Thorax, 1977, 32, 254–261

Studies in chronic allergic bronchopulmonary aspergillosis
1 Clinical and physiological findings

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Malo, J. L., Hawkins, R., and Pepys, J. (1977). *Thorax*, **32**, 254–261. **Studies in chronic allergic bronchopulmonary aspergillosis. 1 Clinical and physiological findings.** This report outlines the clinical and physiological features in 50 asthmatic patients with chronic allergic bronchopulmonary aspergillosis in whom the diagnosis was made from 2 to 25 years ago (mean duration 10·9 years). From a questionnaire and analysis of the peak expiratory flow rate measurements it was found that they were worse in the winter months, corresponding to the maximal concentrations of *Aspergillus fumigatus* in the atmosphere. Nineteen patients reported daily sputum production of up to an eggcupful or more, and 24 had noticed sputum 'plugs' in the previous year. Reduction of vital capacity (VC) was found in 20 patients, of forced expiratory volume in one second (FEV_1) in 38 patients, and of maximal expiratory flow at 50%VC breathing air (V_{50}air) in 47 patients. Nine patients had significantly reduced gas transfer factor (DLCO). Significant improvement (more than 15%) in FEV_1 after inhaled bronchodilator was shown by only 17 patients. There were statistically significant correlations between the degree of reduction in the physiological measurements of VC, FEV_1, and V_{50}air with the age of the patient at the time of the study and the later in life the diagnosis of aspergillosis was made, whereas the reduction in DLCO was also significantly related to the duration of aspergillosis. Prospective studies are needed for a proper assessment of any protective effect of treatment on the pathophysiological changes due to the disease over many years.

In recent years the acute manifestations of allergic bronchopulmonary aspergillosis have been described (Pepys *et al.*, 1959; Henderson, 1968; Golbert and Patterson, 1970) and its different clinical, physiological (McCarthy and Pepys, 1971a), radiological (McCarthy *et al.*, 1970), and immunological (McCarthy and Pepys, 1971b) aspects have been studied extensively. Because this disease was described for the first time in this country only 25 years ago (Hinson *et al.*, 1952), the chronic changes occurring in the affected patients are less well known. A five-year follow-up (Safirstein *et al.*, 1973) analysed the results of different treatments and suggested that those patients on 7·5 mg or more of oral prednisolone per day had fewer new acute shadows, although their functional impairment was greater.

Patients with chronic bronchiectasis are known to develop fixed airways obstruction together with a reduced gas transfer factor (Cherniack and Carton, 1966; Pande *et al.*, 1971; Landau *et al.*, 1974). It has also been shown in patients with allergic bronchopulmonary aspergillosis that bronchiectasis often develops at the site of the acute shadow (Scadding, 1967; McCarthy *et al.*, 1970), and the gas transfer factor was reduced in most of the patients who were tested by McCarthy and Pepys (1971a).

The purposes of the present study are to assess the chronic clinical features and pulmonary function changes in such patients in detail to see whether clinical parameters are related to the degrees of severity and reversibility of the airways obstruction.

Material and methods

Fifty patients with allergic bronchopulmonary aspergillosis are described (Table 1). The criteria

[1] Supported by a fellowship grant of the Medical Research Council of Canada

Table 1 *Diagnostic features*

	No. of patients
Main diagnostic criteria	
Asthma	50
Previous episode of transient shadow in chest radiograph with blood eosinophilia	50
Immediate positive prick test with an extract of *A. fumigatus*	50
Supporting evidence	
Presence of serum precipitins against *A. fumigatus*	
in the past	44
at time of study	42
History of 'plugs' in sputum	37
Culture of *A. fumigatus* from sputum in the past	23
Suggestive chronic changes in chest radiograph	49

for diagnosis were pulmonary shadows with blood eosinophilia in the past and a positive type I prick test reaction to an extract of *Aspergillus fumigatus*. All the patients were also asthmatics. On the day of examination for this study they were asked to answer a questionnaire on their past and present clinical history. Each had a chest radiograph, and blood was taken for immunological tests. Prick tests were performed with a routine battery of 23 common allergens and with two different extracts of *A. fumigatus*. One of these extracts was the commercial solution prepared by Bencard. The other extract was prepared in our department from freeze-dried, dialysed culture filtrates grown at room temperature for five weeks on an histoplasmin synthetic medium. This extract was used for prick testing at a concentration of 1 mg/ml.

The following lung function tests were first carried out before and 20 minutes after four 50 μg inhalations of salbutamol in an aerosol preparation (Ventolin)—forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and maximal expiratory flow volume (MEFV) curves breathing air and a helium(He)-oxygen(O_2) mixture in concentrations of 79% and 21% respectively. Complete lung volumes, airways resistance (Raw), and gas transfer factor (DLCO) were measured one hour later.

FEV_1 and FVC were measured on a Vitalograph (Vitalograph Ltd). The MEFV curve was produced on a wedge spirometer Ohio 840 (Airco Ltd) and traced on an oscilloscope DM 64 (Telequipment Ltd). After the tracing had been made, the patient was connected to a closed circuit and asked to take three slow vital capacity (VC) breaths of the He-O_2 mixture. Another MEFV curve was then produced before the patient was allowed to breathe air. Several curves were recorded, and two curves with a similar VC, one made with air and the other breathing He-O_2, were kept for analysis. The expiratory flows at 50%VC breathing air ($\dot{V}_{50}$air) and the He-O_2 mixture ($\dot{V}_{50}$He) were measured as well as the ratio $\dot{V}_{50}He/\dot{V}_{50}air$.

Lung volumes and Raw were measured in a body plethysmograph according to the technique of DuBois *et al.* (1956a and b). DLCO was assessed by the single-breath technique (McGrath and Thomson, 1959).

Reference values for FE_1, FVC, and lung volumes were taken from Goldman and Becklake (1959), from Cotes (1975) for DLCO, and from Bass (1973) for $\dot{V}_{50}$air. FEV_1, FVC, and VC were regarded as in the normal range if they were 85% or more of the predicted values. The functional residual capacity (FRC) was regarded as normal if between 80% and 120% predicted. Raw was increased if over 0·25 kPa l^{-1} s. DLCO was considered to be reduced if less than 75% of the predicted value. This apparently low threshold was chosen in order to account for the relative underestimation of DLCO by the technique of McGrath and Thomson (1959). This technique measures directly alveolar volume by using helium in the test breath and may underestimate this volume when the gas distribution is uneven.

The measurements of reversibility were expressed in two ways. First, the changes in expiratory measurements after bronchodilator were compared as percentages of the prebronchodilator values. Secondly, we compared the actual difference between the values, expressed in percentages of the predicted, before and after the bronchodilator.

From the time of diagnosis of aspergillosis, these patients attended regular outpatient clinics when their expiratory flow rates (PEFR) were measured. In 41 patients, at least five recordings were available. For every one of these patients the mean PEFR in November, December, and January was compared with the mean at other times of the year. The same information was obtained from a control group of 41 adult asthmatics with similar ranges of age, duration, and age at onset of asthma. All these asthmatics had a negative prick test to *A. fumigatus*. The three months of November, December, and January were chosen since it has been shown that Aspergillus spores are more abundant in the atmosphere at this time of the year (Noble and Clayton, 1963).

Unpaired *t* test, chi square, and linear correlation tests were used for statistical analysis of the results.

Results

The age at the time of the study, age at diagnosis of asthma and bronchopulmonary aspergillosis, and duration of asthma and aspergillosis are shown in the Figure. There were 20 men and 30 women whose age range was between 20 and 72 with a mean of 44·5±13·2 years. Twenty-eight patients developed asthma before 10 years and nine after 30 years of age. Most of the patients were long-standing asthmatics with a mean duration of asthma of 30·4±11·4 years. Bronchopulmonary aspergillosis was diagnosed after the age of 20 in the majority of patients, and the duration of the disease was from 2 to 25 (mean=10·9±5·2) years.

The clinical data obtained from the questionnaire are listed in Table 2. Out of the 50 patients, 39 were full-time workers and 17 of them had lost time off work over the past year. Five patients were admitted to hospital because of acute exacerbations of asthma or aspergillosis. Four patients reported that they had not had asthma or sputum production in the year preceding the visit. The asthma was generally more troublesome during the winter months but was not severe, the majority of patients having less than one attack of wheezing a week. Thirty-nine of the 46 patients judged the control of their asthma to be good. Nineteen patients had up to an eggcupful or more of sputum daily and 24 had noticed 'plugs' in their sputum during the past year.

At the time of their visit the patients were on a variety of treatments listed in Table 3. Twenty-seven were on oral corticosteroids with or without beclomethasone dipropionate, nine on beclomethasone dipropionate only, and four on sodium cromoglycate. As shown in Table 4, the majority of patients had been on different regimes of treat-

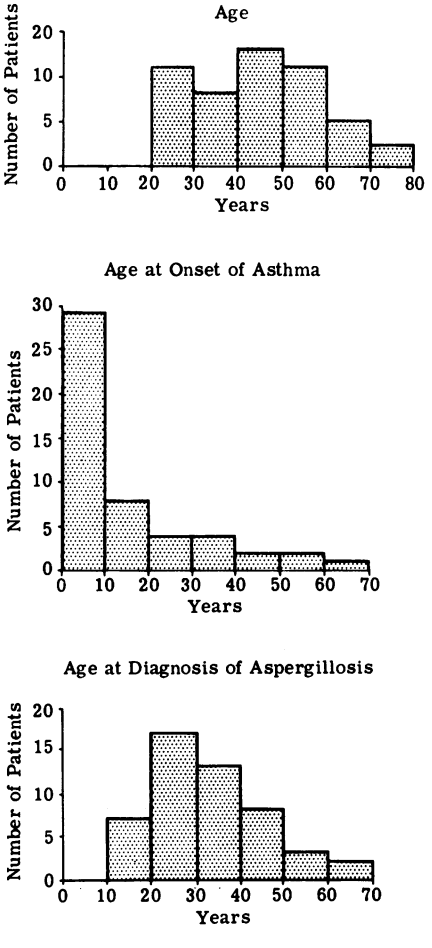

Figure *Histograms of clinical features*

Table 2 *Clinical findings in 50 patients**

	None	*2 weeks*	*2–4 weeks*	*> 4 weeks*
Loss of work**	22	4	9	4
	None	*One*	*Two*	
No. of hospital admissions**	45	3	2	
Characteristics of asthma				
	Night	*Day*	*Same*	
Diurnal preponderance	11	13	22	
	Winter (Oct.–Mar.)	*Summer (Apr.–Sep.)*	*Same*	
Seasonal preponderance	21	3	22	
	Present	*Absent*		
Morning tightness	19	27		
	One attack/wk	*Several attacks/wk*	*One attack every day*	*Continuously wheezing*
Severity	29	5	5	7
	Good	*Fair*	*Poor*	
General control	39	4	3	
Sputum production				
	Every day	*Intermittent*		
Frequency	21	25		
	Small	*Up to an eggcupful*	*Up to a teacupful*	
Daily quantity	27	15	4	
	White–grey	*Yellow–green*		
Usual colour	20	26		
	None	*Intermittent*		
'Plugs'	22	24		

*Except for loss of work where the number of full-time workers is 39, and characteristics of asthma and sputum production where the number is 46 (four patients denied asthma and sputum production in the past year).
**From chest symptoms.

Table 3 *Present treatment*

	No. of patients
Oral corticosteroids	
Continuously	
More than 7·5 mg daily	8
Less than 7·5 mg daily	5
Intermittently	3
With beclomethasone dipropionate	11
Beclomethasone dipropionate	9
Sodium cromoglycate	4
Others (bronchodilators and/or antibiotics)	10

Table 4 *Past treatment*

	No. of patients
Only one regimen	
Oral steroids (more than 7·5 mg daily)	6
Oral steroids intermittently	5
Sodium cromoglycate	3
Others (bronchodilators and/or antibiotics)	7
Mixed regimens	
Oral steroids with sodium cromoglycate and/or bronchodilators and/or antibiotics and/or beclomethasone dipropionate	29

ment since the time of diagnosis of aspergillosis.

The PEFR measurements showed that 28 patients had a lower mean value in November, December, and January compared with 13 in other months of the year. In a control group of 41 asthmatics with negative prick test to *A. fumigatus*, 21 had a lower mean PEFR from November until January and 20 at other times of the year. The difference between the two groups of patients was statistically significant ($P=0{\cdot}005$).

PULMONARY FUNCTION TESTS AT TIME OF VISIT

Table 5 summarises the functional results for FEV_1 (before bronchodilator), VC, FRC, and DLCO. Only 12 patients had a normal FEV_1 and 12 others had severe airways obstruction with an FEV_1 of less than 45% of the predicted values. In 20 patients the VC was reduced. In nine patients the DLCO was less than 75% of the normal predicted. In five of them the values were 65% or less of the predicted and in two under 50%. The FRC was reduced in four patients, normal in 23, and increased in 23. Both FEV_1 and VC were found to be reduced in 18 patients. In 19 subjects airways

Table 5 *Results of pulmonary function tests in 50 patients*

	↓ *VC*	*N VC*	↓ *FRC*	*N FRC*	↑ *FRC*
↓ FEV_1 N ↓ DL_{CO}/DL_{CO}	13/5	17/3	2/1	14/2	14/5
N FEV_1 N ↓ DL_{CO}/DL_{CO}	1/1	10/0	1/0	7/0	3/1
Total no. of patients	20	30	4	23	23

See text for definitions of abbreviations. In addition, ↓ = reduced, ↑ = increased, and N = normal. VC and FEV_1 were considered to be reduced if less than 85% of the predicted values. This limit was 75% for DL_{CO}. Normal values for FRC were considered to be between 80% and 120% of the predicted.

obstruction with a reduced FEV_1 and hyperinflation with an increased FRC were demonstrated.

Eighteen patients had a reduced FVC. V_{50}air was reduced in all patients except three. Raw was increased in 17 patients. The ratio $V_{50}He/V_{50}air$ was over 1·20 in eight patients before bronchodilator and in 12 after.

The degrees of reversibility by bronchodilator aerosol expressed in percentage of the pre-bronchodilator value for FEV_1, FVC, V_{50}air, and V_{50}He are shown in Table 6. The improvement in FEV_1 was greater than 15% in only 17 patients. However, in considering the reversibility of V_{50} of 15% or more, 28 patients were found to improve when breathing air and a total of 32 when breathing $He-O_2$.

Table 6 *Reversibility of airways obstruction by inhaled salbutamol**

	Less than 15%	*15–19%*	*20% and more*
FEV_1	21	8	9
FVC	10	3	5
$\dot{V}_{50}$air**	18	5	23
$\dot{V}_{50}$He**	17	8	24

See text for definitions of abbreviations.
*Measured as changes in expiratory function tests after bronchodilator and expressed as percentages of the pre-bronchodilator values. The patients with a normal FEV_1, FVC or $\dot{V}_{50}$air before bronchodilator are excluded.
**Measured in 49 patients.

In Tables 7 and 8 are the correlations between age at the time of the study, age at diagnosis of bronchopulmonary aspergillosis and asthma, duration of bronchopulmonary aspergillosis and asthma, and the physiological findings. The degree of airways obstruction as measured by FEV_1, V_{50}air, and FVC was greater with increasing age and the later in life the diagnosis of aspergillosis was made. These correlations were statistically significant when the values either before or after bronchodilator were considered. The FVC also showed corresponding correlations with the duration of aspergillosis and the later in life the asthma started.

Table 8 *Direct correlation between clinical features and reduction in lung volumes, gas transfer factor, and ratio of expiratory flow rates*

	VC	*FRC*	*DLco*	$\dot{V}_{50}He/\dot{V}_{50}air$*
Age	$P<0·01$	NS	$P<0·01$	NS
Duration of asthma	NS	NS	NS	NS
Duration of aspergillosis	NS	NS	$P<0·01$	NS
Age at onset of asthma	NS	NS	NS	NS
Age at diagnosis of aspergillosis	$P<0·02$	NS	$P<0·01$	NS

See text for definitions of abbreviations.
NS = statistically not significant.
*Before and after inhaled salbutamol.

The severity of the reduction in gas transfer factor was directly related to the age of the patient and to the history of aspergillosis. The diminution was not linked with the duration and the age at onset of asthma.

The degree of reversibility measured either as a percentage change of the pre-bronchodilator value or as a difference between the pre- and post-bronchodilator values, expressed in percentage of predicted, bore no correlation with the clinical findings except for the FVC. The percentage change in FVC expressed in the two ways mentioned above was significantly larger in older subjects and in those patients whose asthma or aspergillosis had started later in life.

Out of the 50 patients, eight were found to have a positive prick test reaction only to *A. fumigatus* and in six of them the asthma and aspergillosis developed after the age of 40.

There were 36 nonsmokers, 12 former smokers, and 2 smokers among our patients. The values for all the physiological parmeters were not statistically different when the nonsmokers were compared with the smokers and former smokers.

At the time of the study eight patients were on oral corticosteroids at a dosage of 7·5 mg or more

Table 7 *Direct correlation between clinical features and degree of airways obstruction before and after inhaled salbutamol*

	FEV_1		*$\dot{V}_{50}air$*		*FVC*		
	Before	*After*	*Before*	*After*	*Before*	*After*	*Raw after*
Age	$P<0·01$	$P<0·01$	$P<0·001$	$P<0·01$	$P<0·001$	$P<0·001$	NS
Duration of asthma	NS	NS	NS	NS	NS	NS	NS
Duration of aspergillosis	NS	NS	NS	NS	$P<0·01$	$P<0·01$	NS
Age at onset of asthma	NS	NS	NS	NS	$P<0·01$	$P<0·01$	NS
Age at diagnosis of aspergillosis	$P<0·01$	$P<0·01$	$P<0·01$	$P<0·01$	$P<0·001$	$P<0·001$	NS

See text for definitions of abbreviations.
NS = statistically not significant.

daily in order to relieve their wheezing which was more frequent than in other groups. These clinically more severely affected patients had a significantly ($0{\cdot}01<P<0{\cdot}02$) reduced DLCO in comparison with the less severely affected patients who were on beclomethasone dipropionate alone or on bronchodilators and/or antibiotics. There were no other statistical differences between any of the differently treated groups in terms of the mean of all function tests.

The patient on oral corticosteroids at a dosage of 7·5 mg or more daily and continuously since the time of diagnosis of aspergillosis had significantly reduced FEV_1, FVC ($0{\cdot}001<P<0{\cdot}01$), and VC ($0{\cdot}01<P<0{\cdot}02$) as compared with the group on bronchodilator and/or antibiotics only.

Discussion

The acute manifestations of allergic bronchopulmonary aspergillosis have been well described but the chronic changes are less well known. The patients often develop bronchiectasis at the site of acute shadowing as demonstrated by chest radiograph and bronchogram (Scadding, 1967; McCarthy *et al.*, 1970) and it is thought likely that with time repeated episodes would lead to chronic impairment of lung function (Turner-Warwick *et al.*, 1975).

All the patients in our study had asthma. The asthmatic complaints were not on the whole troublesome, the majority having one attack or less a week, and the general control of asthma was considered to be good. The finding that the asthma was preponderantly in the winter months is probably related to the fact that *A. fumigatus* is more abundant in the air at this time of the year (Noble and Clayton, 1963). This is supported by the lower mean PEFR demonstrated from November until the end of January in the patients with aspergillosis in contrast to those without allergy to *A. fumigatus*.

Many of the patients had daily sputum, often copious and of a yellow-green colour. This is more a characteristic of bronchiectasis than of asthma, and indeed McCarthy and Pepys (1971a) reported positive cultures for *Staphylococcus aureus, Haemophilus influenzae*, and pneumococci with precipitins against them in about two-thirds of the cases. Almost half of our patients reported the intermittent production of 'plugs' during the past year.

Thirty-eight patients had airways obstruction as measured by FEV_1 at the time of the study. Forty-seven showed a reduced $\dot{V}_{50}$air. The range of normal values for MEFV curves is still under discussion (Green *et al.*, 1973) but our results nevertheless show that in nine of our patients with an FEV_1 in the normal range airways obstruction was present as shown by a reduced $\dot{V}_{50}$air. Airway resistance was increased in 17 patients, suggesting that the obstruction was predominantly in the larger airways. Among the 38 patients with a reduced FEV_1 one-half had an increased FRC. Airways obstruction with hyperinflation as shown by an increased FRC is a common pattern found in asthma. The functional abnormalities described in patients with bronchiectasis are of an obstructive or restrictive type (Cherniack and Carton, 1966; Pande *et al.*, 1971; Landau *et al.*, 1974). Only four of our patients had both a reduced VC and FRC suggesting a restrictive defect. As mentioned above, a pattern of airways obstruction was more commonly found.

Nine patients had a significantly reduced gas transfer factor. This number of patients with abnormal values may be exaggerated. The technique we used (McGrath and Thomson, 1959), which measures alveolar volume from single-breath helium dilution, may indeed have underestimated the value of DLCO. The apparently low threshold of 75% for normal values was chosen to account for this.

The reduction in gas transfer is considered to be characteristic of the usual form of distal bronchiectasis and proportional to the extent of the disease (Pande *et al.*, 1971). Although the bronchiectasis of allergic bronchopulmonary aspergillosis is known to affect the proximal bronchi (Scadding, 1967; McCarthy *et al.*, 1970), a reduction in lung gas transfer factor has been described as an important physiological abnormality of the disease. McCarthy and Pepys (1971a) found that 25 out of 35 patients with bronchopulmonary aspergillosis had a gas transfer of 75% or less of the predicted. This finding was much less frequent in the present series of patients. The technique that they used to measure gas transfer factor—a steady-state method—is different from the single-breath method in the present study, and this might explain the differences.

An improvement in $\dot{V}_{50}$ after He-O_2 breathing greater than 20% was found in only a small number of our patients. This contrasts with the larger improvement found in normal individuals, in some asthmatics (Despas *et al.*, 1972), and in subjects with mild airways obstruction (Malo and Leblanc, 1975). The severity of airways obstruction is considered to be relevant to improvement of flows after He-O_2 breathing (Benatar *et al.*, 1975), and

this might explain the poor response found in our patients.

Improvement in FEV_1 of 15% or more after inhaled bronchodilator was found in only 17 patients. If our subjects had been only asthmatics without superimposed aspergillosis a larger proportion of them might have been expected to improve. The poor reversibility may be linked with the presence of bronchiectasis. V_{50}air and V_{50}He showed a significant improvement in a larger number of patients. These parameters are thought to reflect the condition of the small airways more than the FEV_1, and our findings may mean greater reversibility of obstruction of the small airways. It has been shown (Scadding, 1967; McCarthy *et al.*, 1970) that the radiographic changes of bronchiectasis due to aspergillosis are in the larger airways and that the small airways are generally preserved.

We found that the reduction of FEV_1, V_{50}air, and VC was directly related to the age of the patient and the age at which the diagnosis of aspergillosis was made. The reduction bore no correlation with the duration of the aspergillosis. These results might be explained in two ways. The first explanation is that aspergillosis might have been present before it was actually diagnosed and might have produced unsuspected shadow and bronchial damage. In all the patients but one, the diagnosis of aspergillosis was not made before they came to us, and in 41 out of 50 the first chest radiograph showed suggestive chronic changes to be already present (Malo *et al.*, 1977). It has been found that up to one-third of acute episodes are asymptomatic (Safirstein *et al.*, 1973) and this is a possible explanation for the delay in making the diagnosis. The other explanation may be that the age at the time of diagnosis of aspergillosis has a direct relationship with the extent of damage so that the later in life it starts the more likely it may be to cause severe damage. If this were so, the fact that the majority (6 out of 8) of patients with a single positive prick test to *A. fumigatus* developed known aspergillosis after the age of 40 may help to identify the patients at risk in this respect.

The reduction in gas transfer factor was nevertheless directly related to the age of the patient, the duration of aspergillosis, and the age at the time of diagnosis of aspergillosis. It bore no correlation with the asthma. This physiological measurement seems, therefore, to be the best index of the severity of the disease.

It was difficult in this retrospective study to assess the results of the treatment. Our patients had been on many different regimes in the past and at the time of the study. As a consequence the treatment groups were small, making statistical analysis less satisfactory. We found, however, that the patients on oral corticosteroids, at a dosage of 7·5 mg or more daily, were those with greater impairment of lung function than the others. These results were also found in a shorter follow-up (Safirstein *et al.*, 1973). This does not mean that steroids are not helpful in the treatment of the condition, and indeed they have been shown to reduce the duration (McCarthy and Pepys, 1971a) and the number (Safirstein *et al.*, 1973) of acute radiographic shadows. It probably means that the patients who were put on oral corticosteroids at the time of diagnosis had already had damage brought about by unsuspected episodes. Protection from further deterioration would be the main function of corticosteroid treatment in these circumstances. Prospective studies of patients diagnosed and selected for treatment at the very start of the disease may be expected to provide answers to the overall value of corticosteroids or other treatment in the prevention of permanent pathological and physiological impairment.

We are grateful to Mrs. J. Nevron-Malo and Mrs. M. Rehahn for help with the statistical work, to Mr. J. Collier of the Medical Records Department, and to the members of the Department of Lung Physiology.

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