Prevalence of exercise-induced bronchial lability in families of children with asthma

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König, P., and Godfrey, S. (1973). *Archives of Disease in Childhood*, 48, 513. **Prevalence of exercise-induced bronchial lability in families of children with asthma.** Exercise tests and skin tests were performed in 65 members of the families of 12 children with asthma. A positive response to skin and exercise challenge frequently, but not invariably, occurred together.

Abnormal exercise-induced bronchial lability was found in 33% of relatives with a past history of asthma, in 40% of those with hay fever, and in 32% of the clinically healthy relatives. The subjects with active asthma chiefly had a tendency to bronchoconstriction, while the other labile subjects chiefly had a tendency to bronchodilatation.

The total proportion of all subjects affected by clinically evident atopic diseases, positive skin tests, or increased bronchial lability was 85%. The importance of using a challenge test to detect a hidden tendency for asthma in family studies is discussed.

A high incidence of atopic disease, and particularly asthma, has frequently been reported in families of patients with asthma (Adkinson, 1920; Cooke and Vander Veer, 1916; Spain and Cooke, 1924; Schwartz, 1952; Van Arsdel and Motulsky, 1959; Leigh and Marley, 1967). In some of these studies comparisons were made between the families of asthmatic patients and the families of subjects not suffering from asthma, from the point of view of clinically manifest asthma or other atopic diseases. In another approach, Parker, Bilbo, and Reed (1965) used inhalation of methacholine to show that some asymptomatic sibs of patients with asthma could develop abnormal bronchoconstriction.

It is now well established that asthmatic patients develop bronchoconstriction after running, even if they are asymptomatic at the time (Jones, Buston, and Wharton, 1962; Jones and Jones, 1966; Connolly and Godfrey, 1970). In addition, this type of exercise-induced bronchial lability has been found in children who suffered from wheezy bronchitis in the past but did not develop clinical asthma (König, Godfrey, and Abrahamov, 1972). It was therefore decided to study the families of asthmatic children to see if there was an abnormal incidence of bronchial lability among the relatives.

Subjects and methods

The *propositi* were 12 unrelated children suffering from asthma as defined by Scadding (1966), who were attending the Paediatric Asthma Clinic of this hospital. The members of their 12 families were studied, including the *propositi* themselves and their first-degree relatives (parents and sibs). The total number of subjects was 65, but this did not include all possible subjects because 8 adults and 1 child were either unable or unwilling to attend for investigation. This meant that 88% of all members of the 12 families were studied, but 4 out of the 9 subjects who were not studied were known to have active asthma from previous records. The subjects were classified in groups as listed in Table I, which were based on the replies to a standard questionnaire about atopic diseases in the subject and his family. A subject was considered healthy if he gave no history, after careful, detailed questioning to supplement the replies in his questionnaire, of having suffered from wheezing or any atopic diseases at any time in his life. If the subject admitted to more than one condition, the most recently active was used for the classification.

Allergic investigation was carried out by prick tests with 24 common allergens in every subject.

The exercise test consisted of continuous running for 6 minutes on a treadmill at a speed and slope which would result in a heart rate of about 170 beats per minute (Connolly and Godfrey, 1970). Peak expiratory flow rate (PEF) was measured with a Wright Peak Flow Meter before, during, and for 15 minutes after the

TABLE I
Prevalence of abnormal bronchial lability and positive skin tests in different groups

	No.	Normal lability	Abnormal lability	Skin test negative	Skin test positive
Propositi	12	2 (17)	10 (83)	0 (0)	12 (100)
Total relatives	53	35 (66)	18 (34)	21 (40)	32 (60)
Relatives with active asthma	8	4 (50)	4 (50)	1 (12)	7 (88)
Relatives with past history of asthma	6	4 (67)	3 (33)	1 (17)	5 (83)
Relatives with hay fever	10	6 (60)	4 (40)	1 (10)	9 (90)
Relatives with eczema	4	4 (100)	0 (0)	3 (75)	1 (25)
Healthy relatives	25	17 (68)	8 (32)	15 (60)	10 (40)
Total subjects	65	37 (57)	28 (43)	21 (32)	44 (68)

Note: Percentage in parentheses.

running. At that stage, a bronchodilator aerosol (salbutamol) was given and a further one-minute run was performed to produce maximum bronchodilatation. The expected values for the PEF were taken from Godfrey, Kamburoff, and Nairn (1970) for children and from Cotes (1968) for adults. The following indices were calculated.

$$\text{Resting PEF \%} = \frac{\text{Initial PEF}}{\text{Expected PEF}} \times 100$$

$$\% \text{ Rise} = \frac{\text{Highest PEF during exercise} - \text{Initial PEF}}{\text{Initial PEF}} \times 100$$

$$\% \text{ Fall} = \frac{\text{Initial PEF} - \text{Lowest PEF after exercise}}{\text{Initial PEF}} \times 100$$

$$\text{Exercise Lability Index (ELI)} = \frac{\text{Highest PEF during exercise} - \text{Lowest PEF after exercise}}{\text{Initial PEF}} \times 100$$

$$\text{Jones Lability Index (JLI, Jones, 1966)} = \frac{\text{Highest PEF during exercise or after bronchodilator} - \text{Lowest PEF}}{\text{Expected PEF}} \times 100$$

The upper limit of normal (mean + 2 SD) for the indices was taken from the work of Silverman and Anderson (1972). The bronchial lability was considered abnormal if either the Jones Lability Index or the Exercise Lability Index was above 22%.

Results

A high incidence of abnormality was found in the relatives, and one family tree is illustrated in Fig. 1. In fact, in those 7 families where both parents were studied, skin tests were positive in 50% of parents and 81% of children, while exercise tests were positive in 36% of parents and 59% of children.

Evidence of atopy as judged by positive skin tests was found in 68% of all the subjects (Table I). All the asthmatic propositi had at least one skin test positive and almost every one had positive tests to more than two allergens. Of the 53 relatives

studied, 15% were actively asthmatic and of these 88% had at least one skin test positive. Another 11% of relatives had a history of asthma in the past and of these 83% had positive skin tests. In the group of relatives with hay fever or allergic rhinitis (19% of the total relatives) skin tests were positive in

FIG. 1.—Prevalence of clinical atopic disease plus exercise-induced bronchial lability in the K family. (Numbers give the ages in years.)

TABLE II

Mean values for exercise lability and average number of positive skin tests per subject in different groups

		Resting PEF (%)	% Rise	% Fall	Exercise Lability Index	Jones Lability Index	No. of positive skin tests per subject
Propositi no. = 12	Mean	82	17	39	55	44	4.8
	SEM	6	4	6	7	5	0.7
All relatives no. = 53	Mean	97	11	8	20	20	1.9
	SEM	2	1	1	7	1	0.3
Relatives with active asthma no. = 8	Mean	90	15	18	33	30	3.8
	SEM	6	3	6	6	5	0.8
Relatives with past history of asthma no. = 6	Mean	89	10	7	17	16	3.2
	SEM	8	3	3	4	3	0.9
Relatives with hay fever no. = 10	Mean	107	13	8	21	22	3.7
	SEM	3	2	3	3	2	0.9
Relatives with eczema no. = 4	Mean	103	7	4	12	13	0.3
	SEM	3	2	2	1	2	0.3
Healthy relatives no. = 25	Mean	97	10	7	17	17	0.6
	SEM	2	2	1	2	2	0.2

90% of cases, and in the relatives with eczema (8% of the total relatives) skin tests were positive in 25% of cases.

There were 47% of the total relatives who were unaffected by asthma or atopic symptoms and skin tests were positive in 40% of these subjects. The number of positive skin tests on average per subject was significantly lower in the healthy relatives and in those with eczema than in the other groups (Table II).

Evidence of abnormal bronchial lability as judged by a positive exercise test was found in 43% of all the subjects (Table I). The highest incidence of abnormal lability was found in the asthmatic group (70% of the combined propositi and actively asthmatic relatives), but there was a very significant incidence among relatives with a past history of asthma (33%), hay fever (40%), and even among the healthy relatives (32%), but not in the relatives with eczema, though there were only 4 subjects in this group.

The exercise-induced bronchial lability of the propositi was much more severe than that of the relatives with active asthma (Table II). The difference between the ELI for the two groups was highly significant ($0.005 > P > 0.001$).

Likewise, the relatives with active asthma had a higher mean lability than those with a history of asthma ($0.05 > P > 0.025$), but there was no difference between the mean lability of the relatives with a history of asthma and either those with hay fever or the healthy relatives. The group of relatives with eczema alone had a normal response

to exercise, but the number of subjects was too small to draw meaningful conclusions.

The results in the present group of healthy relatives can be compared with those from groups of normal children and adults studied in this department (Anderson, 1972; Silverman and Anderson, 1972). The present group of healthy children (not evidently asthmatic or atopic) had a higher mean ELI ($0.01 > P > 0.005$) and JLI ($0.02 > P > 0.05$) than the other normal group; for the adults, the difference between the present group and the other normal adults was not significant either for the ELI ($0.2 > P > 0.1$) or for the JLI ($0.1 > P > 0.05$).

A further analysis was made of the response to exercise in those subjects with an abnormal total

TABLE III

Sex distribution of positive skin tests and exercise results

	Male	Female
<i>Skin tests</i>		
All negative	9	12
1 positive	7	3
2 positive	2	5
More than 2 positive	20	7
Total	38	27
<i>Exercise lability</i>		
<22%	20	17
22-40%	7	9
>40%	11	1
Total	38	27

FIG. 2.—Patterns of exercise liability in subjects with an abnormal response to exercise.

liability (i.e. > 22%). It was found that the liability in the subjects with active asthma (propositi and relatives) was due mainly to the fall in PEF after exercise, while in the other labile subjects it was mainly due to bronchodilatation during exercise or after a bronchodilator (Fig. 2, Table II). Thus the % Rise was equal or bigger than % Fall in only 36% of the active asthmatics, but in 71% of the other labile subjects.

The sex distribution of positive skin tests and exercise results is given in Table III. Males heavily predominated in the groups with multiple positive skin tests and high exercise-induced bronchial liability. The relation between skin testing and exercise liability is shown in Table IV.

The abnormal exercise liability was accompanied by at least one positive skin test in 75% of subjects, but in 7 subjects with abnormal exercise liability the skin tests were negative. From the opposite point of view, among the subjects with positive skin tests, 48% had an abnormal bronchial liability.

Discussion

This study has shown that an abnormal exercise-induced bronchial liability can be found in a high

TABLE IV

Relation between skin testing and exercise liability

	Skin test* positive	Skin test negative
Exercise† positive	21	7
Exercise negative	23	14

*At least one skin test positive.

†Exercise liability or liability index > 22%.

proportion of first-degree relatives of asthmatic children.

The fact that some subjects with a history of asthma or wheezy bronchitis in the past still have abnormal responses to exercise has been noted in other studies (Jones and Jones, 1966; Blackhall, 1970; König *et al.*, 1972). The proportion of abnormal responses in subjects with hay fever in this study (40%) compares very closely with the results of Jones (1966) who found such responses in 6 out of 13 cases (46%).

The most striking finding of the present study was that 32% of apparently healthy relatives had an increased exercise liability. Parker *et al.* (1965), using a methacholine challenge test, found an asthmatic response in only 16% of the healthy sibs and they also found a much lower proportion (10%) of abnormal responses in patients with hay fever. In their study, 90% of the children and all of the adults with asthma had an asthmatic response.

The fact that only 70% of the asthmatics in our study had a pathological liability is in accordance with the results of Silverman and Anderson (1972) who found that on a single exercise test on the treadmill about 75% of known asthmatics give positive results. This percentage can be increased to between 90 to 100% by repeating the treadmill exercise on another occasion, and particularly by using free range rather than uphill treadmill running.

Two of the asthmatics in the present study, who on this occasion had normal responses to exercise, had previously responded with abnormal liability. These results were not included in the present study, because tests were not repeated on other members of family.

One of the interesting findings of the present study was that in cases with a pathological bronchial liability the % Rise was equal to or larger than the % Fall in most subjects without active asthma, while in active asthmatics the % Fall was greater in most cases. This pattern of bronchial liability was very similar to the finding of König *et al.* (1972) who

compared a group of children with active asthma with a group of children with a past history of wheezy bronchitis, but who had been symptom free for several years. In this study the % Rise was larger than the % Fall in 78% of the subjects with a past history of wheezy bronchitis, but in only 48% of subjects with asthma. A rather similar pattern of more dilatation than constriction was recently found in a group of children with cystic fibrosis studied by Day and Mearns (1973). Thus, though the non-asthmatic subject may have labile bronchi, it appears to be mainly an ability to dilate and not to constrict. Since resting PEF values of 90% or so are unlikely to be associated with symptoms, such patients do not have clinical asthma.

The results of the present study could be interpreted as giving support to the hypothesis that bronchial lability is an inherited characteristic which must combine with a triggering mechanism to result in clinical asthma. There was clearly a high incidence of lability among the members of the families of the asthmatics, but only those subjects whose lability was manifest predominantly by constriction had clinical asthma. We have no definite evidence on the nature of the triggering mechanism which caused these subjects to constrict, but one obvious suggestion is IgE-mediated allergy. This need not be the case with every patient because the asthmatic type of exercise response is also seen in skin test negative subjects (Silverman and Turner-Warwick, 1972). The fact that even in the families of asthmatics, 60% of subjects with positive skin tests had normal lability and no asthma, supports the idea that one must inherit more than atopy alone to be an asthmatic. To carry this hypothesis a little further, we might speculate that the broncho-constrictor element of inherited lability might be temporarily switched on by virus infection in those infants who develop wheezy bronchitis. After recovery, they revert to the less constricting type of lability. Of course, persistent or repeated viral infections could be another mechanism of triggering the constrictor type of lability resulting in childhood asthma.

Whether the subjects with no clinical asthma but with an increased exercise-induced bronchial lability will eventually develop asthma is not known, but an interesting hint was given when a comparison was made with groups of normal adults and children selected from the population at large. The fact that the present group of healthy childhood relatives of asthmatics had a significantly higher lability than the general population of normal children, while in adults the difference was not significant, could mean that by adulthood some of these labile children may

develop asthma or hay fever and would no longer be classified as 'healthy'.

The overall incidence of abnormality found in the present study is very high but is similar in some respects to previously published data. Thus, 26% of first-degree relatives in the present series had asthma compared to 26% found by Leigh and Marley (1967). Hay fever occurred in 19% of relatives in the present study and 20% of those reported by Leigh and Marley (1967). The incidence of wheezing among sibs was higher in the present study (58%) compared with the 29% found by Williams and McNicol (1969).

We know of no family studies of bronchial lability shown by exercise testing.

We were unable to study control groups in the present investigation because of the practical difficulties of inducing whole families to exercise. However, there are some data in the literature with which our findings can be compared. Spain and Cooke (1924) found asthma or hay fever in 7% of their normal control group, while Williams and McNicol (1969) found that 11% of all children aged 10 years had had some asthmatic episodes. In their control group of normal children 15% had a history of wheezing in sibs. Likewise, Leigh and Marley (1967) described asthma in 3% of the first-degree relatives of their control group, hay fever or vasomotor rhinitis in 16%, and eczema in 12%.

The total proportion of clinically evident cases of atopic diseases among the relatives (52%), together with the number of relatives with an increased bronchial lability but without clinical disease, gave a total of affected relatives of 68%. If those with positive skin tests are included, this rises to 81%, and if the *propositi* are added, the total proportion of all subjects affected rises to 85%. This incidence of abnormality in the families of asthmatics is much higher than that found in studies based solely on clinically evident diseases.

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