20.4)	36 (16.7)	112 (19.0)
Arthritis/arthralgia*	62 (16.6)	51 (23.7)	113 (19.2)
Asymptomatic	20 (5.4)	9 (4.2)	29 (4.9)
Clubbing†	203 (54.4)	86 (40.0)	289 (49.1)
Acute onset	64 (17.2)	43 (20.0)	107 (18.2)

Values in parentheses are percentages.
* $p<0.05$; † $p=0.001$.

Table 2 Exercise tolerance at presentation

	Men (n=373)	*Women (n=214)**	*Total*
Normal	45 (12.1)	16 (7.5)	61 (10.4)
Breathless			
on hills	132 (35.4)	53 (24.8)	185 (31.5)
on level	80 (21.4)	52 (24.3)	132 (22.5)
≤100 yards	91 (24.4)	69 (32.2)	160 (27.3)
at rest	25 (6.7)	24 (11.2)	49 (8.3)

Values in parentheses are percentages.
Men versus women ($\chi^2=14.5$, $p=0.006$).
* Missing data for one patient.

Table 3 Occupational and smoking history

	Men (n=373)	*Women (n=215)*	*Total*
Asbestos†	79 (21.2)	8 (3.7)	87 (14.8)
Organic dust	72 (19.3)	40 (18.6)	112 (19.0)
Other inorganic dust†	145 (38.9)	20 (9.3)	165 (28.1)
Any dust†	212 (56.8)	62 (28.8)	274 (46.6)
Smoking†			
Current	82 (22.0)	28 (13.0)	110 (18.7)
Ex-smoker	260 (69.7)	78 (36.3)	338 (57.5)
Never	31 (8.3)	109 (50.7)	140 (23.8)

Values in parentheses are percentages.
† p<0.0001 (male versus female).

Table 4 Chest radiographic appearance at entry to study (n=582)

Normal/near normal	14 (2.4)
Fine nodular/short linear	297 (51.0)
Ground glass	30 (5.1)
Ill defined/patchy/confluent	153 (26.3)
Honeycomb/late stage	88 (15.1)

Values in parentheses are percentages.

patients had been breathless for a mean of 15.1 months (median 9.0) before presentation. Slightly fewer patients (n=521, table 1) presented with breathlessness than were recorded to have a reduced exercise tolerance (n=526, table 2). Review of the data confirmed that a very small number of patients presented with other symptoms or an abnormal chest radiograph but, on direct questioning, admitted to a slight reduction in exercise tolerance. Although 5% of patients were asymptomatic at entry – that is, with neither breathlessness nor cough – 209 (36%) were severely disabled by their breathlessness being breathless at rest or on minimal exertion. Exercise tolerance was significantly worse in women (table 2).

Almost half the patients had a history of some dust exposure (table 3) and physicians considered that, of the 87 patients with at least some exposure to asbestos, this was moderate or severe in 19. However, of the four considered to have had severe exposure no evidence of asbestosis was found at post mortem examination in two and the occupational histories suggested that exposure may have been heavy in only one of the other two. Women were significantly less likely to report a history of any dust exposure, as might be expected, with the exception of exposure to organic dust for which there was no difference between the sexes. Women with CFA were much less likely than men to have smoked.

Table 5 Mean (SD) percentage predicted lung function data at presentation

	Men		*Women*		*Total*	
	n	*% predicted*	*n*	*% predicted*	*n*	*% predicted*
FEV_1	364	78.4 (19.8)	202	79.2 (29.5)	566	78.7 (23.7)
FVC	365	78.0 (24.3)	201	79.0 (25.8)	566	78.4 (24.8)
RV	275	69.5 (27.2)	139	74.4 (30.2)	414	71.1 (28.3)
TLC	275	72.4 (20.3)	141	71.6 (19.2)	416	72.1 (19.9)
TLCO*	304	47.9 (19.2)	139	53.4 (22.5)	443	49.7 (20.4)
KCO**	289	58.1 (23.6)	135	65.0 (20.9)	424	60.3 (23.0)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; TLCO = carbon monoxide transfer factor; KCO = carbon monoxide transfer coefficient.
* p=0.08; ** p=0.004 (male versus female).

INVESTIGATIONS

Rheumatoid factor was positive in 90 of 479 patients (19%) and antinuclear factor in 125 of 489 patients (26%). A positive rheumatoid or antinuclear factor was significantly more common in older patients (37% of those aged over 67 years compared with 25% of those aged 67 years or less, p=0.001). Avian precipitins were positive in 24 of 268 patients (9%) although only seven of these had any documented exposure to birds. Various chest radiographic appearances were noted by physicians (table 4), the most common being a fine nodular/short linear shadowing which occurred in 297 (51%). In 2.4% of patients the chest radiograph was considered to be normal.

Lung function tests on presentation (table 5) revealed mild impairment in mean spirometric indices and lung volumes and a moderate reduction in gas transfer factor (TLCO), the latter being significantly lower in men. It should be noted that, while 96% of subjects had spirometric tests at initial evaluation, TLCO was measured in only 75%. Transbronchial biopsy specimens were taken in 164 cases (28%), percutaneous biopsy specimens in six (1.0%), open lung biopsy specimens in 73 (12.4%), and bronchoalveolar lavage fluid in 67 cases (11.3%). In 59.9% of patients none of these four procedures was performed. Inadequate data were obtained in response to questions about the intended purpose or value of such procedures. Whether any procedure was performed was strongly related to age (mean age 63.0 years for those in whom a procedure was performed compared with 70.4 years for those in whom one was not performed, p<0.0001) and to better lung function (forced expiratory volume in one second (FEV_1), p=0.005; forced vital capacity (FVC), p=0.03; gas transfer coefficient (KCO), p<0.001)). There was no relationship between whether a procedure was performed and sex or total lung capacity (TLC), residual volume (RV), or TLCO on presentation. A diagnostic procedure was more commonly performed in patients with a history of exposure to asbestos (47 of 87 (54%) compared with 189 of 501 (38%), p<0.004) but not in patients with exposure to other inorganic or organic dusts. Access to thoracic surgical facilities was not associated with whether or not transbronchial biopsy was performed, but open lung biopsy was more commonly performed when such facilities were on site (44 of 182 (24%) compared with 29 of 403 (7%), p<0.0001).

Table 6 Physicians' reasons for observation of CFA (n = 284)

*Reason**	*No. of patients*	*%*
Asymptomatic/mild symptoms	183	64.4
Stable	169	59.5
Complicating illness	39	13.7
Elderly	103	36.3
End stage	16	5.6
Other	54	19.0
Treatment considered inappropriate†	28	10.0

* Categories not mutually exclusive.
† Response to separate question as to appropriateness of treatment.

Table 7 Physicians' reasons for initiating treatment at presentation (n = 263)

*Reason**	*No. of patients*	*%*
Symptoms warrant treatment	248	93.9
Worsening symptoms	163	61.7
Extensive radiographic change	155	58.7
Worsening chest radiography	46	18.2
Severe lung function deficit	144	54.5
Worsening lung function	35	13.3
Other	20	7.6

* Categories not mutually exclusive.

Table 8 Comparison of presentation, management and outcome variables between subjects with and without a history of any dust exposure (organic, asbestos, or other inorganic)

	History of dust exposure	
	No (n = 314)	*Yes (n = 274)*
Severe breathlessness*	112 (35.8)	97 (35.4)
Smoking†		
Current	48 (15.3)	62 (22.6)
Ex-smoker	176 (56.1)	162 (59.1)
Never	90 (28.7)	50 (18.2)
Procedure performed	125 (39.8)	111 (40.5)
Observed at presentation	142 (45.2)	142 (51.8)
Alive at October 1994	172 (54.8)	150 (54.7)

Values in parentheses are percentages.
* Breathless at rest or at ≤100 yards.
† $\chi^2 = 11.1$, p = 0.004.

TREATMENT

At diagnosis physicians were prepared to observe – that is, to withhold treatment – in 284 patients (48.3%) predominantly on the grounds of few or stable symptoms (table 6). In only 10% of patients, however, was present or future treatment considered inappropriate. Compared with those who were observed, those for whom treatment was initiated at presentation were slightly younger (mean age 66.9 years compared with 68.3 years, p = 0.04) and had very significantly worse lung function – for example, mean predicted FVC 71.2% versus 85.9%, p<0.0001; TLCO 46.9% versus 52.5%, p = 0.02 – with the exception of the percentage predicted KCO which was almost identical in the two groups. The M:F ratio was not significantly different in the two groups. In the 263 patients (44%) who started treatment at diagnosis, 201 (76%) received prednisolone alone, 25 (9.5%) received prednisolone and cyclophosphamide, 10 (3.8%) received prednisolone and azathioprine, and 22 (8%) received other combinations of drugs. Overall, 17% of treated patients received cyclophosphamide or azathioprine, either in combination with other drugs or as sole therapy. Again the decision to initiate treatment was most commonly based on symptom severity (table 7). Forty one patients (7%) were already on some form of treatment at presentation.

Table 9 Comparison of mean (SD) lung function data at presentation between subjects with and without a history of dust exposure (organic, asbestos or other inorganic)

	Exposed		*Not exposed*		
	No.	*Mean (SD)*	*No.*	*Mean (SD)*	*Difference (SE)*
FEV_1 (%)	266	80.2 (27.1)	300	77.2 (19.8)	3.0 (2.0)
FVC (%)	266	81.2 (28.0)	300	75.8 (21.2)	5.4 (2.1)**
TLC (%)	190	76.6 (22.4)	226	68.3 (16.7)	8.3 (1.9)***
RV (%)	191	74.4 (30.6)	223	68.3 (25.8)	6.0 (2.8)*
TLCO (%)	212	50.6 (20.9)	231	48.8 (19.9)	1.9 (1.9)
KCO (%)	204	58.2 (22.6)	220	62.2 (23.2)	−4.0 (2.2)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; TLCO = carbon monoxide transfer factor; KCO = carbon monoxide transfer coefficient.
* p<0.05; ** p<0.01; *** p<0.001.

OUTCOME

By October 1994 266 patients (45.2%) had died. Death was considered to be primarily due to CFA in 53% of cases, partly due to CFA in 28%, and unrelated to the disease in 14%. Of 231 patients with complete information 29 (12.6%) were known to have lung cancer. A preliminary analysis of factors associated with death from CFA revealed that those who had died were older at presentation (mean age 69.7 versus 65.6, p<0.0001) and all indices of lung function were significantly worse – for example, FVC 73.8% versus 82.0%, TLCO 44.1% versus 53.4%, both p<0.0001). Sex, a history of exposure to any dust, the presence of rheumatoid or antinuclear factor, and whether any investigative procedure had been performed were not associated with death.

COMPARISON OF THOSE WITH AND WITHOUT DUST EXPOSURE

Further analyses were performed to ascertain whether subjects with a history of dust exposure differed in presentation, management, or outcome from those without such a history (tables 8 and 9). Those reporting a history of exposure to any dust (including asbestos or other inorganic or organic dust) were significantly more likely to be current smokers and to have slightly higher FVC, RV, and TLC. These differences in lung function persisted in the whole population after adjustment for age, sex, and smoking status. However, the differences appeared to be largely accounted for by women with CFA; for men the only significant difference in lung function between those with and without a history of dust exposure was in TLC (adjusted mean (SE) difference 5.7 (2.3)%). There were no other significant differences between the two populations including duration of symptoms at presentation, comparison of chest radiographic appearances, treatment decision, and mortality at October 1994. A comparison of those merely reporting asbestos exposure with the remainder revealed differences only in the same variables as for any dust exposure – that is, smoking, lung volumes, and the higher rate of diagnostic investigation noted previously in those with asbestos exposure (54% versus 38%).

Discussion

This BTS study of CFA is the largest survey reported to date of a disease of serious prognosis and which is increasing in reported mortality in both the UK and in several other countries.[1 2]

Before reviewing the data obtained we need to consider how robust the diagnosis of CFA was in our patients. Earlier recommendations that biopsy is the gold standard for diagnosis of CFA have come from specialist centres in which the age at presentation is likely to be substantially lower than that reported here.[8 9] The greater age of the more unselected patients in the present study is likely to influence physicians' decisions about the safety and necessity of taking biopsy specimens. More recently it has become accepted that the high resolution computed tomographic (HRCT) scan can be a diagnostic tool,[11] but our study began before HRCT had become well established. We used essentially clinical criteria for the diagnosis of CFA, very similar to those used in past surveys of the disease.[3 6] There is no information on the reliability of a clinical diagnosis of CFA, but clearly physicians in the UK are prepared to diagnose CFA on clinical grounds in most patients since nearly 60% had no diagnostic procedure of any kind in our study. However, having entered patients into the study only a very small proportion were eventually withdrawn after 2–4 years because of alternative diagnoses, although only a few of those who died had a post mortem examination. Given the knowledge that taking biopsy specimens is not routine in patients with suspected CFA, our diagnostic criteria reflected the general perception that CFA is a clinical syndrome, probably heterogeneous in origin.

A substantial number of patients had reported exposure to asbestos and other dust, both inorganic and organic. The question arises as to whether some of these patients may have had pneumoconiosis or extrinsic allergic alveolitis (EAA) rather than CFA. Potential difficulties in this area are highlighted by a study which found post mortem histological appearances similar to CFA in a small number of patients with silicosis (4%), although these were patients with a known diagnosis of silicosis and no clinical or radiographic data were given.[12] On the other hand, CFA has been reported in patients with exposure to asbestos.[13] Our study was specifically designed to include all patients in whom the participating physicians considered CFA to be the most likely diagnosis rather than pneumoconiosis or EAA. To have excluded patients with any history of exposure to dust, however trivial and however unlikely to be the cause of the lung disease, would have seriously biased the sample, effectively excluding many cases occurring amongst the working population. Furthermore, we did evaluate the information provided about dust exposure in every case. For example, review of the occupational histories of those graded as having moderate or severe exposure to asbestos suggested that the severity of exposure tended to be overestimated – indeed, in only one of four graded as severe was asbestosis a possible diagnosis. Less than one third of those with avian precipitins had documented avian exposure. Importantly, while those with exposure to dust had smoked more and had slightly greater lung volumes, they were otherwise indistinguishable in terms of clinical presentation, management, and outcome from patients with no exposure to dust. Overall we are confident that, in nearly all cases, the diagnosis of CFA was correct, although occupational exposure to some dusts previously unrecognised as causing pulmonary fibrosis are probably involved in the aetiology of CFA, as recently reported.[4]

A particular strength of this BTS study is that the data have been obtained prospectively at the time of consultation, rather than by retrospective review of case records as in some previous surveys.[5–7] A possible weakness is the lack of formal validation of the questionnaire in areas such as symptoms and smoking and occupational histories, although areas such as physicians' opinions would be difficult to validate. However, during data cleaning the internal validity of the questionnaire data has been exhaustively checked where possible, and frequent review of original records has also occurred.

Our study shows that CFA is predominantly a disease of the elderly, with a mean age at presentation of 67 years, and that men predominate (M:F ratio 1.7:1). Comparisons with previous studies are difficult, partly because some studies have included patients with connective tissue disorders (making up to one third of the total[5–7]), partly because of differing diagnostic criteria (in one study only 60% had crackles[7]), and also because our study is the only one to have documented clinical features prospectively. Nevertheless, CFA has previously been reported as presenting in much younger patients.[5–7] It is possible that there has been a real increase in the age at presentation or that the disease is increasingly being recognised in the elderly. Of particular importance, however, is the fact that a high proportion of patients in this study have been referred from primary care and seen in district general hospitals. Our data are therefore much more likely to reflect the true presentation of this disease than do earlier studies. With regard to sex differences, previous surveys have suggested either no difference in presentation[5 14] or a male predominance of 2:1[6] or 3:1.[7] As noted above and elsewhere, the male predominance raises the possibility of genetic and occupational factors in the aetiology of the disease. Apart from one study from South Africa[15] there is little information on CFA in non-white patients. In our study only 2% of patients were non-white and their numbers were too small to permit separate analysis. Further work is needed to determine whether ethnic factors may play a part in the aetiology of CFA.

Despite the likely differences in the populations studied, there appear to be few major differences in clinical features or the results of basic investigations from earlier studies where comparisons are possible. One exception would appear to be the high proportion (35%) of patients in our study who were severely disabled

by breathlessness on presentation. Nevertheless, spirometric indices in men (at about 80% predicted) were considerably less impaired than in previous studies, although TLCO was similar (at about 50% predicted[5–7]). Clubbing occurs in about 50% of patients, although others have found the sign in two thirds.[6] Stack *et al*,[14] like ourselves, did not include connective tissue disorders in their study and found a very similar proportion of their patients with CFA with positive autoantibodies. We have not formally reviewed the chest radiographs but appearances were classified at time of entry by the participating physician. It is clear that the appearance we classified as fine nodular/short linear is the most common. Interestingly, our figures for ground glass shadowing (5%) and normal radiographs (2%) correspond to those of Turner-Warwick *et al*[6] of 7% and 2%, respectively.

The diagnosis of CFA in this study was made on clinical grounds in 60% of cases, a proportion similar to that of an earlier more geographically limited study.[3] The most common diagnostic procedure was transbronchial biopsy, an investigation known to be unreliable for the diagnosis of CFA,[16] though we have not reviewed the biopsies in the present study. It may be, however, that physicians reasonably use transbronchial biopsy specimens to exclude other diagnoses such as sarcoidosis which are more readily diagnosable on such specimens. We questioned physicians as to their reasons for using transbronchial biopsy specimens but our data are unfortunately insufficient to shed light on this practical question. Only 12% had an open lung biopsy, the investigation recommended at the time the study started as the diagnostic gold standard.[8 9] Such a recommendation may have been appropriate for the age group of patients in earlier studies[5–7] (mean age 55 or less), but in our patients with a mean age of 67 years the morbidity and mortality from open lung biopsy would be unjustified in a large proportion. Indeed, we have confirmed, perhaps not surprisingly, that age and poorer lung function are the most important factors in the decision whether to investigate, but access to thoracic surgical facilities also influences the decision to obtain an open lung biopsy specimen. The advent of video assisted thoracoscopy may lead to open lung biopsies being more acceptable, although HRCT scanning seems likely to become the investigation of choice[11] and will be particularly attractive for older patients.

In over 50% of patients who were not already on some form of treatment at entry a decision was made to observe rather than to initiate treatment and this decision was most commonly made because of few or stable symptoms. This may at first sight appear to be at odds with the severe prognosis of CFA, generally reported as a median survival of 4–5 years.[6 7 14] The decision to observe may reflect the concerns of the physicians as to the effectiveness and side effects of available treatment, particularly in the elderly, and those observed rather than treated at presentation were, indeed, significantly older and had less impaired lung function. There is little published evidence to support the concept that treatment is more effective when given earlier, despite the apparent plausibility of this hypothesis.[11] A further issue is the widely held view that CFA often remains stable, particularly in the elderly, and indeed the most common reason for observation was the perception that patients had stable or minimal symptoms. The view that CFA may be a benign disease may well be seriously challenged by the eventual mortality data from the present study, as an interim analysis shows a 45% mortality for patients entered only 2–4 years earlier which is considerably higher than in previous reports. Preliminary analysis confirms the association of older age with death from CFA,[5 6 14] although the association with poorer lung function on presentation was previously only found for TLCO.[5] When treatment was given prednisolone was clearly the commonest option (90%), with cyclophosphamide and azathioprine being given to only 17% of patients. Further analysis of treatment and prognosis will be available from the study in due course.

This is by far the largest study of patients with CFA, but how representative are the data? At the time the study was designed there were about 800 reported deaths annually from CFA. We hoped that about 50% of physicians would participate and that at least 50% of their patients would be entered. Our aim was therefore for a total of 400–600 cases over the two year period and this aim was achieved. Previous data[1] suggest that recorded mortality data may underestimate actual numbers of patients with the disease by up to half. Overall, the present study may have enrolled 20–40% of all those eligible nationally. The mean age of patients is very similar to that of more geographically limited studies of patients with CFA.[3 4] Even for participating physicians, however, the study is likely to have missed those who declined rapidly or those in whom the diagnosis was initially uncertain. Given these caveats, we feel the data are likely to be representative of the generality of patients with CFA and certainly represent the most complete picture of the spectrum of the disease that has hitherto been available.

In summary, this is the largest study yet reported of CFA, a disease with a steadily increasing annual mortality. We have shown that in unselected patients the disease presents predominantly in the elderly. In the main, respiratory physicians consider CFA to be a clinical diagnosis. Over one third of patients were severely disabled by symptoms on presentation and we have confirmed that CFA has a poor prognosis, although almost half of the patients in this study did not receive treatment at diagnosis. Of the many unanswered questions about CFA there is an urgent need for therapeutic studies and studies that address the issue of whether early treatment conveys benefit.

We are most grateful to the 150 BTS members who participated in this study which was supported by the Morrison-Davis Trust. Members of the Committee are: R A L Brewis (Chairman), I D A Johnston, R M Rudd (Study Co-ordinators), R Prescott (Statistician), J White, J A R Friend.

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