

## Pulmonary aspergillosis

### A survey of its occurrence in patients with chronic lung disease and a discussion of the significance of diagnostic tests

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The occurrence of pulmonary aspergillosis and of precipitins, positive skin tests, and sputum containing abundant *Aspergillus fumigatus* has been assessed and correlated in a survey of 107 consecutive patients attending hospital in Bristol with various chronic chest diseases. The series included three with aspergilloma, five with allergic aspergillosis, and one with chronic invasive aspergillosis. Of 46 asthmatic patients, 11% had definite and 22% had probable or definite allergic aspergillosis.

Seven patients (15%) in the asthmatic group were found to have chronic upper lobe contraction, probably attributable to long-standing allergic aspergillosis. One of these patients developed aspergilloma, and another, invasive aspergillosis.

The significance of precipitins is discussed, based on the survey patients together with 21 additional patients who had aspergillosis but were from outside the survey. In the survey patients without definite aspergillosis, precipitins and positive sputum were significantly associated and were found most commonly in patients with asthma, bronchiectasis, or cavitated lungs. Two patients with invasive aspergillosis who had weak precipitins are reported. We think that precipitins reflect recent or continuing fungal growth in body tissues or within damaged bronchi, and that their presence can be a useful indication of occult fungal colonization, which might rarely become invasive if host resistance were lowered as by steroids.

Allergic aspergillosis is a more common condition and a more frequent cause of upper lobe damage than has been appreciated.

Pulmonary aspergillosis, in its various forms, is most commonly caused by the species *Aspergillus fumigatus*, the spores of which are widely disseminated in the atmosphere. The fungus colonizes diseased air spaces (Okudaira and Schwarz, 1962) and sometimes grows to form obvious aspergillomas (Dévé, 1938). It can become invasive, usually when host defences are impaired (Finegold, Will, and Murray, 1959; Symmers, 1964), although occasional instances of systemic infection in previously healthy individuals have been reported (Strelling, Rhaney, Simmons, and Thomson, 1966). It may also cause allergic reactions, resulting in episodic airways obstruction, pulmonary shadows, and eosinophilia (Hinson, Moon, and Plummer, 1952; Pepys, Riddell, Citron, Clayton, and Short, 1959).

Culture of *A. fumigatus* from the sputum may indicate only coincidental contamination (Camp-

bell and Clayton, 1964). Conversely, sputum cultures from patients with pulmonary aspergillosis have often not yielded the fungus (Belcher and Plummer, 1960). Serum precipitins and skin tests are of diagnostic value in cases of aspergilloma and allergic aspergillosis but are found also in other patients with lung disease (Pepys *et al.*, 1959; Campbell and Clayton, 1964; Longbottom and Pepys, 1964).

This paper reports the results of a survey of patients with chronic lung disease, studied for evidence of aspergillosis. The significance of positive tests is discussed, with particular reference to those patients who cannot with certainty be shown to have aspergilloma or allergic aspergillosis.

#### SUBJECTS

The survey comprised 107 patients seen in Bristol, representing all new and follow-up patients with

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chronic lung disease who were seen routinely over the course of one year from April 1965 by one of us (A. H. H.).

The discussion on the significance of laboratory findings is based on these 107, together with 21 additional patients with aspergillosis seen by A. H. H. (including the 17 described in this issue (Henderson, 1968) as well as three patients from whom aspergillomas had been resected and one patient with acute disseminated aspergillosis).

#### DEFINITIONS AND METHODS

Methods have been described and definitions of the types of aspergillosis given in previous papers (English and Henderson, 1968; Henderson, 1968). Other definitions are given here.

**ASTHMA** This group contains all patients with a history of asthma, even if fixed airways obstruction had subsequently developed or there was associated bronchiectasis or chronic bronchitis.

**BRONCHIECTASIS** This group contains only patients with clinical or radiological evidence of localized bronchiectasis and excludes patients with asthma.

**NON-SPECIFIC LUNG DISEASE** This group contains patients with chronic bronchitis, emphysema, or both.

**SPUTUM** Two or more specimens from each patient were examined by a medical mycologist.

#### RESULTS

**SURVEY FINDINGS** Table I shows the clinical and laboratory features of patients with aspergillosis and also of all patients with asthma.

Table II shows the features of patients without definite aspergillosis.

There were three patients with aspergilloma, five with allergic aspergillosis, and one with invasive aspergillosis—a total of nine with definite pulmonary aspergillosis. Five (11%) of the 46 patients with asthma had allergic aspergillosis.

Some degree of chronic upper lobe contraction was radiographically evident in seven (15%) of the asthmatic patients, two of whom had established long-standing allergic aspergillosis, and the other five of whom all had probable long-standing allergic aspergillosis (Henderson, 1968). One of these patients developed aspergillomas, and one died with invasive aspergillosis. Four were on steroid therapy.

In patients without definite aspergillosis the proportions of patients with precipitins or positive

TABLE I

ALL SURVEY PATIENTS WITH DEFINITE ASPERGILLOSIS OR ASTHMA: CLINICAL AND LABORATORY FINDINGS

Diagnosis	No. of Patients	No. of Patients with				Patients on Steroids
		Precipitins	Positive Skin Test	Positive Sputum	Eosinophilia	
Aspergilloma (1 with asthma) .. .. .	3	3	3	3	1	0
Allergic aspergillosis .. .. .	5	5	5	5	5	3
Invasive aspergillosis (1 with asthma) .. .. .	1	1	1	1	1	1
Total definite aspergillosis .. .. .	9	9	9	9	7	4
Total asthma (including 7 with aspergillosis) .. .. .	46	12 (26%)	16 <sup>1</sup> (36%)	10 <sup>1</sup> (25%)	24 (52%)	10 (22%)

<sup>1</sup> In patients with asthma, skin test not carried out on 2 cases, sputum not examined in 6 cases. Figures in brackets refer to proportions of patients tested with positive result.

TABLE II

ALL SURVEY PATIENTS WITHOUT DEFINITE ASPERGILLOSIS: CLINICAL AND LABORATORY FINDINGS

Diagnosis	No. of Patients	Patients with				Patients on Steroids	
		Precipitins No. %	Positive Skin Test No. %	Positive Sputum No. %	Eosinophilia No. %	No. %	
Asthma .. .. .	39	5 13	9 (2) 24	3 (6) 9	17 44	6 15	
Bronchiectasis or cavitated lungs <sup>1</sup> .. .. .	13	4 31	2 (1) 17	3 (2) 27	0 0	0 0	
Other non-asthmatic <sup>2</sup> .. .. .	46	1 2	2 (3) 5	0 (3) 0	2 4	7 15	
Total non-asthmatic .. .. .	59	5 8	4 (4) 7	3 (5) 6	2 3	7 12	
Total .. .. .	98	10 10	13 (6) 14	6 (11) 7	19 19	13 13	

Figures in brackets indicate numbers of patients in whom test was not carried out.

<sup>1</sup> 1 Case of cavitated sarcoid (with precipitins and positive sputum), 12 cases of bronchiectasis (2 with both precipitins and positive sputum).

<sup>2</sup> 40 Cases of non-specific lung disease, 4 of bronchial carcinoma, and 2 with diffuse interstitial pulmonary fibrosis.

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sputum were similar in those on steroid therapy and those not on steroid therapy.

LABORATORY AND CLINICAL FEATURES

**Patients with aspergillosis** The findings in patients with aspergillosis are summarized in Tables I and III.

Two patients were shown at necropsy to have invasive aspergillosis. One of these had probably also had long-standing allergic aspergillosis: histological examination of the lungs showed hyphae penetrating the bronchial walls and within giant cell granulomata. The other patient died from acute pneumonic and disseminated aspergillosis after two months of high dosage steroid and azathioprine therapy for pemphigus. The fungus was recovered from the sputum in both cases: it had been present for at least a year in the first case and in each was found in large quantities at necropsy.

**Patients without definite aspergillosis** Tables III and IV show that in survey patients without definite aspergillosis, precipitins and positive sputum were significantly associated. The coincident development of positive sputum and of increasingly strong precipitins is illustrated in the Figure.

Ten survey patients had precipitins. The five with asthma all had positive skin tests, and the five without asthma had negative skin tests. Of

**TABLE III**  
RELATIONSHIP OF STRENGTH OF PRECIPITINS TO DIAGNOSTIC GROUPS (INCLUDING ALL SURVEY PATIENTS AND 21 OTHERS WITH ASPERGILLOSIS NOT IN SURVEY)

Diagnosis	No. of Patients				
	Precipitins (group) <sup>2</sup>				No Precipitins
	A	B	C	D	
Aspergilloma in situ .. .. .	3	0	0	0	0
Aspergilloma resected <sup>1</sup> .. .. .	1	0	0	2	1
Allergic aspergillosis .. .. .	13	0	2	7	0
Invasive aspergillosis .. .. .	0	0	1	1	0
Other with asthma <sup>3</sup> { Sputum positive .. .. .	0	0	0	1	2
{ Sputum negative .. .. .	0	1	0	2	27
Other without asthma { Sputum positive .. .. .	1	0	1	1	0
{ Sputum negative .. .. .	0	0	0	2	49

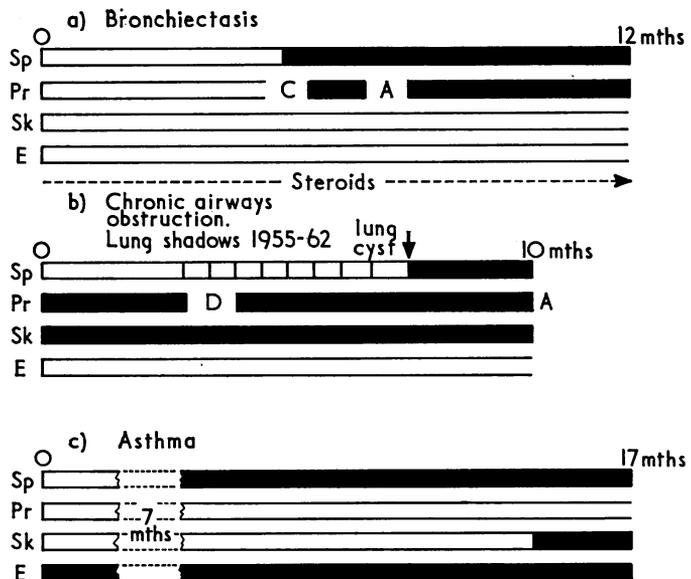
<sup>1</sup> Resected more than 18 months previously, sputum negative  
<sup>2</sup> Survey patients in whom sputum was examined  
<sup>3</sup> Precipitins classified A-D in descending order of strength (see Methods)

**TABLE IV**  
RELATIONSHIP BETWEEN SPUTUM CULTURES AND PRECIPITINS IN SURVEY PATIENTS<sup>1</sup> WITHOUT DEFINITE ASPERGILLOSIS

Precipitins	Total No. of Patients	Positive Sputum Culture	
		No. of Patients	Percentage
Present	9	4	44
Absent	78	2	3

P > 0.00077 by Fisher's Exact Probability Test  
<sup>1</sup> 11 Survey patients excluded because sputum not available

the asthmatic patients, four had probable allergic aspergillosis and one was inadequately studied, being lost to follow-up; sputum was positive in



**FIGURE.** Time relationships of test result in three patients. Sp. = sputum; Pr. = precipitins; Sk. = skin test; E. = eosinophilia; white line = negative result; black line = positive result; broken line = not tested; A-D = strength of precipitins.

one, became positive after the period of the survey in another, and was not examined in a third patient. Of the patients without asthma, one (precipitins strength A) had cavitated sarcoid with positive sputum, and three (precipitins strengths C, D, and D) had bronchiectasis, two with positive sputum; the fifth patient (precipitins strength D) had chronic bronchitis, but no fungus was found in the only specimen of sputum available.

Of the two patients with positive sputum but no precipitins, one had chronic bronchitis with recent asthma, and sputum repeatedly contained *A. fumigatus* hyphae for three weeks but not thereafter. The other (Figure, c) was a young woman with asthma, eosinophilia, and persistently positive sputum for nine months, during which period the skin test became positive on retesting. Precipitins have not been demonstrated in either of these last two patients despite follow-up for a year and the use of concentrated serum.

The development of increasingly strong precipitins was observed in three patients. In two (Figure, a, b) this was coincident with recovery of the fungus from sputum, previous specimens of which had been negative. One patient outside the survey, who had had pulmonary eosinophilia in the past before her asthma was controlled with steroids, had a positive skin test and weak precipitins but no evidence of current fungal infection at necropsy.

#### DISCUSSION

**INCIDENCE OF PULMONARY ASPERGILLOSIS** The incidence of the different types of pulmonary aspergillosis is not known, although necropsy reviews have shown an increasing number of cases of invasive aspergillosis (Heffernan and Asper, 1966). Pepys *et al.* (1959) found that patients with aspergilloma comprised 0.2% of 2,080 patients whose sputum was examined, and Macpherson (1965) found aspergilloma in 0.01% of a population of 60,000 from a review of radiographs taken in the preceding 10 years. The diagnosis of allergic aspergillosis in our survey has been confined to patients fulfilling all the given diagnostic criteria (airways obstruction, pulmonary eosinophilia, positive skin test, and positive sputum), thereby excluding some patients with potential allergy or only limited allergic reactions while under observation. Our finding of allergic aspergillosis in 5 out of 46 patients with asthma (11%) attending hospital is similar to the estimated 8% derived from a combined analysis of two published series (Pepys *et al.*, 1959; Campbell and Clayton, 1964).

The proportions of positive sputum cultures, precipitins, and positive skin tests have been reported in a number of papers but only fully correlated in selected series. Table V has been compiled from an analysis of the published data: our own findings are entered for comparison. Slight differences of technique used in different series make detailed comparisons difficult.

Patients with sputum cultures yielding abundant fungus were found as often in the Bristol series as were total positive cultures in other reported series, possibly reflecting the fact that all specimens were examined by a mycologist. In all patients with allergic aspergillosis the fungus was isolated on examination of no more than three random specimens, none of which contained obvious plugs. The proportions of precipitins in patients with lung disease other than definite aspergillosis are similar to those found by other workers (Longbottom and Pepys, 1964; Mearns, Longbottom, and Batten, 1967). Positive skin tests were found less often in our series than in other published series. This may be related to our use of the intradermal instead of the prick method of testing and to our acceptance only of strongly positive results.

Positive sputum cultures and precipitins were found most commonly in patients with asthma, bronchiectasis, or cavitated lungs.

**UPPER LOBE CONTRACTION** Some degree of chronic contraction of the upper lobes not attributable to other known disease was found in seven (15%) of the asthmatic patients in the survey: all showed evidence of chronic fungal infection and hypersensitivity and probably had long-standing allergic aspergillosis. If these patients are included, the proportion of survey patients with asthma who had allergic aspergillosis becomes 22%.

**PRECIPITINS** The precise significance of precipitins in the diagnosis and pathogenesis of the different types of aspergillosis is not yet fully understood.

Precipitins are strongly present in almost all cases of aspergilloma (Table V) and slowly disappear after resection of the aspergilloma in some cases (Longbottom and Pepys, 1964) (Table III). They occur in almost 10% of non-asthmatic patients with chronic lung disease (Table V), being found most commonly in patients with severely diseased lungs (Brönnestam and Hallberg, 1965; Mearns *et al.*, 1967) and, in our series, in patients with bronchiectasis or cavitated lungs. Their presence

TABLE V  
COMPARISON OF PRESENT FINDINGS WITH THOSE OF OTHER SERIES

	Percentage of Patients with Positive Findings											
	Precipitins		Positive Skin Tests		Positive Sputum Cultures		Eosinophilia		Peripheral Lung Shadows			
	Others	Present Series	Others	Present Series	Others	Present Series	Others	Present Series	Others	Present Series		
Aspergilloma												
In situ (including patients with asthma) . . . .	98 <sup>b</sup> , <sup>c</sup>	100 <sup>d</sup> , <sup>e</sup>	100	240 <sup>b</sup> 25 <sup>c</sup>	100	100	82 <sup>c</sup> 75 <sup>d</sup>	100	42 <sup>c</sup>	50	33	4 <sup>c</sup>
In situ (excluding asthma) . . . .												
Removed . . . .	56 <sup>b</sup>			22 <sup>b</sup> 5 <sup>c</sup>	100							
Allergic aspergillosis . . . .	63 <sup>b</sup> 70 <sup>e</sup>	100		99 <sup>c</sup>	100		98 <sup>c</sup>	100	90 <sup>c</sup>	100		89 <sup>c</sup>
Asthma												
Total . . . .	22 <sup>b</sup> 27 <sup>d</sup>	26		24 <sup>a</sup> 50 <sup>b</sup>	36		17 <sup>a</sup>	24		52		13
Excluding pulmonary eosinophilia . . . .	9 <sup>b</sup> 7 <sup>f</sup>	13		38 <sup>b</sup> 10-20 <sup>g</sup>	24			9		44		0
Other lung disease . . . .	8 <sup>b</sup> 62 <sup>d</sup>	8		14 <sup>b</sup>	7		5 <sup>a</sup>	6		3		0
No lung disease . . . .	0 <sup>b</sup>											

Index letters refer to series summarized below.

- a. Pepys, Riddell, Citron, Clayton, and Short (1959)
  - (i) Series of 103 positive sputum cultures from 315 patients with asthma and 1,000 patients with other chest disease
  - (ii) Series of 41 positive skin tests from 170 patients with asthma
- b. Longbottom and Pepys (1964)
  - Series of 163 positive precipitins from 651 patients, selected on the basis that serum was submitted for examination (85-90% from physicians elsewhere): 57 aspergilloma in situ, 9 aspergilloma removed, 93 asthma with pulmonary eosinophilia, 307 asthma without pulmonary eosinophilia, 185 other lung disease; skin tests performed in c. 80% of asthmatics, c. 50% of aspergilloma, and an unspecified number of patients with other lung disease; sputum findings not given.
- c. Campbell and Clayton (1964)
  - Series of 272 patients (30 included in publication by Pepys, Riddell, Citron, Clayton, and Short (1959) ) selected on the basis of positive sputum or precipitins or both: 23 aspergilloma, 87 allergic aspergillosis; giving data about the presence of aspergilloma, lung infiltration, eosinophilia, precipitins, positive skin tests, and positive sputum cultures.
- d. Brönnestam and Hallberg (1965)
  - Swedish series of 4 patients with aspergilloma, 15 with asthma, and 24 selected patients with other 'grave pulmonary disease', giving precipitin results, and results of sputum cultures in the patients with aspergilloma.
- e. Macpherson (1965)
  - Series of 6 cases of aspergilloma out of 56 patients with cavitated lung, found after review of radiographs 1954-1963 in Argyll; giving precipitin results.
- f. Mearns, Longbottom, and Batten (1967)
  - Series of 60 patients with asthma, giving precipitin results.
- g. Pepys (1966)
  - Cited proportion of positive skin tests in unselected patients with asthma.

is significantly associated with the finding of positive sputum. Further support is lent to the concept that they reflect antigen exposure by the coincident development of precipitins and positive sputum in two patients.

Precipitins were also present in the two cases of invasive pulmonary aspergillosis already briefly reported (Henderson, English, and Stewart-Smith, 1967). They have previously been reported in the invasive disease only by Murray (1966) in a case of renal aspergillosis, and by Redmond, Carré, Biggart, and Mackenzie (1965) in a systemic infection with bone involvement caused by *A. nidulans*. Those found in our two cases were very weak, possibly reflecting low host resistance to the fungus and possibly attributable to steroids.

In allergic aspergillosis, precipitins of varied strength have been found in 60 to 70% of cases (Longbottom and Pepys, 1964; Campbell and

Clayton, 1964) and are said to be present in almost all cases, if the test is carried out with concentrated serum (Pepys, 1966). They were present in all our cases, and there is some evidence that their strength was related to the amount and duration of fungal growth (Henderson, 1968). Precipitins also occur in 7 to 13% of asthmatic patients in whom not all the features of allergic aspergillosis have been demonstrated. The five such patients in this series all showed some features of allergic aspergillosis, and it is possible that most of these patients might have been shown to have allergic aspergillosis if investigated at the appropriate stage of the disease. The weak precipitins present in one asthmatic patient in whom no current fungal lung infection was found at necropsy may relate to previous fungal growth subsequently cleared during symptom-free intervals. Conversely, two patients with asthma did not develop precipitins despite pro-

ducing repeatedly positive sputum: some bronchial damage may be necessary to allow effective antigen exposure.

The evidence here presented indicates that precipitins are associated with present or recent fungal growth in the body tissues or within damaged bronchi, whether with obvious aspergilloma formation or occult fungal colonization of diseased bronchial spaces, and whether there is associated allergic aspergillosis or not. On this interpretation precipitins in allergic aspergillosis will reflect chronic fungal colonization secondary to impaired drainage due either to temporary airways obstruction or to permanent bronchial damage.

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