Clinical Allergy, 1971, Volume 1, pages 261–286

Allergic broncho-pulmonary aspergillosis

Clinical immunology: (1) Clinical features

D. S. McCARTHY* *and* J. PEPYS†
**D. A. Stewart Centre, 668 Bannatyne Avenue, Winnipeg 3, Manitoba, and*
†*Department of Clinical Immunology, Institute of Diseases of the Chest, Brompton Hospital, London*

Summary

In 111 out of 143 U.K. patients with pulmonary eosinophilia evidence of allergic broncho-pulmonary aspergillosis was present, consisting of transitory pulmonary shadows, eosinophilia of blood and sputum, Type I and Type III reactions to prick and intracutaneous tests respectively with *A. fumigatus*. Precipitins were present in 92% of sera tested with and without concentration. Sputum plugs usually with pulmonary shadows were present in 56% and contained fungal mycelium, and the sputum gave positive cultures in 58%. Characteristic proximal bronchiectasis was present and fibrosis, mainly of the upper lobes, was found in chronic cases. These features were absent in the patients with no evidence of allergy to *A. fumigatus*.

Patients with early onset of symptoms had a higher atopic status and a much longer interval before pulmonary eosinophilia appeared than those with late onset symptoms. Episodes of pulmonary eosinophilia with aggravation of all symptoms, with fever and positive cultures in 83% for *A. fumigatus*, were common in the winter months, when there are more spores in the air. Precipitins to one or more of *H. influenzae*, *Str. pneumoniae* and *Staph. aureus* were present in 60% of sputa examined and positive cultures were obtained in 45%, indicating a high incidence of secondary infection.

Increasing airways obstruction with decreasing reversibility was common and some had reduction of CO gas transfer factor. Pulmonary hypertension was uncommon. Corticosteroids reduced sputum plugs, positive cultures and hastened resolution of pulmonary shadows.

Diagnoses such as pneumonia, tuberculosis, bronchiectasis and carcinoma were not uncommonly made before that of allergic broncho-pulmonary aspergillosis.

Introduction

Allergic broncho-pulmonary aspergillosis, first described by Hinson, Moon & Plummer (1952), is the commonest form of asthma and pulmonary eosinophilia in the

Correspondence: Professor J. Pepys, Department of Clinical Immunology, Institute of Diseases of the Chest, Brompton Hospital, Fulham Road, London, S.W.3.

United Kingdom (Pepys *et al.*, 1959; Longbottom & Pepys, 1964). The diagnosis is based on the presence of pulmonary eosinophilia, that is of transitory pulmonary infiltrations together with eosinophilia of the blood and sputum, and of immunological evidence of allergy to *Aspergillus fumigatus*, and possibly rarely to other *Aspergillus* species, as shown by the presence of Type I allergy. The supporting evidence consists of: evidence of Type III allergy, regarded as responsible for the complication of the asthma by the pulmonary infiltrations, as shown by Type III skin and bronchial reactions, the presence in the majority of cases of precipitating antibodies and of culture of *A. fumigatus* from the sputum and from sputum plugs.

The clinical and immunopathological importance of allergic broncho-pulmonary aspergillosis led to the detailed analysis reported here of a large group of 111 patients, fulfilling the above criteria, out of a total of 143 patients with a diagnosis of pulmonary eosinophilia seen at the Brompton Hospital over a period of 2 years. This report supplements others on smaller groups, or groups examined in other ways in the U.K. by Pepys *et al.* (1959), Henderson (1968), Campbell & Clayton (1964), and of reports on isolated cases or very small groups of cases which are being recognized elsewhere among others by Charpin *et al.* (1967), Spotnitz & Overholt (1967), Patterson & Golbert (1968), Slavin *et al.* (1969), Slavin, Milion & Cherry (1970), Warren & Rose (1969), Landrigan, Wasty & Nigam (1968) and Goldstein & Yokoyama (1970).

Materials and methods

Patients

All the patients were admitted for investigation into the Brompton Hospital. Standard procedures were applied uniformly to elicit in detail the clinical and other findings, (1) prior to admission and (2) on admission to hospital. They were divided for a number of analyses into three groups according to the age of onset in the majority of the asthma, and in a small number of pulmonary eosinophilia. Group I started before the age of 10 years, group II between 11 and 30 years and group III at 31 years or more.

Investigations were made as follows:

(1) *Sputum.* Three early morning specimens were collected in sterile containers in hospital. They were cultured for *A. fumigatus* on Sabouraud's medium, being regarded as negative if there was no growth within 4 days. Sputum plugs were looked for especially and were examined by culture, and by direct microscopy and histologically after fixation in formol saline and staining with haematoxylin and eosin or with Grocott's silver impregnation to show fungal mycelium. Examination for eosinophils was made on sputum homogenized by pancreatin and sputum eosinophilia was regarded as present where the proportion of eosinophils estimated from the stained smears was greater than 20% of the white cells.

(2) *Blood tests.* (a) Total white cell counts were made. (b) Wet absolute eosinophil counts were made on three successive mornings between 9 and 11 a.m., counts of $500/mm^3$ or more being taken as a blood eosinophilia. (c) ESR (Westergren) was measured. (d) Total serum proteins were estimated by the Biuret method. The albumin and globulin contents were estimated and the concentrations of α-, β- and γ-globulins were obtained from paper electrophoresis.

(3) *Skin tests.* Prick tests were made with the following routine extracts of common allergens (Bencards): house dust, *Alternaria*, *Aspergillus fumigatus* and *A. terreus*, *Cladosporium herbarum*, dry rot, *Sporobolomyces roseus*, yeast, *Candida albicans*, grass, shrub and tree pollens, milk, egg, wheat, fish, mixed nuts, cat, dog, hen and

horse allergens. Reactions to *A. fumigatus* and *A. terreus* were regarded as a single allergy.

(4) *Serological tests.* (a) Agar gel tests for precipitins to *A. fumigatus.* (b) Precipitin tests for bacterial antibodies against *H. influenzae*, *Str. pneumoniae* and *Staph. aureus* (Burns & May, 1967; Burns, 1968). (c) Viral antibody tests. (d) Antinuclear factor and rheumatoid factor tests.

(5) *Pulmonary function tests.* Respiratory function was assessed on subjective evidence, consisting mainly of exercise tolerance when well, and by the following objective tests for: (a) *Airways obstruction.* Spirometric tests were made of the $FEV_{1\cdot0}$ and FVC using a low inertia, water-sealed spirometer. The lower limit of normal for the $FEV_{1\cdot0}$/FVC ratio was taken as 70%. Reversibility of airways obstruction was determined 5 min after inhalation from a Medihaler Iso of isoprenaline (0·14 mg) or 15 min after subcutaneous injection of 0·5 ml of a solution of Liq. Adrenalini (BP) 1/1000. The peak flow rate was measured with a Wright's peak flow meter. Measurements of airways resistance and residual volume were also made. (b) Measurements of CO gas transfer factor (TLCO) were made with the steady state method and end-tidal sampling at rest and on exercise (Bates, Boucot & Dormer, 1955; McNamara, Prime & Sinclair, 1959). The fractional CO uptake was calculated. Values less than 80% of predicted resting values were considered abnormal. (c) *Blood gas tensions* were measured on brachial arterial bood for (i) oxygen tension (Pa,O_2) and (ii) carbon dioxide tension (Pa,CO_2).

(6) *Intestinal parasites* were looked for as possible causes of pulmonary eosinophilia by (a) examination of one fresh stool, (b) complement fixation tests for antibodies to *Ascaris lumbricoides* and *Toxocara canis*, (c) intracutaneous skin tests were made with *Toxocara* allergen according to the method of Woodruff, Bisseru & Bowe (1966) in twenty-five patients and extracts of *Ascaris lumbricoides* were examined by prick tests in all cases.

Results

1. *Clinical and other findings prior to present investigations*

Age of onset of symptoms and sex distribution (Table 1)
Asthma was present in all except four patients in group III. It started before the age of 10 years, group I, in the majority of cases. There was a slight preponderance of males in group I whereas females predominated in group II and even more so in group III.

Atopic status (Table 2)
This was assessed in terms of the personal and family history of asthma, hay fever and infantile eczema and as suggested by Pepys (1969) in terms of the numbers of reactions to reactions to prick tests. The diagnosis of hay fever was based on a seasonal history and a positive prick test to grass pollen extract. The presence in infancy of a scaly, itchy rash affecting the flexures was taken as evidence of infantile eczema and in 25% of the patients it was still present on examination.

Table 2 shows that group I had the highest clinical atopic status with infantile eczema and hay fever in 51%, compared with 10% and 25% in group II and with 4% and 18% in group III. The family history supports this, being positive in 30% of

group I and II and in only 7% of group III. Group I also shows the highest immunological status with an average of 5·5 prick test reactions to the common allergens, compared with 4 in group II and with 1·6 in group III. The reactions in group I were to house dust (94%), grass pollen (75%) and animal danders (40%). Reactions only

Table 1. Age at onset of asthma and/or pulmonary eosinophilia

	No. of patients	% of total	Males	Females
Group I (below 10 years)	63	57%	33 (52%)	30 (48%)
Group II (11–30 years)	20	18%	8 (40%)	12 (60%)
Group III (31 years or more)	28	25%	10 (36%)	18 (64%)
Total	111		51 (46%)	60 (54%)

to *A. fumigatus* were confined to 43% of the patients in group III; in all the other patients the positive reactions to *A. fumigatus* were accompanied by positive reactions to other allergens. The degree of clinical and immunological atopic status is well shown, with the highest status being present in all respects in the early onset group.

Table 2. Assessment of atopic status of patients with allergic bronchopulmonary aspergillosis

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
Personal history of:				
Asthma	107 (96%)	63 (100%)	20 (100%)	24 (83%)
Infantile eczema	35 (32%)	32 (51%)	2 (10%)	1 (4%)
Hay fever	42 (38%)	32 (51%)	5 (25%)	5 (18%)
Allergic family history (first degree siblings)	27 (24%)	19 (30%)	6 (30%)	2 (7%)
Prick test with twenty-one common allergens				
Average number positive per patient	4·2	5·5	4	1·6
Isolated *Aspergillus* reactivity	12 (11%)	0	0	12 (43%)

Infantile eczema: difference between three groups $P > 0{\cdot}001$.
Hay fever: difference between three groups $P > 0{\cdot}005$.
Allergic family history: difference between three groups $P > 0{\cdot}05$.

Group II are mid-way between group I and group III, the late onset group who have low atopic status.

Past history

The clinical and radiological picture of allergic broncho-pulmonary aspergillosis may be mistaken for other forms of chest disease (Table 3). In the majority of the 111 patients the diagnosis of allergic broncho-pulmonary aspergillosis was made for the first time after admission to Brompton Hospital.

Sixty-six patients (58%) had a history of pneumonia, often recurrent, in recent years. Thirty patients had had radiological confirmation of 'pneumonia'. Carcinoma of the bronchus was suspected more frequently in the late onset group. Both pulmonary tuberculosis and allergic broncho-pulmonary aspergillosis (Henderson, 1968; McCarthy, Simon & Hargreave, 1970) affect mainly the upper lobes, thus accounting for the frequency with which tuberculosis was suspected. The diagnosis of tuberculosis was not established in any of the patients, and 89% of those tested with 10 and 100 TU of Old Tuberculin gave negative reactions. Nine patients had been treated with antituberculous drugs; two had been in sanatoria for more than 1 year. In other cases

Table 3. Past diagnosis

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
'Pneumonia'	66 (58%)	42 (62%)	10 (50%)	17 (61%)
Tuberculosis	35 (32%)	20 (32%)	8 (40%)	7 (25%)
Bronchiectasis	21 (19%)	9 (14%)	7 (35%)	5 (18%)
Lung abscess	5 (5%)	4 (6%)	1 (5%)	—
Carcinoma of bronchus	5 (5%)	—	1 (5%)	4 (14%)
Pneumothorax	5 (5%)	3 (5%)	2 (10%)	—
Cor pulmonale	1 (1%)	1	—	—

antituberculous treatment was not started because of the rapid resolution of the radiographic shadows, whilst sputum culture reports for tuberculosis were awaited.

The majority of the patients lost 4–8 weeks per year from their normal activities. Only one patient in group I was completely incapacitated by the illness. Less than one quarter smoked cigarettes, the largest proportion, ten out of twenty-eight, being in group III.

Environmental factors

Exposure to A. fumigatus. Enquiries were made about the place of dwelling, occupation and possible relationship of onset or exacerbation of disease associated with exposure to *A. fumigatus* which may be abundant in decaying vegetable matter. There were thirteen rural dwellers (12%), of whom eight were farmers handling mouldy hay or vegetable matter. The remainder were urban dwellers. With one possible exception, no clear relationship could be established between exposure to mouldy vegetable matter and the onset of symptoms.

Exposure to birds. Because *A. fumigatus* is a pathogen for birds and it can be cultured from their droppings, the patients were questioned about contact with birds. Fifty-one patients (46%), distributed evenly in the three groups, either had birds, usually budgerigars, in the home or had close contact with them. One was a pigeon fancier and three kept poultry. In relation to the presumed date of onset of the pulmonary eosinophilia, there was avian contact in thirty-two cases before this time; in twelve cases a bird was acquired at about the same time; and after it in seven. The incidence of contact with budgerigars of about 40% of the cases seems high and merits further study.

Seasonal factors

Table 4 shows that all the manifestations, such as asthma, cough and sputum, the presence of plugs, a history of 'pneumonia', and radiographic shadows, were more prevalent in the autumn/winter months, October–March inclusive, than the spring/summer months, April–September. In addition, *A. fumigatus* was cultured from the sputum in the autumn/winter months from 65% of the specimens compared with 35% at other times, and similar proportions were given for hospital admissions. Of twenty patients in group II and III who gave a clear history of the time of the year when the asthma started, in thirteen this was in the autumn/winter months, four out of seven in group II and nine out of thirteen in group III. Some patients had preceding rhinitis for weeks, months or years. Because of the relatively recent onset of acute symptoms

Table 4. Seasonal factors: allergic bronchopulmonary aspergillosis

	Total	Autumn/winter	Spring/summer
Asthma worse	77 (69%)	58 (75%)	19 (25%)
Cough and sputum worse	80 (72%)	75 (94%)	5 (6%)
Past history of plugs	40 patients	32 (80%)	8 (20%)
Past history of 'pneumonia'	88 episodes	63 (72%)	25 (28%)
Radiological shadows recorded			
No. of radiographs	475	281 (59%)	194 (41%)
In 111 patients		96 (86%)	71 (64%)
A. fumigatus in sputum	95 specimens	62 (65%)	33 (35%)
Hospital admissions	100 patients	64 (64%)	36 (36%)

in group III, and less so in group II, their history of onset of symptoms was more reliable than in group I, in whom the remoteness of onset made the dating of the onset inadequate for comparison.

A history of seasonal change in severity of symptoms towards the winter months was obtained in many cases. In sixteen patients (thirteen in group I and three in group II), the symptoms previously worse in the summer became worse in the winter. In eight patients (six in group I and two in group II), the previous summer symptoms became perennial, and in nineteen patients (sixteen in group I, two in group II and one in group III), the previously perennial symptoms became worse in the winter. At the same time the asthma became more severe and continuous. Twenty-seven patients who previously had paroxysmal wheezing developed more severe and unremitting symptoms. At the outset eighty (75%) of the 107 asthmatic patients had paroxysmal asthma, and twenty-seven (25%) had continuous asthma. At the time of investigation the position was reversed and seventy-three (68%) had continuous asthma, compared with thirty-four (32%) who had paroxysmal asthma.

Pulmonary eosinophilia—onset and duration

The onset of pulmonary eosinophilia was taken from the time that transient radiological shadows were first observed. Whilst there were no children younger than 5 years with radiological shadows, it is not known whether it can occur in very young children. There were two main peaks between 15 and 35 years in groups I and II and

50–55 years in group III, when the pulmonary eosinophilia was first observed. Asthma was present before the pulmonary eosinophilia in all cases in group I, in 75% of group II and 54% of group III. Asthma appeared in groups II and III respectively at the same time as the pulmonary eosinophilia in two (10%) and eight (29%) cases and after its onset in three (15%) and three (11%). The average duration of the asthma before the onset of the pulmonary eosinophilia was 24 years in group I, 11 years in group II and 3·5 years in group III.

The duration of the pulmonary eosinophilia dating back to the first pulmonary shadow varied widely from less than 1 month to 27 years, with averages of 6, 9 and 4 years for groups I, II and III respectively. The average numbers of episodes of radiological shadowing in the material available were 3·6 in group I, 4·7 in group II and 2·4 in group III. Prospective surveys with matched observations are however needed for more accurate information.

Role of other allergens and other factors in the asthma

A history of asthma due to common allergens was present in twenty-seven (32%), nineteen in group I and only two in group III. The histories correlated well with the positive prick test reactions to the suspected allergens in 81% of cases. Grass pollen was important in summer in group I and presumably *A. fumigatus* in winter in group III. Group I exhibited the highest and group III the lowest degree of atopy. Other factors were also regarded as relevant, such as emotion (29%), exertion (29%), changes of temperature and humidity (28%), irritants such as smoke, fog and paint (19%). Nocturnal asthma was troublesome in 10%. Half of the patients in group I had lengthy remissions being completely symptom free for 1 year or more, whereas there were none in group III.

Sputum

At the outset, sixty-one (56%) of 109 patients had intermittent, and the remainder continuous, sputum production. At the time of examination this was reversed, with 40% having intermittent and 60% continuous sputum. The volume varied from scanty to $\frac{1}{2}$ cupful in 24 hr. Almost one half of the patients, even when well, produced $\frac{1}{4}$ cupful of sputum per day. It was mucoid in one-third and mucopurulent in the remainder and it increased in volume and purulence during exacerbations. In group I cough and sputum developed, often many years after the onset of asthma. In group III, by contrast, cough and sputum were present before the onset of asthma in 54% and appeared at the same time as the asthma in 43% of cases. In four cases there was only cough and sputum and no wheezing.

Sputum plugs

These are important in the diagnosis and comprise bronchial casts or particles of different sizes, shapes and colours ranging from dirty green to brown or beige. They may be infrequent and special questioning may be needed as they may be forgotten or overlooked. They are firm, friable, usually pultaceous, cylindrical or pellet-like, remaining distinct from the sputum and standing out in relief when it is poured onto a flat surface. Occasionally longitudinal grooves or branching may be seen and the plug may be broken off at one end, suggesting that it is only a portion of a larger plug. The average size is about $0{\cdot}5 \times 1{\cdot}5$ cm but they may be bigger. They may also, on occasion, be spotted with fresh blood. Patients volunteered the information that the

plugs were unusual in nature, being very hard solid lumps, associated with choking attacks and violent bouts of coughing with difficulty in expectoration. The coughing up of the plug was sometimes followed by copious offensive sputum. Many patients felt better after expectoration of the plug and were conscious of its presence in the bronchi. One patient who stated that the breathing on the left side of her chest was blocked off, had complete atalectasis of the left lung. A large plug was removed from the left main stem bronchus by bronchoscopy with re-aeration of the lung.

Plugs were recorded by sixty (54%) of the patients, the sputum being mucopurulent in forty-eight (80%) at the time. Only a 'few plugs', ten or less per year, were noted by forty-nine of these patients, the remainder having more frequent plugs, more than ten per year.

There was no clear relationship between the plugs and the severity of asthma, twenty-nine (48%) of the sixty patients not noticing any relationship. In seventeen (28%) the patient was recovering from an acute exacerbation when the plugs appeared. All the patients in group I, and twelve (70%) of those in group II, noticed the plugs for the first time after the onset of the asthma. In group III, eight out of fourteen patients noticed plugs before or at the time of onset of the asthma. Radiological shadows were present in most cases at the time of the expectoration of a plug.

In sixteen out of eighteen patients the plugs contained fungal mycelium on direct examination of stained material and cultures for *A. fumigatus* were positive. Eosinophil cells predominated in thirteen cases. Nasal plugs with similar macroscopic, histological and cultural features were examined in two patients and were recorded in eleven (10%) of the 111 patients.

Febrile episodes

These were frequent in the patients with allergic broncho-pulmonary aspergillosis, lasting from half an hour to hours or days, together with 'flu-like' symptoms. They were present in seventy-six (68%) and in most of the patients were associated with cough and sputum, though not necessarily wheezing. In eleven out of sixteen with records the temperature rose to 38·5°C, and in one patient to 40°C. Soaking night sweats occurred in six patients. Radiographic shadows were present in the lungs in twenty out of sixty patients at the time of the febrile episodes which were more frequent in, though not confined to, the winter months.

Haemoptysis

Slight infrequent blood streaking of the sputum was present in 85%, usually associated with daily cough and sputum. Haemoptysis was more common in group I (56%) and group II (75%) than in group III (32%). Four patients with severe haemoptysis, a cupful or more, were in groups I and II. One patient coughed up more than a pint with clots over a period of 6 hr. The haemoptysis followed the episodes of pulmonary eosinophilia in thirty-nine (66%) patients.

Chest pain

Sixty-one (55%) of the patients had chest pain, pleuritic in forty-four. Pulmonary shadows were present in twenty out of twenty-three examined at the time, the pain being related to the region of the shadowing.

2. *Clinical and other findings in present investigation*

Clinical examination

All the patients were assessed clinically at the first visit and forty-one were examined further during acute episodes of pulmonary eosinophilia. Evidence of generalized airways obstruction was present in 88% on admission to hospital. No clinical evidence of airways obstruction was present in thirteen patients, three each in groups I and II and seven in group III. Local wheezing and rhonchi were present in fifteen patients, in eleven in the upper zones.

Crepitant rales of medium intensity were heard in thirty-six patients (32%). There were no fine rales and coarse rales clearing on coughing are not included. In the majority (78%) the rales were of localizing value, being heard over areas of pulmonary shadowing or evidence of local irreversible bronchial damage. They were heard over the upper zones in 75% of the subjects, generalized rales being heard in eight cases.

Clubbing of the fingers was present in eight patients, seven of whom had cough and sputum each day. No other significant abnormalities were found.

Clinical features during episodes of pulmonary eosinophilia in forty-one patients

The constitutional manifestations during these episodes varied, four patients (10%) being quite well, the radiographic shadow being found incidentally. The majority (86%) complained of malaise and half of them could not carry on their normal

Table 5. Physical signs (forty-one patients)

	Patients	%
Airways obstruction, rhonchi and wheeze	35/41	85
Localized	1/35	3
Generalized	34/35	97
Localizing signs	18/41	44
Crepitant rales	13/41	32
Localized	13/13	100
Generalized	0	
Air entry diminished	15/41	37
Dullness of percussion	7/41	17
Signs of consolidation	3/41	7
No localizing signs detected	23/41	56
Apparently normal chest	6/41	15

activities. Only two were obliged to go to bed. The chief symptoms were anorexia, headache, generalized aches and pains and loss of energy.

In eight patients the temperature was not raised, two of these being on corticosteroids at the time. In twenty-eight (68%) it varied between 37 and 39·5°C, and between 39·6 and 40°C in five cases. The pyrexia lasted with treatment between 1 and 15 days with an average of 4–5 days.

There were acute attacks of wheezy dyspnoea or its aggravation in thirty-six (88%) of the patients. Chest pain in twenty-one patients (51%) was of pleuritic type in

fourteen (67%), corresponding with the region of the shadow in eleven cases. A pleural rub was heard in two cases and there were no pleural effusions. In thirty-nine (95%) of the patients cough and increased sputum (mucoid in 8%, muco-purulent in 69% and purulent in 23%) were features. The 24 hr volume of sputum ranged from 100 to 300 ml. In thirteen patients sputum plugs were present and streaky haemoptysis occurred in five.

The physical signs (Table 5) show some evidence of localizing value in almost one half of the cases of pulmonary eosinophilia, in the form of localized crepitant rales, diminution of air entry and dullness on percussion.

Radiological features

The radiological features of the allergic broncho-pulmonary aspergillosis in all 111 cases have been reported in detail by McCarthy *et al.* (1970). They consisted of a variety of types of radiographic shadows. Massive homogeneous shadows were present, consisting of patchy clouding (eighty-three), lobar consolidation (thirty), irregular shadows of about half a lobe (fifteen), triangular shadows less than a segment (fifty-one), oblong shadows about 2 cm in length (twenty-two), 'V' shaped gloved-finger shadows (eleven) and circular shadows (twenty-six). The upper lobes were affected more frequently than the middle and lingular or lower lobes, the shadows being unilateral in thirty-nine and bilateral in seventy-two cases. Lobar shrinkage also affected the upper lobes (thirty-one out of forty cases) more frequently than the lower lobes. Radiographs examined over the course of the disease showed incidences of the different shadows as follows: massive consolidation in 71%, patchy massive shadows in 75%, nodular in 23%, avascular areas in 23%, appearances like those of advanced fibrosing alveolitis in 10%, lobar shrinkage in 36%, atalectasis of a lung, lobe or segment in 14%, and parallel line or ring shadows in 79%. Shadows termed 'tram-line', consisting of parallel hair-line shadows corresponding to the width and direction of the normal bronchus and extending out from the hilum were present in twenty-three cases and were often the only abnormality in a radiograph. Parallel line shadows wider than the normal bronchus and shown by bronchogram to be dilated bronchi, were present in seventy-seven cases. Band-like 'toothpaste' shadows 2–3 cm long and 5–8 mm wide, representing secretions in dilated bronchi, were present in thirty-seven cases. 'Gloved-finger' shadows representing secretions in a dilated and occluded bronchus were present in twelve cases. Honeycomb shadows were present in thirty-seven and ring shadows in fifty-one cases.

Gross abnormalities were found in bronchograms of all thirty-two cases examined. These took various forms, consisting in some cases of dilatation and occlusion of some proximal bronchi like that of conventional bronchiectasis due to infection. In others with similar degrees of dilatation there was normal filling of the bronchus peripheral to the dilatation, representing localized bronchial lesions, as described by Scadding (1967) and McCarthy (1968). Cystic bronchiectasis was also seen and all three appearances were found in close proximity in some cases.

Blood counts

Peripheral blood eosinophilia. The absolute eosinophil counts/mm^3 are given in Table 6 for all the patients and for thirty patients during episodes of pulmonary eosinophilia. Of the thirty-eight with less than 1000/mm^3, ten were on prednisone 10–15 mg daily; counts in excess of 2000/mm^3 were obtained in two others on pred-

nisone 5 mg daily. In thirty patients not on corticosteroids during episodes of pulmonary eosinophilia the count was above 1000/mm^3. During the episodes of pulmonary eosinophilia the counts were higher than in the total group, but none of these patients were on corticosteroids at the time. All the patients had sputum eosinophilia (Table 7).

Table 6

Eosinophil count per mm^3	No. of patients*	During pulmonary eosinophilia†
500–1000	38 (34%)	
1001–2000	50 (45%)	8 (27%)
2001–3000	15 (14%)	14 (47%)
3001–4000	5 (5%)	5 (17%)
4001–6000	3 (2%)	3 (10%)

* Total 111. † Total 30.

Total white cell counts were within the normal range in thirty-six (33%). In 44% there was an increase to below 15,000/mm^3 and in 17% it was up to 20,000/mm^3, and up to 25,000/mm^3 in the remaining six.

Sedimentation rate. The ESR was greater than 20 mm/hr in 75%, between 21 and

Table 7. Percentage eosinophils in the sputum

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
15–30% eosinophils	79 (71%)	46 (73%)	11 (55%)	22 (78%)
31–60% eosinophils	16 (14%)	9 (14%)	4 (20%)	3 (11%)
61–90% eosinophils	16 (14%)	8 (13%)	5 (25%)	3 (11%)

40 mm/hr in 31%, 41–70 mm/hr in 32%, and above 70 mm/hr in 12%. The haemoglobin and packed red cell volume were within normal limits in forty-five patients so tested.

Serum proteins. Estimations were made on sixty-five patients of whom thirty-five were having acute exacerbations. There were only slight increases in the globulin fractions, the commonest finding being increases in the α_2-globulin.

Serological tests

(a) Serological tests by the agar-gel Ouchterlony method for precipitins to *A. fumigatus* (Longbottom & Pepys, 1964) in ninety-nine of the 111 patients are discussed further by McCarthy & Pepys (1971). Of the ninety-nine, seventy-one gave positive reactions with unconcentrated serum. Further tests on sixteen of the negative sera after concentration three- to four-fold, gave a further nine positive reactions. Thus, out of the total of eighty-seven sera tested with the aid of concentration, positive reactions were obtained in eighty (92%).

(b) Serial tests in eleven patients for antibodies against influenza A, B and C, adenoviruses and syncytial respiratory virus were negative in all cases. No cold agglutinins were found in eight sera tested, nor ornithosis antibodies in five.

(c) Tests in seventy-seven patients for rheumatoid and antinuclear factor were

Table 8. Serological tests—bacterial precipitins

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
No. of patients tested	70 (63%)	34 (54%)	15 (75%)	21 (75%)
Bacterial precipitins present	42 (60%)	21 (62%)	7 (47%)	14 (67%)
H. influenzae				
Precipitins	28 (67%)	12 (57%)	6 (86%)	10 (71%)
Positive culture	5 (18%)	1 (8%)	3 (50%)	1 (10%)
Pneumococcus				
Precipitins	24 (57%)	13 (62%)	4 (57%)	7 (50%)
Positive culture	4 (17%)	2 (15%)	1 (25%)	1 (14%)
Staph. aureus				
Precipitins	20 (48%)	11 (52%)	3 (43%)	6 (43%)
Positive culture	6 (30%)	5 (45%)		1 (17%)

Table 9. Sputum culture—pathogenic bacteria

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
Pathogens isolated in:	50 (45%)	30 (48%)	11 (55%)	9 (32%)
One pathogen	33 (66%)	25 (84%)	3 (27%)	5 (56%)
Two pathogens	13 (26%)	4 (13%)	6 (55%)	3 (33%)
Three pathogens	4 (8%)	1 (3%)	2 (18%)	1 (11%)
Organisms cultured in fifty patients				
Staph. aureus	32 (64%)	21 (70%)	7 (64%)	4 (44%)
Resistant	19 (59%)	12 (57%)	5 (71%)	2 (50%)
Sensitive	13 (41%)	9 (43%)	2 (29%)	2 (22%)
H. influenzae	20 (40%)	7 (23%)	9 (82%)	4 (44%)
Pneumococci	12 (24%)	5 (17%)	4 (36%)	3 (33%)
Ps. pyocyaneus	8 (16%)	3 (10%)	3 (27%)	2 (22%)

uniformly negative. LE cells were sought but not found in three tests on each of eighteen patients.

(d) *Bacterial precipitins.* Table 8 shows that precipitins were present in 60%, a high proportion of these against *H. influenzae* (67%), *Str. pneumoniae* (57%) and *Staph. aureus* (48%), some having precipitins to all three bacteria.

Sputum culture

(a) Sputum cultures for pathogenic bacteriae (Table 9) show positive cultures in 45% of the patients. *Staph. aureus* was the commonest (64%), then *H. influenzae*

(40%), pneumococci (24%) and *Ps. pyocyaneus* (16%). (b) Sputum cultures for *A. fumigatus* on three specimens per patient (Table 10) show that 58% were positive, the majority on one of the three specimens, 39% on two and only a few on all three specimens. In the sixty-four patients giving positive cultures (Table 11), pulmonary eosinophilia was present at the time in thirty-six (56%), absent in twenty-three (36%) and there was no current radiograph present for the remainder. Direct microscopic

Table 10. Sputum culture: *A. fumigatus*

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
Negative	47 (42%)	27 (43%)	7 (35%)	13 (46%)
Positive	64 (58%)	36 (57%)	13 (65%)	15 (54%)
One of the three specimens	36 (56%)	20 (56%)	6 (46%)	10 (67%)
Two of the three specimens	25 (39%)	14 (39%)	6 (46%)	5 (33%)
All three specimens	3 (5%)	2 (5%)	1 (8%)	0

examination of the sputum was made of only a limited number of specimens, usually because plugs were present. Of thirty-five specimens, seventeen showed fungal mycelium. In fifteen with plugs, mycelium was seen in thirteen and all the specimens gave positive cultures for *A. fumigatus*. In the twenty specimens without plugs mycelium was seen in four and *A. fumigatus* was cultured in sixteen.

Cytology of the sputum

In at least one of the three specimens from all the patients there were moderate or large amounts of white cells. Many of the specimens were mucopurulent or purulent.

Table 7 shows that eosinophil cells were abundant in almost all the specimens.

Table 11. Pulmonary eosinophilia and culture of *A. fumigatus* from the sputum

	Total	Group I	Group II	Group III
No. of patients	64	36	13	15
Pulmonary eosinophilia present at time of sputum examination	36 (56%)	16 (44%)	9 (69%)	11 (73%)
A. fumigatus in sputum	30 (83%)	13 (81%)	7 (78%)	10 (91%)
A. fumigatus not present	6 (17%)	3 (19%)	2 (22%)	1 (9%)
Pulmonary eosinophilia not present	23 (36%)	16 (44%)	3 (23%)	4 (27%)
No chest radiograph	5 (8%)	4 (12%)	1 (8%)	0

Cultures for M. tuberculosis

The three specimens of sputum were examined by direct microscopy and culture for acid-fast bacilli, and this was repeated in thirty patients on at least one later admission. All the tests were negative.

Table 12. Respiratory function tests performed

	Total	Group I	Group II	Group III
No. of patients	111	63	20	28
Ventilatory capacity				
Spirometry	86 (77%)	50 (79%)	14 (70%)	22 (79%)
PEFR	28 (25%)	22 (35%)	3 (15%)	3 (11%)
Airways resistance	16 (14%)			
Lung volumes	16 (14%)			
Diffusing capacity	35 (32%)			
Blood gases, before and after exercise test	3 (3%)			

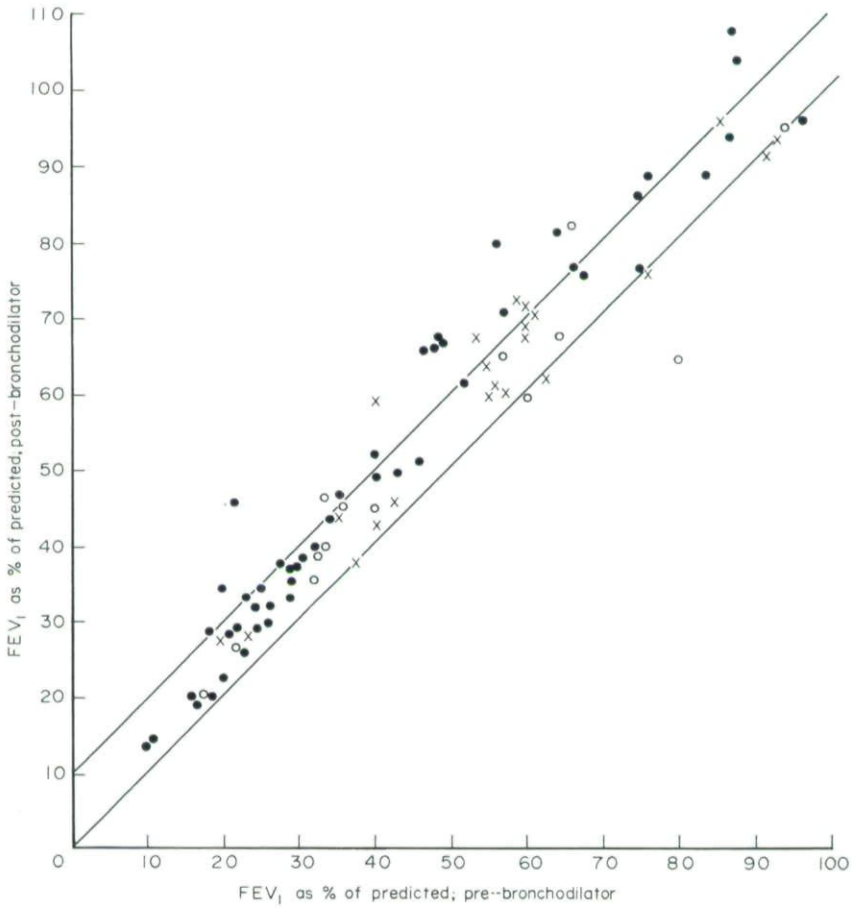

Fig. 1. $FEV_{1\cdot0}$ values before and after inhalation of isoprenaline expressed as % of predicted values. ●, Group I; ○, group II; ×, group III. Forced expiratory volume in 1 sec ($FEV_{1\cdot0}$) in eighty-six patients before and after bronchodilator. The majority of patients had moderate to severe airways obstruction which showed only limited reversibility towards normality following bronchodilator. Reversibility was especially limited in patients with severe respiratory dysfunction. The second parallel line represents a 10% improvement. The character of airways obstruction was similar in the three groups of patients.

Respiratory function tests

Clinical exercise tolerance. In fifty-three patients 'exercise' tolerance was normal; it was slightly reduced in twenty-five, moderately in thirty-one and severely in two. Exertion provoked undue shortness of breath without noticeable increase in wheezing in one third of the patients.

Respiratory function tests. These are listed in Table 12. They were made when a level regarded as 'normal' for the patient was attained, as judged by exercise tolerance

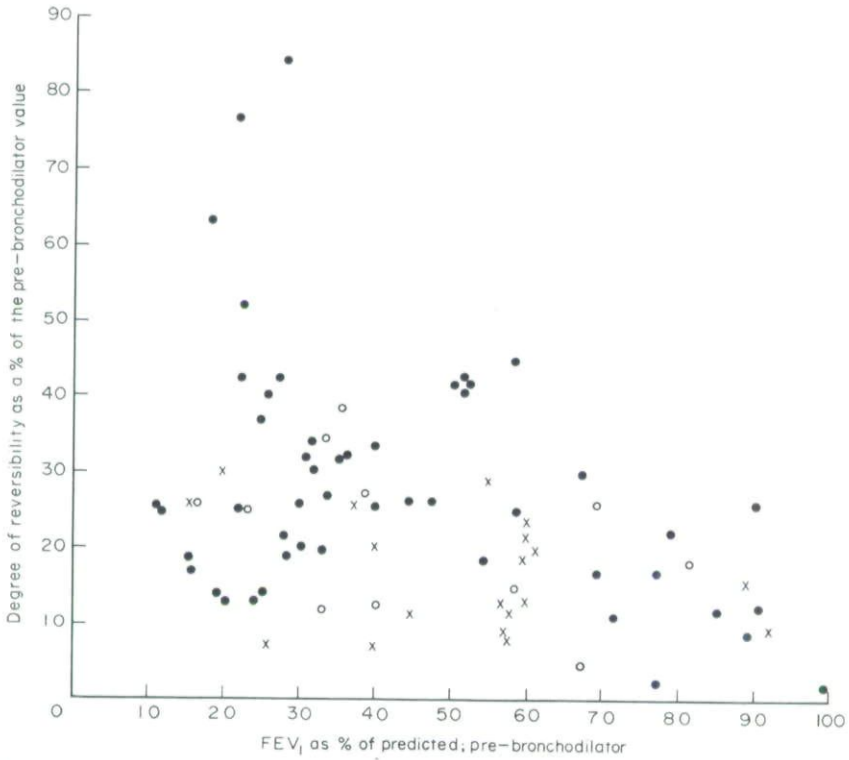

Fig. 2. Degree of reversibility by inhalation of isoprenaline as a percentage of the pre-bronchodilator value. ●, Group I; ○, group II; ×, group III. Some improvement in $FEV_{1\cdot0}$ following bronchodilator was obtained in virtually all patients. It is especially noteworthy that patients with severe airways obstruction retain a degree of reversibility which may be important in terms of the patient's comfort and exercise tolerance though the improvement expressed as a percentage of predicted normal $FEV_{1\cdot0}$ is very small.

and previous measurements. Reversibility of the airways obstruction was estimated by repetition of the tests 5 min after the inhalation of isoprenaline from a Medihaler Iso, or 15 min after an injection of 0·5 ml Liq. Adrenalini (BP) 1/1000.

Forced expiratory volume in 1 *sec* ($FEV_{1\cdot0}$)

Fig. 1 shows in eighty-six patients that the $FEV_{1\cdot0}$ calculated as a percentage of predicted value was reduced in almost all cases and that there was only a small change after inhalation of isoprenaline, especially in those with $FEV_{1\cdot0}$ measurements of about 35% of the predicted level. Out of thirty-five such patients, twenty-six had improvements of less than 10%.

$FEV_{1\cdot0}$ values as a percentage of predicted were also taken (Fig. 2) as a base line for reversibility by isoprenaline. The degree of reversibility was expressed as a percentage of the value prior to the inhalation in seventy-three patients. Fig. 2 shows that whilst there was only a very limited response in terms of predicted values, even patients with severe airways obstruction retained an appreciable degree of reversibility, in terms of their performance before the isoprenaline inhalation.

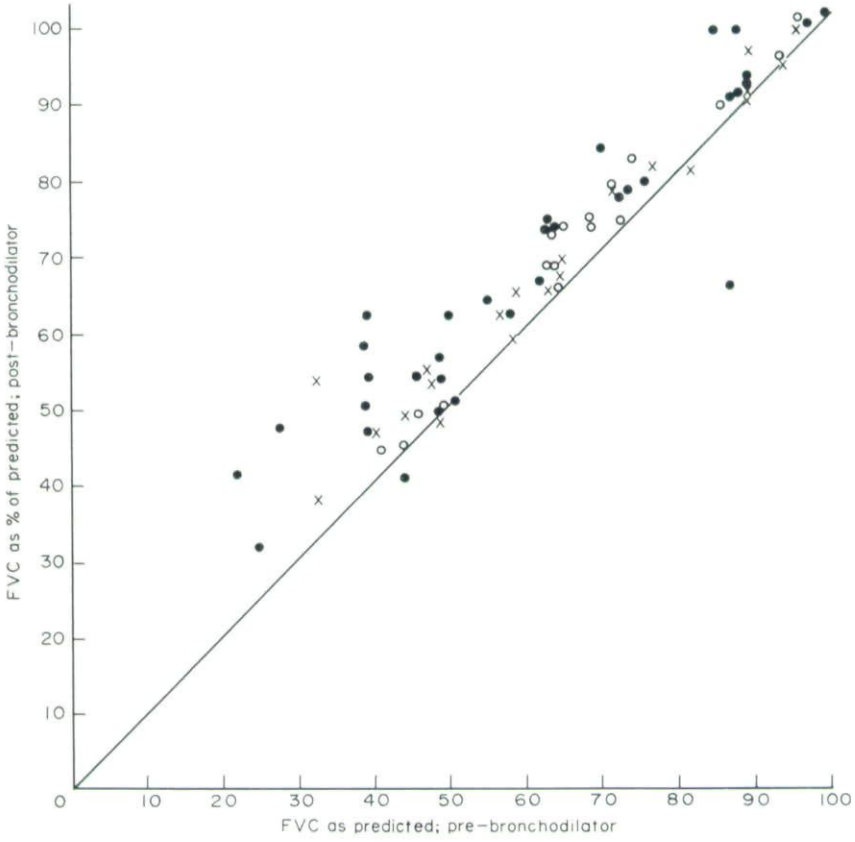

Fig. 3. FVC before and after inhalation of isoprenaline. ●, Group I; ○, group II; ×, group III. The differences in severity of airways obstruction and the limited reversibility following bronchodilator in moderately or severely affected patients are shown.

Forced vital capacity (FVC)

This too was reduced as a percentage of predicted values in most cases, though not as markedly as the $FEV_{1\cdot0}$, and there was also a small amount of reversibility after inhalation of isoprenaline (Fig. 3).

$FEV_{1\cdot0}$/FVC ratio

The ratio was reduced in most cases below 70% which was taken as normal. In twenty patients it was less than 40% and it changed little with bronchodilator treatment, in some cases being reduced further because of a disproportionate increase in FVC as compared with the $FEV_{1\cdot0}$.

Peak expiratory flow rate (PEFR)
This was reduced in all except four patients and also showed a limited reversibility being poorest in those with a PEFR of less than 30% of predicted values.

Measurements by body plethysmography
The total lung capacity (TLC) was greater than predicted in five of the sixteen patients tested and less in the remainder, of whom four had values less than 80% of that

Table 13. Body plethysmography in sixteen patients

TLC / Predicted (%)	RV% TLC / Predicted (%)	Airways resistance Before bronchodilator	Airways resistance After bronchodilator	FEV_1 % predicted Before bronchodilator	FEV_1 % predicted After bronchodilator	$D_{L,CO}$ (% pred.)	$D_{L,CO}$ (% extraction pred.)
4600/5500 (84)	58/37 (157)	4·0	4·0	56	81	—	—
7900/6500 (122)	69·6/24·1 (348)	3·34	3·0	75	78	64	95
5800/5900 (98)	51·6/26·7 (192)	3·81	2·37	23	26	63	66
5700/5000 (114)	57·2/27·0 (211)	2·93	2·5	26	33	56	78
4400/4600 (96)	72·4/26·3 (277)	10·0	10·2	21	32	—	—
6400/7500 (85)	52·5/25·0 (208)	4·32	3·74	35	45	45	70
4200/3800 (111)	66/25 (264)	9·05	9·68	24	40	—	—
6100/6800 (90)	45·8/27·0 (170)	2·84	2·34	43	54	92	75
2700/6900 (92)	58·5/24·5 (236)	3·52	4·05	50	69	60	57
5200/4700 (110)	53/23 (230)	4·1	4·4	30	39	45	56
5300/5700 (93)	62/33 (188)	4·8	4·3	16	19	—	—
5100/5700 (89)	72/30 (240)	3·34	2·63	16	20	31	59
5500/7300 (75)	45·1/27·7 (161)	2·6	2·4	69	77	37	71
9250/5890 (156)	64·0/26·6 (237)	4·9	4·23	18	29	53	61
4300/4400 (98)	48/27 (178)	2·77	2·6	57	65	53	72
6400/6500 (98)	45/28 (161)	2·61	2·38	96	96	70	93

predicted (Table 13). In view of the severity of the airways obstruction in many of the patients the TLC was lower than expected. The residual volume was increased in all the patients, being double the predicted value in nine patients, indicating considerable air-trapping. Airways resistance was increased in all cases, though only slightly in three cases. Patients with low percentage $FEV_{1.0}$ values compared with predicted values tended to have high airways resistance.

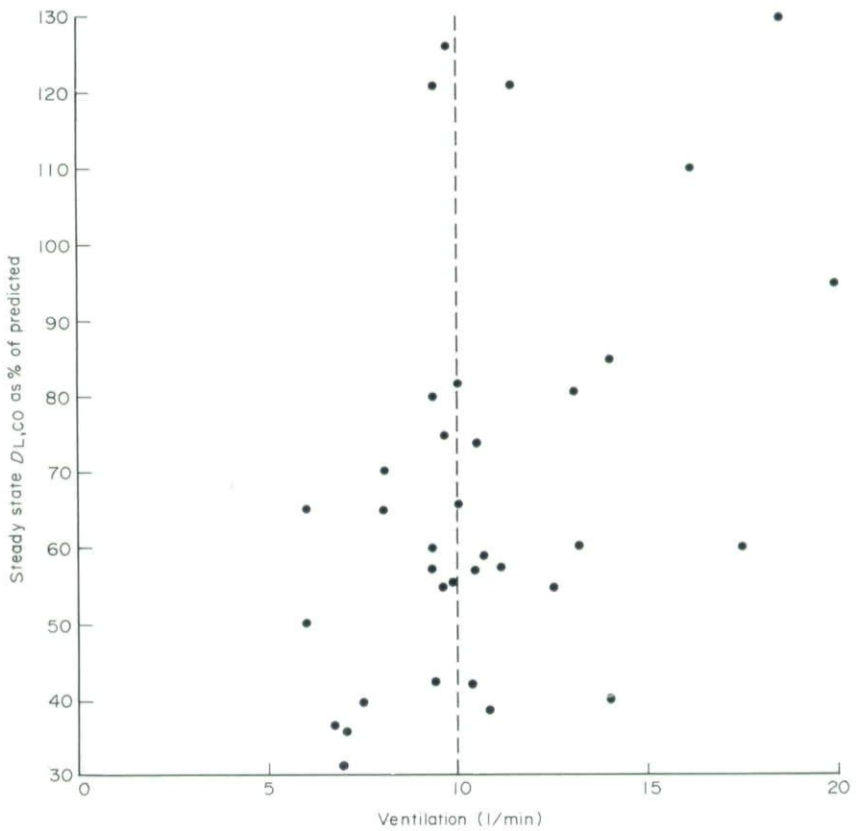

Fig. 4. Transfer factor for carbon monoxide (D_L,CO) at rest (thirty-five patients). The D_L,CO at rest as estimated by the steady state method was reduced in many patients.

CO gas transfer factor

As estimated by the steady state method (Fig. 4) the DL,CO was reduced at rest in most of the thirty-five patients tested. On exercise the DL,CO showed only a small increase despite considerable increases in minute ventilation.

The percentage extraction of CO was reduced in most patients and in twenty-four out of the thirty-five tested values of less than 80% predicted were obtained.

Blood gases and acidity were measured in three patients before and after stepping on and off a platform 23 cm high at a rate of 20–25 steps/min. Only one patient continued for 5 min, the other two stopping after $2\frac{1}{2}$ and 3 min. All three (Table 14)

showed a fall in arterial oxygen tension and a rise in arterial CO_2 tension and fall in blood pH. This contrasts with the usual response to limited exercise in uncomplicated asthma, where there is a fall in arterial oxygen tension, but little change in pH and possibly a fall in CO_2 tension.

Table 14. Blood gas: pH measurements in three patients before and after exercise

		Blood gases			FEV_1 (%	$D_{L,CO}$ (%	$D_{L,CO}$ (% extraction
	pH	Pa,CO_2	Pa,O_2	Sa,O_2	pred.)	pred.)	pred.)
					87	90	80
Rest	7·38	35	76	89			
Exercise	7·2	47	60	81			
					36	56	78
Rest	7·35	58	61	83			
Exercise	7·1	70	36	60			
					20	38	49
Rest	7·36	45	70	90			
Exercise	7·3	61	56	74			

Electrocardiographic examination

Out of seventy-two patients examined the electrocardiogram was normal in sixty-six; showed evidence of right heart strain in four and ischaemic changes in two.

Para-nasal sinuses and nasal plugs

Nasal plugs like those expectorated from the bronchi were present in 10% of the patients, and usually yielded *A. fumigatus* on culture, as often did the sinus washings. In forty-six patients radiographs showed past or present evidence of infection of the maxillary sinuses.

Bronchoscopic findings

Bronchoscopy was performed in thirty-one patients for diagnostic (87%) or therapeutic reasons (13%). In older patients carcinoma of the bronchus was suspected because of pulmonary shadows of undetermined cause. Bronchoscopy was used therapeutically to investigate and relieve the cause of bronchial obstruction, responsible for atelectasis of lobes or even an entire lung. In seventeen patients plugs were seen in the larger bronchi in relation to the area of radiographic shadowing.

Histopathological findings in bronchial and lung tissue

Bronchial biopsy was made in seven patients who had bronchial epithelium described as normal in some, and hyperaemic or pale, or oedematous and boggy in others. Secretions were usually profuse, mucopurulent, and tenacious. Plugs were firmly attached to the bronchial wall and had to be removed piecemeal, the underlying mucosa appearing granulomatous in some patients. Histological examination showed oedema, hyperaemia, polymorphonuclear neutrophil infiltration and eosinophilia. The mucus glands were hypertrophied and there were many goblet cells. The cilia were absent or atrophic in some cases. The bronchial wall was infiltrated with polymorphonuclear neutrophil and eosinophil cells and squamous metaplasia was also

observed. In areas of consolidated lung the alveoli contained numerous eosinophil cells, the appearance of so-called eosinophil pneumonia. Where pulmonary collapse predominated there were scattered clumps of eosinophil cells. The walls of the alveoli appeared normal. Gross bronchiectasis, mucous membrane polyps and emphysema were reported in one specimen. In two resection specimens the findings were similar. No abnormality of blood vessels was shown.

Effects of treatment

Corticosteroid treatment and pulmonary shadows. Two groups of twenty patients were chosen in whom each had at least two episodes of pulmonary eosinophilia over the previous 2 years and the most recent episodes were analysed (Table 15). This

Table 15. Effect of corticosteroids on pulmonary shadows*

New shadow clear in:	Corticosteroid treatment	No corticosteroid treatment
1 week	5 (13%)	2 (5%)
2–4 weeks	18 (45%)	7 (18%)
5–8 weeks	10 (25%)	11 (28%)
9–12 weeks	3 (8%)	11 (28%)
13–24 weeks	2 (5%)	4 (10%)
1–6 months	1 (2%)	3 (8%)
Up to 1 year	1 (2%)	2 (5%)

* Total number of shadows in each group = 40.

assessment was mainly retrospective, without comparable standardized radiographic studies, and with some patients on prednisone dosages varying between 20 and 40 mg/day. Table 15 suggests that the corticosteroid treatment reduced the duration of the pulmonary shadows. Atalectasis cleared rapidly under treatment, the more confluent shadows resolving more slowly.

Corticosteroid and antibiotic treatment and sputum production. The effects of treatment were assessed 48 hr after the start of corticosteroid treatment. The response to treatment varied in patients with repeated exacerbations, the corticosteroids being completely effective when given alone in some episodes, whilst in others antibiotic treatment alone was effective. The airways obstruction responded to corticosteroids in all cases, 75% of the patients requiring such treatment for control of symptoms. In eighty-two patients on corticosteroids the sputum cleared completely in twenty-two, of whom twenty had intermittent sputum production; it decreased in volume and purulence in forty, and there was no change in twenty. Of thirty patients with *A. fumigatus* cultured from the sputum, negative cultures were obtained in twenty cases within 48 hr after the start of prednisone treatment with doses of 40 mg/day or more.

The corticosteroid treatment reduced the expectoration of plugs in 24% and stopped them in 45% of a group of forty-five patients. The production of plugs stopped within 12 hr in one patient who had a pulmonary shadow and had produced numerous plugs over the previous 7 days. In seven patients there were at first more plugs in the sputum after corticosteroid treatment; five of these ceased to expectorate them in less than

1 week. Four of the latter patients had not expectorated plugs previously suggesting that the treatment enabled pre-formed plugs to be coughed up. There was no change in the number of frequency of expectoration of plugs in the remaining eight patients, and of these four were receiving less than 7·5 mg prednisone daily; suggesting that higher doses are necessary to suppress the formation of plugs.

Antibiotic treatment during exacerbations with tetracycline or ampicillin and without other changes in therapy, was associated with occasional good responses in about 70% of the cases, as judged by improvement in the sputum, in the constitutional upset and the pyrexia, within 48 hr.

Intracutaneous tests with A. fumigatus and effects of injections of A. fumigatus extracts for treatment purposes

In addition to the presence of Type I prick test reactions to routine extracts of *A. fumigatus*, all the cases gave Type III reactions as well to intracutaneous tests with the protein fraction of *A. fumigatus*. These are discussed further by McCarthy & Pepys (1971).

The influence of this dual skin test reactivity was seen in fifteen patients in whom attempts were made at hyposensitization with weak extracts of *A. fumigatus*, starting with 0·1 ml of a 10^{-6} concentration. In one patient even this low dose caused a Type III reaction, measuring 150×200 mm, after several hours. In the others increasingly severe local reactions developed with each increase in dose; in four patients asthmatic attacks developed after 4 hr or more and lasted 48–72 hr, and in two patients, one on corticosteroid treatment, new pulmonary shadows occurred during the course of injection treatment. Similar complications were frequent in other patients with allergic broncho-pulmonary aspergillosis, not included in this survey.

Examinations for intestinal parasites

Because of the possible association of intestinal parasites and pulmonary eosinophilia the stools of all the patients were examined and gave negative results. Complement fixation tests in ten patients for *Ascaris lumbricoides* and *Toxocara canis* were negative. Intracutaneous tests for *Toxocara canis* in twenty-five patients were negative and none of the 111 patients reacted to prick tests with extracts of *Ascaris lumbricoides*.

Clinical features of patients with pulmonary eosinophilia and no evidence of Aspergillus allergy

Of the total of 143 patients with asthma and pulmonary eosinophilia, there was no evidence of *Aspergillus* allergy in thirty-two. Brief comment is made on twenty-seven of these, the full clinical details to be reported later. They were divided into two groups, the first consisting of thirteen with onset of symptoms before the age of 10 and the second consisting of fourteen starting after that age. There were five male and eight females in the first group and three male and eleven females in the second, the later onset group thus resembling the later onset group of patients with allergic broncho-pulmonary aspergillosis in having a higher proportion of female patients. The younger group also had a higher atopic status with a history of infantile eczema and/or hay fever in about one-half as against none in the later onset group. This was supported by their higher atopic immunological status, with ten out of thirteen giving positive prick test reactions to an average of three allergens, compared with one out of ten reacting to one allergen in the later onset group. Negative reactions were given in

all twenty-seven patients to prick and intracutaneous tests with *A. fumigatus* and in five cases to inhalation tests. In ten cases prick tests were made not only with *A. fumigatus* and *A. terreus*, but also with *A. flavus*, *A. glaucus*, *A. nidulans* and *A. niger*, all being negative. In three patients sputum plugs were expectorated, but the sputum cultures for *A. fumigatus* were negative. In three patients, one specimen of sputum from each gave a positive culture for *A. fumigatus*. All the tests for intestinal parasites were negative. In two cases polyarteritis developed later. No evidence was obtained on the etiology of the pulmonary eosinophilia in any of these cases.

Discussion

In 111 out of 143 U.K. patients with pulmonary eosinophilia, the characteristic features of allergic broncho-pulmonary aspergillosis were present. The most important diagnostic criteria, present in all cases, were transitory pulmonary shadows, eosinophilia of blood and sputum, and evidence of allergy to *A. fumigatus*. Other supporting features were the expectoration of sputum plugs (56%) containing fungal mycelium and sputum giving cultures of *A. fumigatus* (58%), and bronchograms showing localized bronchiectasis of the proximal bronchi, with normal filling of the relevant peripheral bronchi (Scadding, 1967; McCarthy, 1968; McCarthy *et al.*, 1970). Localizing signs corresponding to the areas of radiographic shadows in the form of pleuritic type chest pain was found in some cases together with localized crepitant rales, decreased air entry and local dullness in about half of the cases during episodes of pulmonary eosinophilia.

The allergic responses to *A. fumigatus* are more important in diagnosis than sputum cultures. The latter may be positive coincidentally because the spores are ubiquitous and they are not infrequently negative in affected subjects. The relationship of the Type I reaction to prick tests with asthma and pulmonary eosinophilia is shown by its immunological role. The presence of precipitins is relevant to the appearance of Type III allergic reactions to which the pulmonary eosinophilia is attributed and they provide strong supporting evidence. But there is much evidence in man (Pepys, 1969) and in experimental animals (Henson & Cochrane, 1969) to show that immune-complex, Type III reactions require a preceding reaction of the immediate type for their development. The Type I reaction is therefore a necessary feature for the development of the Type III reactions.

In patients with asthma and pulmonary shadows in whom diagnoses such as pneumonia, tuberculosis or carcinoma may be made, a Type I prick test reaction is of high diagnostic value, since if positive a diagnosis of allergic broncho-pulmonary aspergillosis is strongly indicated and the other features of the disease are likely to be found, whereas if negative this is unlikely to be the case.

Passive transfer tests in the monkey with the sera of patients with reagins only or with reagins and precipitins have shown that only the latter sera transfer to the monkey the capacity to give Type III skin test reactions and pulmonary infiltrations on inhalation tests with extracts of *A. fumigatus* (Golbert & Patterson, 1970).

Comparison of patients with pulmonary eosinophilia who did not give prick test reactions to *A. fumigatus*, with those who did, shows that cultures of the fungus were obtained in only one specimen each for three of the patients out of a total of twenty-seven negative reactors examined in detail, compared with 58% of the total group of 111 positive reactors and with 83% of those examined during episodes of pulmonary eosinophilia. Sputum plugs were expectorated by three out of the twenty-seven

negative reactors and these did not contain fungal mycelium or yield positive cultures. By contrast, sputum plugs were present in 54% of the patients with allergy to *A. fumigatus*, and those which were examined contained fungal mycelium and gave positive cultures. Similar nasal plugs were also recorded in 10% of the positive reactors. The distribution of the radiographic shadows also differed, tending to be peripheral in their distribution in the negative reactors and lying in the region of the proximal bronchi, often in relation to plugs in the positive reactors. The allergic sensitivity to *A. fumigatus*, shown by the prick test, discriminates well between patients with allergic broncho-pulmonary aspergillosis and those with pulmonary eosinophilia of, as yet, unknown etiology.

The precipitins against *A. fumigatus* are helpful in support of the diagnosis, the serum requiring concentration in a number of cases in order to obtain a positive reaction. Out of eighty-seven sera tested both with and without concentration, eighty (92%) were positive.

The division of the patients into three groups according to the age of onset of the symptoms showed a high clinical and immunological atopic status in the group starting before 10 years of age and a low atopic status in those starting at 31 years or more. The group starting between 11 and 30 years lay intermediate between these.

In the early onset group the interval between the onset of asthma and the appearance of pulmonary eosinophilia averaged 24 years, compared with 11 years in the middle group and 3·5 years in the late onset group. This suggests that in the more highly atopic subjects prolonged antigenic stimulation by *A. fumigatus* was needed for the appearance of the precipitins and of the Type III allergy, which is almost invariably present in such subjects. In the subjects of low atopic status, of whom almost one half were the only ones to be allergic to *A. fumigatus* solely, the precipitins would seem to have developed more rapidly, possibly in concert with the reaginic antibody. These differences present problems of interest in relation to the effects of the immunological reactivity of the subject on the mode of presentation of the clinical manifestations in response to *A. fumigatus* and very probably to other allergens as well.

Some authors have suggested that exposure to large concentrations of spores of *A. fumigatus* may be related to the disease (Hinson *et al.*, 1952; Strelling, 1961), and Henderson (1968) suggested that it was more common in agricultural conditions. In the present study most of the subjects were urban dwellers, so that whatever the effects of heavy rural or agricultural exposure may be, the disease is common under urban conditions. The high incidence of 46% with exposure to birds, mainly budgerigars, in the home, requires further study to see if this is relevant. The findings by Maunsell (1954) and Noble & Clayton (1963) that the spores of *A. fumigatus* are far more common in the air in winter is supported by the frequent supervention in winter of episodes of pulmonary eosinophilia, in patients with previously uncomplicated asthma, and of aggravation of symptoms and recurrent episodes of pulmonary infiltrations. These were not, however, confined to this season. The asthmatic manifestations which were usually paroxysmal to start with, became more continuous and severe with the development of pulmonary eosinophilia. Protracted remissions which were not uncommon in group I who start early in life, were rare in group II and absent in group III. This is relevant to the assessment of response to treatment and of the need to classify the patients in their appropriate groups of age of onset and atopic status.

Cough and sputum as well as the asthma were all worse during exacerbations of

the allergic broncho-pulmonary aspergillosis and fever was often present. There may be difficulty in deciding the relative importance of the immunological reactions in this or of secondary bacterial infection.

An important role for bacterial infection in patients with allergic broncho-pulmonary aspergillosis is shown by the high incidence of bacterial precipitins and sputum cultures for pathogenic bacteria. Bacterial precipitins were found in forty-two (60%) of seventy subjects tested; *H. influenzae* represented 67% of the positives, *Str. pneumoniae* 57% and *Staph. aureus* 48%. The high incidence of *H. influenzae* precipitins is evidence of chronic infection being comparable to that found by Burns & May (1967) in chronic bronchitis and much higher than the 8% of positives they found in uncomplicated asthma. Sputum cultures supported these findings, being positive in 45% of the patients for one or more of the following, *Staph. aureus*, *H. influenzae*, *Str. pneumoniae* and *Ps. pyocyaneus*. It is difficult to assess the role of these bacteria, antibiotic treatment being of help in some exacerbations, but far less effective than corticosteroid treatment.

There is little information in earlier reports on respiratory function in allergic broncho-pulmonary aspergillosis. The mechanisms of the reactions and of the physiological changes in the dual asthmatic reactions which are excited on challenge and which are discussed in detail by McCarthy & Pepys (1971) are not well understood, at least as far as 'late' asthmatic reaction is concerned. Nor is anything known about the possible reactions in the peripheral lung tissues in allergic broncho-pulmonary aspergillosis.

Completely reversible airways obstruction was usually present at first, followed by increasingly worse airways obstruction with less and less reversibility and decreasing exercise tolerance. The subjective changes consisted of a prolonged course of widely fluctuating airways obstruction in groups I and II, while in group III there was rapid progression to poorly reversible obstruction. The peak expiratory flow and $FEV_{1\cdot0}$ were reduced in most patients and the increase in airways resistance, which occurred only when the $FEV_{1\cdot0}$ was markedly reduced, together with the increase in residual volume confirmed the airways obstruction and gas trapping.

Total lung capacity (TLC) was smaller than predicted in some, and the same or even greater in others. In patients with loss of lung tissue and severe airways obstruction the TLC may be misleading. In these circumstances a normal or low TLC may be compatible with air trapping. In two patients with normal predicted TLC there was radiological evidence of shrinkage of the upper lobes and severe airways obstruction.

The reduction in CO gas transfer factor at rest and on exercise found in the patients with allergic broncho-pulmonary aspergillosis may be due to various causes. Firstly, the test may be unsatisfactory in patients with severe airways obstruction because equilibrium between the gas mixture containing CO and the air in the patients' lungs is difficult to achieve, giving an incorrect end tidal sample. The mismatching of ventilation and perfusion is probably the main reason for the low diffusing capacity. Loss of lung tissue due to the commonly present lobar fibrosis and contraction and to areas of local emphysema may be important as well. There was also a rise in arterial CO_2 in two out of three of the patients on exercise, not usually present in uncomplicated asthma.

Further information on respiratory function in this disease is needed regarding the location of the airways obstruction and the mechanisms responsible for the abnormality in gas-exchange. Contrary to what might be anticipated in the patients with

gross lung damage, pulmonary hypertension was uncommon and cor pulmonale was not seen.

Specific immunological treatment by attempts at hyposensitization is unsatisfactory because of the local and asthmatic reactions, presumed to be of a Type III nature, which are provoked. Bronchodilator drugs and disodium cromoglycate have their place in treatment, but corticosteroid treatment is the most effective, though there are many problems in deciding how best to use it. It leads to rapid improvement of asthma and systemic manifestations and decrease in the sputum, plugs seldom being seen with adequate dosage (20–40 mg/day) after the first 2 days, and the sputum becoming negative for *A. fumigatus* on culture. Slavin, Milion & Cherry (1970) report that the precipitin test may become negative under corticosteroid treatment. It may take a week or so for maximal improvement in the airways obstruction. The radiographic shadows may clear within a few days or take several weeks. Corticosteroids suppress the Type III skin and inhalation test reactions and there is some evidence that the continued use of corticosteroids reduced the pulmonary infiltrations. This may be of help in decreasing the development of further bronchiectasis. The presence of severe asthma makes it easier to decide on corticosteroid treatment. It is more difficult to decide this where the asthma is not severe and pulmonary infiltrations are the main feature. Doses higher than 5 mg prednisone a day are needed, since in fifteen patients this did not prevent recurrent pulmonary infiltrations. The diagnosis of allergic broncho-pulmonary aspergillosis needs to be considered in all patients with pulmonary shadows, mimicking pneumonitis from various causes, pulmonary tuberculosis or even carcinoma of the bronchus, and the presence of eosinophilia of the blood and/or the sputum is a useful pointer. Constitutional disturbance with fever may occur with limited evidence of airways obstruction, or a radiological shadow may be found coincidentally in an asymptomatic patient. Bronchiectasis of an infective origin may be suspected but the characteristic cylindrical or saccular bronchiectasis of the proximal bronchi, usually together with normal filling of the bronchi peripheral to it, described by Scadding (1967), McCarthy (1968) and McCarthy *et al.* (1970), is a useful pointer to the diagnosis. Allergic broncho-pulmonary aspergillosis should be suspected in all asthmatic patients with histories of pneumonic episodes or radiographic abnormalities. Fibrosis of the upper lobes in chronic cases is common as reported by Henderson (1968).

Whilst allergic broncho-pulmonary aspergillosis has a course extending over many years with recurrent episodes of pulmonary eosinophilia and progressive, insidious, deterioration, many patients with marked functional defects nevertheless continue with their work. A 'burnt-out' stage (Plummer, 1958) also seems to occur. Prospective long-term studies are needed to give a clear picture of the behaviour of this disease.

Acknowledgments

We wish to thank the clinicians of the Brompton Hospital for referring the patients to the laboratories, and for their support in these investigations.

References

Bates, D.V., Boucot, N.G. & Dormer, A.E. (1955) The pulmonary diffusing capacity in normal subjects. *Journal of Physiology*, **129**, 237.

Burns, M.W. (1968) Precipitins to pneumococcal C-substance polysaccharide in the serum of patients with chronic bronchial disorders. *Lancet*, **i**, 223.

BURNS, M.W. & MAY, J.R. (1967) *Haemophilus influenzae* precipitins in the serum of patients with chronic bronchial disorders. *Lancet*, **i,** 354.

CAMPBELL, M.J. & CLAYTON, Y.M. (1964) Bronchopulmonary aspergillosis. A correlation of the clinical and laboratory findings in 272 patients investigated for bronchopulmonary aspergillosis. *American Review of Respiratory Diseases*, **89,** 186.

CHARPIN, J., OHRESSER, PH., BOUTIN, C. & AUBERT, J. (1967) Aspergillose pulmonaire allergique. *Journal Français de Médecine et Chirurgie Thoraciques*, **21,** 517.

GOLBERT, T.M. & PATTERSON, R. (1970) Pulmonary allergic aspergillosis. *Annals of Internal Medicine*, **72,** 395.

GOLDSTEIN, G.B. & YOKOYAMA, M. (1971) Studies of the dual antibody response in allergic broncho-pulmonary aspergillosis. *Journal of Allergy*, **46,** 340.

HENDERSON, A.H. (1968) Allergic aspergillosis: review of 32 cases. *Thorax*, **23,** 501.

HENSON, P.M. & COCHRANE, C.A. (1969) Antigen–antibody complexes. Platelets and increased vascular permeability. *Cellular and Humoral Mechanisms in Anaphylaxis and Allergy* (Ed. by H. Z. Movat), p. 129. Karger, Basel.

HINSON, K.F.W., MOON, A.J. & PLUMMER, N.S. (1952) Bronchopulmonary aspergillosis. *Thorax*, **7,** 317.

LANDRIGAN, P.L., WASTY, G. & NIGAM, S. (1968) Pulmonary aspergillosis; report of seven cases. *Canadian Medical Association Journal*, **98,** 642.

LONGBOTTOM, J.L. & PEPYS, J. (1964) Pulmonary aspergillosis: diagnostic and immunological significance of antigens and C-substance in *A. fumigatus*. *Journal of Pathology and Bacteriology*, **88,** 141.

MAUNSELL, K. (1954) Respiratory allergy to fungus spores. *Progress in Allergy*, vol. 4, p. 457. Karger, Basel.

MAY, J.R. (1954) Pathogenic bacteria in chronic bronchitis. *Lancet*, **ii,** 839.

MCCARTHY, D.S. (1968) Bronchiectasis in allergic broncho-pulmonary aspergillosis. *Proceedings of the Royal Society of Medicine*, **61,** 503.

MCCARTHY, D.S. & PEPYS, J. (1971) Allergic broncho-pulmonary aspergillosis. Clinical immunology: (2) Immunological features. *Clinical Allergy*, **1** (in press).

MCCARTHY, D.S., SIMON, G. & HARGREAVE, F.E. (1970) The radiological appearances in allergic broncho-pulmonary aspergillosis. *Clinical Radiology*, **21,** 366.

MCNAMARA, J., PRIME, F.J. & SINCLAIR, J.D. (1959) An assessment of the steady state carbon monoxide method of estimating pulmonary diffusing capacity. *Thorax*, **14,** 166.

NOBLE, W.C.N. & CLAYTON, Y.M. (1963) Fungi in the air of hospital wards. *Journal of General Microbiology*, **32,** 397.

PATTERSON, R. & GOLBERT, T.M. (1968) Hypersensitivity disease of the lung. *University of Michigan Medical Center*, **8,** 1968.

PEPYS, J. (1969) *Hypersensitivity Diseases of the Lungs due to Fungi and Organic Dusts*. Karger, Basel.

PEPYS, J., RIDDELL, R.W., CITRON, K.M., CLAYTON, Y.M. & SHORT, E.I. (1959) Clinical and immunological significance of *Aspergillus fumigatus* in the sputum. *American Review of Respiratory Diseases*, **80,** 167.

PLUMMER, N.S. (1958) In: *Fungous Diseases and their Treatment* (Ed. by R. W. Riddell and G. T. Stewart), p. 234, Butterworth, London.

SCADDING, J.G. (1967) The bronchi in allergic aspergillosis. *Scandinavian Journal of Respiratory Diseases*, **48,** 372.

SLAVIN, R.G., MILION, L. & CHERRY, J. (1970) Allergic broncho-pulmonary aspergillosis: characterization of antibodies and results of treatment. *Journal of Allergy*, **46,** 150.

SLAVIN, R.G., STANCZYK, D.J., LONIGRO, A.J. & BRAUN, S.O.S. (1969) Allergic broncho-pulmonary aspergillosis—a North American rarity. *American Journal of Medicine*, **47,** 306.

SPOTNITZ, M. & OVERHOLT, E.L. (1967) Mucoid impaction of the bronchi associated with aspergillosis. *Diseases of the Chest*, **52,** 92.

STRELLING, M.K., RHANEY, K., SIMMONS, D.A.R. & THOMSON, J. (1966) Fatal acute pulmonary aspergillosis in two children in one family. *Archives of Diseases of Childhood*, **41,** 34.

WARREN, W.P. & ROSE, B. (1969) Hypersensitivity broncho-pulmonary aspergillosis. *Diseases of the Chest*, **55,** 415.

WOODRUFF, A.W., BISSERU, B. & BOWE, J.C. (1966) Infection with animal helminths as a factor causing poliomyelitis and leprosy. *British Medical Journal*, **i,** 1576.