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THE EVALUATION OF SKIN TESTS IN RESPIRATORY ALLERGY

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Since Blackley showed in 1873 that hay-fever patients reacted to scratch tests with pollen by forming urticarial weals, the practice of skin testing in allergy has become widespread and great diagnostic importance has been attributed to it. Recently however, the validity of skin tests has been questioned. (Urbach, 1946, and others). It is the purpose of this paper to show their limitations in the diagnosis of respiratory allergy.

METHOD

We have investigated 300 patients with respiratory allergy and 100 normal subjects as controls. Their ages ranged between 5 and 75 years and no particular age group predominated. Of the patients more than half suffered from bronchial asthma, many of these severely so. The remainder suffered either from perennial rhinitis or hay-fever. Every patient attending the asthma clinic was included if a diagnosis of one of the above conditions was made. In many of these cases no particular allergen had been revealed by careful history taking. In the selection of control subjects, all those with a history of possibly allergic disease, tuberculosis or recent antibiotic therapy were excluded.

The prick test was chosen as method of skin testing, having less disadvantages than the intracutaneous and the scratch test. The former sometimes causes severe anaphylactic reactions, the latter is a trauma to the more sensitive skin. The main setback of the prick test is the impossibility of achieving a constant depth of penetration. This depends not only on the force applied and the point of the instrument used, but also on the texture of the skin which varies considerably in different subjects.

As test fluids we have used allergenic extracts more concentrated than those commonly employed for scratch testing. We are obliged to Messrs. Bencards for supplying the most concentrated extracts they were able to produce of 12 different allergens. They were: Mixed Grass Pollen, Mixed Tree Pollen, Mixed Autumn Pollen, Horse-hair and Dander, Cat and Dog-hair, House-dust (this was a 1:100 crude antigen according to Rimington & Maunsell, 1951), Fresh Sage-leaves, Orris Root, Mixed Moulds (containing *Alternaria*, 4 sp. of *Aspergillus*, 3 sp. of *Mucor*, 2 sp. of *Penicillium*, *Rhizopus* and *Cladosporium*) and three different bacterial extracts including different types of *Streptococci* and *Staphylococci*. The Sage extract, the Orris Root and Bacterial Extracts were intended to act as controls. The commonly used saline controls seemed unsatisfactory as some subjects respond positively to any foreign protein but not to saline. Their positive response would therefore be unspecific though this would not be revealed by the use of saline controls. It was our intention to test with a number of extracts whose widely differing characteristics would render it unlikely that a subject with specific sensitivity or sensitivities would react to all of them. For this reason the sage, orris root and bacterial extracts were included.

The comparatively small number of allergens used limits to a certain extent the validity of our results. Of the more common allergens we have not included foodstuffs or fabrics, and it is possible that some of the subjects who have given only negative reactions, would have given positive reactions

to such other allergens. This error however can never be completely excluded as some subjects may react positively only to a single allergen which is either not represented in the test extracts or only as one constituent of a mixture and therefore too weak to elicit a positive reaction. We should have had to employ a multiple of 12 extracts in order to reduce this error to a minimum.

The different degrees of antigenicity of the various extracts used created a further difficulty in the evaluation of the results. It is obvious that the more concentrated an extract, the more often positive reactions must be expected. As no satisfactory standardization of extracts has been achieved so far, they show wide variations of antigenic potency. It is therefore possible and even likely that the high proportion of positive reactions to one particular extract may be due to its high potency and vice versa. One would expect such an extract frequently to give a positive reaction in the absence of any other positive reactions. Our horsehair and dander extract gave such isolated positive reaction in a number of cases; on the other hand the total of positive reactions to this extract was far less than half, and there were some subjects who reacted positively to many other extracts, but not to horse-hair and dander. The same applies, to a lesser extent, to the housedust extract. It must be kept in mind that housedust is an allergen to which a large section of the population is continually exposed. The same is true of horsehair which is widely used in mattresses, pillows and upholstery. It may be, therefore, that the frequency of positive reactions to horsehair and housedust is less due to the potency of the extract than to the ubiquity of the allergens.

We have considered standardizing the antigenicity of extracts by selecting the concentration which does just not cause a positive reaction in normal subjects. This would have necessitated circumstantial preliminary tests with large numbers of normal subjects and the outcome would be doubtful: Although in some patients the skin reactions are very pronounced, there are many others in whom they are of the same intensity as in

many normals. Most probably, therefore, we should have missed, by using weaker extracts, a large number of positive reactions in patients.

The tests were carried out on the flexor surface of one forearm and 15–20 minutes after pricking the weals and flares were outlined with ink and immediately recorded by transferring them to a sheet of tissue paper gently pressed on the forearm. We have regarded as positive all reactions which showed a persistent flare. A weal without a flare was regarded as positive if it was clearly larger than the controls and at least 3 mm. in diameter.

We have also looked for the so called delayed or late reactions which have very often been regarded as of no clinical significance. They show a central redness, often slightly papulous, decreasing towards the periphery. They never have a flare and are similar to the Tuberculin type of reaction. We found that such reactions occurred frequently. The time of their appearance varied from 5 to 24 hours or more after pricking, and their duration was usually 12 hours, but often several days. We cannot be sure that we have seen all the late reactions which might have occurred in our subjects, as the majority were outpatients and therefore not under continuous observation. If they seemed intelligent and co-operative they were asked to inspect their own arms after 12, 24 and 36 hours and to take tissue paper prints if there was any difference between the individual reactions. The patients who were obviously unable to record the late results objectively were asked to come after 24 hours for inspection. In these patients, reactions developing after the first reading and disappearing 10–12 hours later would have escaped observation. This may well have taken place as we have observed such reactions in some of the comparatively few patients whom we were able to inspect every few hours.

Both immediate and late reactions often occurred in the same patients. For instance, there might be an immediate reaction to one allergen, and a late reaction to another. In cases where there were several late reactions to different allergens,

they often appeared after and persisted for different periods. When the immediate reaction was strong it often persisted for more than 12 hours. In such cases the reaction was termed "immediate and continuous". In a few inpatients however who were under continuous observation it was seen that the immediate reaction disappeared after the first 4 or 5 hours but reappeared after a further 12 hours or more. We were convinced that such reappearing reactions were true late reactions. It is therefore possible that in those cases in which the second inspection was only made after a lapse of 12 hours and the immediate positive reactions were found to be still present, and termed "immediate and continuous", we may in fact have been dealing with late reactions. Nevertheless, such reactions have not been listed as "late".

An attempt has been made to correlate the positive skin reactions with the clinical history and environmental evidence. This has been easy in many cases of monovalent allergy, as, for instance, in grass pollen asthma. In many subjects with perennial asthma, in whom the skin reacted positively to some pollen, animal hair, and housedust, such correlations could not be found. One cannot expect to find such correlations in many such cases, as the patients with multiple hypersensitivity are exposed to at least one of their allergens during any time of the year. Moreover it would be difficult for a patient to relate an allergic reaction to a particular allergen if it does not immediately follow exposure.

In a number of cases the bronchial test was used to investigate further the significance of the skin test. This was done with the same extracts and by the method described previously (Herxheimer 1951). The time required for bronchial tests limited the number of these investigations.

RESULTS

Variability.

In 21 patients we have repeated the tests using the same technique on different days, and in some cases at different

TABLE 1
Typical Examples of the Variability of Skin Reactions.

Patient	Clinical diagnosis	Positive reactions in first test	Positive reactions in second test	Positive reactions in bronch. test
An.	grass pollen asthma	123459 10	3459	1
Ar.	dust asthma and some other allergen	12469	146	6
Cr.	dust asthma	468	14	6
El.	perennial asthma	12456	146	6
Li.	perennial asthma	1467	123456	169
Na.	grass pollen asthma and some other all.	12345	123567	1
Ov.	grass pollen asthma	123467	12347	1
Va.	dust asthma	1346	346	6
Wh.	perennial asthma emphysema	6	456	-
Le.	perennial asthma	14569	13456789	9

Explanation of figures: 1 = grass pollen. 2 = tree pollen. 3 = autumn pollen. 4 = horse hair and dander. 5 = cat and dog hair. 6 = house dust. 7 = sage leaves. 8 = orris root. 9 = mixed moulds. 10 = streptococcus.

times of the year (Table 1). In a few of these patients the tests were carried out a third time. Only in 3 patients did two consecutive tests give exactly the same result. In the other 18 patients there was considerable variation: either one or several of the reactions which were positive in the first test had become negative in the subsequent test, or vice versa. It also occurred that a reaction which in the first test became positive only after 12 hours, in a subsequent test became positive immediately. One of the most striking examples of this variability occurred in a woman of 45, who gave a history of 2 years asthma, mainly during August and September. Autumn pollens were suspected as the cause, and at the first test the skin gave a positive reaction only to autumn pollen. At the second skin test, both autumn pollen and grass pollen gave weakly positive reactions, but horse hair and dander were strongly positive. A bronchial test with autumn pollen was

TABLE 2
*Percentage of Positive and Negative Skin Reactions in 100 Normal Subjects and
 300 Patients with Respiratory Allergy.*

	Neg.	Immed. pos.	Late pos.	Either immed. pos. or late pos.	Either immed. pos. or contin. or late pos.	Either immed. pos. or cont.	Total of immed. pos.	Total of late pos.
100 normal subjects	49	25	17	5	2	2	34	24
300 patients	5	32	11	7	20	25	84	38

carried out, but had a negative result. A third skin test now gave positive reactions again to horse hair and dander and in addition a late positive reaction to house dust. A bronchial test with house dust gave a pronounced late reaction. Obviously, some of the skin reactions had been misleading, and the allergen causing the asthma was house dust, possibly in conjunction with an unidentified seasonal allergen acting in autumn.

Frequency of Reactions in Normal Subjects and Patients.

About 95 % of our patients and about 50 % of our normal subjects had one or more positive skin reactions (Tables 2, 3 and 4). Only two of the 13 patients with negative skin reactions were typical asthmatics with a long history. Seven of them were elderly, between 50 and 65, and their complaint had started only a few years before, usually as a winter bronchitis, which at a later stage was accompanied by typical asthmatic attacks. Two others were children with mild chronic bronchitis and mild and transient attacks of bronchial spasm. In one other patient psychological trigger factors were so pronounced that it appeared doubtful as to whether an allergic mechanism was still operating. The remaining patient had a perennial rhinitis. It seems therefore that in 9 out of these 13 patients a chronic bronchitis had been the first sign of illness before symptoms of asthma appeared. In the great

TABLE 3
*Percentage Distribution of the Positive Skin Reactions obtained with
 12 different antigenic Extracts.*

Allergenic extracts		1	2	3	4	5	6	7	8	9	10	11	12
1138	immed. positive reactions (patients)	17	10	9	19	8	15	5	4	7	2	2	2
64	immed. positive reactions (norm. subj.) ...	20	12	12	24	5	12	2	3	3	3	1	3
204	late positive reactions (patients)	4	4	8	9	18	26	4	8	6	2	5	5
36	late positive reactions (norm. subj.) ...	6	6	9	14	22	39	0	3	3	0	0	0

Explanation of extract numbers in first line: 1 = grass pollen. 2 = tree pollen. 3 = autumn pollen. 4 = horse hair and dander. 5 = cat and dog hair. 6 = house dust. 7 = fresh sage leaves. 8 = orris root. 9 = mixed moulds. 10 = strept. Lancefield group. 11 = strept. viridans group. 12 = staphylococcus.

majority of the other patients chronic bronchitis, if present, was secondary and had developed in the course of the asthma.

The frequency of positive reactions varied considerably with the different allergens. Considering all immediate and immediate and continuous reactions together, grass pollen, horse hair and house dust each produced positive reactions in about 67 % of all patients. The other pollen groups and cat and dog hair each produced positive reactions in about 33 % of all patients. Mixed moulds gave positive reactions in 28 % of patients, orris root in 14 %. The three bacterial extracts caused positive reactions in only 4 to 7 % of patients. The late reactions showed a different distribution. House dust caused a late-positive reaction in 15 %, and cat and dog hair and horse hair each in 6 % of all patients. Autumn pollen caused late-positive reactions in 6 %, orris root in 5 %, mixed moulds in 4 % and sage and grass pollen each in 3 % of all patients.

In Table 3 the percentage of reactions to specific allergens in the total of all positive reactions is shown separately for immediate and late reactions. It will be seen that the majority of immediate reactions occurred in the pollen and horse hair groups. In the late reactions these groups are in the minority,

TABLE 4
*Percentage Distribution of the Positive Skin Reaction obtained
 with two groups of allergenic extracts.*

Groups		Three pollen extracts (1 + 2 + 3)	Cat and dog hair, house dust (5 + 6)
1138	immed. pos. reactions (patients)	36	23
64	immed. pos. reactions (normal subjects)	44	17
204	late pos. reactions (patients)	17	44
36	late pos. reactions (normal subjects)	21	61

and the house dust and cat and dog predominate. The same predominance of one group of allergens in the immediate reactions and another group in the late reactions is present also in the normal subjects. This is shown more clearly in Table 4, in which the three pollen groups are contrasted with the combined house dust and cat and dog groups.

Correlation of Skin Tests with Clinical Evidence.

We have tried to correlate the results of the skin tests with the clinical evidence of specific allergy. For this purpose, we separated 100 patients with immediate skin reactions into three categories:

1. Those with definite clinical evidence of sensitivity to one or more known specific allergens.
2. Those with definite variations in the intensity of their complaint and suspected of sensitivity to one or more periodically active allergens, but without adequate clinical evidence to incriminate a specific allergen.
3. Those with a perennial complaint without any seasonal variation (except perhaps in very cold and dry weather) and without any clinical evidence of the action of a specific allergen.

These three groups were approximately equal numerically.

In the first group (51 patients) it was found that in 6 patients none of the skin reactions correlated with the clinical evidence: the skin did not give a positive reaction to the allergen incriminated on clinical evidence. In the remaining 45 patients, at least one skin reaction did correlate with the clinical evidence, but there was also one or more additional positive skin reactions and one or more of these additional reactions was not compatible with the clinical evidence. For instance, the clinical picture may have been that of a typical grass pollen asthma stopping abruptly in mid July with skin tests positive not only to grass pollen, but also to tree pollen and autumn pollen. In another case, a patient was clinically sensitive to house dust, but the skin reacted not only to house dust, but also to grass pollen and cat and dog hair. There was no evidence that the asthma was more severe during the grass pollen season: there had been no animals in the home during the last five years, and occasional contact with cats or dogs did not provoke an asthmatic attack. It is clear therefore that in the great majority of these cases, the clinically active allergen does manifest itself by giving a positive skin reaction. However, a number of other allergens may also give positive skin reactions, and there is no way of telling from the skin test procedure which of these allergens is responsible for the clinical attacks.

It would appear from these findings that even in those patients with a clinically well defined allergy the skin reaction does not necessarily mirror the offending allergen. In almost all cases, some skin reactions are positive which have no correlation whatsoever with the clinical evidence. In the second group (47 patients) and the third group (52 patients) the clinical evidence of an offending allergen was either vague or absent; correlation of the skin tests was therefore restricted in the former and impossible in the latter. In 9 patients of the second group the skin tests could definitely not explain the allergic symptoms. In the patients of the third group who all

suffered from a perennial complaint, 28 were found skin sensitive to house dust, whilst in 18 others the positive skin tests could not explain a perennial complaint.

Skin Reaction and Bronchial Reaction.

In 52 patients 71 tests were carried out. As these tests require much time, it proved impossible to test the patients against many different allergens. We therefore cannot present a complete comparison of bronchial and skin testing against the same series of allergens. In those cases in which the skin tests were positive to many allergens, the bronchial test was carried out with one to three of those allergens which from the clinical evidence promised a positive result.

In 46 tests, i.e. in about two thirds, the bronchial test and the skin test were both positive to the same allergen. In 15 tests where the skin reaction was positive, the bronchial reaction was negative, and in 10 tests the negative skin reaction was accompanied by a positive bronchial reaction. If the skin reaction was a late one, the bronchial reaction was often immediate, and vice versa. We have seen only 4 patients in whom both skin and bronchial reactions were delayed. In all patients in whom a positive bronchial reaction was obtained, there was complete correlation with the clinical evidence. As only a comparatively small number of bronchial tests have been carried out, it is possible that some discrepancies would have been found with larger numbers.

DISCUSSION

There are various sources of error in our method which may impair its value:

- 1) Difficulty in pricking to a constant depth.
- 2) The necessarily limited range of antigens employed.
- 3) The different antigenicity of the extracts.
- 4) The probability that some late reactions may have escaped our observation.

Elimination of (2) and (4) would have increased the proportion of positive reactions whilst (1) and (3) may have affected both positive and negative reactions.

The variable result of repeated tests on the same subject—only 3 of 21 subjects had identical reactions on 2 occasions—can only partly be attributed to the error listed under (1). Another important factor is the reactivity of the subject which may vary under the impact of preceding exposure to the antigen, endocrine disturbances (menses) and also, according to an observation by Frankland (1954), with vasoconstriction and vasodilatation. In these circumstances it must be considered whether skin testing on a single occasion is accurate enough for any clinical conclusion to be drawn. We doubt it, and we would prefer to take notice only of those reactions which have been repeatedly positive or negative. However for our present evaluation this inaccuracy is of little importance, for it is balanced by the large number of subjects.

The frequency of positive reactions in our normal subjects and patients is well in accordance with that described by other authors. Simon and Rackemann (1935), Grow and Herman (1936) and Ehrström (1950) found an incidence of about 50 % in, altogether, over 200 normal subjects. Bruun (1945), Winkenwerder and Gay (1937), Schwartz (1952) and Thacker (1946) found an incidence of 95 %–100 % in asthma or vasomotor rhinitis. Others have found percentages as low as 25 % in normal subjects and 40 % in asthmatics. Thus our findings are close to the highest percentages so far found; they are, however, not strictly comparable, for we have included the late reactions, omitted by previous observers; this increased our percentage of positives. But on the other hand we have not tested with such allergens as fabrics and food-stuffs, and this must have decreased our percentages.

It must be considered whether our results indicate too great an antigenicity of our extracts. It is obvious that a more concentrated antigen solution will elicit a positive reaction in more normal subjects than will a weak one. For example Rimington and Maunsell (1950) found that a comparatively

weak solution of their house dust antigen produced positive reactions in only 4 % of their normal subjects. We should expect, had our extracts been too concentrated, to have obtained a higher percentage of positives than found by other authors. As this was not the case, we have no reason to assume that we have made a decisive error in this direction. At one time we suspected that our horse hair and dander extract was too strong since we found a number of subjects whose skin was sensitive only to this allergen. But on the other hand there were quite a number who were sensitive to many other extracts but not to horse hair and dander. It must also be remembered that many people must have had long and intimate contact with this allergen.

If our results and those of many earlier observers are valid, presence or absence of positive skin reactions in a patient do not seem to be of great diagnostic importance, since they occur in almost half of normal subjects. However, if such a patient has *no* positive reactions at all, this points strongly against an allergic disorder. The 5 % of patients in our series with no positive reactions included a number in whom the allergic nature of their complaint was doubtful, and it may well be that negative skin reactions occur in much less than 5 % of true allergic patients.

We must ask ourselves what a positive skin test may mean. Some authors firmly believe that it indicates that a liability to allergic symptoms is present even if they have never existed, and they call this latent allergy. But as half of all normal subjects have positive skin reactions latent allergy would have to be a normal occurrence, and in many of these normal subjects allergic symptoms ought to occur sooner or later. As this is not so, this concept of latent allergy should be abandoned. A positive skin reaction probably means no more than that some foreign substance has acted on some body substance and that, consequently, antibody has appeared in the skin. This does not necessarily mean that any other organ has formed antibody, nor that allergic disease is present or will develop. The observation by Ehrström (1950) on North Greenlanders

clearly shows that long and intimate contact with foreign matter will lead in many cases to a positive skin reaction. Only one of his 19 cases with a positive skin reaction developed allergic disease, and it is clear that some additional factor, as yet unknown, must be present to lead to this happening. In this connection it is interesting to note that specific allergens have caused positive reactions in similar proportions of patients and normal subjects. This may mean that the way in which these skin reactions are brought about is the same in allergic and normal subjects. It must be emphasized that in respiratory allergy the only allergens that matter are those which affect the respiratory organs. The skin is a different organ, and allergens affecting it do not necessarily affect the respiratory tract or vice versa.

The frequent occurrence of late reactions is also worth noting. When Simon and Rackemann (1935) injected guinea-pig serum into normal subjects at weekly intervals, they found that after the second injection a late reaction occurred. Some weeks later the reaction would cause an immediate reaction, often followed by a late one. The same sequence of events was also seen in allergic subjects. Other authors, Jones and Mote (1934), Stevens and Jordani (1936) also report the occurrence of immediate reactions followed by late reactions in the same subjects during the same test, and also the change from immediate at one time to late at another. Late reactions to, for example, penicillin have been found by Peck et al. (1948) and Rostenberg and Welch (1945) in 5 % of subjects who had had no prior contact with this substance.

These observations show that late reactions cannot be rare. It is difficult to understand why so little attention has been paid to them in clinical practice. Their practical importance, if any, is the same as that of the immediate reactions. In those of our cases in whom a positive skin reaction agreed with the clinical evidence or the bronchial reaction, this skin reaction often was a late one.

In the light of these observations the relative value of clinical evidence, bronchial test and skin test must be con-

sidered. The clinical evidence—in most cases an accurate history—is decisive if it is clear and unmistakable. For instance, when grass pollen asthma is present at exactly the period of grass pollen dissemination, no further confirmation by skin or bronchial testing is necessary, and the history is equivalent to an environmental test. There are, however, many cases in which the history is not so clear, and the identification of the allergen becomes necessary. Moreover, many cases present no clue to the offending allergen mainly because the patient is a late reactor and naturally fails to recognise the action of an allergen with which he has been in contact many hours before the attack.

In the numerous cases in which the offending allergen is uncertain, identifying tests must be carried out. Stevens (1934) has demonstrated many years ago that moderately positive skin tests could be confirmed by bronchial test only in a proportion of 1:9 cases. Other authors (Lowell and Schiller, 1948; Herxheimer, 1951; Colldahl, 1953; ten Cate and Orie, 1953) have also reported discrepancies between skin reaction and bronchial reaction. Our present investigations have shown that although in the majority of positive bronchial reactions a positive skin reaction to the same allergen is found, the reverse is not the case. Of the many positive skin reactions only some have been confirmed by bronchial testing—this result will need further investigations in greater numbers—and there is also a minority of cases in which positive bronchial tests are accompanied by negative skin tests. Those who use a positive skin reaction without clinical evidence as the basis for hyposensitization treatment will do well to remember that skin and respiratory passages are different organs and many react differently to the same allergen. The only advantage a positive skin reaction offers is that it may act as a guide for the selection of the bronchial or nasal test substance.

The bronchial test has proved much more reliable. In every case its outcome has been correlated with the clinical evidence, and in many it has provided the main clue to the

diagnosis. This is natural, as the inhalation of the allergen imitates closely the natural conditions in which an attack may occur. The bronchial test should therefore be used more widely as a means to establish the diagnosis. In the mild and moderate asthmatic it is a harmless procedure provided that overdosage is avoided. In severe asthma, it may be difficult to avoid overdosage, and bronchial testing should therefore not be undertaken lightly. In such cases the diagnostic advantage offered by bronchial testing is usually not pronounced as multiple allergic sensitivity is present and specific treatment difficult, and here bronchial testing appears unnecessary and can be avoided.

SUMMARY

1. In 300 patients with respiratory allergy and 100 normal subjects, skin tests with a number of allergens were carried out. In 95 % of the patients and 51 % of the normal subjects, one or more skin reactions were positive. This result is in good accordance with those of other authors. The high rate of positive skin reactions in normal subjects considerably limits their value in the diagnosis of respiratory allergic disease. Their absence makes allergic disease unlikely, although it does not absolutely exclude it.

2. In a great number of patients the skin reacted positively to allergens which were not causal as judged by the clinical evidence. On the other hand, the bronchial reaction was always compatible with the clinical evidence. The wide discrepancy thus shown to exist between the reaction of different shock organs (skin and respiratory membrane) makes it impossible to rely on the outcome of skin tests for the identification of a causative allergen. Skin tests may possess, however, some limited value for this purpose if no other evidence of specific allergy is available. In such cases, their outcome may give some guidance for the direct testing of the respiratory shock organ.

3. Skin testing should therefore be limited to cases in which (a) it is suspected that the symptoms are due to non-

allergic causes, (b) precise clinical evidence of a specific allergen is lacking in an undoubted allergic disorder.

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