

The prognosis of cryptogenic fibrosing alveolitis

B. H. R. STACK,¹ Y. F. J. CHOO-KANG, and B. E. HEARD²

Chest Unit, City Hospital, Edinburgh, Respiratory Diseases Unit, Northern General Hospital, Edinburgh, and Department of Pathology, University of Edinburgh

The course of cryptogenic fibrosing alveolitis (CFA) in 96 patients is described. The mean survival from the onset of the first symptom until death was 47.4 months in all the 59 fatal cases, 49.6 months in those dying from CFA only, and 48.4 months in those dying from CFA in whom the course of the illness was not influenced by corticosteroids. There was a wide variation in the natural course of the disorder, varying from death within a year of the onset of symptoms in five patients to prolonged survival with slow or arrested progress in four patients not treated with corticosteroids. Most patients died from CFA but five developed bronchial carcinoma and two died after lung biopsy.

The main factor influencing the prognosis was the effectiveness of corticosteroid drugs. Only 16% of the treated patients had a worthwhile (grade 2) response to these drugs and the five-year survival of this group was 67%. In those patients in whom the course of the illness was uninfluenced by corticosteroids the five-year survival rate was only 20%. The histological appearances on lung biopsy gave a rough guide to the likely effect of corticosteroid therapy.

Other factors influencing the prognosis were the degree of dyspnoea on presentation, the vital capacity, and the presence of arterial hypoxaemia. Patients who had had symptoms for more than four years before the first hospital attendance had a relatively good prognosis.

By contrast, neither the extent of radiographic abnormality nor the presence of circulating rheumatoid and antinuclear factors influenced subsequent survival.

A feature of earlier reports of this condition (then more commonly called diffuse interstitial pulmonary fibrosis) was the marked variability in the course of the disorder. Hence, although all the patients described by Hamman and Rich (1944) died within 12 months of the onset of symptoms, Scadding (1960) considered a less acute course to be more usual and reported several patients who survived more than five years. Moreover, occasional dramatic improvement following corticosteroid therapy had by then been reported (Schechter, 1953; Tuft and Girsh, 1958; Douglas, 1960).

Most of these earlier papers were individual case reports or general reviews which contained little reference to the overall prognosis of cryptogenic fibrosing alveolitis (CFA) or to factors which might influence this. The object of this

paper is to review the prognosis in a large series of well-documented cases seen in Edinburgh during the past 17 years.

CLINICAL MATERIAL

Forty-nine males and 47 females were investigated in the Edinburgh Chest Units between 1953 and 1 January 1970 (Table I). Most of the patients described by Stack, Grant, Irvine, and Moffat (1965) were included in this series. Essential criteria for inclusion were a history of progressive non-episodic dyspnoea

TABLE I
AGE AND SURVIVAL OF SERIES

Age (years)	< 40		40-49		50-59		60-69		> 70	
	M	F	M	F	M	F	M	F	M	F
No. of patients:										
Alive	0	2	5	4	5	2	7	9	2	1
Dead	0	1	4	3	5	6	10	11	11	8
Total	0	3	9	7	10	8	17	20	13	9

¹Present address: Respiratory Diseases Unit, Knightswood Hospital, Anniesland, Glasgow G13 2XG

²Present address: London Chest Hospital, London E.2

without wheeze, and bilateral crepitations on auscultation of the chest. All patients had diffuse bilateral pulmonary opacities on the chest radiograph and these were either confined to the lower zones or were more widespread. The forced expiratory volume in one second (FEV_{1.0}) and the forced vital capacity (FVC) were measured in all patients except in two of the earlier cases. Only patients with an FEV_{1.0}/FVC ratio of more than 60% were included in the series. Blood gas analysis was carried out in 78 patients. Patients whose arterial carbon dioxide tension (Paco₂) was raised above 46 mmHg were excluded, except when this was recorded in the terminal stages of the illness. The carbon monoxide transfer factor (TF) was measured in 34 patients, in 27 by the single breath technique and in 7 by the steady state method. It was less than 60% of the predicted normal value in all except six of these patients.

Histological confirmation of the diagnosis by lung biopsy and/or necropsy was obtained in 48 patients. The essential criteria for inclusion were alveolar wall thickening by fibrous tissue infiltrated with chronic inflammatory cells or more advanced fibrotic changes in which inflammatory cells were sometimes less conspicuous.

The presence of other similar disorders, such as sarcoidosis, pneumoconiosis, and allergic alveolitis, was eliminated as far as possible. No patients who developed or who already suffered from frank systemic lupus erythematosus or rheumatoid arthritis were included, although of 62 patients investigated, 30% had positive serological tests for anti-nuclear factor and 13% for rheumatoid factor. Eight of the 18 patients (44%) with a positive anti-nuclear factor test and four of seven (57%) with positive tests for rheumatoid factor were female.

METHOD

Details of the patients' progress were obtained from case records of their hospital admissions and outpatient attendances. In the majority, regular outpatient reviews were carried out and these consisted of a full clinical assessment, chest radiography, and simple spirometric tests. In the eight patients not followed up at the clinics, details of progress were obtained from their general practitioners and/or other hospitals.

RESULTS

Fifty-nine of the 96 patients (61%) had died before this analysis was undertaken. The mortality was higher in the older age groups, 68% of those over 60 having died, compared with only 42% of those under 50. This was far in excess of that expected in a matched normal population calculated from actuarial life expectancy tables (Table II). Even allowing for the fact that these were based on the mortality in England and Wales derived from the 1951 census, the mortality rate

TABLE II
OBSERVED AND EXPECTED MORTALITY

Age Group (years)	Males		Females	
	Actual	Expected	Actual	Expected
< 50	4	0.08	2	0.19
50-59	3	0.71	5	0.41
60-69	11	2.48	11	1.75
70 or over	13	4.58	10	1.86

TABLE III
MEAN SURVIVAL OF FATAL CASES

	No. of Patients	Survival (months)
All deaths	59	47.4
Deaths from CFA	41	49.6
Deaths from CFA uninfluenced by corticosteroids	28	48.4

in our series was more than three times greater in males and more than four times greater in females than that of the general population ($P < 0.05$).

The mean survival from the onset of the first symptom until death in the 59 fatal cases was 47.4 months with a range of 5 months to 20 years (Table III). In all those who died from fibrosing alveolitis, the mean survival was 49.6 months. In those patients who died from fibrosing alveolitis and who either did not receive corticosteroids or did not respond to them, the mean survival was similar (48.4 months).

Five patients died from fibrosing alveolitis within one year of the onset of symptoms. These comprised four males, two of whom were under 50 and all of whom received corticosteroids without benefit, and one female aged 72 who was not treated with these drugs.

Thirty-seven patients were alive at the time of analysis. Twenty-eight of these had survived for more than two years after the onset of symptoms and seven had survived for more than 10 years. Of particular interest is a group of four patients (three males aged 40, 66, and 74, and a female aged 56) who are still alive, having survived for between four and 13 years from the onset of symptoms without corticosteroid therapy. In two of these patients the disease appears to have undergone spontaneous arrest.

CAUSE OF DEATH In 40 of the 59 patients who died (68%), the cause of death was fibrosing alveolitis, associated cor pulmonale, and infection (Table IV). A noteworthy feature was the high incidence of apparently unrelated cardiovascular deaths (20%). Eight patients died from myocardial infarction, three from cerebro-vascular accident,

TABLE IV
CAUSE OF DEATH

	No. of Patients	Percentage
Fibrosing alveolitis	40	68
Cardiovascular disease	12	20
Bronchial carcinoma	4	7
Lung biopsy	2	3
Others	1	2

and one from a pulmonary embolism. Only two of these 12 patients (17%) were polycythaemic.

Bronchial carcinoma developed in five patients and the incidence was compared with that expected in this series based on mortality rates for Scotland (1958). In three males, evidence of carcinoma was present at first hospital attendance and these were excluded from statistical analysis. The observed incidence of two deaths from bronchial carcinoma among the remainder was much in excess of that expected ($P=0.08$).

All five patients with bronchial carcinoma were cigarette smokers and four died before the end of the period of study. Two had oat-cell carcinomas, one, a poorly differentiated squamous carcinoma and one, an adenocarcinoma. Material for histological examination was not obtained from one patient.

Thirty patients underwent lung biopsy, in 24 by thoracotomy and in six by drill biopsy. One of these died of cardiac and respiratory failure within 24 hours of thoracotomy. One patient died 10 days after drill biopsy having developed an empyema; the ultimate cause of death was probably pulmonary embolism. Both were receiving corticosteroids at the time of biopsy.

FACTORS INFLUENCING THE PROGNOSIS

1. CORTICOSTEROID THERAPY In 69 patients the duration of corticosteroid therapy was long enough to allow assessment of its effect. The usual initial daily dose was between 20 and 40 mg of prednisolone. After between two and eight weeks, the drug was either withdrawn completely or reduced to a maintenance daily dose of about 5 to 10 mg. The response to corticosteroids was graded as:

Grade 0 No effect

Grade 1 Slight symptomatic improvement, vital capacity increased by up to 10% and/or slight radiological improvement

Grade 2 Substantial relief of dyspnoea, vital capacity increased by more than 10%, and considerable or complete radiological clearing

Some improvement on corticosteroid therapy occurred in 28 of the 69 patients (41%) (Table V). The results of treatment were better in women, a response being observed in 17 out of 33 females (52%) compared with only 11 of 36 males (31%).

TABLE V
RESPONSE TO CORTICOSTEROIDS

Age (years)	< 50		50-59		60-69		> 70		Total	
Sex	M	F	M	F	M	F	M	F	M	F
Corticosteroid response:										
0	5	2	4	5	10	7	6	2	25	16
1	2	1	2	0	1	8	2	1	7	10
2	1	5	1	1	1	0	1	1	4	7
Total	8	8	7	6	12	15	9	4	36	33

A grade 2 corticosteroid effect was obtained in only 11 of 69 patients (16%). Five of these were women under the age of 50. A grade 1 corticosteroid effect occurred in 17 patients (25%). Eight of these were women in the 60-69 age group.

The five-year survival rate for all the patients who responded to corticosteroid therapy was 43%, compared with only 20% in the group uninfluenced by corticosteroids. Of the eleven patients showing a grade 2 response to corticosteroids, eight are still alive, and six of these have survived more than five years from the start of treatment. CFA was the cause of death in only one of the three fatal cases, none of whom survived five years. The five-year survival rate in this group is thus 67%.

2. RESPIRATORY DYSFUNCTION In order to assess the relationship between initial respiratory dysfunction and the natural course of the disease, we considered only those patients who were not treated with corticosteroid drugs or who did not respond to them.

(a) *Dyspnoea* A rough correlation was seen to exist between the degree of dyspnoea on presentation and the survival from first hospital attendance (Fig. 1). Individual patients are represented by points placed in one of the four vertical columns according to the degree of dyspnoea on presentation. This was classified into four grades (Wood, 1956):

(1) dyspnoea provoked by more than average activity, e.g., hurrying on the level, walking up hills

(2) dyspnoea on ordinary activity, e.g., walking at normal pace on the level

(3) dyspnoea on less than ordinary physical activity

(4) total incapacity, dyspnoea at rest or on slight exertion

It can be seen that the majority of those patients presenting with grades 2 to 4 dyspnoea died within four years. By contrast, among five patients with grade 1 dyspnoea on presentation there were no deaths in the subsequent two years and three have survived for more than five years.

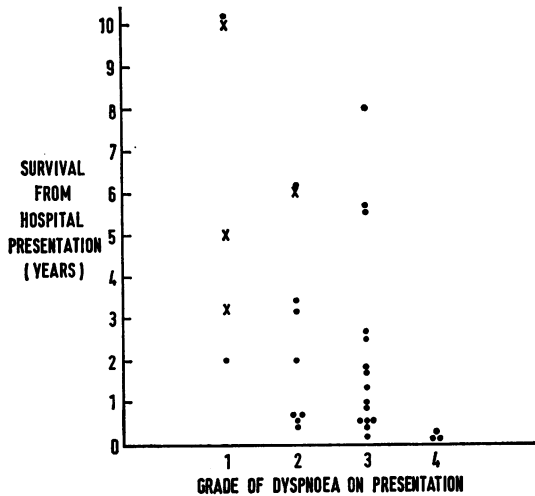


FIG. 1. Survival from first hospital attendance related to grade of dyspnoea on presentation: ● died of CFA, course uninfluenced by corticosteroids; × alive, course uninfluenced by corticosteroids. ● alive, course influenced by corticosteroids.

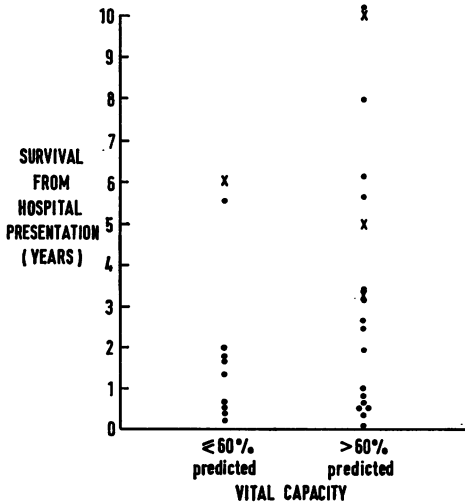


FIG. 2. Survival from first hospital attendance related to the vital capacity on presentation. Symbols as in Fig. 1.

(b) *Vital capacity* A similar diagram (Fig. 2) relates the initial vital capacity, expressed as a percentage of the predicted normal, to the subsequent survival of patients in whom the course of the illness was not influenced by corticosteroid therapy. All except two of the patients who presented with a vital capacity of less than 60% of the predicted normal died within two years. However, a vital capacity of more than 60% of the predicted was no guarantee of longer survival, as nearly half of the patients in this group (8 out of 19) died within two years.

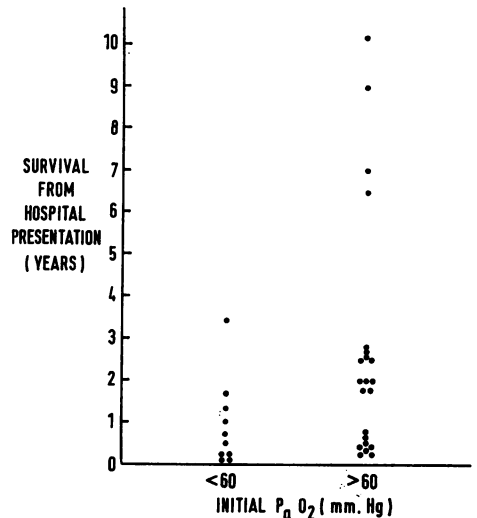


FIG. 3. Survival from first hospital attendance related to degree of hypoxia on presentation in patients who died from CFA, cardiovascular disorders or following lung biopsy and in whom the course of the illness was not influenced by corticosteroids.

(c) *Hypoxia* Figure 3 shows a similar relationship between the initial presence of significant hypoxia, defined as a resting arterial oxygen tension (PaO_2) of less than 60 mmHg, and the subsequent survival of the patients in this group. All of the patients who were initially hypoxic died within four years, all except one within two years. By contrast, over half the remainder survived longer than two years and four out of 18 survived more than four years.

3. *Histological appearances.* Slides of 16 lung biopsy specimens were available and suitable for assessment. Patients were divided into two groups depending on the histological appearances. In group I there was generally a highly cellular picture with many lymphocytes and plasma cells in

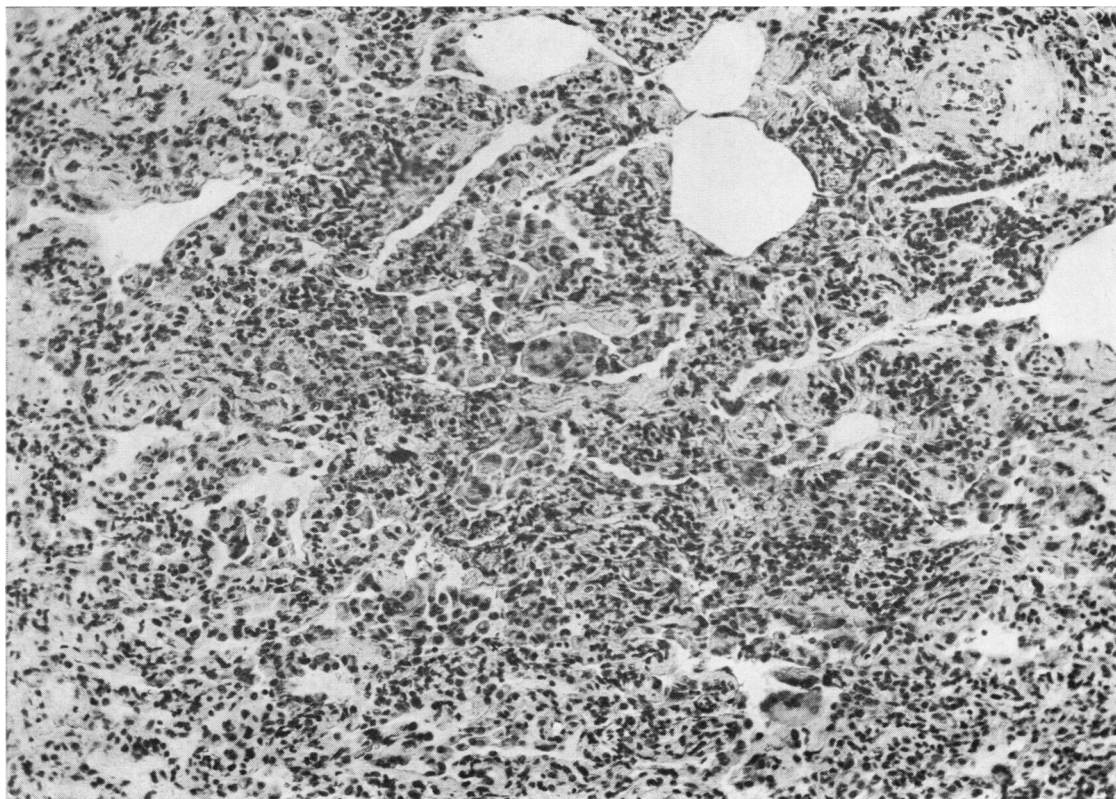


FIG. 4. Cellular histological appearance of a lung biopsy from a patient in group I. The alveolar walls are thickened and contain many lymphocytes and plasma cells. The alveolar lumina contain clusters of larger cells which are probably a mixture of histiocytes and desquamated large alveolar lining cells (H. and E. $\times 155$).

the alveolar and bronchiolar walls, and also many intra-alveolar cells (Fig. 4). The lymphocytes were commonly collected into nodules and sometimes germinal centres were also present. There was only a little fibrous thickening of the alveolar walls and honeycombing was never present. In group II the picture was less cellular. The degree of fibrosis was more marked and it was inert in appearance (Fig. 5). In some specimens, pronounced honeycombing was a feature.

TABLE VI
CORTICOSTEROID RESPONSE RELATED TO HISTOLOGICAL APPEARANCES OF LUNG BIOPSY SPECIMENS

	Group I	Group II
Corticosteroid responders	6	0
Non-responders to corticosteroids ..	3	6
Not treated with corticosteroids ..	0	1
Total	9	7

Table VI shows the relationship between the histological picture of the lung biopsy specimens and the subsequent response to corticosteroids. The majority of patients with a cellular picture responded to these drugs. In contrast, there was no response in those patients with less cellularity and more marked fibrosis.

4. Duration of symptoms In all except seven of the patients in whom three- and five-year survival rates could be calculated, the duration of symptoms was less than four years. It can be seen from Table VII that, within this group, the chance of surviving three or five years was not influenced by the length of the previous history. However, there is a suggestion that patients with a history of more than four years' duration before presentation have a better prognosis as six out of the seven patients survived more than five years after first hospital attendance.

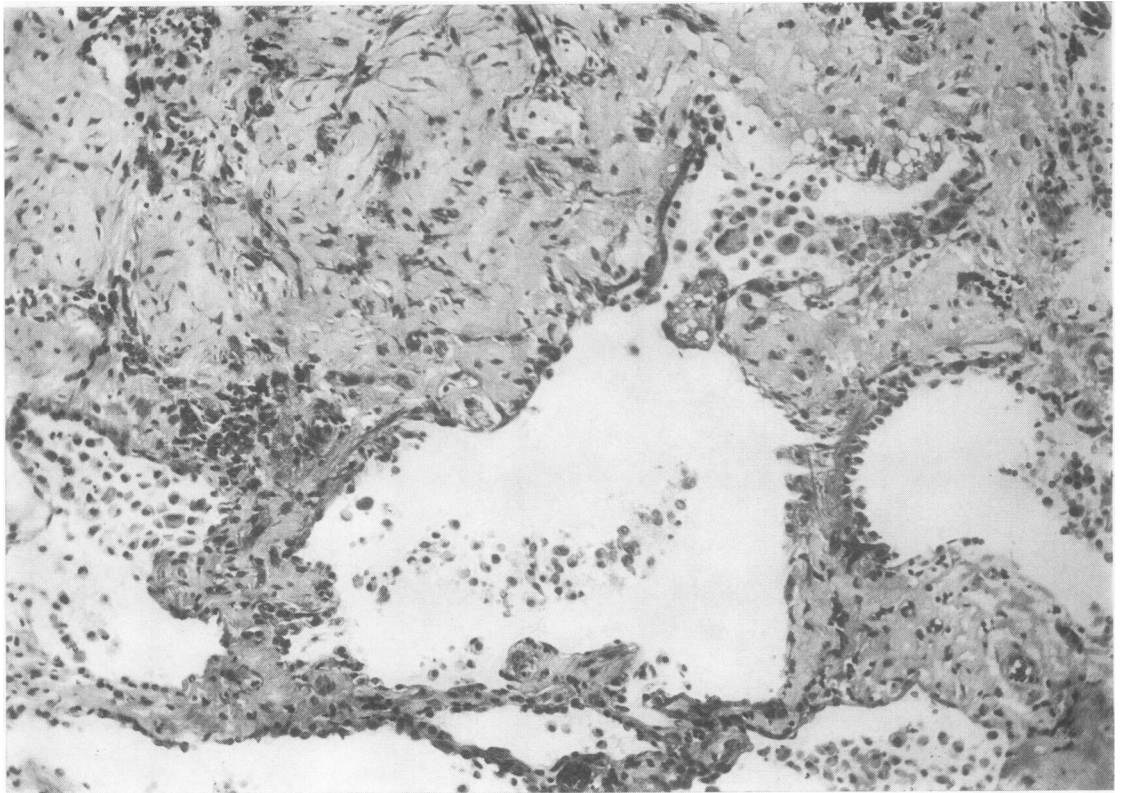


FIG. 5. *Non-cellular pattern from lung biopsy of a patient in group II. Large honeycomb spaces are present, surrounded by a considerable amount of dense fibrous tissue. There is conspicuously less cellular infiltrate of the interstitial tissue than is shown in Fig. 4 (H. and E. $\times 155$).*

TABLE VII

SURVIVAL FROM FIRST HOSPITAL ATTENDANCE
RELATED TO DURATION OF PREVIOUS HISTORY

Duration of History (yr)	No. of Patients Surviving 3 yr	Total No. of Patients	% 3-year Survival	No. of Patients Surviving 5 yr	Total No. of Patients	% 5-year Survival
< 1	9	30	30	5	30	17
1-2	5	15	33	3	13	23
2-4	6	23	26	5	23	22
> 4	6	7	86	6	7	86

FACTORS WHICH DID NOT INFLUENCE THE PROGNOSIS

1. **RADIOGRAPHIC CHANGES AND PROGNOSIS** Points were awarded according to the degree of abnormality in each lung zone of the first chest radiograph taken after attendance at clinic or hospital and the sum of these was used to express the total abnormality. No relationship was found between the subsequent survival and either the total abnormality or the presence of elevation of both hemi-

diaphragms. An incidental finding was that chest radiographs taken more than three years before the development of symptoms of fibrosing alveolitis were abnormal in 10 patients and that in eight of 27 patients dying from fibrosing alveolitis there was no significant radiographic deterioration even during the terminal illness.

2. **CIRCULATING NON-ORGAN SPECIFIC AUTOANTIBODIES** Fifty-nine patients had serological tests for both rheumatoid and antinuclear factors. Positive tests for one or both of these were obtained in 22 patients (37%), 54% of whom were males, and occurred with equal frequency in the different age groups. The five-year survival rate in patients with positive serological tests was 18% compared with 24% in those with negative tests. The mean survival from first hospital attendance until death was 24 months in patients with positive tests and 30 months in those with negative tests.

DISCUSSION

The mean duration from the onset of symptoms until death in those patients who died from CFA and in whom the course of the illness was unaffected by corticosteroid drugs was just over four years. This is similar to the mean survival of four and a half years reported in seven cases by Scadding (1960). Our findings also confirm the marked variability of the course of the illness which he described. Five patients died within one year of the onset of symptoms and were thus similar to the original four cases described by Hamman and Rich (1944). In contrast, the disease progressed very slowly or underwent spontaneous arrest in four patients not treated with corticosteroids. Such patients may constitute a separate clinical entity and account for the relatively good prognosis of patients who present with a history of more than four years' duration (Table VII).

The majority of deaths were the direct result of fibrosing alveolitis. Among the other causes of death, the predominance of elderly patients in this series and the prevalence of cardiovascular disease in the community account for the high proportion dying from this cause. In two of the 12 patients, polycythaemia may have been a contributory factor. Of particular interest was the occurrence of bronchial carcinoma in five patients (all males). In two the carcinoma developed three and five years after first hospital attendance with CFA. This incidence is considerably higher than would be expected in a population of males of similar age distribution and suggests that there may be an association between the two conditions although the total number of cases in the series is still too small to allow a definite conclusion to be reached. Other evidence that CFA predisposes to lung carcinoma includes the finding of carcinoma in individual cases (Tesluk and Ikeda, 1970) and in reported series (Scadding, 1960; Livingstone, Lewis, Reid, and Jefferson, 1964; Haddad and Massaro, 1968), the occurrence of carcinoma in relation to lung fibrosis (Spencer, 1968), and the presence of hyperplastic changes of the bronchiolar epithelium in CFA (Stack *et al.*, 1965). No particular histological variety of carcinoma predominated either in our patients or in the reported series. However, in view of the alveolar wall changes described in CFA it is of interest that patients have occasionally developed alveolar-cell carcinoma (Fox and Risdon, 1968; Jones, 1970).

Two patients died shortly after lung biopsy. One of these was among six patients who had a drill

biopsy. Of 24 patients undergoing lung biopsy by thoracotomy, one died. This mortality rate of 4% can be compared with that reported for biopsy by thoracotomy in diffuse lung disorders by Wolf and Cole (1964—2%) and by Scadding (1970—3%). This risk and the discomfort to the patient make the routine use of the procedure for diagnostic confirmation unjustifiable especially as sero-immunological tests recently developed may prove to be of diagnostic value in this condition (Turner-Warwick and Haslam, 1971). It should therefore be reserved for special problem cases.

Histological examination of the lung biopsy specimens showed that clinical improvement occurred with corticosteroid drugs in most of the patients whose alveolar walls were heavily infiltrated by chronic inflammatory cells and where there were many desquamated alveolar lining cells and histocytes in the lumen. Presumably the cellular picture implied an active inflammatory reaction which could be suppressed by corticosteroids. On the other hand, when the biopsy showed severe fibrosis and honeycombing but fewer inflammatory cells there was little or no response to these drugs. Scadding and Hinson (1967) made similar observations which suggest that corticosteroids can suppress an active inflammatory condition but fail to reverse established dense fibrosis.

Our investigation has shown that the most important factor determining the prognosis of a new patient presenting with incapacitating dyspnoea due to CFA is the presence or absence of improvement with corticosteroid drugs. Improvement occurred in 41% of treated patients and was substantial (grade 2) in 16%. This compares with an overall improvement of 34% in 64 patients described in four published reports (Herbert, Nahmias, Gaensler, and MacMahon, 1962; Ford, Giacobine, Madoff, and Sachs, 1964; Livingstone *et al.*, 1964; Ander, 1965). From three of these reports it is possible to estimate that a substantial improvement, corresponding to our grade 2, occurred in 15% of patients. In the report of Livingstone *et al.* (1964), four out of seven of the patients who improved with corticosteroid therapy were women under the age of 50 and in our series also the best response to corticosteroid drugs occurred in this group.

It was to be expected that the subsequent survival of patients not treated with corticosteroids or not improved by these drugs would be related to the degree of respiratory dysfunction on presentation. This was confirmed for three indices of respiratory function: the degree of dyspnoea, the vital capacity, and the arterial PO_2 . The poor

correlation between the severity of the disease process and the radiographic abnormality is a recognized feature of CFA. Particularly in patients with a desquamative process (Liebow, Steer, and Billingsley, 1965), the radiograph may be normal despite the presence of symptoms, and conversely we and others (Livingstone *et al.*, 1964) have observed bilateral radiographic abnormalities which have preceded symptoms by several years. Hence it is not surprising that the extent of the radiographic changes was not a useful guide to the prognosis.

Finally, our findings did not support the belief that the presence of circulating non-organ specific antibodies is commoner in younger patients and indicates more active earlier disease with a better prognosis.

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