

OBSERVATIONS ON THE SPECIFICITY OF THE SKIN TEST

The Incidence of Positive Skin Tests in Allergic and Nonallergic Children

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FOR nearly half a century the skin test has been the backbone of allergic diagnosis, the key to specific therapy. It is generally appreciated that it has shortcomings. It may fail to reveal clinical sensitivity and it may exhibit a positive reaction that is not clinically significant. False negatives are the rule rather than the exception in drug hypersensitivities and false positives are commonly encountered with bacterial antigens. Little use is therefore made of drug and bacterial antigens in practice. Barring these major exceptions, however, the skin test is regarded as a reasonably accurate guide to evaluate specific hypersensitivity. Environmental (provocation) tests are admittedly more accurate but present difficulties; hence the skin test has stayed with us and has retained a place of honor.

Accepted allergic procedures are, however, not infrequently criticized by nonallergists and sometimes by allergists themselves¹ for not having a sufficient basis of critical scientific observation. It was with this in mind that the present studies were undertaken. Our purpose was to attempt to obtain a definitive answer to three questions: (1) How frequently is a positive skin test obtained to commonly employed antigens in a nonallergic subject? (2) How frequently does the allergic subject react positively to such tests? (3) How significant of specific hypersensitivity is a positive test obtained in a clinically allergic subject? Previous efforts to answer these questions have been surprisingly few. Rackemann and Simon² tested 60 subjects who had a variety of nonallergic complaints, only 4 of whom had a history of allergy. Eight different antigens were used. Fifty per cent of these subjects gave positive reactions to one or another antigen, the highest percentage of reactions being found to ragweed. Grow and Herman³ tested a group of 150 apparently normal medical students, of whom 110 had no history of allergy. Thirteen common antigens were employed and 55.5 per cent of the entire group showed one or more positive reactions. In the smaller group with no allergic history, the incidence of positive reactions was virtually the same—54.4 per cent. The most common

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Received for publication March 15, 1963.

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reactants were house dust (38.6 per cent) and orris (34.6 per cent). Efron and Boatner^{4, 5} studied skin reactions to house dust and ragweed in normal and allergic individuals, and reported a high incidence in the latter group as compared to the former. Lindblad and Farr⁶ studied skin reactions in 100 normal subjects with five inhalant antigens: ragweed, dust, mixed trees, mixed grasses, and mixed molds. Up to 50 per cent showed positive reactions, depending on the dosage employed. In order to ascertain whether these false positive reactants were primary irritants, passive transfer studies were made with house dust and with ragweed; 5 out of 8 such tests with dust were positive and 3 out of 8 with ragweed. To the best of our knowledge comparatively few reports are available on normal children that have been systematically skin tested with a variety of antigens, a defect we have undertaken to remedy.

EXPERIMENTAL STUDIES

The subjects of this study were 200 children between the ages of 2 and 11 years who were admitted to the general pediatric outpatient clinic of Bellevue Hospital during the year 1960 for a variety of minor complaints, none of them suggestive of allergy and none of them serious enough to warrant admission to the hospital. The patients were from a lower socioeconomic group and were

TABLE I. INCIDENCE OF POSITIVE SKIN REACTIONS IN ALLERGIC AND NONALLERGIC PATIENTS

ANTIGENS	CONCENTRATION (PNU/C.C.)	NO. PATIENTS TESTED	ALLERGIC PATIENTS (% POSITIVE REACTIONS)	NONALLERGIC PATIENTS (% POSITIVE REACTIONS)
<i>Inhalants</i>				
Dust concentrate		200	88	42
Feathers	1,000	200	59	7
Pyrethrum	1,000	200	28	5
Penicillium	1,000	182	9	5
Alternaria	1,000	200	35	2
Horse dander	1,000	168	19	2
Wool	1,000	200	28	2
Cat dander	1,000	176	26	1
Cottonseed	1,000	200	17	1
Orris root	1,000	150	12	1
Ragweed	500	200	56	1
Timothy	500	200	44	1
Dog dander	1,000	194	24	0
Plantain	500	200	32	0
<i>Foods</i>				
Strawberry	3,500	66	33	20
Spinach	3,500	62	26	18
Chocolate	3,500	113	19	11
Orange	3,500	117	25	5
Pork	3,500	64	9	3
Wheat	3,500	123	26	1
Rye	3,500	70	20	1
Codfish	100	66	45	0
Cow's milk	3,500	124	15	0
Egg white	100	122	16	0
Lamb	3,500	61	13	0
Peanut	100	63	9	0

predominantly of Puerto Rican origin. A past history of allergy and a family history of allergy were not obtained upon interrogation. Skin tests were carried out with 28 commonly employed antigens, 14 foods and 14 inhalants. Half of the children (100) were tested with the 14 food antigens and the other half with the 14 inhalant antigens. The 14 tests were carried out on two visits, 7 tests being applied at each visit.

Another group of 200 allergic children of similar age and racial and socioeconomic background, between the ages of 2 and 11 years of age, who had been referred to the Pediatric Allergy Clinic of Bellevue Hospital with the diagnosis of asthma or hay fever, were tested with the same materials used in the group of nonallergic children. Not all of these children were tested with each antigen, some antigens being employed more frequently than others, depending on leads obtained from the history.

The tests were recorded as slight, moderate, or marked. A wheal reaction about $\frac{1}{8}$ inch in diameter was considered as slight; a wheal of $\frac{1}{2}$ to $\frac{3}{4}$ inch was moderate, and a larger wheal with pseudopods was called marked. Approximately 0.02 c.c. of the test material was injected into the deltoid area intradermally and the tests were read within 15 minutes. Questionably positive reactions were counted as negative; only the moderate and marked reactions were considered positive for the study. Table I shows the nature of the extracts and their strength, expressed in protein nitrogen units.*

RESULTS

The data on the tests with the 28 different antigens, each of which was tested on 100 normal children, are tabulated in Table I. It can be seen that substantial percentages of positive reactions were obtained with several antigens: 42 per cent reacted to house dust, 20 per cent to strawberry, 18 per cent to spinach, 11 per cent to chocolate, and 7 per cent to feathers; the incidence of positive reactions to orange, pyrethrum, and penicillium was 5 per cent. Other antigens showed less frequent reactions, and nine of the antigens, including cow's milk and egg albumin, showed no positive reactions.

The numbers of tests performed with each antigen and the percentage of positive reactions obtained in the allergic group of children are shown in Table I and are contrasted with the percentages of reactions found with the same antigens in the nonallergic children. Regardless of the selection used in performing these tests it is quite apparent that the incidence of reactors to all antigens is much higher in allergic than in nonallergic subjects. All of the antigens used gave at least some positive responses and for every antigen the percentage of positive reactions was higher and often markedly higher than in the nonallergic group. In the allergic group, the highest percentage of positive reactions was found with house dust—88 per cent of all subjects tested. Multiple positive reactions were common as is evident from the total of 732 positive reactions in the 200 subjects tested.

*The test extracts were prepared by Margaret B. Strauss in the Allergy Laboratory at University Hospital, New York City. The usual procedure was followed involving defatting, extraction in phosphate buffered saline at pH 7.0, filtration, dialysis concentration by evaporation, and a final Seitz filtration.

COMMENT

What practical deductions can be made from these data? Certainly, one is obvious. If nearly half of a group of nonallergic subjects reacts positively to house dust, testing with this antigen is of relatively little value in pinpointing specific hypersensitivity to this antigen and does not provide justification for specific therapy. Evidence to incriminate house dust must be sought elsewhere. An environmental (provocation) test may serve to establish such sensitivity, but unless carried out meticulously by alternate withdrawal and challenge, this, too, may give misleading information. An illustration of this was recently provided by the environmental study of house dust sensitivity carried out by Long and his co-workers at the Massachusetts General Hospital.⁷ Fourteen children with asthma who were skin-sensitive to house dust were hospitalized with prompt relief of the symptoms. On being transferred to another room which, without their knowledge, had been sprayed with house dust collected from their own homes in a vacuum cleaner, not a single one suffered an exacerbation of symptoms. A minority are said to have relapsed when returned to the home environment.⁸ Had only the elimination without the subsequent specific challenges been attempted one might easily have concluded that house dust was the specific offender. We are not prepared to accept the conclusion of these investigators that the benefit from hospitalizing these subjects was the result of removal from untoward psychogenic factors in the home. There are many other possible variables that might have been concerned. What does seem clear, however, is the fact that in all these cases the skin test gave false information about house dust sensitivity.

The lower incidence of skin reactions to other antigens in our study does not mean that a positive skin reaction to one of these is more likely to be significant than in the case of house dust. These less frequent reactions may have no greater clinical significance in the individual case than does the house dust reaction. It is of interest that the Massachusetts study mentioned above included one case of an asthmatic child with a skin reaction to wheat, a child who had lived near a flour mill but could eat wheat with impunity.

Of interest in the present study was the failure to encounter positive skin reactions to cow's milk and egg white. Dubois and his co-workers⁹ showed some years ago that infants after ingesting a food for the first time would develop a condition that has been called "physiological allergy" as shown by positive skin tests and precipitin reactions. This was, however, of relatively brief duration, persisting for a matter of weeks or a few months. Presumably our subjects, none of whom were infants, had lost such physiological allergy to foods as they may have had.

A tempting interpretation of these findings is the traditional one that because the skin responses are so much more frequent in the allergic patient they must be indicative of specific allergy. It must be pointed out, however, that another explanation is equally possible. The many skin reactions which the allergic subject exhibits may indicate only that his skin is more reactive than that of a nonallergic individual. The skin response may have much the same

significance as does eosinophilia. The value of the skin test rests on the alleged parallel between the reactivity of the skin and that of the so-called shock organ. The concept that a reasonably close parallel exists between the skin and the shock organ is a fundamental tenet of allergy. It rests rather heavily on "clinical experience," finding little support from critically controlled studies. A large number of asthmatics are now designated as having "intrinsic asthma"¹⁰ because they fail to respond to control of extrinsic factors, such as elimination of antigens to which many of these patients show positive skin reactions. The literature on allergy contains reports¹¹ of the frequency of house dust asthma in patients who fail to give a positive skin test to house dust, and the lack of correlation appears to be frequent. Correspondence between the skin test, the history, and the provocation test was found in only 17 per cent of asthmatics studied by Fagerberg,¹¹ although he quotes four other reports in which it was stated that it was as high as 25 per cent. In a group of asthmatics who were skin sensitive to molds, Duchaine and Spapen¹² carried out inhalation tests and were able to demonstrate bronchial sensitivity in only 29 per cent. There is certainly a lack of parallelism between the responsiveness of the skin and that of the bronchial mucosa to antihistaminics. A lack of parallelism between skin sensitivity and mucous membrane sensitivity is by no means rare in our own experience. For example, we recently saw a patient who had suffered most of his adult life from ragweed hay fever. His skin reacted strongly to ragweed, but it also reacted to cat epidermis. When scratched by the family cat this patient developed marked whealing, but close contact with the house cat caused no symptoms of respiratory allergy; there is obvious dissociation between skin sensitivity and sensitivity of the respiratory mucosa. A Cassandra might predict that this individual is headed for trouble and should avoid cats. But how does Cassandra know this? Where is her statistical evidence from controlled observations? This individual is now in his sixty-eighth year and Cassandra has not caught up with him yet.

The clinical experience of the allergist who often sees favorable results from therapy agreeing with the positive skin test is not to be denied. It should be pointed out, however, that it is exceedingly difficult to carry out controlled observations in office practice. Indeed it is impossible to do so from an ethical standpoint if one is convinced of the efficiency of a particular procedure. Treatment of the allergic patient usually involves more than one therapeutic measure. In addition to specific elimination or hyposensitization it may involve drug therapy, various environmental changes, and perhaps a change in a way of life, any one of which may have been responsible for clinical benefit.

SUMMARY

A series of allergic children skin tested with 28 common antigens was found to give a markedly higher incidence of positive reactions than a comparable group of nonallergic children.

Reasons are given for questioning the significance of the skin reaction as an indicator of the specific antigen responsible for allergic symptoms. It

appears likely that in the case of house dust, at least, the skin test has little practical significance.

It seems to the writers that, if the skin test is to retain its place of eminence in the diagnosis of specific allergies, a firmer body of support in the form of rigorously controlled studies than is now available is required.

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