

THE INCIDENCE OF POSITIVE INTRADERMAL REACTIONS AND THE DEMONSTRATION OF SKIN SENSITIZING ANTIBODY TO EXTRACTS OF RAGWEED AND DUST IN HUMANS WITHOUT HISTORY OF RHINITIS OR ASTHMA

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DESPITE the importance of the intradermal test as a diagnostic aid for the identification of causative agents in allergic rhinitis and asthma, only a few studies are available in which the incidence of positive reactions has been recorded when the extracts used for such testing are studied on individuals without rhinitis or asthma. Some of these important control studies were concerned with only one concentration of multiple allergens,^{1, 2, 3} a few with multiple concentrations of a single allergen,^{4, 5} but none have been concerned with multiple concentrations of several allergens tested on the same group of individuals. Accordingly, the present experiment was undertaken to determine the incidence of positive intradermal tests when graded concentrations of extracts from ragweed, mixed grasses, mixed trees, mixed molds, and dust were injected into the skin of individuals who denied ever suffering from the usual nasal or pulmonary symptoms thought to be associated with allergic phenomena. Some additional studies were also done to determine whether some of the positive reactions observed were due to nonspecific irritation, or were due to the presence of passively transferable skin sensitizing antibody.

METHOD

Test Subjects.—Subjects for this investigation were chosen at random from graduate nurses, medical students, patients attending Falk Medical Out-Patient Clinic, and patients admitted to the ward of Presbyterian Hospital, Pittsburgh, Pa. The criteria used for including a given subject in this study were (a) a completely negative history of nasal or respiratory symptoms which could in any way be interpreted as being on an allergic basis, (b) the absence of steroid, bronchodilator, or antihistamine medication as part of the treatment of other current disease states, and (c) a history of living 5 or more years in the Pittsburgh area. Only 100 of the first 136 subjects tested fulfilled all the above criteria. Of those who did fulfill these criteria, 51 were white, 49 Negro, 55 female, and 45 male. The age range was from 16 to 81 years, and 76 were over the age of 40.

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Antigens.—The antigens used in this experiment were prepared by the Allergy Laboratory, Montefiore Hospital, Pittsburgh, Pa. The pollen antigens were extracted from dry defatted pollens by incubation in Coca's solution* for 24 to 48 hours. After Seitz filtration, glycerin was added and the solutions were diluted with buffered saline† so that the most concentrated pollen extracts used for skin testing contained 0.1 mg. N per milliliter and 6.0 per cent glycerin. The dust and mold extracts were prepared in a similar fashion to the pollen extracts, except that no glycerin was added. The concentrated dust extract contained 0.009 mg. N per milliliter and the concentrated mold extract contained 0.015 mg. N per milliliter.

The five antigenic substances used in this study were extracts of ragweed, mixed trees, mixed grasses, mixed molds, and house dust; the two control solutions tested on each subject were glycerin-saline and histamine-saline. The concentrated ragweed antigens contained equal parts of extracts of tall ragweed and short ragweed with 6 per cent glycerin. The concentrated mixed tree antigens contained equal parts of extracts of maple, elm, poplar, hazelnut, birch, ash, hickory, black walnut, sycamore, oak, and beech with 6 per cent glycerin. The concentrated mixed grass antigens contained equal parts of extracts of timothy, orchard grass, redtop, June grass, sweet vernal, and perennial rye with 6 per cent glycerin. The concentrated mixed mold antigens contained equal parts of extracts of alternaria, hormodendrum, aspergillus, and penicillium. The concentrated dust extract was made from vacuum cleanings from carpets, pillows, mattresses, and upholstered furniture. The concentrated glycerin-saline control contained 6 per cent glycerin in buffered saline. The concentrated histamine control was a 1:1000 solution of histamine phosphate in buffered saline. Each of the seven concentrated test substances was diluted 1:10 and 1:100 in buffered saline.

Testing.—Subjects were first given intradermal injections of approximately 0.02 ml. of the 1:100 dilutions of the seven concentrated test solutions. Disposable plastic syringes with disposable No. 27 needles were used, the test sites were one inch apart on the lateral surface of the arm, and the results were read 15 minutes after injection. Based on the observations of Grow,¹ a wheal 5 mm. or greater in diameter was the preselected size considered to be a positive intradermal test. Erythema was not used as a criterion because it could not be evaluated on pigmented skin and 49 per cent of the subjects were of the Negro race. If a test with the 1:100 dilution of any particular extract was negative after 15 minutes, the subject was retested with the 1:10 dilution. Finally, if the 1:10 dilution was also negative for a given substance, the most concentrated test solution was applied. During the waiting period between these series of tests, details of the personal and family allergic history were obtained from each patient.

*Coca's solution contains 70 Gm. NaCl, 38.4 Gm. NaHCO₃, and 56 Gm. of phenol dissolved in 14,000 ml. of distilled water.

†The buffered saline contains 75 Gm. NaCl, 5.5 Gm. KH₂PO₄, 16 Gm. Na₂HPO₄ · 7H₂O, and 58 Gm. phenol dissolved in 15,000 ml. of distilled water.

RESULTS

Pollen Extracts.—The data shown in Table I summarize the incidence of positive intradermal tests observed with each concentration of each antigen and each control solution. Most of the information contained in Table I is self-explanatory, but it is noteworthy that a positive test was obtained in 16 per cent of the subjects injected with the 6 per cent glycerin-saline control solution. That the 6 per cent glycerin was responsible for these positive reactions rather than the buffered saline is evidenced by the fact that none of the subjects responded to 0.6 or 0.06 per cent glycerin suspended in the same diluent. The data also suggest that positive reactions to the 6 per cent glycerin-saline solutions were on the basis of a nonspecific irritation because of the 16 subjects, who reacted to the 6 per cent glycerin-saline control solution, only 7 responded to all three antigens containing the same per cent of glycerin, only 12 responded to at least two of the antigens containing the same glycerin, 14 responded to at least one other of the concentrated antigens, and 2 responded to the 6 per cent glycerin-saline control solution alone. Had the glycerin response been specific, almost all of the subjects responding to glycerin in saline should also have responded to the same concentration of glycerin present in the ragweed, grass, and tree antigens.

TABLE I. INCIDENCE OF POSITIVE INTRADERMAL SKIN TESTS IN A POPULATION OF 100 INDIVIDUALS WITHOUT HISTORY OF RHINITIS AND/OR ASTHMA

	0.1 MG. N/ML. WITH 6% GLYCERIN	0.01 MG. N/ML. WITH 0.6% GLYCERIN	0.001 MG. N/ML. WITH 0.06% GLYCERIN
Ragweed with glycerin	28%	8%	0
Mixed grasses with glycerin	35%	2%	0
Mixed trees with glycerin	30%	3%	0
Saline diluent with glycerin	16%	0	0
	Conc.	1:10	1:100
Mixed molds without glycerin	17%	2%	1%
Dust extract without glycerin	50%	19%	4%
	1:1000	1:10,000	1:100,000
Histamine phosphate	100%	100%	92%

Regarding the results obtained with the dilute solutions of the grass, ragweed, and tree pollens, it is highly significant that none of the 100 control subjects responded with a positive test to the antigen containing only 0.001 mg. N per milliliter. These findings are in contrast to an incidence of approximately 85 per cent positive skin reactions when this concentration of this ragweed extract was tested on 66 subjects with a well-documented history of rhinitis and/or asthma during the ragweed season.⁶

Dust and Mold Extracts.—It can be seen in Table I that the dust extracts used in these studies caused more positive skin reactions than did the pollen or mold extracts. The positive reactions observed with glycerin are of no concern to the dust and mold extract results since these extracts contained no glycerin.

The Incidence of Multiple Positive Skin Tests.—The incidence of multiple positive skin tests to the five antigens and the glycerin diluent in the patients presented in Table I is summarized in Table II. It may or may not be significant that 5 of the 8 persons responding to 0.01 mg. N per milliliter of ragweed also responded to the 1:10 dilution of dust extract, but no other cross-reactivity patterns were noted with respect to skin testing with the antigens employed. It is apparent in Table II that the most concentrated extracts used for this study elicited too many positive reactions in asymptomatic individuals to be of much assistance as a diagnostic aid in the identification of offending substances in cases of rhinitis or asthma. Even the five 1:10 dilutions of the concentrated antigens elicited one or more reactions in almost 25 per cent of the patients. As mentioned above, reactions to the 1:100 dilution of the concentrated antigens were extremely uncommon in asymptomatic individuals and, therefore, a positive reaction to this dilute antigen becomes a highly significant observation when associated with a compatible clinical history.

TABLE II. THE INCIDENCE OF MULTIPLE POSITIVE SKIN TESTS TO THE FIVE ANTIGENS AND THE ANTIGEN DILUENTS IN THE PATIENT GROUP PRESENTED IN TABLE I

ANTIGEN OR DILUENT CON- CENTRATIONS	1 OR MORE POSITIVE TESTS (%)	2 OR MORE POSITIVE TESTS (%)	3 OR MORE POSITIVE TESTS (%)	4 OR MORE POSITIVE TESTS (%)	5 OR MORE POSITIVE TESTS (%)	6 OR MORE POSITIVE TESTS (%)
Concentrated	71	48	25	19	11	2
1:10	24	5	3	3	0	0
1:100	4	1	0	0	0	0

Positive Intradermal Tests as Related to Other Factors.—An attempt was made to relate the incidence of skin sensitivity with the five test antigens to the past history of allergic manifestations other than rhinitis and asthma. Such a consideration was necessary because 46 of the subjects gave a history of having had intermittent hives, poison ivy, or drug reactions sometime in the past. As seen in Table III there was no correlation between such personal histories and skin sensitivity to the test antigens employed except in the case of subjects who previously had contact dermatitis. Of those having a personal history of contact dermatitis (primarily poison ivy), 95 per cent reacted to one or more of the concentrated antigens and 37 per cent reacted to one or more of the 1:10 antigen dilutions, but only 5 per cent reacted to the 1:100 dilution. These results may be significantly different from the data collected from individuals having no personal history of contact dermatitis, among whom only 65 per cent reacted to the concentrated antigen, only 21 per cent to the 1:10 dilution, and 4 per cent to the 1:100 antigen dilution. These data are in keeping with the previous suggestion that the skin of individuals having had contact dermatitis is hyper-reactive to nonspecific irritation⁷ since the post contact dermatitis group was not hyperreactive to the dilute solution of antigen where skin testing becomes highly specific.

The data relative to family history, race, sex, and age are summarized in Table IV. No correlation could be made between the occurrence of positive intradermal tests and a family history of hives, eczema, asthma, or hay fever. In

TABLE III. THE PER CENT OF ONE OR MORE POSITIVE SKIN TESTS IN PATIENTS WITH A HISTORY OF ALLERGIC CONDITIONS OTHER THAN RHINITIS AND/OR ASTHMA

	NO. OF CASES	1:100 ANTIGEN (%)	1:10 ANTIGEN (%)	CONC. ANTIGEN (%)
1. History of hives	28	4	21	64
No history of hives	72	4	25	74
2. History of contact dermatitis	19	5	37	95
No history of contact dermatitis	81	4	21	65
3. History of drug reactions	18	0	11	50
No history of drug reactions	82	5	27	76
4. History of either 1, 2, or 3	46	4	26	67
No history of 1, 2, or 3	54	4	21	74
5. Average of all patients	100	4	24	71

addition, there was no significant difference in the incidence of positive tests as related to age or race, but there was a rather marked tendency for males to have more positive tests to the lower concentrations of antigen than was observed among the females (Table IV). If significant, the reason for the difference is not clear.

TABLE IV. THE PER CENT OF ONE OR MORE POSITIVE SKIN TESTS AS RELATED TO SEX, RACE, AND FAMILY HISTORY OF ALLERGY

	NO. OF CASES	1:100 ANTIGEN (%)	1:10 ANTIGEN (%)	CONC. ANTIGEN (%)
1. Females	55	0	15	73
2. Males	45	9	36	69
3. Under age of 40	24	8	33	66
4. Over age of 40	76	3	21	72
5. White	51	6	24	63
6. Negro	49	2	24	80
7. With family history of allergy	19	0	16	53
8. Without family history of allergy	81	5	26	75
9. Average of all patients	100	4	24	71

Passive Transfer Studies.—The question arose as to whether the positive reactions observed with the intermediate concentrations of antigen were due to skin sensitizing antibody, or whether they were due to a nonspecific irritation effect. Accordingly, 0.1 ml. of serum from each of the 5 patients responding to both the 0.01 mg. N per milliliter of ragweed extract and to the 1:10 dilution of dust extract, and from each of the 3 patients reacting to the 0.01 mg. N per milliliter of ragweed alone, was injected intradermally into a normal recipient. Forty-eight hours after application to the normal recipient, all 8 sites were challenged with ragweed antigen containing 0.1 mg. N per milliliter without glycerin. Of the 8 sera tested, 3 were clearly shown to have passively transferable skin sensitivity antibody as evidenced by fully developed Prausnitz-Küstner (P-K) test reactions with wheals, pseudopodia, erythema, and itching. As controls for this experiment, 1:10,000 histamine applied to the recipient was positive, and three normal sites on the recipient were unequivocally negative to this concentration of ragweed extract.

Forty-eight hours after the recipient sites were challenged with ragweed extract, the same 8 sites were again challenged with the 1:10 dilution of dust extract. On this occasion, 4 of the 5 sera from patients with positive direct tests to the 1:10 dust extract had strongly positive reactions and all 3 of the sera from patients with negative direct tests were also negative to the P-K test. Three normal sites on the recipient did not respond to the 1:10 dilution of dust extract. Details of this experiment are presented in Table V, and it was concluded from these data that skin sensitizing antibody to dust or to ragweed was indeed present in 5 of the 8 sera tested.

DISCUSSION

It is not possible to compare directly the results obtained in this study with previous reports in the literature because (a) a variety of methods have been used to express the concentration of extracts used for testing, (b) the presence of multiple antigens in pollen extracts limits the significance of any attempt made to quantitate the amount of antigen in a given extract, and (c) it is highly unlikely that any two extracts prepared from dust or mold, or from plant, weed, or tree pollen would contain equal concentrations of the multiple antigens known to be present in each instance. In general, however, the data in Table I are in reasonable accord with the existing literature which describes the incidence of positive intradermal tests when the antigens and the concentrations of antigens similar to those used for this study were injected into asymptomatic individuals.¹⁻⁵ For example, Efron and Boatner⁵ observed 5 per cent positive reactions with 0.002 per cent of their solution of "purified pollen extracts" and 10 per cent positive reaction with 0.02 per cent of the same ragweed antigen solution.

The incidence of positive and of negative intradermal tests, when antigens are injected into the skin of asymptomatic individuals, has considerable bearing upon the interpretation of results when the same antigens are tested on patients with problems involving rhinitis and asthma. For example, a positive reaction obtained with a 0.001 mg. N solution of the pollen extracts of trees, ragweed, and grasses used for this study becomes a highly significant clinical finding when a patient has physical manifestations of allergic disease during the season of the year when such antigens are known to be present in the air of the local environment. Conversely, a positive reaction to the most concentrated extracts used in this study are of little diagnostic aid when found to occur on the skin of a patient with perennial rhinitis or asthma of unknown etiology. When confronted with a patient with symptoms of unknown etiology, it is difficult to assign a casual relationship between a positive skin test with a concentrated antigen and the symptoms when approximately 50 per cent of an asymptomatic population have two or more positive reactions when tested with a battery of only five of the concentrated antigen solutions.

The demonstration of passively transferable antibody in the sera of 5 of the 8 positive reactors to the intermediate concentrations of ragweed and dust indicates that at least 5 per cent of the asymptomatic individuals studied had

TABLE V. PASSIVE TRANSFER STUDIES ON THE SERA FROM 5 ASYMPTOMATIC INDIVIDUALS WITH POSITIVE INTRADERMAL TESTS TO RAGWEED AND DUST AND 3 ASYMPTOMATIC INDIVIDUALS WITH A POSITIVE INTRADERMAL TEST TO RAGWEED ALONE

	PATIENT									
	C. M.C.	M. T.	P. M. P.	K. M.	N. M.	F. I. J.	W. G.	C. L. G.		
Age	25	60	24	66	64	54	74	35		
Sex	F	M	M	M	F	M	M	M		
Race	W	W	W	W	N	W	N	N		
Diagnosis	Rheumatic heart disease	Essential hypertension	Normal student	Degenerative joint disease	Normal housewife	Diabetes mellitus	Peptic ulcer	Malignant hypertension		
Reaction recorded*	Wheal; erythema	Wheal; erythema	Wheal; erythema	Wheal; erythema	Wheal	Wheal; erythema	Wheal	Wheal		
Direct test 0.6% glycerin (control)	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.		
Direct test ragweed (0.01 mg. N/ml.)	5 × 5 mm. + P† 15 × 15 mm.	5 × 5 mm. 20 × 20 mm.	5 × 7 mm. 25 × 25 mm.	5 × 6 mm. 0	6 × 6 mm.	6 × 6 mm. 20 × 20 mm.	5 × 5 mm.	5 × 5 mm.		
P-K test ragweed (0.1 mg. N/ml.)	8 × 8 mm. + P 30 × 30 mm.	10 × 7 mm. + P 35 × 35 mm.	Neg.	Neg.	6 × 6 mm. 25 × 25 mm.	Neg.	Neg.	Neg.		
Direct test (1:10 dust)	5 × 6 mm. + P 15 × 20 mm.	6 × 6 mm. 20 × 20 mm.	7 × 6 mm. 30 × 30 mm.	7 × 7 mm. 10 × 10	7 × 7 mm. + P	Neg.	Neg.	Neg.		
P-K test (1:10 dust)	8 × 8 + P 25 × 25 mm.	9 × 7 mm. + P 30 × 30 mm.	7 × 6 mm. 15 × 15 mm.	7 × 7 mm. 20 × 20 mm.	Neg.	Neg.	Neg.	Neg.		

*Erythema not recorded on pigmented skin.

†P = pseudopodia.

positive intradermal tests associated with the presence of skin sensitizing antibody in their sera. The 5 per cent incidence indicated is undoubtedly an underestimate since the passive transfer studies were not done on all sera from positive reactors. The other sera were not tested because of an unwillingness to run the additional risks of inoculating recipients with the B virus responsible for serum hepatitis. If one assumes that the incidence of positive P-K tests would have been approximately the same with the 16 additional sera from subjects who had a direct positive test to the 0.01 mg. N per milliliter of pollen extracts, or the 1:10 dust or mold extracts, then it would appear that detectable amounts of skin sensitizing antibody against one or more of the five antigens were present in the sera of over 10 per cent of the asymptomatic individuals in this study.

Regarding nonspecific irritation as a cause for positive tests, some of the weak responses in the ragweed group may well have been caused by a nonspecific irritation. In addition, 16 per cent of the subjects reacted to the 6 per cent glycerin-saline control solution. That these reactions were also nonspecific is suggested by the fact that only 7 of the 16 subjects reacted to all three of the antigens containing the same concentration of glycerin. It is probable that the converse of this situation also occurred in that some patients must have responded to the irritating effects of 6 per cent glycerin in one or more of the concentrated antigens at a time when the test with the 6 per cent glycerin control solution was negative. These findings are probably best interpreted as an indication that many nonspecific positive reactions occurred when test antigens containing 6 per cent glycerin were employed, but that some of the positive reactions to the concentrated pollen, mold, and dust extracts may also have been on the basis of a specific antigen-antibody interaction.

The clinical significance of a positive test due to specific antigen-antibody interaction on the skin of an asymptomatic individual is not entirely clear. Chambers and Glaser⁸ and Ratner⁹ present convincing evidence that some of the asymptomatic individuals, particularly children, with positive skin tests to ragweed pollen develop clinical symptoms of seasonal pollinosis in subsequent years. On the other hand, as pointed out by Feinberg¹⁰ and by Fuchs,¹¹ it is most unusual that an individual will develop clinical symptoms of seasonal pollinosis after the age of 40. In the present study, 67 of the positive results obtained with the 1:10 and 1:100 dilutions of the concentrated antigens were elicited on the skin of individuals older than 40. Since many of the positive results with the 1:10 and 1:100 dilutions of antigen were probably due to specific antigen-antibody interactions, it follows that most of the older age group individuals with positive tests will not develop seasonal pollinosis in the future despite the fact that their sera contained skin sensitizing antibody. This complete lack of correlation between positive intradermal tests and clinical symptoms is not surprising in view of the fact that a high degree of skin reactivity can and frequently does remain when clinically sensitive patients become asymptomatic as a result of specific hyposensitization.¹² A striking example of this situation was recently observed in a patient who had severe symptoms of ragweed pollinosis for 3 years prior to becoming completely asymptomatic without

specific therapy. At the end of his second asymptomatic season, this individual had a 4+ reaction to 0.0001 mg. N per milliliter of the ragweed antigens used for the present tests.¹³

The present experiments indicate that skin sensitizing antibody can be detected in the sera of a relatively large number of individuals who do not have clinical manifestations of asthma or rhinitis. It is equally true that detectable skin sensitizing antibody to ragweed, for example, is usually present in the serum of a patient with rhinitis or asthma during the hay fever season. Although it seems likely that skin sensitizing antibody must be present in order for a patient to have symptoms of seasonal pollinosis, it is also evident that skin sensitizing antibody can be present without clinical manifestations of allergy. This relationship between the presence of antibody and clinical manifestations of allergy is similar to the experimental allergic fevers produced in rabbits immunized with crystalline bovine serum albumin (BSA).^{14, 15} In this experimental model: (a) normal rabbits do not respond with fever when challenged with intravenous BSA, (b) about half of a group of rabbits immunized with BSA respond with fever when challenged with intravenous BSA, (c) some of the nonresponding rabbits have more circulating anti-BSA than those who do respond with fever, and (d) the capacity to respond with fever following intravenous administration of BSA can be passively transferred to normal rabbits by means of serum, but not by means of cells.^{16, 17} Thus, antibody is probably necessary for both the fever reaction in rabbits and for seasonal pollinosis symptoms in man, but fever and pollinosis do not necessarily result when antibody is present.

CONCLUSIONS

1. The incidence of positive intradermal reactions has been studied when 100 asymptomatic individuals were tested with graded concentrations of each of five antigen extracts.
2. The incidence of positive reactions to these antigens ranged from 50 to 0 per cent, depending upon the antigen and the concentration of extract used.
3. Six per cent glycerin, a commonly used stabilizer of skin test antigens, elicited positive intradermal tests in 16 per cent of the individuals tested; 0.6 per cent glycerin in saline did not elicit any positive intradermal tests.
4. At least 5 per cent of the asymptomatic individuals studied had positive intradermal tests associated with the presence of skin sensitizing antibody in their sera. The 5 per cent incidence is undoubtedly an underestimate since the passive transfer studies were attempted with only 8 sera.
5. Positive intradermal tests and passively transferable skin sensitizing antibody against ragweed and dust were found in some individuals older than 40 years of age and who are probably destined to remain asymptomatic for the rest of their lives.

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