An analysis of skin prick test reactions in 656 asthmatic patients

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Hendrick, D. J., Davies, R. J., D'Souza, M. F., and Pepys, J. (1975). Thorax, 30, 2-8. An analysis of skin prick test reactions in 656 asthmatic patients. Of 656 asthmatic patients referred specifically for allergy assessments, 544 (84%) gave positive immediate skin prick tests to at least one of 22 common allergens used routinely. Comparison of these skin test positive patients with the 102 (16%) who were skin test negative showed a number of significant differences. The majority of the skin test positive patients (52%) were less than 10 years old at the time of onset of the asthma, whereas, of the skin test negative patients, 56% were aged over 30 years at the time of onset. Seventy per cent reported rhinitis compared with 48% of the skin test negative patients, and 29% reported infantile eczema compared with 9%. Symptoms attributed to house dust, pollens, and animals were noted two to three times more frequently by the skin test positive patients, while corticosteroid drugs had been used more commonly by the skin test negative patients (45% compared with 35%).

No significant differences were observed with the other factors studied, namely, history of urticaria or angio-oedema, family history of 'allergic' disease, and awareness of sensitivity to foods, aspirin or penicillin.

Prick test reactions in the skin test positive patients were most commonly seen to house dust or the acarine mite, *Dermatophagoides farinae* (82%), followed by pollens (66%), animal danders (38%), foods (16%), *Aspergillus fumigatus* (16%), and other moulds (21%). There was a highly significant association of positive history with positive prick test for all allergens studied.

Although the association between immediate wealing skin reactions and asthma has been recognized for many years (Coca and Cooke, 1923), the specificity of these tests, their relation to aetiology, and their clinical significance has been in dispute. Rackemann (1947) suggested that the presence of positive skin reactions on routine prick testing with common inhalant and food allergens should place the asthmatic into the extrinsic (allergic) category where usually the onset of symptoms is early in life and the prognosis more favourable than in the intrinsic (non-allergic) category (Rackemann and Edwards, 1952; Rackemann, 1958).

Raised serum IgE levels have been found in

63% of allergic asthmatics compared to only 5% of intrinsic asthmatics (Johansson, 1967), and a good correlation has been demonstrated between the number of positive skin reactions to a routine number of allergens and the total amount of serum IgE (Stenius, Wide, and Seymour, 1972). Further, the weal size of the individual skin prick tests has been shown to correlate well with the amount of specific serum IgE for that allergen (Stenius *et al.*, 1971).

Close correlations have also been demonstrated for a number of allergens between the clinical history, skin prick tests, serum levels of specific IgE, and bronchial provocation tests (Pepys, Chan, and Hargreave, 1968; McAllen, Assem, and Maunsell, 1970; Stenius *et al.*, 1971). In some cases the combination of a positive clinical history with a positive skin prick test has shown an even closer correlation with bronchial provocation

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tests than has the serum level of specific IgE (Aas and Johansson, 1971). The clinical history and the results of skin prick tests may therefore be of considerable value in determining aetiological factors in asthma.

The purpose of this investigation was to compare allergic and other factors in two categories of asthmatic patients distinguished by the presence or absence of positive immediate skin prick tests, and to study the relationship between the presence of positive prick tests and the history of provocation by the appropriate allergens.

MATERIALS AND METHODS

PATIENTS The 656 patients were selected at random from those attending the clinical immunology outpatient department of the Brompton Hospital between 1969 and 1971. They had been referred by general practitioners, by other departments of the Brompton Hospital, and by other hospitals or chest clinics. The data were recorded on standardized questionnaires during the course of routine clinical assessment. The results were transferred to punch cards from which the analysis was made.

The patients were classified according to age at onset—group 1 <10 years, group 2 10–30 years, group 3 >30 years. There were 365 males and 301 females.

HISTORY The diagnosis of asthma was accepted if there was a history of intermittent wheezing. In most cases reversible airways obstruction had been observed by the referring physician. The occurrence of other 'allergic' disease was similarly accepted from the history alone if the major clinical characteristics were described, namely, weeping, pruritic eruptions of the flexures within the first 12 months of life for infantile eczema; recurrent episodes of undue sneezing, nasal discharge or blockage for rhinitis; pruritic wealing eruptions for urticaria; and acute swelling of the face, lips, tongue or throat for angio-oedema.

A positive family history was recorded if at least one first-degree relative (parent, sibling or child) had asthma, rhinitis, infantile eczema, urticaria or angio-oedema.

The use at any time of corticosteroid drugs in the management of the asthma was also noted.

The capacity of specific allergens to provoke symptoms was assessed from the history by a physician of the department before the skin tests were carried out.

SKIN PRICK TESTS These tests were carried out with a series of 22 routine allergens or allergen groups which fell into five classes:

1. House dust
Dermatophagoides farinae, 10 mg/ml; house dust
2. Pollens
Grasses (B2); shrubs (B1); trees (B3)

3. Animal danders
Cat; dog; feathers; horse
4. Foods
Egg; fish; milk; nuts; wheat
5. Moulds
Alternaria; *Aspergillus fumigatus*; *Aspergillus terreus*; *Candida*; *Cladosporium herbarum*; *Merulius lacrymans*; *Sporobolomyces*; yeast
Controls
Carbol/saline; Gaine's dog meal; yeast.

All the allergens were prepared by Bencards Limited apart from the cat, dog, and horse extracts, which were obtained from Dome Limited, and *D. farinae*, which was made up in the Brompton laboratory (Stenius *et al.*, 1971). Separate controls of Gaine's dog meal and yeast were used with this allergen as these constituted the media on which the mite was grown. *Dermatophagoides pteronyssinus*, which is chiefly responsible for the allergenicity of house dust in the UK, is less readily cultured, and extracts for skin tests were not readily available for routine use at the time of this study. Prick tests with extracts of *D. farinae*, however, have been shown to give comparable results (Pepys *et al.*, 1968), and so this species was used as the source of *Dermatophagoides* allergen.

The volar aspect of one forearm was used but the skin at the edges, the wrist, and the antecubital fossa was avoided. The 22 routine prick tests together with controls were arranged in three rows in a standard order, the site of each test being marked by Biro. A gauge 25 needle (Gillette size No. 17) held at 45° to the surface, bevel downwards, was pressed vertically and gently through a drop of test extract so that its point penetrated the epidermis and, on withdrawal, raised the skin. This method rarely drew blood. If it did, the test was repeated. A separate needle was used for each test. The distal row was prepared and tested first, followed by middle and proximal rows, thus avoiding smearing. When all the tests were completed absorbent tissue was carefully applied to remove the residual extract, and the sleeve was rolled down to keep the arm warm. The patient was instructed not to scratch, and the tests were read after 10 to 20 minutes.

A positive immediate (type 1) reaction was taken to be present when there was a measurable weal of 1 mm or more, surrounded by a flare in the absence of any equivalent reaction in the control test. Small weals were confirmed by palpation. A flare alone was disregarded. In cases of doubt, individual tests were repeated in triplicate. Reactions in patients with dermatographism were not included unless individual weal sizes were at least twice that of the control.

Patients were not tested if they had had any anti-histamine drugs within the preceding 48 hours. Sodium cromoglycate, corticosteroids, catecholamines, and methylxanthines were not considered to be a bar to testing.

STATISTICS The χ^2 test was used for all statistical comparisons.

RESULTS

Of the 656 patients in the series, 554 (84%) gave positive immediate prick test reactions to at least one of the 22 routine common allergens. There was no immediate skin reactivity in the remaining 102 (16%). There was a marked difference in the distribution according to age at onset of the asthma between skin test positive and skin test negative patients (Fig. 1). The relative proportions of skin test positive to skin test negative patients in each age group are shown in Figure 2.

FIG. 1. Distribution of 656 asthmatic patients according to skin prick test reactivity and age at onset.

FIG. 2. Relative proportions of skin test positive to skin test negative patients in each age group.

HISTORY Table I shows the prevalences of other 'allergic' diseases, positive family history, previous use of corticosteroids, and possible provoking factors in both skin test positive and skin test

negative patients. Rhinitis and eczema were significantly more common in the skin test positive subjects, as were histories of provocation by house dust, pollens, and animals ($P<0.001$). The use of corticosteroids before presentation was more common in the skin test negative patients ($P<0.05$). There were no significant differences with respect to urticaria or angio-oedema, family history of 'allergic' diseases or histories of provocation by foods, aspirin, and penicillin.

TABLE I
HISTORY

	Skin Test Positive		Skin Test Negative	
	No. 554	% 100	No. 102	% 100
Other 'allergic' diseases				
Rhinitis	388	70	49	48
Eczema	159	29	9	9
Urticaria/angio-oedema	88	16	11	11
Rhinitis and eczema	121	22	5	5
Rhinitis, eczema and urticaria/angio-oedema	26	5	0	—
Family history	212	38	41	40
Corticosteroids	192	35	46	45
History of provoking factors				
House dust	297	54	20	20
Pollens	199	36	11	11
Animals	156	28	8	8
Foods	150	27	22	22
Aspirin	23	4	4	4
Penicillin	22	4	9	9

SKIN PRICK TESTS The reactions given by the skin test positive patients are shown in Table II.

Prick test reactions in the series as a whole were most commonly seen to house dust (59%) and *D. farinae* (58%) (69% giving reactions to one or the other or both), followed by pollens (56%), animal danders (32%), foods (14%), *A. fumigatus* (13%), and other moulds (18%).

Of the 168 skin test positive patients whose skin was unreactive to house dust, all but eight

TABLE II
PRICK TEST REACTIONS IN SKIN TEST POSITIVE PATIENTS

	No. 554	% 100
House dust and/or <i>D. farinae</i>	454	82
House dust	386	70
<i>D. farinae</i>	380	69
Pollens	365	66
Animal danders	209	38
Foods	89	16
<i>A. fumigatus</i>	86	16
Other moulds	116	21
Single positive	111	20
Multiple positives	443	80

gave positive prick test reactions to *D. farinae*, grass pollen or *A. fumigatus*. The use of these four allergens alone would consequently have detected 546 (99%) of the 554 skin test positive patients. No other combination of four individual allergens would have produced as high a yield.

SEX Males were more common than females (3:2) in the skin test positive patients whose asthma began under the age of 10 years, but the sexes were distributed evenly in all other age groups. There were significant differences between the skin test positive males and females with regard to histories of provocation by pollens (males 32%, females 40%— $P<0.05$), animals (males 22%, females 36%— $P<0.001$), and foods (males 23%, females 32%— $P<0.025$) but not by house dust, aspirin or penicillin. Prick test reactions to animal danders were also more common in females (males 33%, females 44%— $P<0.01$), but with the other allergens little difference was seen between the sexes, as was the case with family history and the previous use of corticosteroids. The numbers of skin test negative patients were generally too small for significant differences between the sexes or age groups to be apparent.

AGE Eczema, but not rhinitis or urticaria/angio-oedema, was reported less by the older skin test positive age groups (group 1 42%, group 2 18%, group 3 10%— $P<0.001$). A history of animal provocation in these patients was also reported less with increasing age at onset of the asthma (group 1 35%, group 2 27%, group 3 13%— $P<0.001$), while aspirin sensitivity appeared to become more common (group 1 1%, group 2 5%, group 3 9%— $P<0.001$). There were no significant variations with age in the previous use of corticosteroids in either skin test positive or negative patients, but in the latter a positive family history was obtained less commonly in the older age groups (group 1 66%, group 2 44%, group 3 30%— $P<0.025$).

With all test extracts, except foods, the prevalence of positive prick test reactions decreased with increasing age at onset, though in the case of *A. fumigatus* this was not statistically significant. The proportion giving positive reactions in group 3 was approximately two-thirds of that in group 1. The older age groups showed a corresponding increase in the proportion of patients giving a single positive skin reaction (group 1 14%, group 2 24%, group 3 30%— $P<0.001$).

ASSOCIATION OF HISTORY WITH SKIN PRICK TEST REACTIVITY (Fig. 3, Table III) With all allergens, those patients with positive histories gave appropriate positive skin test reactions in greater proportion than those with negative histories. Conversely, again with all allergens, those showing positive skin test reactions gave positive histories in greater proportion than those without skin sensitivity. The details are presented in Fig. 3. The association of positive history with positive skin reaction was highly significant for all allergens ($P<0.001$ —Table III).

TABLE III
SIGNIFICANCE OF ASSOCIATION OF POSITIVE HISTORY
WITH POSITIVE PRICK TEST IN SKIN TEST
POSITIVE PATIENTS

	House Dust and/or <i>D. farinae</i>	House Dust	<i>D. farinae</i>	Pollens	Animals	Foods
χ^2 $P<$	19.84 0.0005	11.84 0.001	11.88 0.001	32.22 0.0005	62.75 0.0005	20.53 0.0005

DISCUSSION

The proportion of this series of asthmatic patients falling into the immediate skin prick test positive and hence extrinsic category (84%) is rather higher than the 64% showing 'allergic factors' reported by Williams *et al.*, (1958), 68% by Pearson (1958) or 54% by Ford (1969). This may be due in part to the use of a single defining criterion—prick test reactivity—and in part to the selection of patients, all of whom were specifically referred for allergy assessment. In a further series of 1,000 asthmatics, Pepys (1973) found 78% to be skin test positive. Smith (1973) performed prick tests with a similar range of allergens on a similarly selected group of children aged 5 to 18 years who suffered from asthma and other 'allergic' diseases. At least one positive reaction was obtained in 95%, which may be compared to the group in this study aged under 10 years at onset of their asthma, 94% of whom gave positive reactions.

Comparison of the skin test positive with skin test negative patients revealed a number of significant differences. The incidence of skin test positive asthma appeared to diminish with increasing age, while that of skin test negative asthma appeared to increase. It is possible that the age differences between the skin test positive patients (predominantly children) and the skin test negative patients (predominantly adults) were independently partly responsible for some of the other

FIG. 3. Association of history with prick test reactivity in skin test positive patients.

differences observed, and some significant variations with age were indeed seen. The numbers in the skin test negative age groups, however, were too small for direct statistical comparisons with each skin test positive age group.

Rhinitis was reported half as commonly again by the skin test positive patients, and infantile eczema appeared to be three times as common, while provocation of 'allergic' symptoms by house dust, pollens, and animals (inhaled allergens) was reported two to three times more commonly. Overall 77% of the skin test positive patients gave positive histories of allergy to one or other of the allergens studied compared to 47% of the skin test negative patients.

While the skin test positive patients differed from the skin test negative patients in the above respects, no significant differences were observed with the other factors studied, namely, history of urticaria or angio-oedema, family history of 'allergic' disease, and history of provocation by foods, aspirin, and penicillin (ingested allergens). The similar percentages (38% and 40% respec-

tively) reporting a positive family history of 'allergic' disease in at least one first-degree relative are particularly interesting, Forgacs (1973) having recently reported the same observation. Pearson (1958) showed little difference in family history of asthma between asthmatics showing predominant psychogenic or infective factors and those who were predominantly allergic. Pepys (1973), however, considered the total numbers of first-degree relatives affected by asthma, rhinitis or infantile eczema, and showed a positive correlation with the skin reactivity (number of positive prick tests) of asthmatic patients.

Prick test reactions were most commonly seen to house dust or *D. farinae* followed by pollens, animal danders, and foods. The same order of precedence was reported by Pearson (1958), Ford (1969), and Smith (1973), Pearson and Ford having considered other criteria of allergy in addition to the prick test. The same order was seen in the skin test positive patients of the present series with respect to history of provocation by each of the allergen groups, but in the

skin test negative patients food sensitivity was reported with the greatest frequency.

The well recognized higher prevalence of asthma in boys was seen in skin test positive patients aged under 10 years at onset, but the sexes were evenly balanced in all other groups. Similar findings were reported by Ford (1969), though other workers have found a bias in favour of females in older asthmatics (Pearson, 1958; Williams *et al.*, 1958). Otherwise little variation was seen between the sexes. Skin prick test positive females gave positive histories of allergy to pollen, animals, and foods half as commonly again as did males, and this was accompanied by a higher prevalence of prick test reactivity to animal danders.

In the skin test positive patients there was a highly significant association ($P < 0.001$) of positive history with positive skin prick test for all the allergens studied, positive prick tests being generally more common than positive histories. McAllen *et al.* (1970) showed in a group of 21 asthmatics that when history to house dust and skin prick test to the house dust mite, *Dermatophagoides pteronyssinus*, were both positive, immediate asthmatic reactions were obtained in 18 (86%) on specific bronchial challenge. Using house dust, Aas and Johansson (1971) obtained positive asthmatic reactions in only 34% of their subjects selected in a similar way, but with birch and timothy pollens, horse, and fish, positive reactions were seen in 89% to 100%. It is interesting that in the present study positive prick tests to house dust and *D. farinae* were, equally, the least discriminatory of all the allergens used with regard to positive histories. This suggests that a reliable history of house dust allergy is the least easy to obtain, or that the skin prick test preparations used are the least specific—or possibly both.

In conclusion we feel that the skin prick test coupled with a carefully taken clinical history provides two major advantages in the investigation and subsequent management of asthmatic patients. First, routine skin testing with a selection of common allergens can identify subjects from the population at large in whom allergic factors (particularly inhalant allergens) are most likely to be present and whose asthma is most likely to respond to sodium cromoglycate. Secondly, and more specifically, the test supplies supporting evidence or otherwise to a history of immediate hypersensitivity and so may influence treatment by environmental control or specific desensitization. The relation of an allergen to symptoms must remain in doubt where a positive skin prick

test is obtained in the absence of a positive history, or where the history is not supported by the skin test. Where the relevance of a particular allergen is of special importance, nasal or bronchial provocation tests may be considered if the history and skin test prove discordant.

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After 29 years' continuous service, which included 25 years as editor, Mr. N. R. Barrett is losing his direct connection with *Thorax*.

The Editorial Committee takes this opportunity of extending to Mr. Barrett their deep appreciation of his vital role in the establishment and subsequent continuing success of the journal and of his very considerable contribution to the literature of thoracic surgery. The Committee hopes that Mr. Barrett will continue to maintain an active interest in the journal for many years ahead.