

Cystic fibrosis—immunological reactions to *A. Fumigatus* and common allergens

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Summary

Immunological studies of forty-three patients with cystic fibrosis showed that positive prick tests to at least one common allergen were obtained in 70%, to multiple allergens in 28% and to *A. fumigatus* in 50%. Specific IgE antibodies against these allergens were found in the appropriate subjects. In spite of this evidence of type 1, IgE, sensitization none of the patients had a history of infantile eczema.

Intracutaneous tests with *A. fumigatus* extract gave types 1 and 3 reactions in sixteen patients (37%), only seven of whom were among the sixteen (37%) who gave positive precipitin tests.

Raised levels of total serum IgG and IgA were found as compared with healthy controls and asthmatic subjects. No differences were found in total serum IgM and IgD levels.

The high incidence of allergy to *A. fumigatus* in cystic fibrosis is confirmed.

Introduction

Transient pulmonary infiltrations in cystic fibrosis due to allergic aspergillosis were described in two patients by Mearns, Young & Batten (1965). Subsequently Mearns, Longbottom & Batten (1967) reported precipitins against *Aspergillus fumigatus* in 31% of 112 patients with cystic fibrosis and positive prick tests with *A. fumigatus* extract in 39% of eighty-six patients. McCarthy, Pepys & Batten (1969) examined thirty-seven patients with cystic fibrosis for hypersensitivity to *A. fumigatus*. In sixteen out of eighteen patients with positive prick tests, they found dual skin reactions (type 1 and type 3) to intracutaneous testing with *A. fumigatus* extracts. Precipitins against *A. fumigatus* were found in ten patients and surprisingly only in five of those with dual skin reactions. This was unlike allergic broncho-pulmonary aspergillosis where the dual skin reaction is accompanied by positive precipitin tests in more than 90% of cases (McCarthy & Pepys, 1971).

The object of the present study was to confirm the previous observations made on reactions in cystic fibrosis to *A. fumigatus* and by examination of the blood for precipitins against *A. fumigatus*, and assay of total and specific immunoglobulins, to see if the nature of this hypersensitivity could be elucidated. A battery of common allergens were also tested and the findings in cystic fibrosis patients were compared with those in patients with asthma and with allergic broncho-pulmonary aspergillosis.

Materials and methods

Subjects investigated

(1) A group of forty-three patients with cystic fibrosis who attended the Brompton Hospital and Queen Elizabeth's Hospital for Children, Banstead was studied. The clinical diagnosis of cystic fibrosis was confirmed in the patients by a high sweat sodium, i.e. a concentration greater than 90 mEq/l. The ages of the patients studied ranged from 2 to 34 years, and they were both inpatients and outpatients. They were selected by their own, or their parents, agreement to the study and their willingness to attend the hospital for the tests. The study was done from February to September 1971.

A standard questionnaire was used to obtain a history of atopic disease in the patient and their family. This group was compared with two other groups (2 and 3) of cystic fibrosis subjects previously studied.

(2) 112 cystic fibrosis patients investigated by Mearns *et al.*, 1967.

(3) Thirty-seven cystic fibrosis patients investigated by McCarthy *et al.*, 1969.

(4) 1000 asthmatic patients attending the Allergy Clinic at the Brompton Hospital for the first time (Pepys, 1973).

(5) 123 asthmatic patients and an equal number of healthy blood donors with no history of asthma, hay fever or eczema undergoing immunological investigation at the Brompton Hospital (BTTA Asthma Immunology Study, in preparation).

(6) Eighty patients with allergic broncho-pulmonary aspergillosis investigated by McCarthy & Pepys (1971).

Skin tests

Prick tests were made in all of the patients with a control extract and extracts of the following twenty-three allergens: *Alternaria*, *Aspergillus fumigatus*, *A. terreus*, *Cladosporium herbarum*, *Sporobolomyces spp.*, yeasts, *Candida albicans*, *Merulius lacrymans*, grass, shrub and tree pollens, milk, egg, wheat, fish, nuts, cat, dog, hen and horse epidermal extracts, house dust, *Dermatophagoides pteronyssinus* (Beechams Ltd) and *D. farinae* prepared in our own laboratory.

Intracutaneous tests. The concentrations of *A. fumigatus* crude extract and of the protein fraction prepared in our own laboratory, which were used for intracutaneous tests (0.01–0.02 ml) were determined by serial prick tests with concentrations of 0.1, 1.0 and 10 mg/ml respectively. The concentration giving a weal not greater than 3 mm diameter was used for the intracutaneous test. In patients giving negative prick tests the 10 mg/ml concentration was used for the intracutaneous test.

The tests were examined at 30 min for immediate, type 1, wealing reactions and at 4–6 hr for late, type 3, reactions (Pepys, 1968). The latter are usually large, oedematous and poorly defined.

Nasal tests. Intranasal tests were made with one drop of the extracts of *A. fumigatus*,

using the concentration employed for the intracutaneous test. Pricking sensations in the nose, nasal congestion and sneezing were regarded as a positive reaction. If no symptoms occurred with 10 min the test was repeated with the next, higher, concentration. Patients were asked to observe if any symptoms developed after the immediate ones had resolved.

Serological tests. Blood was taken at the initial investigation for the following serological tests.

1. *Precipitin test.* (a) Agar-gel double diffusion (Ouchterlony) tests for precipitins to extracts of *A. fumigatus* containing 10 mg of freeze-dried extract per ml were made as in the previous investigations (McCarthy *et al.*, 1969; Mearns *et al.*, 1967).

(b) *Precipitating antibodies to allergens.* These were measured by the direct radioimmunodiffusion test (direct RID test) as described by Pepys *et al.* (1973a).

(c) *IgG, IgA and IgM antibodies to allergens (specific IgG, IgA and IgM).* These were examined by the indirect radioimmunodiffusion test (indirect RID test) as described by Dolovich *et al.* (1970).

2. *IgE tests.* (a) Total serum IgE was measured by the radioactive, single, radial immunodiffusion method of Rowe (1969). The British Research standard 68/341 was used for reference.

(b) Specific IgE antibodies to *A. fumigatus*, *D. pteronyssinus* and grass pollen were measured by the RAST—radioallergosorbent—test of Wide, Bennich & Johansson (1967).

(c) Total serum IgG, IgA and IgM levels were measured by Tri-partigen immunodiffusion plates (Behringwerke).

(d) Total serum IgD levels were measured by the same method as for total IgE, using the British Research standard 67/37 for reference.

Results

Atopic status

In the group of forty-three cystic fibrosis patients, three had hay fever, four had asthma and one had both and six had nasal polyps. There was a family history of hay fever in three and asthma in two patients.

Table 1. The prevalence of positive prick test reactions to common allergens, asthma, rhinitis, infantile eczema and family history of these in the various groups

		No. of patients	Skin test positive	Infantile eczema	Rhinitis	Asthma	Family history
Asthma (Pepys, 1973)	Group (4)	1000	77%	23%	84%	100%	59%
Allergic broncho-pulmonary aspergillosis (McCarthy & Pepys, 1971)	Group (6)	80	100%	32%	38%	96%	24%
Cystic fibrosis present study	Group (1)	43	70%	0%	7%	10%	7%

Prick test reactions, incidence of asthma, rhinitis and infantile eczema in the patients and their first-degree relatives

Table 1 shows that 70% (thirty/forty-three) of the cystic fibrosis group (1) gave positive type 1 prick test reactions, comparable to the 77% in group (4) consisting of 1000 asthmatic patients. Of these thirty patients, twenty-five gave positive reactions to *A. fumigatus* and sixteen of the latter reacted to other allergens as well. Table 2

Table 2. Skin hypersensitivity in various groups. Prick test positive

		Single	Multiple	Total
Asthma (Pepys, 1973)	Group (4)	14%	63%	77%
Allergic broncho-pulmonary aspergillosis (McCarthy & Pepys, 1971)	Group (6)	12%	88%	100%
Cystic fibrosis (McCarthy <i>et al.</i> , 1969)	Group (3)	16%	41%	57%
Present study	Group (1)	42%	28%	70%

shows that 28% of the cystic fibrosis group (1) gave multiple reactions; the proportions were higher in the asthma group (4) and allergic broncho-pulmonary aspergillosis group (6).

Infantile eczema (Table 1) was absent in the cystic fibrosis group compared with 23% in the asthma group (4) and 32% in the allergic broncho-pulmonary aspergillosis group (6).

Asthma was present in 10% of the cystic fibrosis group (1) and rhinitis in 7%. In the asthma group (4), 84% had rhinitis. In the allergic broncho-pulmonary aspergillosis group (6), 96% had asthma and 38% had rhinitis. The cystic fibrosis group showed an incidence of 7% of positive family history of asthma, rhinitis or infantile eczema as compared with 24% in the allergic broncho-pulmonary aspergillosis group (6) and 59% in the asthma group (4).

Table 3. Skin test and precipitin reactions to *Aspergillus fumigatus*

		No. of patients	Prick tests Immediate	Intracutaneous tests Dual	Precipitins
Asthma	Group (4) (sub-group)	554	13%	—	—
Allergic broncho-pulmonary aspergillosis	Group (6)	80	100%	97%	92%
Cystic fibrosis:					
(Mearns <i>et al.</i> , 1967)	Group (2)	112	39%	n.a.	31%
(McCarthy <i>et al.</i> , 1969)	Group (3)	37	43%	43%	27%
Present study	Group (1)	43	58%	37%	37%

Skin tests and precipitins to A. fumigatus (Table 3)

In the three cystic fibrosis groups, immediate reactions to prick tests with *A. fumigatus* extract were obtained in 39–58% compared with 100% in the allergic bronchopulmonary aspergillosis groups, with 13% in the new asthmatic patients (group 4), and with 2% in a general healthy population (Horn & Gregg, personal communication).

Intracutaneous tests gave dual, immediate and late skin test reactions in 37–43% in two of the cystic fibrosis groups compared with almost all of the allergic bronchopulmonary aspergillosis groups.

Precipitins were present in from 27 to 37% of the cystic fibrosis groups (1, 2 and 3), compared with 7% of a group of asthma patients (Longbottom & Pepys, 1964) and 92% of the allergic broncho-pulmonary aspergillosis group (6).

Comparison of skin tests in cystic fibrosis (group 1) and allergic broncho-pulmonary aspergillosis (group 6) (Table 4)

The allergic broncho-pulmonary aspergillosis group show much higher degrees of sensitivity in that 26% gave dual reactions to prick tests and almost all to intracutaneous tests. In the cystic fibrosis group there were no dual reactions to prick tests, 25% gave only immediate reactions to intracutaneous tests and 37% gave dual reactions.

Table 4. Comparison of prick and intracutaneous testing to *Aspergillus fumigatus* in cystic fibrosis and allergic broncho-pulmonary aspergillosis

		No. of patients	Immediate reactions only	Dual-immediate plus late reactions
<i>Allergic broncho-pulmonary aspergillosis (Group 6)</i>				
	Prick	80	74%	26%
	Intradermal	80	3%	97%
<i>Cystic fibrosis (Group 1)</i>				
	Prick	43	58%	0%
	Intradermal	43	25%	37%

Nasal tests in cystic fibrosis (group 1) and allergic broncho-pulmonary aspergillosis (group 6) (Table 5)

In the allergic broncho-pulmonary aspergillosis group dual reactions were elicited by

Table 5. Nasal provocation testing with *Aspergillus fumigatus* extracts in cystic fibrosis and allergic broncho-pulmonary aspergillosis

		No. of patients	Immediate	Dual
Allergic broncho-pulmonary aspergillosis (McCarthy & Pepys, 1971)	Group (6)	8	12.5%	87.5%
Cystic fibrosis Present study	Group (1)	43	54%	0%

nasal tests in seven out of eight patients, whereas there were only immediate but no late reactions in the forty-three patients of the cystic fibrosis group.

Skin and precipitin test reactions to A. fumigatus in cystic fibrosis (group 1) (Table 6)

In two patients blood for precipitin tests was not obtained. The forty-one remaining cystic fibrosis patients can be divided into six sub-groups. In group (a), ten patients, all the tests were negative and in group (b), four patients, the precipitin test only was

Table 6. Distribution of skin hypersensitivity and precipitins to *Aspergillus fumigatus* in cystic fibrosis (Group 1)

Sub-groups	No. of patients	Skin prick test	Intradermal test		Nasal challenge	Positive precipitins
			Immediate	Late		
a	10	0	0	0	0	0
b	4	0	0	0	0	4
c	6	6	6	0	5	0
d	5	3	5	0	2	5
e	9	9	9	9	9	0
f	7	7	7	7	7	7
Total	41	25	27	16	23	16

positive. In group (c), six patients, immediate reactions only were elicited by skin and nasal tests and the precipitin test was negative. In group (d), five patients, only immediate skin and nasal reactions were elicited and precipitins were present. In group (e), nine patients, dual reactions were elicited in the skin tests, immediate reactions in nasal tests and the precipitin test was negative. In group (f), seven patients, dual skin reactions were elicited, immediate nasal reactions and all had had precipitins. Of the total of sixteen with precipitins to *A. fumigatus*, four had no skin reactions, five had type 1 reactions and seven had dual skin test reactions.

Table 7. Skin hypersensitivity and serum specific IgE to *A. fumigatus* and total IgE levels in cystic fibrosis

Sub-groups	Immediate skin test	Specific IgE mean/counts per minute	Total IgE mean units/ML	No. of positive skin tests to other allergens
a	0	185	85	3
b	0	195	90	2
c	6	430	300	2
d	5	600	840	2
e	9	700	900	7
f	7	500	920	5

Total IgE and specific IgE to A. fumigatus in cystic fibrosis (group 1) (Table 7)

The total IgE levels were higher in group (c), in whom positive skin tests were present than in groups (a) and (b) who were prick test negative. The groups (d)(e)(f) with precipitins or dual skin test reactions or both had higher values than group (c) which had neither.

Mean values for specific IgE antibody to *A. fumigatus* were also higher in groups (d)(e)(f) than in the skin test negative groups (a) and (b) and group (c) which gave only immediate skin test reactions, and had negative precipitin tests.

Prick tests and specific IgE to A. fumigatus, grass pollen and D. pteronyssinus (Table 8)

For *A. fumigatus*, fifteen out of twenty-one positive prick test reactors had counts greater than 300/min, compared with none out of fourteen negative prick test reactors. For *D. pteronyssinus* three out of five positive prick test reactors had counts above 1500/min compared with none out of twenty-seven negative prick test reactors, and

Table 8. RAST (counts per min) for specific IgE antibody to *A. fumigatus*, *D. pteronyssinus* and grass pollen

	No.	< 300 cpm	301 or more	Mean/range		
<i>A. fumigatus</i>						
Prick test—positive	21	6	15	637 (187–1384)		
negative	14	14	0	202 (153–277)		
		< 800 cpm	801–900	901–1500	1501 or more	Mean/range
<i>D. pteronyssinus</i>						
Prick test—positive	5	0	1	1	3	1606 (900–2510)
negative	27	14	8	5	0	809 (595–1263)
		< 800 cpm	801–1200	1201–1500	2000 or more	Mean/range
<i>Grass pollen</i>						
Prick test—positive	9	1	1	0	7	5064 (781–11605)
negative	23	8	8	6	1	1212 (591–7211)

for grass pollen seven out of nine prick test reactors had counts above 2000/min compared with one out of three negative prick test reactors.

The positive prick test reactors to *A. fumigatus*, grass pollen and to *D. pteronyssinus* had higher specific counts per minute respectively in the RAST test than did the negative reactors.

Serum IgG, IgA, IgM and IgD levels

Tables 9 and 10 show that the cystic fibrosis group had higher levels of IgG and IgA than the controls and asthmatic subjects.

There were no significant differences in levels of IgM or IgD (Tables 11 and 12).

Radioimmunoassay (RIA) tests for specific antibody to A. fumigatus (Table 13)

Positive reactions for specific antibody were given by the RID tests with ¹³¹I labelled *A. fumigatus* with a number of sera giving negative precipitin tests by the Ouchterlony method. Of ten negative sera in group (a), the direct RID test gave positive reactions

Table 9. Comparison of immunoglobulin levels in cystic fibrosis, asthmatic and control populations

		No.	Geometric mean IgG mg/100 ml	Serum IgG values	
				s.d. (log ₁₀ value)	'p' value
*Controls	Group (5)	123	1177	0.0876	—
*Asthma	Group (5)	123	1293	0.0887	<0.001
Cystic fibrosis	Group (1)	35	1716	0.1822	<0.001
Present study					

* BTTA Asthma Immunology Study.

Table 10. Serum IgA values

		No.	Geometric mean IgA mg/100 ml	s.d. (log ₁₀ value)	'p' value
*Controls	Group (5)	123	174	0.1652	—
*Asthma	Group (5)	123	208	0.1985	<0.01
Cystic fibrosis	Group (1)	35	258	0.2968	<0.001
Present study					

* BTTA Asthma Immunology Study.

Table 11. Serum IgM values

		No.	Geometric mean IgM mg/100 ml	s.d. (log ₁₀ value)	'p' value
*Controls	Group (5)	123	157	0.1505	—
*Asthma	Group (5)	123	168	0.1742	n.s.
Cystic fibrosis	Group (1)	34	166	0.2112	n.s.
Present study					

* BTTA Asthma Immunology Study.

Table 12. Serum IgD values

		No.	Geometric mean IgD units/ml	s.d. (log ₁₀ value)	'p' value
*Controls	Group (5)	123	15.1	0.3482	—
*Asthma	Group (5)	123	22.8	0.3926	0.01
Cystic fibrosis	Group (1)	35	16.9	0.4534	n.s.
Present study					

* BTTA Asthma Immunology Study (Clinical Allergy, 1975. In Press)

with four. The indirect RID test showed that five had IgG antibody. A total of six positive sera were found. In group (b) all three positive precipitin reactors were positive on direct RID test and two had IgG and 1 IgA antibody. In group (c), three

Table 13. Serum antibodies to *A. fumigatus* in cystic fibrosis patients (Group 1) comparison of radioimmunodiffusion (RID) and double-diffusion tests

Groups	No.	Direct RID	Indirect RID			Gel diffusion	Total positive sera, by all tests
			IgG	IgA	IgM		
a	10	4/10	5/10	0	0	0/10	6
b	4	3/3	2/3	1	0	4/4	4
c	6	2/4	2/4	0	0	0/6	3
d	5	3/5	5/5	1	0	5/5	5
e	9	3/8	2/8	0	0	0/9	4
f	7	6/6	6/6	2	1	7/7	7

out of four sera with negative precipitin tests were positive on direct RID test and two had IgG antibody. In group (d) out of five with positive precipitin tests, three were positive on direct RID test and on indirect RID test all five had IgG and one had IgA antibody. In group (e) of nine sera giving negative precipitin tests, three out of eight tested were positive on direct RID test and two on indirect RID test had IgG antibody. A total of four positive reactions were obtained with both tests. In group (f) out of seven sera giving positive precipitin tests, four out of six tested were positive on direct RID test and all six had IgG antibody on indirect RID test, two had IgA and one had IgM antibody. The indirect RID test was more sensitive than the direct RID test and gave positive reactions with all the sera giving positive precipitin tests and also provided a number of positive reactions with the precipitin negative sera.

Eosinophil count

Six of the cystic fibrosis patients (Group 1) had a blood eosinophilia of more than 500/mm³ at the time of investigation and three of these had a history of asthma.

Discussion

The present investigation confirms previous reports in cystic fibrosis of a high incidence of sensitivity to *A. fumigatus* (Mearns *et al.*, 1967; McCarthy *et al.*, 1969), with 58% giving type 1 prick test reactions as compared with 12% in new asthmatic patients presenting at the Brompton Hospital; 37% gave dual, types 1 plus 3 reactions to intracutaneous tests and 37% gave positive precipitin reactions. There was a high incidence (70%), comparable to that of asthmatics, of type 1 prick test reactions to common allergens. Specific IgE antibodies were found in the RAST test against *A. fumigatus*, *D. pteronyssinus* and grass pollen, corresponding well with the prick test positive reactions, thus confirming that these were mediated by reaginic antibody as in atopic subjects. In 328 healthy children, siblings of children attending mainly for respiratory illness, Horn & Gregg (personal communication) found that 23% gave positive prick test reactions to common allergens. When they excluded those with a positive family history of asthma, rhinitis and infantile eczema, the incidence of

positive skin test reactors fell to about 5%, and of these children 14% had a history of eczema. These skin test findings correspond with those of Curran & Goldman (1961) in their investigation of skin test reactions in the normal population. Multiple positive prick test reactions like those in subjects with moderately high or high atopic status were obtained in 28% of the cystic fibrosis patients. In spite of this enhanced capacity of the cystic fibrosis patients to develop IgE antibody, the incidence of rhinitis and asthma was low. Infantile eczema, an outstanding feature of atopic subjects, was notably absent. There was also a much lower incidence of family history of asthma, rhinitis or infantile eczema in the cystic fibrosis group. The capacity to produce IgE antibody to common allergens in atopic subjects is attributed in part to increased permeability of mucosal membranes (Leskowitz, Salvaggio & Schwartz, 1972), possibly arising from deficiency of secretory IgA antibody which may be only temporary (Taylor *et al.*, 1973; Salvaggio *et al.*, 1973). It may be that the mucosal abnormality of cystic fibrosis may be responsible for penetration of common allergens with the stimulation of IgE antibody by the IgE producing plasma cells, which have been shown by Tada & Ishizaka (1970) to lie in the lymphoid tissues of mucosal membranes. These findings in cystic fibrosis are in favour of mucosal abnormality as being an important and perhaps the main factor responsible for the IgE antibody production to common allergens in atopic subjects. Values for total serum IgE levels were also raised above the usual normal range in the prick test positive subjects as is the case in atopic subjects with multiple sensitivity.

The precipitins against *A. fumigatus* were found by indirect radioimmunodiffusion tests to be mainly in the IgG and also to a lesser extent in the IgA and IgM classes of immunoglobulin. Precipitating antibodies are regarded as responsible for the Type III skin test reactions in allergic broncho-pulmonary aspergillosis. In this disease there is a very close correlation between the precipitins and the presence of reaginic antibody and the production of Type III reactions (McCarthy & Pepys, 1971). There is evidence that the Type I reaction acts as an introductory mechanism for Type III reactions (Cochrane, 1971). In the 37% of cystic fibrosis patients giving Type III skin test reactions, these were preceded in all cases by Type I reactions. They differed however from allergic bronchopulmonary aspergillosis, in that whilst 37% also have precipitins, these did not correspond so closely with the Type III reactions. In five subjects with Type I reactions and precipitins, the Type III reaction was absent. It is possible that a higher dosage of *A. fumigatus* extract may have elicited this reaction. There were however nine subjects with Type I plus III reactions in whom the precipitin test was negative. The mechanism for the Type III reaction in these subjects is not known, though in a previous study (Pepys *et al.*, 1968(a)), immunofluorescent studies of a Type III reaction to *A. fumigatus* extract in a precipitin test negative patient with cystic fibrosis showed the presence of immunoglobulins and β_1C component of complement in the perivascular and vascular tissues. This suggests that precipitins may be present but may not be demonstrable by the tests used. The possibility that the antibodies to *A. fumigatus* demonstrated by radioimmunodiffusion tests on sera giving negative precipitin reactions in the usual double diffusion tests, may be playing a part in the Type III reactions of these subjects has to be considered. More evidence is needed of the immunoglobulin sub-class of these antibodies and of their complement fixing capacity.

There are suggestions that IgE antibody may itself mediate Type III reactions in subjects without demonstrable precipitins to ragweed pollen (Dolovich *et al.*, 1973), because of the absence of complement and immunoglobulins in skin biopsies of such

cases and the presence of eosinophil cells and the production of Type III reactions with anti-IgE serum. The eosinophils are likely however to be evidence of the preceding IgE reaction rather than part of the mechanism responsible for the Type III reaction itself. In the present study direct and indirect radioimmunodiffusion tests showed the presence of IgG, IgA and IgM antibodies in sera giving negative double-diffusion precipitin test reactions. Further search is needed for precipitating and possibly other antibodies in patients giving Type III reactions and negative precipitin tests.

In the Type III reactions to anti-IgE serum described by Dolovich *et al.* (1973) the IgE is acting an antigen and the anti-IgE antibodies are of the precipitating type. It cannot be assumed that such reactions are the same as reactions in which the IgE is participating as antibody.

Nasal provocation tests gave only Type I reactions in the cystic fibrosis patients with and without precipitins, whereas almost all patients with allergic broncho-pulmonary aspergillosis gave dual reactions (McCarthy & Pepys, 1971), indeed the latter subjects also gave dual bronchial reactions. The cystic fibrosis group were not suitable for bronchial tests because of their pulmonary impairment.

Measurements of serum immunoglobulin levels showed a highly significant increase in IgG and IgA in the cystic fibrosis group as compared with controls and asthmatic subjects. There were no differences in the IgM and IgD levels.

To what extent the immunological reactions to *A. fumigatus* demonstrated in these studies contribute to the lung damage in patients with cystic fibrosis with sensitivity to this fungus is not known. Katz & Kniker (1973) have reported the presence of immunoglobulins, complement and aspergillus antigen in the vascular lesions of allergic broncho-pulmonary aspergillosis thus supporting the role of Type III allergy in this disorder. Two of the patients in the present study had been diagnosed as allergic broncho-pulmonary aspergillosis several years before a high sweat sodium was found. Bronchiectatic changes typical of those seen in allergic broncho-pulmonary aspergillosis (Scadding, 1967) have been demonstrated by bronchography in cystic fibrosis (Simon, 1970). Broncho-pulmonary aspergillosis has been observed in five patients with cystic fibrosis (Batten, 1966). The skin reactivity to *A. fumigatus* would imply that allergic broncho-pulmonary aspergillosis can be a serious problem in cystic fibrosis but the lack of late reactions on challenge of the respiratory tract and frequent absence of precipitins in these patients may mean either that the hypersensitivity is not often significant in the lungs or that other immunological mechanisms than those thought to be operative in allergic broncho-pulmonary aspergillosis are present.

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