

Exercise-induced bronchoconstriction, skin sensitivity, and serum IgE in children with eczema

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Price, J. F., Cogswell, J. J., Joseph, M. C., and Cochrane, G. M. (1976). *Archives of Disease in Childhood*, **51**, 912. **Exercise-induced bronchoconstriction, skin sensitivity, and serum IgE in children with eczema.** Forty-two children with eczema were studied for exercise-induced asthma (EIA), skin sensitivity to prick testing, blood eosinophil count, and immunoglobulins. 29 had a fall in peak expiratory flow rate after exercise greater than 20% and of these, 23 had symptoms of wheezing. 13 of the eczematous children showed a fall of less than 20%. The children with EIA showed greater cutaneous sensitivity ($P < 0.001$) and a higher total serum IgE ($P < 0.025$). 3 of the group with a fall of less than 20% had allergic rhinitis with skin sensitivity to grass pollen. The remaining 10 had no clinical evidence of allergic disease, other than eczema and skin sensitivity, and total IgE fell within the normal range. It is suggested that in a proportion of children with eczema there is little evidence of reaginic allergy.

Bronchoconstriction after exercise is a physiological characteristic which helps to distinguish asthmatic children from normals (Jones, Buston, and Wharton, 1962). Abnormal bronchial lability has also been shown in adults (Jones and Jones, 1966) and in children with a past history of wheezing (König, Godfrey, and Abrahamov, 1972). Asthma and eczema are commonly associated in individuals and families (Edgren, 1943; Stifter, 1965). These conditions, together with allergic rhinitis, urticaria, and certain food allergies, have become grouped under the heading 'atopy', though when the term was originally conceived (Coca and Cooke, 1923) infantile eczema was regarded separately. Atopic subjects typically show the capacity to synthesize IgE reaginic antibody, and show skin sensitivity to one or several common allergens.

High levels of total and specific IgE have been observed in patients with atopic eczema (Juhlin *et al.*, 1969; Ogawa, *et al.*, 1971; Stone, Muller, and Gleich, 1973; Johnson *et al.*, 1974; Hoffman *et al.*, 1975). Many of the patients in these studies also had clinical evidence of wheezing. The purpose of this study was to investigate the incidence of exercise-induced asthma (EIA) in a group of children with eczema, and to examine the relation between EIA, skin sensitivity, and total IgE.

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Patients

Ninety children were invited by a letter to their parents to take part in the study, and 42 were studied with parental consent. A paediatric dermatologist's diagnosis of atopic eczema and an age range between 5 and 14 were the only two criteria for selection. Mean age of the 42 children (24 males, 18 females) was 9 years. The diagnosis of atopic eczema was made on clinical grounds; a personal or family history of atopy, flexural distribution, and severe pruritus with lichenification. A further 15 children (12 males, 3 female) who were sibs of the eczematous patients were also studied and their ages ranged from 5-13 years (mean 9 years).

Method

The children attended the Respiratory Function Laboratory for about 2 hours when the following were carried out. (1) A clinical history and examination. (2) Physiological tests of ventilation before and after exercise challenge. (3) Prick tests to determine skin sensitivities to 23 common allergens. (4) Venous blood samples taken for blood eosinophil count and serum immunoglobulins.

The studies were carried out during July to October 1974, in a constant hospital environment. No observations were made of airborne allergens or local weather conditions.

Clinical evaluation. One of us (J.J.C.), independently of the other observers, carried out a full history and examination using a standard questionnaire.

A history from the patient of a periodic wheeze or breathlessness was accepted as a positive history of asthma. Clinical quantification (mild, moderate, severe) of the skin lesions was made. None of the children was receiving systemic steroids, and none had been given bronchodilator therapy for 6 hours or antihistamines for 24 hours before the study. No child had been given hyposensitization immunotherapy during the year before the study.

Physiological assessment. A standard exercise test was performed by all children (Connolly and Godfrey, 1970) of running down a flat hospital corridor for 6 minutes at a speed sufficient to produce a pulse rate of 170/min. Peak expiratory flow rate (PEFR) was measured each minute with a Wright Peak Flow Meter before, during, and for 15 minutes after running. At that stage a bronchodilator aerosol (200 µg salbutamol) was given and a further one-minute run performed to produce maximal dilatation. The expected values for PEFR were taken from Godfrey, Kamburoff, and Nairn (1970).

The results are expressed as % fall in PEFR calculated:

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

In the presentation of the data the normal range for EIA was taken from the work of Silverman and Anderson (1972).

Skin tests. Skin sensitivity was assessed using the prick test with 23 common allergens. Standard test solutions were used (manufactured by Bencard, Beecham Group Ltd.). The presence of a wheal of 3 mm in diameter at 15 minutes was regarded as a positive reaction. In one case a 2 mm wheal reaction occurred to the control solution and there a 5 mm wheal was taken as positive.

Serum immunoglobulins. Sera were separated at room temperature and stored at -70°C until tested. Serum IgA, IgG, and IgM were measured by radial immunodiffusion. Serum IgE levels were measured by using Phadebas Radioimmunosorbent Test Kits. Standard curves were generated using an IgE standard calibrated against the World Health Organization, British Research Standard for Human Serum Immunoglobulin E 68/341. Duplicate assays were set up simultaneously for all samples and standards. The test was repeated if there was a variation $>2\%$ from the mean of the percentage binding of the duplicates. Results were expressed as units (IU) relative to the reference standard. All unknown serum samples were diluted ten times with buffer before assay. Correction was made for serum factor interferences by multiplying the Mean Count Rate of the Zeros (MRCO) by a factor of 0.96. The count rate for each of the unknown sera was expressed as a percentage of this serum factor

corrected MRCO. The method is then regarded as being accurate over the range 10–4000 IU IgE/ml, with a coefficient of variation in our hands of 15%.

Analysis. The means of the indices for the different groups were compared by Student's 't' test. Differences were considered significant when $P < 0.05$.

Results

The 42 children with eczema were divided into two clinical groups comprising 23 children with a history of present and past wheezing, and 19 in whom there was no history of respiratory symptoms. The physiological response to exercise in the two clinical groups is shown in Fig. 1. Children with

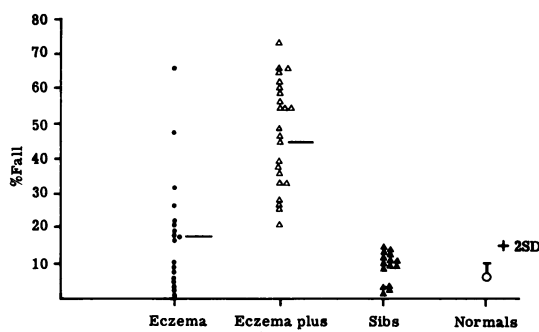


FIG. 1.—Percentage fall in peak expiratory flow-rate (PEFR) after exercise of 19 children with a history of eczema only and 23 with a history of wheezing past or present. The normal range is taken from Silverman and Anderson (1972).

a history of asthma showed a mean fall in PEFR of 47% (21–74%). The 19 nonwheezy eczematous children showed a lower mean of 17% but a wide range (0–66%). 10 had a fall in PEFR greater than 11%, the upper limit of normal quoted for EIA (Silverman and Anderson, 1972). 9 sibs showed borderline responses.

Using the physiological data it was decided to divide the eczematous children into 3 groups, those with a per cent fall in PEFR after exercise $<20\%$ (group 1), between 20 and 40% (group 2), and $>40\%$ (group 3) (Fig. 2). An upper limit of normal of 20% fall in PEFR was chosen arbitrarily, as this would comprise a group with indisputable abnormal broncholability. 13 of the 19 children with eczema only had a fall $<20\%$ in PEFR, while all children with both eczema and respiratory symptoms had a fall of at least 20%.

The age distribution (Table I), morphology, and distribution of skin lesions, and family history of atopic disorders was similar in the three groups.

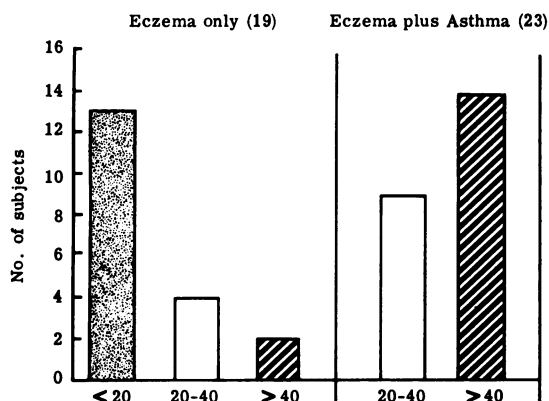


FIG. 2.—Histogram showing the number of subjects in each clinical group with a % fall in PEFR after exercise of <20%, 20–40%, or >40%.

However, those children with a fall of >40% tended to have the earliest age of onset, and to be the least severely affected by their eczema (Table II).

A comparison was made of skin sensitivity, serum total IgE, and eosinophil counts in the three groups. The results of the relative skin sensitivities are shown in Fig. 3. Skin tests were not completed in one child who had a percentage fall in PEFR of 55%. The children in group 1 had significantly fewer positive skin tests than those in groups 2 and 3 ($P < 0.001$). A 3 mm or greater wheal in re-

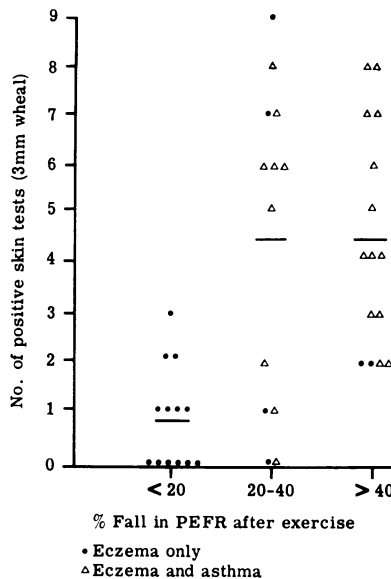


FIG. 3.—Total number of positive skin tests related to % fall in PEFR after exercise.

sponse to *Dermatophagoides pteronyssinus* or *D. farinae* occurred in only one child in group 1 but was seen in 10 out of the 15 tested in group 3 (Table III).

The total blood eosinophil count per mm³ showed considerable overlap in all three groups (Table IV).

TABLE I

Age distribution of children with eczema after division into the groups defined by the fall in PEFR after exercise

Group	% Fall in PEFR on exercise	No.	Sex M:F	Mean age (yr)	Age range (yr)
1	<20	13	4:9	9.4	6–12
2	20–40	13	8:5	8.7	5–14
3	>40	16	12:4	10.0	5–13

TABLE II

Clinical data relating the age of onset of eczema and severity of eczema to the three groups defined by fall in PEFR after exercise

Group	Age of onset of eczema (yr)			Severity of eczema			
	0–1	1–5	5	0	+	++	+++
(1) <20% fall in PEFR on exercise (n=13)	7	5	1	1	5	4	3
(2) 20–40% fall in PEFR on exercise (n=13)	9	3	1	1	7	3	2
(3) >40% fall in PEFR on exercise (n=16)	13	2	1	3	4	9	0

TABLE III
Skin reaction to *D. pteronyssinus* or *D. farinae*

No.	% Fall in PEFR	Skin reaction to house mite (wheal diameter)		
		3 mm-5 mm	5 mm-10 mm	Total
13	<20	0	1	1
13	20-40	4	4	8
15	>40	5	5	10

TABLE IV
Mean blood eosinophil count related to the fall in PEFR after exercise

No.	% Fall in PEFR	Eosinophils/mm ³ (mean ± SD)	No. with count >350/mm ³
12	<20	262 ± 66	3
12	20-40	465 ± 91	7
15	>40	654 ± 127	11

However, there was a significant difference between the means in group 1 and group 3 ($P < 0.02$), and the means of groups 2 and 3 were outside the normal range quoted by Horn *et al.* (1975). The eosinophil count was not measured in 3 children.

The children all had normal levels of IgG and IgM and there was no difference among the three groups. One child in group 1 had IgA deficiency. Total IgA tended to be lower in the group with normal broncholability.

The results for total IgE are shown in Fig. 4. IgE is plotted on a log scale. The mean for each group is indicated. The normal range is based upon the figures quoted for Berg and Johansson by Havnen *et al.* (1973). Levels >600 IU/ml were considered to be high for children over the age of 5 years, i.e. >2 SD from the mean. Results achieved with the Phadebas IgE test have been shown to be comparable with those obtained with the radioimmunosorbent technique used by Berg and Johansson (Havnen *et al.*, 1973). All 13 children in group 1 had total serum IgE levels within the normal range. 6 in group 2 and 10 in group 3 had levels >600 IU/ml. Group 1 is significantly different from group 2 ($P < 0.025$) and group 3 ($P < 0.005$).

Discussion

This study has confirmed that eczematous children with a history of wheezing have exercise-induced asthma which distinguishes them from normals (Silverman and Anderson, 1972). The children with eczema as the only symptom showed a mixed physiological response to exercise, 9 of the

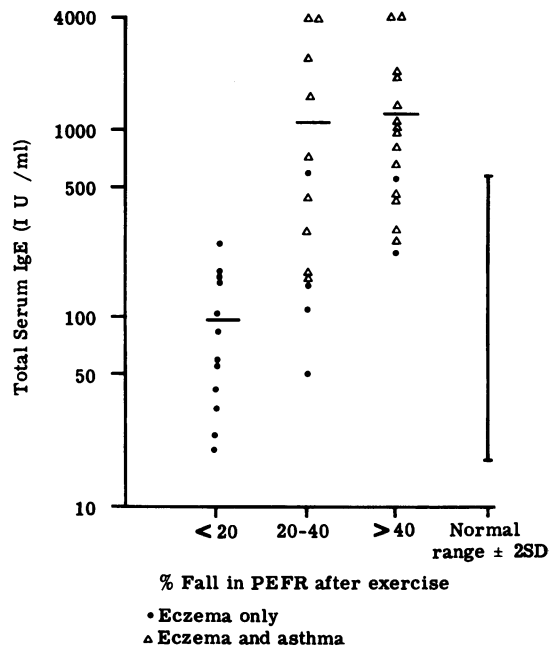


FIG. 4.—Total IgE related to % fall in PEFR after exercise. IgE levels are expressed in IU/ml on a log scale. The bars indicate the mean in each group. Normal values are taken from Berg and Johansson.

19 with a normal response, 10 out of 19 showing a percentage fall of greater than 11%, and 6 of them showing a clearly asthmatic response to exercise with a percentage fall of greater than 20%. The

clinical severity of the eczema was not necessarily related to the presence of, or degree of, bronchoconstriction and in 3 of the 5 children graded as having severe eczema there was no EIA.

The effect of exercise in increasing airways resistance in asthmatics is well documented (Jones *et al.*, 1962; McNeill *et al.*, 1966; Fitch and Morton, 1971). Increased airways resistance after exercise has also been shown in nonasthmatic relatives of asthmatic children (König and Godfrey, 1973) and in children with a past history of wheezy bronchitis (König *et al.*, 1972). In an epidemiological study of 817 12-year-old children, Burr, Eldridge and Borysiewicz (1974) found that children with a history of wheezing showed a fall in PEFR on exercise, while children with other atopic disorders showed something of the same tendency though their percentage fall in PEFR after exercise overlapped those of the control group. The results of the present study showed a similar overlap. Whether children with eczema and abnormal bronchial lability will eventually develop symptoms attributable to asthma is not yet known, but it is of interest that 2 children in group 2 have attended paediatricians with asthmatic symptoms since the study was carried out. However, it is not possible to say whether these children have developed asthma or are now aware of the mechanism of their previous symptoms, but the impression is that before the study their bronchial lability was not severe enough to lead to symptoms.

The study has shown that eczematous children with a bronchial response to exercise of less than a 20% fall in PEFR have normal serum IgE levels (<600 IU/ml). Significantly higher levels of IgE were found in those children with increased bronchial lability. Other workers have also found that serum IgE levels are highest in those children who have two or more atopic disorders together (Havnen *et al.*, 1973; Wood and Oliver, 1972; Berg and Johansson, 1969).

Some patients with atopic eczema as the only symptom have been reported to have very high serum IgE concentrations (Juhlin *et al.*, 1969). This has not been our experience in this study except in one eczematous child who showed an abnormal physiological response to exercise. In those children with a history of wheezing attacks the majority, but not all, had serum IgE levels above the normal range (600 IU/ml).

We have shown that eczematous children who show abnormal bronchial lability have a greater number of hypersensitivity reactions to common allergens on skin testing. House mite sensitivity

was greatest in the group with the most labile bronchial reactions to exercise. In view of our findings of high IgE levels in the abnormally labile group, the skin testing results are not expected since a relation between skin sensitivities and IgE levels in atopic subjects has been established (Wood and Oliver, 1972; Havnen *et al.*, 1973). Eosinophil counts tended to be higher in those eczematous children with the most labile bronchi but there was considerable overlap in all three physiological groups. It has recently been suggested that in adults 350 eosinophils/mm³ is the upper limit of normal (Horn *et al.*, 1975) and it is of interest that the majority of overtly wheezy children had counts above this level. In the group of children with a fall in PEFR of less than 20% in response to exercise 3 had an eosinophil count > 350 eosinophils/mm³ but 2 of these had symptoms of allergic rhinitis. 29 of our 42 children had a fall in PEFR greater than 20% after exercise. This group with clearly abnormal bronchial responses were also characterized by increased cutaneous sensitizations and high serum IgE levels.

Our data indicate that the majority of children with eczema who present at a dermatology clinic will have a history of wheezing, a high eosinophil count, a high IgE level, a number of skin sensitivities, and exercise-linked asthma. In the majority of our eczematous patients there is a predisposition to develop asthma and an interdependent inheritance is suggested. However, 13 eczematous children showed no evidence of EIA. 3 of these gave a history of allergic rhinitis and showed a positive skin reaction to grass pollen. The remaining 10 children, with a morphologically identical dermatitis gave no history of allergic disease other than eczema, had little skin sensitivity and normal levels of IgE. It may be that eczema and bronchial lability are inherited independently but in the majority of patients both occur and only in a minority is eczema inherited alone. Thus patients with eczema and no evidence of EIA, normal levels of IgE, and lack of skin sensitivity may well constitute a separate group with a different pathophysiological mechanism for their eczema; or eczema in all patients is not associated with reaginic allergy but the raised IgE levels and skin sensitivity found in the majority of patients with eczema is dependent on the tendency for combined inheritance of asthma and eczema.

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