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ALLERGEN-SPECIFIC IgE IN ATOPIC DERMATITIS

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Abstract. Allergen-specific IgE was studied in 36 adults and 24 children with atopic dermatitis. A higher number of positive skin tests and positive RAST (radioallergosorbent test)-reactions against common allergens was found in patients with high serum-IgE values than in patients with normal levels. The agreement between RAST and intradermal tests depended to a large extent on the allergen tested. The largest discrepancies were seen with extracts from horse, cow, house dust, and food. In children and adults with atopic dermatitis alone and no coexisting asthma or allergic rhinitis, circulating reagins against common allergens could be demonstrated using the RAST. No correlation was found between the number of circulating basophils and the serum IgE concentration. The eosinophil leucocytes were increased in patients with a high serum IgE level and here a slight correlation was found. In the adult group the frequency of heterophile antibodies to BGG was similar to that in healthy adults.

For diagnosing hypersensitivity in atopic patients, scratch and intradermal tests with various allergens have been used in clinical practice. In 1967 the reagins or skin-sensitizing antibodies were shown to belong to a new class of immunoglobulins, IgE (6, 7). With the radioallergosorbent test (RAST) of Wide et al. (16) a new and in vitro method was introduced to determine allergen-specific IgE antibodies. This technique has been used to study circulating reagins in patients with asthma and allergic rhinitis, and comparisons have been made between RAST, intradermal tests and provocation tests in these groups of patients (2, 4, 12, 13, 16).

In the present study the results obtained with intradermal tests and RAST using common allergens have been compared in adult patients with atopic dermatitis who have elevated and normal IgE values. The occurrence of heterophile antibodies to bovine gammaglobulin (BGG) was also investigated in these patients. Since it has often been claimed that circulating eosinophil and basophil leucocytes are involved in allergic reactions, their number was studied in relation to the serum IgE levels. Finally, in a selected group of children with atopic dermatitis alone, allergen-specific IgE against a standard set-up of common allergens was determined using the RAST method.

MATERIALS AND METHODS

Patients

I. Twenty patients with a high IgE level (> 1000 ng/ml) in serum; 10 males and 10 females, aged 17 to 35 years. They were randomly selected from a previous study of serum IgE levels in a large number of patients with atopic dermatitis (17). Nineteen of the 20 patients also had had symptoms of asthma and/or allergic rhinitis during the previous 3 years. Eight patients had a dermatitis graded as a mild, 7 as moderate and 5 as severe.

II. Sixteen patients with an IgE level in serum within normal limits (125 to 500 ng/ml), 4 males and 12 females, aged 16 to 37 years. They were also selected at random from the previous study (17). Seven of the 16 patients had had symptoms of asthma and/or allergic rhinitis during the previous 3 years. In 9 patients the dermatitis was classified as mild, in 5 as moderate and in 2 as severe.

III. The 9 children with the highest serum IgE values (R.V. $\geq +0.4610$) and atopic dermatitis alone in the aforementioned study (17) were asked to come for a follow-up investigation a year later. In 8 patients new blood samples could be collected, the patients were examined, and a new case history with special regard to allergic manifestations was once more taken.

IV. From the same study (17) a random selection of 20 patients was made from the children over 3 years of age with only atopic dermatitis and serum IgE values within normal limits (R.V. ± 0.2666). Seventeen patients were able to come a year later and were examined in the same way as the children with high IgE levels.

V. Thirty-six healthy blood donors, aged 20 to 58 years, with no history of atopy were selected randomly for control of heterophile antibodies.

Allergen extracts

The following 13 commercially available allergen extracts were used in the RAST and skin tests in the adult group: dander from horse, cow (Vitrum AB, Sweden), dog and cat (Dome Chemicals, Inc., New York, N.Y., USA); pollens from birch, timothy, dandelion and ox-eye daisy (Vitrum AB); wool and house dust (Dome Chemicals); unboiled egg

yolk, unboiled milk and fish (Vitrum AB). The same batches of allergen extracts were used in both the RAST and skin tests. The only exception to this was birch pollen, but here the two extracts used were compared with the RAST-system (10) and found to be of a very similar quality.

In the intradermal tests the following types and numbers of allergen extracts were also included: dust (1), excelsior (1), mold mixture (1), foods (9), feathers (1), pollens (3) and plants (7) (Vitrum AB, Sweden).

In the child group, the same batches of allergen extracts were used as in the study of Berg et al. (2), except for horse dander (Vitrum AB) and our own preparations of egg white and milk. These allergens are listed in Tables IV and V.

Intradermal tests

0.1 ml of each extract was injected intradermally in the back of the patient. The standard dilutions used were 1:1000 of extracts from Vitrum AB, and 100 PNU of extracts from Dome Chemicals. Coca's solution was used as a control and histamine 1:10 000 as a reference standard. The tests were read after 20 minutes and were considered positive when the sum of two diameters of the wheal, measured at right angles, was 20 mm or more. A sum of 30 to 40 mm was graded 2+, and 40 to 50 mm as 3+, etc. The histamine reaction could be regarded as a 3+ reaction in all patients except 4. When correction was made for this, only two of the test results listed in Table I had to be changed.

IgE and RAST analyses

In the adult group, venous blood samples were drawn immediately before the intracutaneous tests. In the child group, venous blood samples could also be collected since, with one exception, only children over 3 years of age were selected for the study. All the sera were separated after 2 to 3 hours at room temperature and stored at −20°C until analysed.

The IgE determinations were carried out according to the technique described previously (17).

The reaginic antibodies of IgE type against the 13 allergens used in the adult study were estimated using the radioallergosorbent technique (RAST) (16) as described in detail in (8). In the child group a modification was used with paper discs as the insoluble matrix (14, 15) instead of cellulose particles.

The standard serum used for quantitative estimation in RAST was obtained from an untreated, birch-pollen-sensitive patient with a high concentration of IgE antibodies. This standard serum was divided into aliquots and stored at −20°C. The concentration of reagins to any allergen is then given in per mille of the standard serum used as described by Johansson et al. (8). For convenience a scale of 1 to 7 is often used where 1 means a value of 3 to 5.6 per mille and 7 a value of more than 1000 per mille. Since the allergen content in the extracts varies considerably both on a quantitative and on a qualitative basis, the results cannot, as a rule, be compared between different allergens. However, for each allergen the results in different individuals can be compared, as well as in different serum samples from the same individual.

Heterophile antibodies

The amount of heterophile antibodies in serum, i.e. antibodies directed against gamma-globulin from cows and related species, was determined in groups I and II and the controls using the following radioimmunological technique: gamma-globulin from sheep was coupled to CNBr-activated cellulose particles (1), 1 mg gamma-globulin per 100 mg particles. Bovine gamma-globulin (BGG) was labelled with ^{125}I as has been described previously for IgE (9). The particles were suspended in 0.05 M phosphate-buffered saline, pH 7.4, with 1% Tween 20 and 1% human serum albumin (HSA), and 0.2 mg of the particles were incubated overnight at room temperature with 0.05 ml of the patient's serum. After washing with saline and centrifugation, 0.1 ml of ^{125}I-labelled BGG corresponding to approximately 60 000 counts per minute (cpm) was added for a second incubation overnight. After washing, the radioactivity bound to the particles was measured in a gamma scintillation counter. The serum from an individual (TF) with a known high concentration of heterophile antibodies was used as a reference standard and arbitrarily given a concentration of 1000 units. The amount in the sample was expressed in arbitrary units calculated from the standard curve. Values above 2 units were considered as positive.

Blood cells

The number of white blood cells (WBC) per mm^3 and circulating eosinophil leucocytes per mm^3 was determined with the routine laboratory techniques using venous blood collected in EDTA-containing test tubes. The basophil leucocytes in blood were determined as described by Shelley & Juhlin (11).

RESULTS

Adults

The skin tests with the 36 allergens showed a greater number of positive reactions in the patients with a high IgE level. This group had an average of 9.2 positive skin tests (range 2 to 19), occurring in all 20 patients. Those with a normal IgE level had an average of 4.4 positive skin tests (range 0 to 12), occurring in 12 of 16 individuals. The number of strongly positive reactions (3 to 4+) was also larger in the patients with a high IgE in serum (25, occurring in 13 of 20 patients) as compared with those with normal IgE values (2, occurring in 2 of 16 patients). Most of the strongly positive reactions were encountered with pollen.

Patients with a high IgE level also had a greater number of positive RAST reactions. They had an average of 4.6 positive reactions (in 17 of 20 patients), compared with an average of 1.3 (in 11 of 16 patients) for those with a normal IgE. In the same manner the number of strongly positive RAST reactions (RAST 5 to 7) was greater in the patients with high IgE, 18 (in 8 of 20 patients) versus 2 (in 2 of 16 patients) in the group with normal IgE.

In Table I the results are listed from the compar-

Table I. *Comparison of RAST and intradermal tests in adult patients with atopic dermatitis*

	Strength of intradermal test reaction															
	0				+				++				+++			
	RAST				RAST				RAST				RAST			
Allergen	0	1	2–4	5–7	0	1	2–4	5–7	0	1	2–4	5–7	0	1	2–4	5–7
Horse	12	2	2	0	7	2	2	0	4	0	1	0	1	0	2	1
Dog	25	1	2	0	1	3	1	0	0	0	2	1	0	0	0	0
Cat	17	1	3	0	3	1	4	0	1	1	4	1	0	0	0	0
Cow	10	1	0	0	15	0	3	0	6	0	0	0	0	0	0	1
Wool	33	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0
Birch	20	1	2	0	1	0	1	0	0	0	4	2	0	0	1	4
Timothy	20	4	0	0	4	1	0	0	4	0	0	0	0	0	3	0
Ox-eye daisy	19	1	0	0	6	0	0	0	2	1	1	0	1	0	2	3
Dandelion	23	1	1	0	3	0	2	0	0	0	2	2	1	0	0	1
House dust	8	0	1	0	9	0	0	0	7	0	8	3	0	0	0	0
Egg yolk	33	0	2	0	0	0	0	0	0	0	1	0	0	0	0	0
Milk	26	1	6	0	1	0	1	0	1	0	0	0	0	0	0	0
Fish	30	2	3	0	1	0	0	0	0	0	0	0	0	0	0	0
Total	276	15	23	0	51	7	15	0	25	2	23	10	3	0	8	10

ative study of intradermal tests and RAST with thirteen allergens. The results from both the group with high and normal IgE values have been pooled.

When studying the sum of all tests, they agreed, that is both were either positive or negative, in 75% of the 468 test pairs.

In 79 (17%) of the test pairs, the skin test was positive but the RAST negative. Three of these positive skin tests were graded 3 + (+ + +), one was for horse dander, one for ox-eye daisy and one for dandelion pollen (Table I). Both pollen reactions were recorded in a patient with severe dermatitis. He had RAST reactions positive to several animal danders, to birch pollen, to milk and fish, and a history of allergic rhinitis, at least when exposed to birch pollen. The skin test strongly positive to horse occurred in a patient who had not been in contact with horses for many years.

The RAST reaction was negative in 25 tests where the intra-dermal tests were graded as 2 +. The discrepancies were mostly seen with extracts from house dust, cow, horse and timothy and occurred to the same extent in patients with high and normal serum IgE values.

Of the positive intradermal tests graded as 1 +, 51 had a corresponding RAST reaction which was negative. This means that more than two-thirds of the 1 + skin tests had a negative RAST result. The finding was especially common with extracts from cow, house dust, horse and ox-eye daisy. For house dust, the discrepancy was as common in the group with high as with normal serum IgE. For the other extracts, it was more commonly seen in the patients with a high IgE level.

The finding of a positive RAST reaction, where the corresponding intradermal test was negative, occurred in 15 + 23 tests = 38 tests. The isolated RAST-positive reaction was never stronger than 3. It was mostly encountered for the food extracts used and also for some of the animal danders and most common in the group with high serum IgE levels. Three patients with a high IgE value accounted for 15 of the 23 negative intradermal reactions in the group with RAST 2 to 4.

The 9 adult patients with only atopic dermatitis and no asthma and/or allergic rhinitis had altogether 9 positive RAST reactions of strength 1 to 3, occurring in 5 patients. Four of the reactions were positive to pollen, two to animal dander, two to milk and one to house dust. The intradermal test in these 9 patients showed 1 + reactions (14 patients) and 2 + reactions (9 patients). None of the 1 + reactions had a corresponding positive RAST. In one RAST of strength 3 the intradermal test was 2 + and RAST strength 2 had a positive intradermal reaction in 3 of 5 tests.

Comparison of test results and history of allergy

No provocation tests were done, but all the patients were questioned on several occasions about allergic

Table II. *Comparison between case history of symptoms and intradermal test reactions to thirteen allergens in adult patients with atopic dermatitis*

The figures indicate the number of tests

	Case history positive		Case history negative	
	High IgE	Normal IgE	High IgE	Normal IgE
Skin test positive	56	18	54	26
Skin test negative	23	24	127	191

manifestations when they were exposed to the allergens which had given positive test reactions. There was agreement with the history of illness in 48 % of the positive skin tests and in 51 % of the RAST-positive reactions. A history of intolerance on exposure to an allergen was obtained in 13 % of the patients with negative intradermal tests and in 15 % of the patients with a negative RAST. Further details are given in Tables II and III.

Heterophile antibodies

Heterophile antibodies were found in 67 % of the patients studied. There was no difference between the groups with high or normal IgE values. In the normal controls, heterophile antibodies were found in 86 % of the studied sera.

Eosinophil and basophil leucocytes

The mean value of eosinophil leucocytes in the peripheral blood was higher ($p < 0.01$) in patients with a higher serum IgE level (479/mm³, S.D. 395) as compared with those with a normal serum IgE level (154/mm³, S.D. 115). In those patients with high serum IgE values, there was a slight correlation between IgE value and the number of circulating eosinophils (correlation coefficient 0.7; partial correlation coefficient 0.6, when considering such factors as severity of dermatitis and coexisting asthma or allergic rhinitis). In patients with normal serum IgE levels, those with a moderate or severe type of dermatitis had a slightly greater number of eosinophils ($p < 0.05$) than those with a mild dermatitis. Such a difference could not be found in the group of patients with a high serum IgE level. No significant differences in the number of eosinophils between those with dermatitis alone and the group with coexisting asthma and/or allergic rhinitis could be found in patients with a normal IgE level. No such comparison could be made in the group with high serum IgE levels as here only one patient had only dermatitis.

The mean value of circulating basophils did not differ significantly between patients who had a high serum IgE value and those with a normal one (24/mm³, S.D. 21.2 and 16.6/mm³, S.D. 12.8 respectively). Nor was there any correlation between the patient's IgE value and the number of circulating basophils.

Children

The results for children with an initially high IgE value are given in Table IV. The IgE value had dropped remarkably in patient no. 1. In the other 7 patients the IgE value had remained almost stable or decreased only slightly. RAST analyses were performed in only 7 of the patients as no venous sample could be obtained from patient no. 8 due to her tender age. Four of them had circulating reagins against pollen. Two of the patients also had reagins against animal dander and food extracts. Many of the reactions were strongly positive. In 2 of the patients with positive RAST, symptoms of allergic rhinitis had developed since the time when they were first studied.

The results for the children who, in the first study, had a normal serum IgE value are given in Table V. In 3 children (nos. 11, 22, 25) the serum IgE value had risen to a high level. In 4 children (nos. 12, 16, 21, 24) there was an obvious decrease. The RAST analyses showed that 7 of the 17 patients had circulating reagins against the tested allergens. All 3 patients whose IgE values now were high, belonged to this group. Four of the patients had reagins against pollen, 2 against animal dander and 2 against food extracts.

The atopic dermatitis was still active and of about

Table III. *Comparison between case history of symptoms and RAST reactions to thirteen allergens in adult patients with atopic dermatitis*

The figures indicate the number of tests

	Case history positive		Case history negative	
	High IgE	Normal IgE	High IgE	Normal IgE
RAST positive	47	11	45	10
RAST negative	32	30	136	209

Table IV. *Results of serum IgE determinations and RAST analyses in children with atopic dermatitis and initially high IgE values*

Patient no.	Sex	Age in years 1969–70	IgE ng/ml Winter 1969–70	IgE ng/ml Winter 1970–71	RAST analyses (1–7) Horse	Dog	Cat	Cow	Birch	Timothy	Ox-eye daisy	Dandelion	House dust	Egg white	Fish	Milk
1	♀	3	880	123												
2	♂	8	1 140	802												
3	♂♀	4	1 750	2 222		1			5					2	5	2
4	♂♂	1.7	3 350	4 320[a]	6	4	4	7	6	3	4	4	5	7	2	5
5	♂	3	440	310[a]					6	2						
6	●	6	570	400					5	3						
7	♂	8	570	620												
8	♀	1.6	400	678	Not done											

[a] Developed allergic rhinitis.

the same degree as the foregoing year in all the examined patients. In the group with initially normal serum IgE values, none had developed symptoms of asthma or allergic rhinitis during the year.

DISCUSSION

A higher number of positive RAST and intradermal tests was observed in patients with a high IgE level than in those with normal IgE values. The difference was especially pronounced for the number of strongly positive reactions. This might very well be expected as the IgE level in serum reflects the amount of circulating reagins. The higher IgE value is likely to reflect not only reagins against a larger number of allergens but also a higher reagin titre against some of the allergens. A determination of the serum IgE

Table V. *Results of serum IgE determinations and RAST analyses in children with atopic dermatitis and initially normal IgE values*

Patient no.	Sex	Age in years 1969–70	IgE ng/ml Winter 1969–70	IgE ng/ml Winter 1970–71	RAST analyses (1–7) Horse	Dog	Cat	Cow	Birch	Timothy	Ox-eye daisy	Dandelion	House dust	Egg white	Fish	Milk
9	♂	4	260	473												
10	♂♀	14	280	623		1										
11	♀	4	240	919					6							
12	♂	9	120	44												
13	♂♀	5	110	91												
14	♀	4	100	51												
15	♀	5	90	117							4	3				
16	♂	8	150	56												
17	♀♂	4	170	168	3			3	4							
18	♂♀	9	160	184												
19	♂	3	100	87												
20	♂	3	270	161					5							
21	♂	12	170	50												
22	♀♂	6	280	985									4	1		
23	●	9	270	310												
24	♂♀	9	170	58												
25	♀	4	250	774										3		

level was therefore found to be of help in predicting pronounced intradermal reactions and thereby making it possible to avoid their occurrence.

In previous studies (4, 12, 13) the comparisons between intradermal tests and RAST had been made with some selected allergens in patients whose main symptoms were asthma or allergic rhinitis. In this study of patients with atopic dermatitis, many also had asthma or allergic rhinitis which had usually been less pronounced. Since we have a different selection of patients and also have studied a larger number of various allergens, our figures cannot be directly compared with those of previous reports.

The birch pollen extract showed the best agreement between the RAST and intradermal tests, as can be seen from Table I. We do not know if this is due to the quality of the extract or whether we have selected people with an active birch-pollen allergy. In favour of a good quality of birch extract is the fact that it is known to be the allergen giving the best agreement with intracutaneous and provocation tests in asthma and allergic rhinitis.

The largest discrepancy between the RAST and intradermal tests was obtained with extracts from horse, cow and house dust. They often gave a negative reaction in the RAST but were positive in the skin test. It is worth noting that we have used the same antigen batches in both test methods. It is possible that the patients with this pattern of reaction have reagins only in the skin and not in the serum, or at least circulating in very small quantities. The house dust extract often represents a heterogeneous mixture of compounds and it is also possible that here some nonspecific factors are responsible for the release of vasoactive substances in the skin. Finally, it is also possible that the coupling of the allergen to the matrix in the RAST procedure is more difficult to accomplish with some antigens. For instance, if the ratio antigen:total protein content in the extract is small, a lot of unspecific protein will bind to the matrix and might thereby exclude the small, but important, antigenic fraction from the binding sites.

It is of interest that the food extracts tested accounted for a large proportion of the test pairs with a RAST-positive reaction and a negative skin test. The RAST reactions graded as 1 might be borderlin evalues and will therefore not be considered. Of the 23 test pairs with a negative skin reaction and a RAST of strength 2 to 4, eleven tests were positive to food extracts. It is difficult to say whether this reflects the fact that more food reagins are circulating than are fixed to the skin or whether it is due to an instability of the extracts when used for skin testing, compared with the freeze-dried or fresh state of the extracts coupled to the solid phase in the RAST procedure. Fifteen of the 23 discordant tests occurred in only 3 patients, but we have no explanation for this. They accounted for 7 of the 11 discordant food tests. These 3 patients had a serum IgE value close to or above 10 000 ng/ml. There is a possibility that in these patients the positive RAST might be a nonspecific finding. It cannot be excluded that, in some patients with a very high serum IgE, some IgE will attach to the Sephadex particles regardless of what allergen they are coated with.

All of the strongly positive RAST reactions had a corresponding positive skin test. In three of the strongly positive skin tests the RAST was negative however. Two of these were in patients with normal histamine and control tests. It therefore seems less likely that they are due to an increased nonspecific reactivity of the skin. One explanation could be that they have no circulating reagins but a large amount fixed in the skin. The patients were tested in the off-season for pollen when the RAST reaction can be of low strength (3).

There are difficulties in making an overall comparison between the intradermal test and RAST. The result varies between the different allergens and, in some instances, only a few patients accounted for a large part of a discrepancy.

Five of the 9 adult patients with only dermatitis had circulating reagins against some common allergens. In two of the nine positive RAST reactions, there was a correlation with the case history. Here, also, the intradermal test was positive. We still know very little about the extent to which one may have circulating reagins which do not cause symptoms, or what the factor may be that determines whether or not they give rise to allergic manifestations.

Three of the children with dermatitis alone and normal IgE levels (nos. 15, 17, 20) also had circulating reagins against some of the common allergens tested. None of these 3 patients had thus far noticed any allergic symptoms when exposed to these allergens. A longer period of observation would be of interest here.

In the absence of provocation tests, the degree of agreement between the case history and the test results is very difficult to evaluate. This is evident from Tables II and III where we have also listed

the number of tests where a positive case history with symptoms on exposure to an allergen could not be verified in the tests. The mechanical irritation by wool is often interpreted by the patients as an allergy, but the results were negative in 17 of the skin and RAST tests despite complaints. A certain number of patients are also likely to overestimate the influence of certain allergens they know might cause allergic symptoms.

The serum IgE level was fairly stable in most of the children when it was determined a year later. An initially high IgE value dropped considerably in one patient and high values were found in 3 patients who previously had normal levels. The change in IgE level was not associated with any obvious change in the clinical picture.

Two of the 25 studied children had developed allergic rhinitis during the year. They both belonged to the group with initially high IgE values. These figures are too small to allow any conclusions but would fit the theory that patients with a high serum IgE level could develop asthma or allergic rhinitis (5). In support of such a theory would also be the fact that we have found few adult patients with a high IgE level and atopic dermatitis alone. None of the children in the group with initially normal IgE values had experienced symptoms of asthma or allergic rhinitis during the year, although the IgE level had risen high in 3 of them. Here, a longer period of observation would also be of interest. It should be remembered, however, that the serum IgE can be looked upon as the sum of all reagins, and titres against only a few allergens might not be reflected as an increased IgE level.

The number of eosinophil leucocytes was significantly higher in our adult patients with a high serum IgE level. Factors such as the severity of dermatitis and coexistent asthma or allergic rhinitis must be considered when investigating for a correlation between serum IgE values and the number of eosinophils. In favour of the possibility that the IgE level and eosinophils are correlated or regulated by the same factor is the fact that the partial correlation coefficient is close to the total ($r = 0.6$; 0.7). That, in the group of patients with a normal IgE, those with a severe atopic dermatitis might have a slightly higher eosinophil count than those with a mild dermatitis does not contradict such a possibility since the eosinophils are here within normal limits.

The presence of heterophile antibodies, that is antibodies directed against gamma-globulin from cows and related species, were studied using the premise that there might be a difference in the permeability of the gut mucosa between atopic individuals and normal controls. If the atopic patient has an increased permeability in his mucosa to food proteins to which he might then develop IgE antibodies, he might also develop, as a parallel phenomenon, heterophile antibodies of the type studied. Or, if all individuals have a similar permeability of the gut mucosa, the atopic patient would have an increased tendency to react with antibody formation on a broad base against the large protein molecules he is absorbing. Our findings of the same or a slightly higher frequency of heterophile antibodies in normal compared with atopic individuals, do not support any of these hypotheses. However, only adults have been studied and it is possible that other figures will be found in children.

As could be expected, reagin titres against common allergens were found more often in patients with high IgE levels. Interesting differences were found in the results obtained with skin tests and the RAST method. Further studies of this type will show whether these differences are more specifically bound to certain groups of allergens. The RAST might also be of special value in atopic patients with concomitant dermatitis as it will make the testing procedure independent of the skin condition.

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