Cystic fibrosis, atopy, and airways lability

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SUMMARY In a survey of cystic fibrosis (CF) in the Avon area, 48 children with CF from 40 families together with 71 of their parents were studied by spirometry, exercise tests, and pinch tests. A control group of 42 young adults was similarly tested; control data for children were taken from previously published work. The prevalence of atopy (any positive prick test) in children with CF was 48%. Sensitivity to grass pollens and house dust mite was no more common in these children (29%) than in a normal population (34%). Hypersensitivity to *Aspergillus fumigatus* was found in 35% of children with CF and was associated with severe lung disease. The parents had a normal pattern and prevalence of atopy. Exercise-induced airways obstruction was present in only 22% of children with CF; its association with severe lung disease rendered interpretation difficult. The parents had a normal response to exercise. Both hypersensitivity to *A. fumigatus* and exercise-induced airways lability had the features of acquired characteristics. There was nothing in the present study to support the hypothesis that the possession of a CF gene predisposed to atopy.

The prevalence and importance of allergic disease in children with cystic fibrosis (CF) is a topic of dispute. Some studies have shown a high prevalence of allergic (or atopic) respiratory disease (Warren *et al.*, 1975; Warner *et al.*, 1976a), whereas others have failed to show any difference in prevalence between children with CF and normal children (Kulczycki *et al.*, 1961; Rachelefsky *et al.*, 1974). Likewise, it has been suggested by some that atopic hypersensitivity in CF is associated with severe lung disease (Warner *et al.*, 1976a), and by others, with relatively mild lung disease (Rachelefsky *et al.*, 1974).

Similarly, the prevalence of allergic disease in the parents of children with CF has varied in different studies. Some workers have found an association between atopy and the CF gene (McFarlane and Allan, 1976; Warner *et al.*, 1976b), while the evidence of others seems to contradict this (Counahan and Mearns, 1975). Many studies have been based on data collected at specialist referral centres, patients attending such centres being highly selected and unrepresentative of the total population of patients with CF.

We studied prospectively, the families of children with CF living within a defined geographical area. As well as measuring lung function and atopic hypersensitivity, we assessed airways lability in the children and their parents.

Subjects and methods

Children with CF currently living within the Avon area were traced through their records at the Royal Hospital for Sick Children and Southmead Hospital, Bristol. 40 of 42 families approached (48 children and 71 parents) agreed to take part in the study (Table 1). Six single-parent families and 3 parents who refused to co-operate accounted for the missing parents. 42 medical students acted as controls. No subject had received any bronchodilator, anti-histamine, or antiasthma drug on the test day.

After a history had been recorded for each subject, peak expiratory flow rate (PEFR) was measured using a Wright peak-flow meter, and a forced expiratory spirogram, for calculating forced expiratory volume in one second (FEV₁), maximum mid-expiratory flow rate (MMFR), and forced vital capacity (FVC), was recorded using a Vitalograph spirometer. Normal values for lung function for

Table 1 Subjects

	CF children	Parents	Adult controls
Total no.	48	71	42
Mean age (years)	7.6	36	22
Sex (M/F)	24/24	32/39	28/14
Tests			
pulmonary function	42	69	42
exercise	36	68	42
prick tests	48	71	42

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children were taken from Godfrey *et al.* (1970) and Cogswell *et al.* (1975), and for adults from Cotes (1975). Not all the children were old enough to perform lung function tests, or the exercise tests which followed (Table 1); heart disease and advanced pregnancy were reasons for some of the parents not completing all the investigations.

Exercise testing consisted of continuous running for 6 min on a treadmill set at a speed and slope calculated to produce a final heart rate of about 170/min (Silverman and Anderson, 1972). PEFR (the best of 3 attempts on each occasion) was recorded before, during, and for 20 min after exercise. Pulse rate was counted at the end of exercise. Two indices of airways liability were calculated: (1) the rise in PEFR during exercise (% of the initial value), and (2) the fall in PEFR after exercise (% of the initial resting value). The values of these indices in 60 normal children were obtained from Anderson (1972).

Prick (intracutaneous) tests were performed on the forearm, by a standard technique (Pepys, 1975), using the following 10 Bencard extracts of common antigens: *Dermatophagoides pteronyssinus*, mixed grasses, *Cladosporium*, *Alternaria*, *Aspergillus fumigatus*, *Candida* species, milk, egg, cat, and dog. A weal of more than 2 mm at 15 min was accepted as positive, in the absence of any reaction to the control solution. In the present study atopy is defined as the manifestation of immediate hypersensitivity to at least one of the antigens tested. The prevalence of atopy in normal children was obtained from Godfrey and Griffiths (1976).

For each child with CF, a recent chest x-ray was inspected by one of us (I.R.S.G.) without knowledge of any other result, and assessed according to the system of Chrispin and Norman (1974), to give the x-ray score. The higher the score, the worse the disease.

Approval for the study was obtained from the Bristol Health District Ethical Committee.

Results were analysed by χ^2 tests (including Yates's correction for small numbers) or by *t* tests for unpaired samples (Swinscow, 1977).

Results

Atopy. The prevalence of atopy (as defined above) of 48% (Table 2) was higher in children with CF than in normal schoolchildren, but the difference was not significant ($\chi^2 = 3.49$; $0.1 > P > 0.05$). Considering only hypersensitivity to *D. pteronyssinus* and grass pollens, 29% of CF children were atopic and the distribution of hypersensitivity to these 2 agents was not significantly different from the value of 34% in normal children (Godfrey and Griffiths,

Table 2 Prevalence of atopy

	Children		Adults	
	CF	Controls*	Parents	Controls
No. tested	48	303	71	42
Overall prevalence (%)	48	34	34	40
Sensitive to (%)				
<i>D. pteronyssinus</i>	13	26	20	26
Mixed grasses	25	24	18	26
<i>A. fumigatus</i>	35	—	0	0

*From Godfrey and Griffiths (1976).

1976). Among the parents, neither the overall prevalence of atopy nor the distribution of hypersensitivity was significantly different from that in normal adult controls (Table 2). Nor was there any association between atopy in the children with CF and in their parents ($\chi^2 = 0.38$; $P > 0.5$).

However 35% of CF children showed immediate hypersensitivity to *A. fumigatus* extract. The prevalence of hypersensitivity to *Aspergillus* appeared to increase with age up to 12 years, in contrast to the relatively stable prevalence of immediate hypersensitivity to other allergens (Figure). There were too few children in the 13–16 age group to draw any conclusions on the prevalence of *Aspergillus* sensitivity in the oldest children.

When the total population of children with CF was divided into 3 groups according to atopic status (Table 3), several differences became apparent. The *Aspergillus* hypersensitive group was significantly older than the others, and respiratory disease, assessed radiologically or by means of lung function tests, was significantly worse in children with

Figure Changing prevalence of hypersensitivity with age in children with cystic fibrosis.

Aspergillus hypersensitivity than in the other 2 groups. When the age difference between the *Aspergillus* hypersensitive group and the other 2 groups was eliminated by age-matching, the *Aspergillus* hypersensitive patients still had significantly higher mean scores in their chest x-rays and lower mean PEFR and MMFR. An association was found between hypersensitivity to *A. fumigatus* and hypersensitivity to other allergens ($\chi^2 = 4.31$; $P < 0.05$), suggesting that hypersensitivity to *A. fumigatus* was more likely to be found in an otherwise atopic patient than in an otherwise nonatopic patient.

The nonatopic CF children and the group sensitive to allergens other than *A. fumigatus* were similar in respect to their mean ages, x-ray scores, and PEFRs. However the nonatopic patients had a lower mean MMFR ($t = 2.5$; $P < 0.05$), implying more severe airways obstruction.

Airways[†] lability. Exercise-induced airways lability (Table 4) was no more severe in CF children or their parents than in controls and there was no association between airways lability in CF children and their parents ($\chi^2 = 0.32$; $P < 0.5$).

Although numbers were small, the children with higher airways lability (fall in PEFR after exercise of greater than 10%) appeared to have a greater

prevalence of hypersensitivity to *A. fumigatus* than did those children with normal airways lability (Table 5), as well as a lower MMFR ($t = 3.69$; $P < 0.02$). The prevalence of hypersensitivity to allergens other than *A. fumigatus* was similar in the 2 groups.

The parents of CF children taking similar exercise to the control adults, had a lower mean heart rate at the end of exercise than did the control subjects ($t = 2.2$; $P < 0.05$). This difference (8 beats/min) may be explained by the difference in mean ages of the 2 groups, as the mean maximum heart rate at 36 years (187 beats/min) is 9 beats/min less than at 22 (Astrand and Rodahl, 1970).

Discussion

Atopy and CF. The association between CF and allergic disorders of the respiratory tract has been a topic of discussion for many years. Largely retrospective studies suggested an incidence of respiratory tract allergy of 10–14%, little different from normal (Abbott *et al.*, 1951; Van Metre *et al.*, 1960). Later studies which used skin testing to define allergy gave a higher prevalence of 17–24% (Kulczycki *et al.*, 1961; Rachelefsky *et al.*, 1974). Recently, studies which included tests for hypersensitivity to *A. fumigatus*, have given prevalence rates for atopy of 56–77% (Allan *et al.*, 1975; Counahan and Mearns, 1975; Warren *et al.*, 1975; Warner *et al.*, 1976a).

In the present study the relatively high prevalence of atopy in children with CF was not due to hypersensitivity to the common allergens *D. pteronyssinus* and grass pollen (the 'normal' pattern of atopic hypersensitivity), as the children were no more frequently sensitive to these allergens than were normal schoolchildren (Godfrey and Griffiths, 1976). In fact, the data of Warren *et al.* (1975) and Warner *et al.* (1976a) contain very similar figures for mite and pollen hypersensitivity in CF, but this information is disguised by the high prevalence of *Aspergillus*

Table 3 Clinical features in relation to atopy and *Aspergillus* hypersensitivity in CF children

	Nonatopic	Atopic	
		Sensitive to <i>A. fumigatus</i> ($\pm$ other allergens)	Sensitive to other allergens only
No.	25	17	6
Age (years)	6.5 (4.3)	9.8 (3.9)	6.2 (3.4)
Chest x-ray score	5.9 (4.2)	10.3 (6.5)	5.8 (3.7)
PEFR (% predicted)	102 (24)	68 (21)	105 (33)
MMFR (% predicted)	56 (18)	35 (24)	84 (29)

Mean values $\pm$ 1 SD.

Table 4 Exercise-induced airways lability

	Children	Adults	
	CF	Controls*	Parents Controls
No.	36	60	67 42
PEFR before exercise (% predicted)	90 (25)	97 (14)	102 (15) 96 (11)
Rise in PEFR during exercise (%)	9.0 (9.3)	8.2 (5.4)	7.6 (5.4) 6.0 (3.5)
Fall in PEFR after exercise (%)	6.4 (9.3)	3.5 (5.4)	4.3 (5.7) 4.5 (3.4)
Heart rate at end of exercise (per min)	170 (14)	172 (—)	166 (14) 174 (15)

Mean values $\pm$ 1 SD.

*From Anderson (1972).

Table 5 Clinical features in relation to exercise-induced airways lability in CF children

	Airways lability	
	Normal	High†
No.	28	8
Age (years)*	8.5 (4.3)	8.8 (3.6)
Chest x-ray score*	7.3 (4.2)	8.1 (6.3)
PEFR (% predicted)*	92 (23)	76 (29)
MMFR (% predicted)*	62 (27)	30 (15)
Sensitive to <i>A. fumigatus</i>	10 (36%)	5 (63%)
Other allergens	10 (36%)	2 (25%)

*Mean value $\pm$ SD.

†Fall in PEFR of over 10% after exercise.

hypersensitivity. Thus homozygosity for the CF gene was not associated with atopic hypersensitivity of the 'normal' pattern either in the present study, or in the studies of Warner *et al.* (1976a). Similarly, in the present study, the parents of children with CF were no more frequently atopic than a group of normal young adults (Table 2). We thus found no evidence to support the hypothesis put forward by Warner *et al.* (1976b) that heterozygosity for the CF gene was associated with atopy. There are two reasons to suspect that the study of Warner *et al.* (1976b) gave misleading results. Firstly, Warner *et al.* relied for adult controls on self-selected friends of CF parents, only 25 of whom were actually skin-tested, leaving much room for bias. Secondly, their study was carried out at a specialist referral centre with a highly selected group of CF patients, unrepresentative of CF patients and their families in general.

Hypersensitivity to *A. fumigatus* was numerically important in the present study and was clearly associated with severe lung disease (Table 3). Its prevalence appeared to increase with age, up to 13 years (Figure), in contrast to the normal prevalence of 'normal pattern' atopy which was affected little by age. These observations suggest that hypersensitivity to *A. fumigatus* may be secondary to lung disease, although it would appear that atopic children with CF are more likely to acquire hypersensitivity to *A. fumigatus* than are nonatopic children. (This is not surprising, as Warren *et al.* (1975) showed that immediate hypersensitivity to *A. fumigatus* in CF is mediated by IgE.) The suggestion of Warner *et al.* (1976a) that allergy in CF is associated with severe chest disease is probably an over simplification, since they do not distinguish between allergy to commonly sensitising antigens and allergy to *A. fumigatus*.

Although numbers were small, it would appear that the CF children with the best overall clinical condition were those who were atopic but who had *not yet* developed hypersensitivity to *A. fumigatus* (Table 3). This association between 'allergy' (Van Metre *et al.*, 1960), or atopy (Rachelefsky *et al.*, 1974), and relatively mild CF has previously been noted. However, it cannot be concluded that atopic CF children have a better long-term prognosis than do nonatopic CF children, because it would appear that the atopic group are more likely eventually to develop *A. fumigatus* hypersensitivity and, by association, severe lung disease. A longitudinal study of CF in children would be necessary to demonstrate this.

Airways lability in cystic fibrosis. Airways obstruction in CF is largely fixed in character. A small and

variable response has been shown to sympathomimetic drugs (Featherby *et al.*, 1970; Zapletal *et al.*, 1971; Landau and Phelan, 1973), particularly when the effort-independent indices have been measured. In response to exercise, many children with CF have been reported to develop airways obstruction (Day and Mearns, 1973; Counahan and Mearns, 1975). A fall in PEFr of greater than 10% after a standard treadmill running test has been considered to indicate abnormal degree of lability (Silverman and Anderson, 1972), and by this criterion 8 (22%) out of 36 CF children in the present study were abnormal. This is somewhat less than the 40% reported by Counahan and Mearns (1975) using an identical test. Using a free-range running test, known to provoke greater fall in PEFr than treadmill running (Anderson *et al.*, 1971), Day and Mearns (1973) demonstrated significant airways lability after exercise in 46% of their patients. The bias introduced by these workers studying patients at a referral centre could account for the difference from the present study. The figure of 22% of abnormally labile CF children may reflect the true situation in relatively unselected patients.

In asthmatic children the severity of exercise determines the degree of subsequent airways lability (Silverman and Anderson, 1972). In the present study the target heart rate of 170/min may have been produced by less energy expenditure in the more severely affected patients. This may have produced a lower prevalence of airways lability than would have been found had fixed work loads been used.

The present study confirms the observations of Day and Mearns (1973) that those children with apparently greater airways lability had more severe lung disease. Since the fall in PEFr after exercise is expressed as a proportion of the initial value, it could be argued that in those CF children who initially had severe airways obstruction (hence a low PEFr), a relatively small fall in PEFr after exercise would produce a spuriously high value for exercise-induced airways obstruction. However, in asthmatic children, exercise-induced asthma has been shown to be independent of the severity of airways obstruction in individual subjects (Silverman, 1973). If this applies also to children with CF then the association between airways lability and severe lung disease was a real phenomenon. If it does not apply, the prevalence of exercise-induced airways lability in CF would have been even lower than the 22% found here. It is not known which alternative is correct and it is therefore unhelpful to try to identify exercise-induced airways lability in individual CF children who have significant airways obstruction at rest.

As noted by Jones (1975) in his comment on the paper of Counahan and Mearns (1975), the rise in

PEFR during exercise is greater when the initial PEFr is low. There is therefore no useful information to be gained by studying the rise in PEFr during exercise. However, an estimate of airways lability in CF patients who have little airways obstruction at rest may help in understanding their disability, and may occasionally permit the rational trial of bronchodilator drugs.

Conclusions

There was no association between the 'normal' pattern of atopy and the possession of a CF gene either by children with CF or their parents. Hypersensitivity to *A. fumigatus* was common in CF children and was associated with severe lung disease. The precise relationship between severe lung disease and hypersensitivity to *A. fumigatus* remains to be elucidated by detailed prospective studies. However, the importance of *A. fumigatus* sensitivity seems likely to increase as patients with CF survive longer, and these patients may be at risk of developing allergic bronchopulmonary aspergillosis. Early recognition of this difficult condition may be aided by prior knowledge of the atopic status of CF children, since *Aspergillus* hypersensitivity is more likely to develop in a previously atopic child.

In a condition such as CF in which a history of wheezing may be of little help in the recognition of coexisting asthma, the exercise test, a simple and reliable method of demonstrating airways lability, may be of help in management, although there are difficulties in the interpretation of exercise-test results in patients with severe airways obstruction.

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