

The Reproducibility of Skin Prick Tests in Childhood Asthma

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ABSTRACT

Thirty-eight children with chronic perennial asthma were skin prick tested with extracts of 17 common allergens at least once a year for a mean of 7 years. All had multiple responses, the response to house dust extract being positive in 95% of all the skin testing sessions. Over the whole follow-up period, the house dust response was consistently positive in 33 of the 38 children and positive in greater than 85% of sessions in 3 more. Consistent responses were noted to other major allergens though in less children. The mean wheal size reaction of the house dust extract and the mean number of skin prick test positive responses increased with age, reaching their peak near the end of puberty, a period of time when bronchial hyperresponsiveness is known to decrease. This study would support the suggestion that differing populations of mast cells in connective tissue and mucosae might account for the different patterns of response that occur in man.

INTRODUCTION

An association between immediate whealing skin reactions and asthma has been recognised for many years,⁽¹⁾ with a close relationship in children.⁽²⁻⁴⁾ For a number of allergens, good correlation has been shown between positive skin prick tests and specific and total IgE,^(5,6) the wheal size correlating well with the amount of total IgE and to the response to bronchial challenge with antigen.⁽⁷⁾ However, skin prick test reproducibility was questioned by Herxheimer et al.⁽⁸⁾ They reported that only 3 subjects of 21 had identical reactions when tested on different occasions, although close study of their results shows that reactions to the most potent of their test materials, horse dander, were reproduced in 8 of the 10 subjects reported. Barbee et al.⁽⁹⁾ were in no doubt that skin prick testing was a highly reproducible test procedure. They showed that more than 95% of 1389 subjects were consistently either negative or positive when skin prick tested with identical concentrations of Bermuda

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grass and more than 90% of 2443 subjects were consistently either negative or positive with repeated testing 1 year later.

During the course of a long-term prospective follow-up of asthmatic children,⁽¹⁰⁾ regular skin prick tests were performed. This report concerns the reproducibility of positive responses and the relationship between skin reactivity and the clinical progress of the disease.

SUBJECTS AND METHODS

Thirty-eight children were skin prick tested at least once a year for a mean 7 years (1.2 – 10.9 years) in a prospective study designed to follow the course of the disease throughout childhood and puberty.⁽¹⁰⁾ Their mean age of entry to the study was 8.7 years (3.9 – 13.8 years), and their mean age at the end was 15.7 years (10.9 – 20.0 years).

Skin prick testing was carried out on the volar aspect of one forearm with 22 common antigens and control solutions (Bencard, Brentford Middlesex) by the modified skin prick test described by Pepys.⁽¹¹⁾ Over the study period, only two people other than the author were involved in skin testing. On reviewing the individual tests over the years of follow-up, five extracts — *Alternaria*, *Cladosporium*, *Aspergillus terreus*, nuts, and fish, — were not consistently available and have been dropped from this study. The remaining 17 antigens used every 6 months were house dust extract, *Dermatophagoides farinae* (10 mg/ml), mixed grass pollen, shrub pollen, tree pollen, cat fur, horse hair, dog hair, rabbit hair, feathers, milk, egg, cereal, shellfish, *Aspergillus fumigatus*, *Candida*, and *Merulius lacrymans* (dryrot).

Immediate (type 1) reactions were recorded at 15 min and were graded as follows: 0 = no wheal; 1+ wheal = 1 – <3 mm; 2+ wheal = 3 – <5 mm; 3+ wheal = 5 – <7 mm; 4+ wheal = 7 mm or more.

The classification of puberty into five stages by Tanner⁽¹²⁾ has been used in this study.

The Fisher-Yates analysis of variance by ranks was used to compare the 17 antigen skin prick test positive responses. Regression lines were calculated by the method of least squares, and Student's *t*-test was used for differences between the means.

RESULTS

All 38 children in this study had multiple immediate skin prick test reactions in the 336 skin testing sessions carried out during the 7 years of follow-up. House dust extract was significantly more frequently positive ($p < 0.001$) than the house dust mite extract, and both were significantly more frequently positive ($p < 0.001$) than any other allergen tested (Table 1). The remaining reactions were grouped into clusters showing significant differences between clusters.

Throughout the many years of follow-up, 33 of the 38 patients had a consistently positive response to the house dust prick test (Table 2). Three more were positive in over 85% of sessions, and even the 2 remaining patients had many prick test positive responses, one having an 83% reproducibility with a mean wheal score of 1.8+ and the other a 72.8% reproducibility with a mean wheal score of 2.1+. Only slightly less constant were the house dust mite results; 24 patients had consistently positive responses and 9 were positive in over 85% of sessions. The 33 patients with a reproducibility of over 85% to the house dust mite prick test were the same 33 patients who showed a 100% reproducibility to the house dust prick test. The 5 patient not achieving 100% reproducibility to the house dust prick test did not have a reproducible house dust mite prick test. In addition, Table 2 emphasizes that other major allergens could be consistently positive, such as grass pollen, cat fur, and horse hair, and there were significant specific allergens for individual children, for example, dog hair, tree pollen, milk, and *Aspergillus fumigatus*.

The remaining allergens tested (feathers, shrub pollen, rabbit hair, cereal, *Candida*, shellfish and dry rot) were all noted to be weakly positive at times, but the pattern was capricious and inconsistent.

Since the house dust prick test was positive in 95% of all skin testing sessions, it was possible to

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TABLE I. FREQUENCY AND MEAN WHEAL SIZE SCORE OF SKIN PRICK TEST POSITIVE RESPONSES OBTAINED TO EACH ALLERGEN IN ALL SKIN TESTING SESSIONS PERFORMED THROUGHOUT PERIOD OF FOLLOW-UP

<i>Allergen</i>	<i>Frequency of skin prick test positive responses</i>	<i>Mean wheal size score</i>
House dust	95%	2.6 +
House dust mite	87%	2.7 +
Cat fur	67%	2.2 +
Horse hair	66%	1.9 +
Grass	59%	2.5 +
Dog hair	43%	1.6 +
Tree	24%	1.6 +
Shrub	22%	1.4 +
Feather	20%	1.4 +
Milk	20%	1.5 +
Rabbit	18%	1.4 +
<i>Aspergillus fumigatus</i>	17%	1.4 +
Egg	12%	1.5 +
Cereal	9%	1.6 +
<i>Candida</i>	9%	1.2 +
Shellfish	5%	1.3 +
Dry rot	4%	1.0 +

The frequency in each row is greater ($p < 0.001$) than that in the row below.

observe any change that occurred in the degree of reactivity over the long period of follow-up. A gradual rise in the size of the mean skin wheal reaction occurred throughout the whole period, leveling off at stage 4 and 5 of puberty (Fig. 1). A regression line fitted to these results gave a highly significant correlation ($r = 0.8076$, $p < 0.01$).

A gradual rise in the mean number of skin prick test responses was also observed over the long period of follow-up, leveling off at stage 4 and 5 of puberty (Fig. 2). A regression line fitted to these results gave a highly significant correlation ($r = 0.8164$, $p < 0.01$).

DISCUSSION

In this study of a select group of chronic perennial childhood asthmatics, every child had multiple positive responses to a standard set of skin prick tests when regularly tested throughout the long period of follow-up. Some allergens showed a high degree of reproducibility. Skin prick tests have been shown to be highly reproducible over the period of 1 year,⁽⁹⁾ and this study has extended this time to a mean 7 years.

Voorhorst et al.⁽¹³⁾ first suggested that the house dust mite was the principal allergen in house

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TABLE 2. NUMBER OF PATIENTS WITH CONSISTENT SKIN PRICK TEST POSITIVE RESPONSE IN 100%, AND OVER 85%, OF SKIN TESTING SESSIONS PERFORMED THROUGHOUT PERIOD OF FOLLOW-UP

Allergen	Strong constant reaction				Mild constant reaction			
	Patients with 100% reproducibility	Mean wheal size score	Patients with 85% reproducibility	Mean wheal size score	Patients with 100% reproducibility	Mean wheal size score	Patients with 85% reproducibility	Mean wheal size score
House dust	31	2.7+	1	2.1+	2	1.8+	2	1.8+
House dust mite	23	2.8+	9	2.6+	1	1.8+		
Grass	10	2.5+	4	3.2+	1	1.8+		
Cat fur	13	2.5+	3	2.5+	1	1.8+	1	1.9+
Horse hair	5	2.6+	2	2.5+			2	1.7+
Dog hair	1	2.4+						
Milk							2	1.5+
Tree					1	1.5+		
<i>Aspergillus fumigatus</i>							1	1.9+

Strong constant reaction: Mean wheal size score $> 2+$ (3–5 mm).

Mild constant reaction: Mean wheal size score $< 2+$.

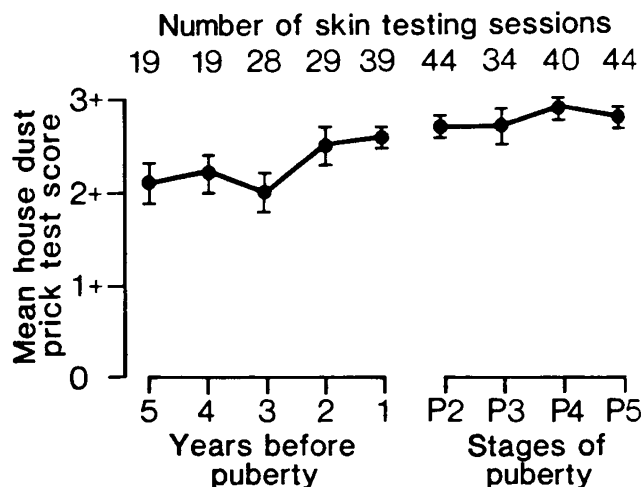


FIG. 1. The mean wheal size scores for the house dust prick test ($\pm$ SE) in the 36 children who reached puberty.

dust, and since then it has been shown to be one of the commonest allergens in Europe to which asthmatic patients are sensitized.⁽¹⁴⁾ Morrison Smith et al.⁽¹⁵⁾ found an 85% incidence of skin prick test positive reactions to *D. farinae* in 302 childhood asthmatics, and Sarsfield⁽¹⁶⁾ found an 84% incidence to *D. pteronyssinus* skin prick tests in 133 childhood asthmatics. This present study not only supports these results but shows their remarkable reproducibility. Thirty-three of the 38 patients had a consistently positive response to the house dust prick test, and the remaining 5 patients almost achieved this. It is of interest to note that it was only in these 5 patients that the house dust mite response was not reproducible. Presumably positive house dust reactions in these patients reflected

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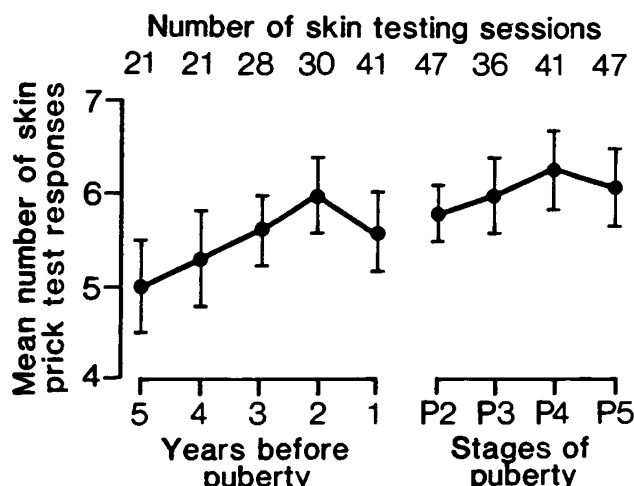


FIG. 2. The mean number of skin prick test responses ($\pm$ SE) for the 36 children who reached puberty.

the presence of other allergens in the house dust extract, which were less reactive and more unpredictable. Similarly, other common allergens, mixed grass pollens, cat fur, horse and dog hair, showed remarkable reproducibility, with the individual child showing a milder though still highly reproducible reaction to tree pollen, milk, and *A. fumigatus*. Positive reactions were seen occasionally with all other allergens tested, but none showed reproducibility.

The skin prick test can suffer from a poor standardization of allergen extracts, in both composition⁽¹⁷⁾ and concentration.⁽¹⁸⁾ Even so, the results were thought to be valid, since extracts from a single laboratory (Bencard) have always been used, and by having sufficient tests repeated on each patient over the long period of follow-up, within-patient and patient-to-patient variation should be eliminated.⁽¹⁹⁾

Constant exposure to allergens appeared to cause a gradual increase in skin reactivity, which was presumably independent of its effect on the lung. Pearson⁽²⁰⁾ found that sensitivity to inhalant substances was at its greatest in subjects between 15 and 30 years, and Morrison Smith⁽²⁾ supported this when he studied the size of positive prick tests in children before and after 5 years of age. He noted a tendency for the reaction to increase with time. This phenomenon was demonstrated even more clearly in this study. Both the number of skin prick test positive responses and the house dust prick test wheal size gradually increased as puberty approached and continued to rise as puberty progressed, a period of time when it has been shown that asthma improved in this same group of children.⁽¹⁰⁾

Hill et al.,⁽²¹⁾ in noting an improvement in their childhood asthmatics over a 5-year follow-up period, observed that this coincided with a fall in the levels of both IgE and IgG house dust mite antibodies. They concluded that the overall improvement in asthma resulted from a diminished clinical and immunological responsiveness to the house dust mite. However, this present study also demonstrated an increase in skin reactivity with age. This could be due to the nonspecific responsiveness of the skin either affecting mediator release from connective tissue mast cells or the response of the skin to those mediators. But if this were so, it would occur at a time when it was known that the nonspecific hyperresponsiveness in the bronchioles had decreased. In fact, during puberty, when the house dust prick test response was at its most flamboyant, exercise-induced asthma was shown to disappear in this same group of children as they became symptom free.⁽²²⁾ A more intriguing explanation arises from recent evidence suggesting that, in rodents, mast cells found in connective tissue differ from mast cells in the mucosae morphologically, histochemically, biochemically, and pharmacologically.⁽²³⁾ Although a heterogeneity of mast cell function has so far not been demonstrated in man,⁽²⁴⁾ it is tempting to speculate that this might account for the apparent paradox noted in this study, whereas constant exposure to a perennial allergen, such as the house dust mite, was associated

both with a progressive increase in skin reactivity and a gradual reduction in bronchial hyperresponsiveness.

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