

Potentialiation of IgE production to common environmental allergens by storage house dust mite *Dermatophagoides farinae*

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Summary

Total serum IgE and IgE antibodies against ten common antigens, including *Dermatophagoides farinae* (D.f.), moth, ragweed, orchard grass, cryptomeria, alternaria, aspergillus, dog dander, cat dander and tetanus toxoid, were determined using the PRIST and the Sepharose-RAST, respectively, in 100 clinically non-allergic Japanese subjects and interrelations of IgE responses to these antigens were investigated. We obtained following results. (1) The number of positive RAST antigens, to which the subjects responded, increased in parallel to their total serum IgE levels. (2) Among ten antigens, D.f. and moth antigens contributed a great deal to the elevation of total serum IgE level as compared with other antigens. (3) When the relationship between IgE response to D.f. and similar responses to the other nine antigens was investigated, positive RAST responses to various antigens occurred selectively in the subjects with positive RAST for D.f., and the number of positive RAST antigens to which the subjects responded increased depending upon their D.f. specific RAST levels. (4) Such an association was not found between IgE response to moth and the other nine antigens. These findings suggest that non-specific activation of IgE-producing B cells occurs as a result of continuing stimulation by D.f.

Introduction

Atopic persons usually possess IgE antibodies against a greater number of allergens than non-atopic subjects [1-3]. Until the present, the mechanism causing the polyclonal increase of IgE synthesis is not clear. Marsh *et al.* [4] postulated that an IgE-regulating gene controlling basal serum IgE level non-specifically modulates specific IgE responses. Moreover, Orr & Blair [5] have shown that helminth infection in

animals potentiates IgE responses to unrelated antigens. Soluble factors involved in the potentiation have been demonstrated during *in vitro* experiments [6]. It is now generally agreed that the potentiation is due to a non-specific activation of IgE-producing B cells. It has been a controversial subject whether or not helminth infection in humans enhances IgE responses to non-helminth antigens [7-9]. These observations, however, suggest a possibility that such a stimulus as repeated exposure to potent environmental allergen can promote a non-specific activation of IgE producing B cells. In the present study, to further investigate this problem, we determined IgE antibodies against a panel of ten common antigens by use of the Sepharose®-RAST in clinically non-allergic subjects and analysed the interrelations of the specific IgE responses to these antigens.

Materials and methods

Subjects

The subjects studied were healthy male volunteers ranging in age from 15 to 20 years, who were students at Tsukuba University in Ibaraki Prefecture and at senior high schools in the surrounding area. Their previous histories and present conditions regarding asthma, allergic rhinitis and flexural eczema with pruritus were investigated by allergy specialists and 100 subjects without any of these allergy symptoms were selected. Measured serum IgE levels of the subjects ranged from 4 to 1900 IU/ml, with arithmetical mean value of 252 ± 410 (SD) IU/ml and geometric mean of 79.4 ± 5.7 IU/ml.

Antigens

Freeze-dried antigens of *Dermatophagoides farinae* (D.f.), moth (silk-worm moth), ragweed (short ragweed), orchard grass and cryptomeria (*Cryptomeria Japonica*) pollens, alternaria, aspergillus, and cat and dog danders were supplied by Torii Co., Ltd., Tokyo. *Dermatophagoides pteronyssinus* (D.pt.) was kindly supplied by Dr M. Takaoka of Saitama Prefectural Institute of Hygiene. Tetanus toxoid antigen was purchased from Takeda Chemical Co., Ltd, (Osaka, Japan).

Sepharose-RAST

Three mg of each antigen was coupled to 300 mg (dry weight) of CNBr-activated Sepharose-4B (Pharmacia, Sweden). The antigen-coupled particles (ACP) was suspended in RAST buffer (0.1 M KH_2PO_4 - K_2HPO_4 , pH 7.4, 1% Tween 20) at a concentration of 10 mg/ml.

The Sepharose-RAST was performed on the basis of the method described by Wide *et al.* [10] with some modifications. In the first step, 50 μl of each of ACP suspension (10 mg/ml) was added to 10 $\times$ 70 mm plastic test tube for radioimmunoassay (Sionogi Ltd., Tokyo, Japan), followed by 50 μl of test serum. The tubes were capped and rotated at 60° angle at 20 rpm for 2 hr at room temperature. The ACP was washed three times with 4 ml of RAST buffer by centrifugation at 2000 rpm for 5 min and aspiration leaving 200 μl RAST buffer. Finally, 200 μl of RAST buffer with ACP was centrifuged and the supernatants were further aspirated by a suction device with needle (0.4 mm diameter) and stopper leaving 50 μl of RAST buffer together with the particles in the tube. In the second step, 50 μl of ^{125}I -labelled anti-IgE (approximately 25000 cpm) obtained from Phadebas® RAST kits (Pharmacia, Sweden) were added to each tube

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and further incubated for 16 hr at room temperature. Excess of labelled anti-IgE was washed away by the same procedure with 0.15 M NaCl solution containing 1% Tween 20. The radioactivity of the ACP in 200 μ l wash solution was measured in a gamma-counter. RAST determinations were done in duplicate and mean percentage of binding was calculated by dividing the counts bound to ACP by total counts added to the tube $\times 100$. We examined negative control using 2% human serum albumin (HSA) solution in each RAST assay. The response parameter of RAST was expressed as a percent control; the percent binding of the test sample divided by the percent binding of the HSA negative control $\times 100$.

To determine the cut-off point between RAST positivity and negativity, RAST were similarly assayed using IgE myeloma (PS) preparation which was diluted to 2000 IU/ml in phosphate buffer with 2% HSA, normal non-allergic serum showing negative skin test reactivity to any one of ten antigens, as negative controls, and allergic serum pool from three allergic patients showing positive skin test reactivity (2 + 2) to a total of ten antigens, as positive control. Ten trials were performed in RAST for each antigen. The cut-off points were taken as a 300% of the average binding of 2% HSA for each antigen RAST.

Paper disc RAST

Paper disc RAST was performed as described by Ceska *et al.* [11] with some modifications. D.f. antigen (10 mg) was dissolved in 1 ml of 0.1 M NaHCO₃ buffer containing 0.5 M NaCl and was coupled to twenty paper discs activated with CNBr. Each paper disc was incubated for 2 hr with 50 μ l of test serum on a horizontal shaker. After thorough washing, the discs were further incubated 16 hr with 50 μ l ¹²⁵I-labelled anti-IgE (approximately 25000 CPM) (Phadebas RAST kits, Pharmacia, Sweden). After washing to remove excess labelled anti-IgE, the radioactivity bound to the disc was measured in a gamma-counter. RAST determinations were carried out in duplicate and the result was expressed as mean percentage binding.

Serum IgE levels

Serum IgE levels were determined by paper radioimmunosorbent test (PRIST) (Pharmacia, Sweden) in duplicate.

RAST inhibition test

RAST inhibition tests were performed using test sera (No. 45, 55, 58) as described by Arbesman *et al.* [12] with some modifications.

Serial four-fold dilutions of each of the ten antigens (2 mg/ml) in 2% HSA were prepared and 100 μ l of each were incubated with 100 μ l serum aliquots on a horizontal shaker overnight. The last tube contained diluent alone. The serum-inhibitor mixture was then subjected to the RAST procedure. As a background binding, 2% HSA RAST was similarly run. Percentage inhibition was calculated using the following formula:

$$\left[1 - \frac{\text{RAST binding with inhibitor} - \text{background binding}}{\text{RAST binding without inhibitor} - \text{background binding}} \right] \times 100.$$

Semilogarithmic paper was used for plotting percentage inhibition *vs* dose of inhibitor added. The concentration of the antigen solution required for 50% RAST inhibition was read from the inhibition curve.

Statistics

Statistical analyses were performed at Science Information Processing Center of Tsukuba University using statistical package for Social Science-SPSSH.

Results

Comparison of Sepharose-RAST with paper disc RAST

IgE antibody against D.f. antigen was assayed by the Sepharose-RAST and the paper disc RAST in thirty clinically non-allergic subjects included in the present study. As shown in Fig. 1, the RAST levels (percent of negative control) in Sepharose-RAST were definitely higher than those in the paper disc RAST. The background bindings yielded by IgE myeloma preparation (2000 IU/ml) in Sepharose-RAST and in paper disc RAST were 186 ± 27 (SD)% and $211 \pm 41\%$ of the negative control, respectively. When the cut-off point between RAST positivity and negativity was taken as a 300% of the average binding of 2% HSA, the background bindings were significantly lower than the cut-off value.

Using a sample serum, the reactivity of D.f.-specific IgE to solid phase allergen was compared by the aforementioned RAST methods with decreasing amount of serum (Fig. 2). In Sepharose-RAST, there was a linear relationship from four to sixty-four fold dilutions, while the reactivity approached a saturation level at lower dilutions and became to control level at higher dilutions. In paper disc RAST, the reactivity was nearly linear up to sixty-four fold dilution. The Sepharose-RAST showed higher reactivities at any dilutions of serum than paper disc RAST. The final dilution of the serum which produces RAST positivity was 128 and thirty-two fold in Sepharose-RAST and paper disc RAST, respectively. Thus, the Sepharose-RAST has a higher sensitivity than the paper disc RAST for the detection of low levels of IgE antibody.

To confirm that the cut-off points exceed the upper limit of the non-specific binding of the sepharose-RAST, we tested IgE preparation (2000 IU/ml) from myeloma PS and non-allergic normal serum as negative controls and serum pool sensitive to a total of ten antigens as positive control in the Sepharose-RAST. As shown in Table 1, the average bindings of the negative controls were significantly lower than the cut-off values for each antigen (*t*-tests, $P < 0.01$). On the other hand, positive control showed high RAST bindings with ranges from 628% to 2512%. Since the highest serum IgE level in our given subjects was 1900 IU/ml, the cut-off values thus defined can discriminate the positive RAST response from the non-specific binding of IgE.

RAST for ten antigens

Using the Sepharose-RAST, IgE antibodies against 10 antigens were determined in 100 young adult subjects who were clinically non-allergic. As shown in Fig. 3, D.f. and moth antigens showed high RAST reactivities, but others were very low. When the cut-off point between RAST positivity and negativity was taken as a 300% of the average binding of 2% HSA for each antigen, positive RAST responses to D.f. and moth were found in fifty-five and forty-six subjects, respectively, whereas occurrences of positive RAST responses to other antigens were definitely low.

Relationship between total serum IgE and specific IgE responses to ten common antigens

As shown in Table 2, when all 100 subjects were divided into six groups according to their total IgE levels, positive RAST responses to each antigen tended to occur in the groups with high total IgE levels and furthermore the increase in the number of positive

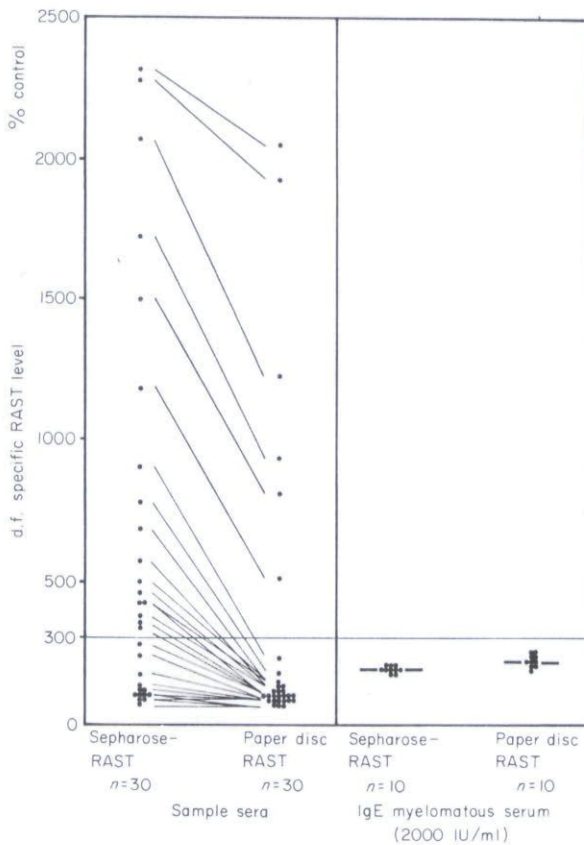


Fig. 1. Comparison of Sephadex-RAST with paper disc RAST. Left column shows RAST bindings for *D.f.* in thirty clinically non-allergic subjects. Right column shows RAST bindings produced by IgE preparation (2000 IU/ml) from IgE myeloma PS. Horizontal bars in the right column represent the average binding of ten RAST determinations. A line at a 300% control represents a cut-off level between RAST positivity and negativity.

RAST antigens, to which the subjects responded, coincided well with their serum total IgE levels.

It remains unknown from this data whether total IgE influences the specific IgE responses to common antigens. These findings, however, suggest that IgE responses to various antigens occur depending upon non-specific activation of IgE producing B cells, which is closely associated with total IgE levels.

*Relationship between IgE response to *D.f.* and similar responses to other antigens*

As shown in Table 3, when the subjects were divided into five groups according to their *D.f.* specific RAST levels, positive RAST response to moth occurred almost evenly from the second to the fifth group. Such responses were rare in the first group with negative RAST for *D.f.* Positive RAST responses to other antigens tended to occur in the groups with high RAST levels for *D.f.* (Group IV and Group V). The mean number

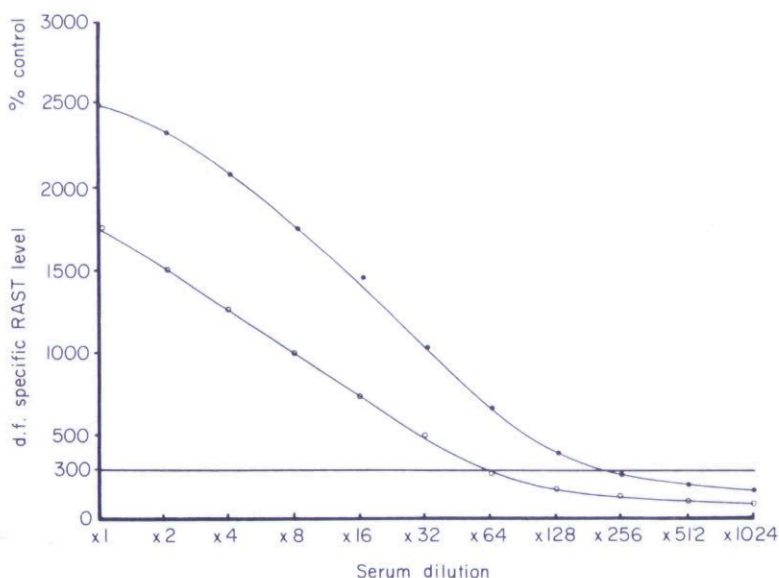


Fig. 2. Comparison of D.f.-specific IgE levels measured by the Sepharose-RAST (●—●) and the paper disc RAST (○—○). The test serum from a study subject was serially diluted to 1024 fold by 2% HSA solution. A line at a 300% control indicates the cut-off level between RAST positivity and negativity.

Table 1. RAST binding of negative control sera and positive allergic serum

Antigen	Mean % control		
	IgE myeloma (2000 IU/ml)	Non-sensitive serum	Sensitive serum pool
D.f.	211 ± 23*	126 ± 14	2512 ± 99
Moth	196 ± 26	112 ± 15	2358 ± 71
Ragweed	207 ± 30	116 ± 29	915 ± 153
Orchard grass	237 ± 16	137 ± 16	2533 ± 99
Cryptomeria	227 ± 27	211 ± 30	920 ± 198
Alternaria	162 ± 13	84 ± 17	841 ± 120
Aspergillus	152 ± 23	87 ± 23	748 ± 195
Dog dander	181 ± 42	172 ± 31	1340 ± 167
Cat dander	143 ± 31	114 ± 9	671 ± 91
Tetanus toxoid	204 ± 13	86 ± 13	628 ± 116

* Mean percent control $\pm$ s.d.; the percent binding of the test sample divided by the percent binding of the HSA negative control $\times 100$. When the cut-off level between RAST positivity and negativity were taken as a 300% control, the mean RAST bindings produced by IgE myelomatous serum and non-sensitive serum were significantly lower than the cut-off level in each antigen RAST (*t*-test, $P < 0.01$).

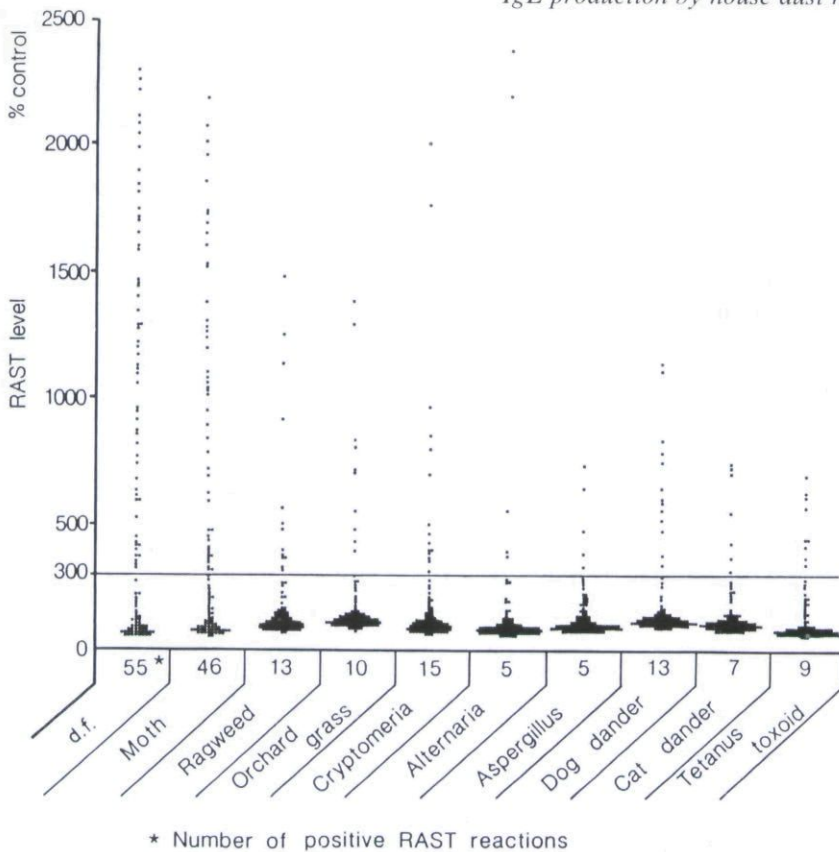


Fig. 3. RAST levels and frequencies of positive RAST reactions to ten common antigens. A line at a 300% control represents the cut-off level between RAST positivity and negativity. (See materials and methods.)

of antigens to which subjects responded increased in parallel to their D.f. specific RAST levels.

Relationship between IgE response to moth and similar responses to other antigens

All the subjects were similarly divided into five groups according to their moth-specific RAST levels (Table 4). This time, although the incidence of positive RAST response to each antigen were very low in the first group in which most subjects concomitantly lacked D.f. response, they were almost even from the second to the fifth group. The mean number of positive RAST antigens did not significantly change from the second to the fifth group. These findings indicate that the non-specific activation of IgE producing B cells can occur as a result of continuing stimulation by an environmental antigen, D.f.

Comparison of RAST levels between D.f. and other antigens

The RAST levels were compared between D.f. and moth antigens (Fig. 4). As can be seen, the relationship was not linear; when D.f. specific IgE reached some threshold level (300% control), IgE antibody production against moth frequently occurred.

Although there was a very weak correlation ($r=0.299$, $P<0.01$) in the total 100 subjects, no significant correlation was obtained ($r=-0.088$, $P>0.9$) in the case of the fifty-five subjects with positive D.f. RAST. The comparison of RAST levels for D.f. and cryptomeria was depicted in Fig. 5. IgE antibodies against cryptomeria were frequently found in the subjects with D.f. specific IgE exceeding 500% of HSA control.

Comparison of RAST levels in various combinations of antigens

When the RAST levels for ten common antigens were compared in various combinations of antigens, there was no intimate correlation in any antigen pairs (Table 5). These results indicated that D.f.-specific IgE response does not affect the magnitudes of the IgE response to various antigens once it has occurred.

RAST inhibition experiments

To exclude the possibility that the clustering of positive RAST responses to various antigens in D.f. responding subjects is attributable to antigenic cross-reactivity between D.f. and other antigens, RAST inhibition experiments were performed using three sera from our volunteer subjects. As shown in Table 6, the amounts of antigens required for 50% inhibition of the RAST for the corresponding antigen were 0.4–42 µg/ml, whereas the concentrations of D.f. antigens required for 50% RAST inhibition for other antigens were more than 2000 µg/ml.

Table 2. Relationship between total serum IgE levels and RAST responses to ten common allergens

Antigens	No. of positive RAST responses					
	Groups by serum IgE levels (IU/ml)					
	I <50*	II 50 –100	III 100 –200	IV 200 –400	V 400 –800	VI >800
D.f.	<i>n</i> =39 6	<i>n</i> =10 2	<i>n</i> =21 18	<i>n</i> =11 10	<i>n</i> =10 10	<i>n</i> =9 9
Moth	7	2	14	6	9	8
Ragweed	1	1	1	1	3	6
Orchard grass	0	1	1	0	4	4
Cryptomeria	0	0	3	1	2	9
Alternaria	0	0	1	1	0	3
Aspergillus	0	0	0	1	1	3
Dog dander	0	1	2	2	4	4
Cat dander	0	1	0	0	1	5
Tetanus toxoid	0	1	0	0	4	4
Total	14	9	40	22	38	55
Mean	0.4	0.9	1.9	2.0	3.8	6.1

* Total serum IgE levels (IU/ml).

Table 3. Relationship between D.f. specific RAST levels and the number of positive RAST responses to nine other antigens

Antigens	No. of positive RAST responses				
	Groups by D.f. specific RAST levels				
	I < 300*	II 300-500	III 500-1000	IV 1000-1500	V > 1500
	<i>n</i> = 45	<i>n</i> = 10	<i>n</i> = 14	<i>n</i> = 15	<i>n</i> = 16
Moth	6	7	12	11	10
Ragweed	1	0	4	3	5
Orchard grass	0	1	0	3	6
Cryptomeria	1	0	3	3	8
Alternaria	1	0	0	1	3
Aspergillus	0	0	1	3	1
Dog dander	0	1	0	6	6
Cat dander	0	0	1	1	5
Tetanus toxoid	0	0	2	2	5
Total	9	9	23	33	49
Mean	0.2	0.9	1.6	2.2	3.1

* D.f. specific RAST levels. The cut-off point between RAST positivity and negativity was a 300% of HSA negative control.

Table 4. Relationship between moth specific RAST levels and the number of positive RAST responses to nine other antigens

Antigens	No. of positive RAST responses				
	Groups by moth specific RAST levels				
	I < 300*	II 300-500	III 500-1000	IV 1000-1500	V > 1500
	<i>n</i> = 54	<i>n</i> = 14	<i>n</i> = 8	<i>n</i> = 12	<i>n</i> = 12
D.f.	15	13	7	9	11
Ragweed	0	5	2	3	3
Orchard grass	1	4	1	3	1
Cryptomeria	3	6	1	3	2
Alternaria	2	0	1	1	1
Aspergillus	1	1	0	2	1
Dog dander	2	2	3	2	4
Cat dander	1	3	1	1	1
Tetanus toxoid	1	2	3	3	0
Total	26	36	19	27	24
Mean	0.5	2.6	2.4	2.3	2.0

* Moth specific RAST levels. The cut-off point between RAST positivity and negativity was a 300% of HSA control.

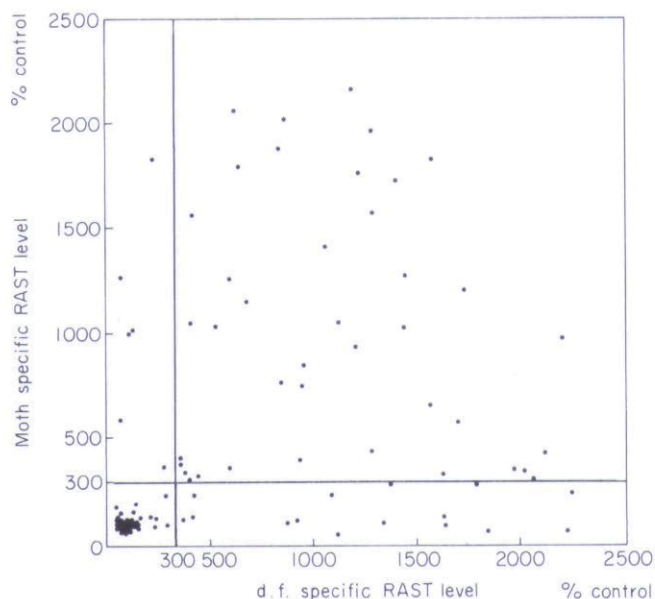


Fig. 4. Comparison of RAST levels for D.f. and moth antigens. Coefficient of correlation was 0.299 ($P < 0.01$). The inner lines in the figure show cut-off level between RAST positivity and negativity for each antigen.

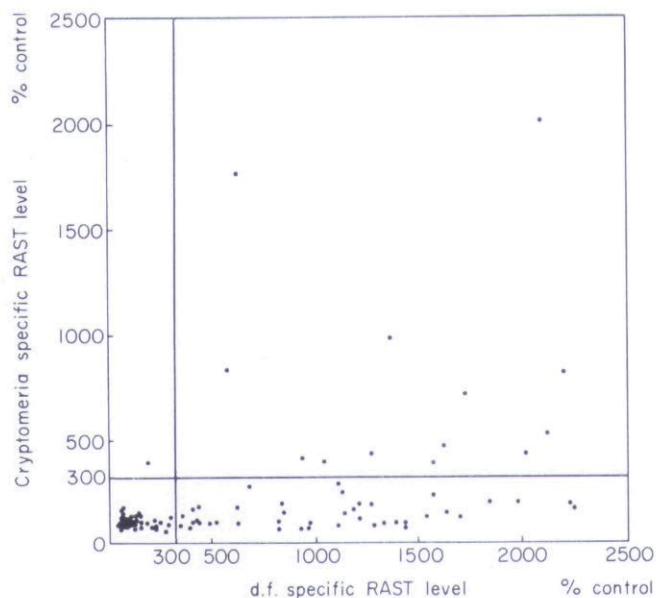


Fig. 5. Comparison of RAST levels for D.f. and cryptomeria. ($r = 0.285$, $P < 0.01$). The inner lines in the figure show the cut-off level between RAST positivity and negativity for each antigen.

Table 5. Comparisons of RAST levels in various combinations of antigens in total 100 subjects

Pearson's correlation coefficients					
	D.f.	Moth	Ragweed	Orchard grass	Cryptomeria
D.f.	—				
Moth	0.299	—			
Ragweed	0.285	0.284	—		
Orchard grass	0.381	0.129	0.219	—	
Cryptomeria	0.405	0.183	0.243	0.139	—
Alternaria	0.181	0.005*	0.075*	0.410	0.124*
Aspergillus	0.435	0.342	0.370	0.509	0.219
Dog dander	0.482	0.503	0.375	0.482	0.232
Cat dander	0.358	0.226	0.371	0.315	0.226
Tetanus toxoid	0.533	0.199	0.300	0.419	0.369

	Alternaria	Aspergillus	Dog dander	Cat dander	Tetanus toxoid
Alternaria	—				
Aspergillus	0.516	—			
Dog dander	0.232	0.428	—		
Cat dander	0.173	0.359	0.503	—	
Tetanus toxoid	0.409	0.536	0.532	0.524	—

* Statistically not significant $P > 0.05$.

Comparison of RAST levels for *D.f.* and *D.pt.*

Both *D.f.* and *D.pt.* are dominant allergenic species of house dust mites in Japan [13]. Since the RAST levels for *D.f.* were very closely correlated with those for *D.pt.* ($r = 0.945$, $P < 0.01$), we presented here only *D.f.* RAST results.

Discussion

It has been reported that 10–50% of subjects free from allergy symptoms have some degree of skin test reactivity to common local allergens [14, 15]. In the present study, IgE antibodies to common environmental allergens were demonstrated in some 60% of clinically non-allergic subjects. The high prevalence rate may be attributable to the following reasons. (1) Occurrence of *Dermatophagoides* mites in Japanese house dust is ubiquitous [13]. (2) The subjects studied were male teenagers who were found to have maximal immunologic capacity to produce IgE [15]. (3) The Sepharose-RAST used was a sensitive method in the determinations of low levels of IgE antibodies.

The geometric mean serum IgE level in our non-allergic subjects was 79 ± 5.7 IU/ml (arithmetic mean 252 ± 410 IU/ml) which was higher than the European and North American standard [16]. In the recent study, it has been reported that the average IgE level in school children in middle Japan is geometric mean of 70.8 ± 76 IU/ml (arithmetic mean 297 ± 686 IU/ml) [17]. The elevated serum IgE may be also related to the high prevalence rate of *D.f.* specific IgE in this country.

In the present study, we demonstrated that occurrence of IgE responses to common antigens are limited to the *D.f.* responding subjects. Furthermore, the number of antigens to which the subjects responded was closely associated with the magnitudes of

IgE responses to the D.f. These findings strongly suggest that non-specific activation of IgE-producing B cells can occur as a result of continuing stimulation of an environmental antigen, house-dust mite. Burdett & Frick [18] reported that immunization of animals with house dust mite antigen and appropriate adjuvant potentiates IgE production to unrelated antigens such as ovalbumin and keyhole limpet haemocyanin. House dust mite is a dominant environmental antigen in Japan and it seems likely that the mite antigen acts as a non-specific potentiator of IgE production in humans.

In addition, our results suggested that the presence of D.f.-specific IgE response influenced the occurrence of IgE response to various antigens, but it did not affect the degree of the IgE response once it happened. Therefore, the potentiation may be due to an increase in the number of IgE B cells capable of responding to various antigenic stimuli, rather than that of IgE-producing plasma cells.

Inhibition experiments revealed that this association was not attributable to the antigenic cross-reactivity between the mite and the other antigens.

The polyclonal increase of IgE synthesis was also closely correlated with total serum IgE levels. Similar observations have been reported by several authors [1, 2] in atopic patients. This phenomenon is in part attributable to the fact that the increase in the number of antigens to which subjects responded invariably follows the elevation of total IgE. In our given subjects, however, total serum IgE levels ($\log_{10}$ of total IgE) were significantly correlated with RAST levels for D.f. ($r=0.755$, $P<0.01$) and for moth

Table 6. Amounts of antigens required for 50% RAST inhibition

RAST	Antigens used for inhibition	Amounts required for 50% RAST inhibition ($\mu\text{g/ml}$)		
		Sample No. 45	Sample No. 55	Sample No. 58
D.f.	D.f.	42	21	7
Moth	D.f.	2000	2000	ND*
	Moth	22	6	ND
Ragweed	D.f.	2000	ND	ND
	Ragweed	12	ND	ND
Orchard grass	D.f.	ND	ND	2000
	Orchard grass	ND	ND	0.4
Cryptomeria	D.f.	ND	2000	ND
	Cryptomeria	ND	19	ND
Alternaria	D.f.	ND	ND	2000
	Alternaria	ND	ND	11
Aspergillus	D.f.	ND	ND	2000
	Aspergillus	ND	ND	0.5
Dog dander	D.f.	ND	2000	ND
	Dog dander	ND	1.6	ND
Cat dander	D.f.	ND	2000	ND
	Cat dander	ND	4.2	ND
Tetanus toxoid	D.f.	ND	ND	2000
	Tetanus toxoid	ND	ND	4

* ND = not done.

($r=0.526$, $P<0.01$) and furthermore strongly with sum total of RAST levels for these two antigens ($r=0.803$, $p<0.01$) (Data was not shown). This indicates that total serum IgE level varies depending upon the amounts of specific IgE against a small number of potent environmental antigens such as D.f. and moth, rather than upon the number of responding antigens. Furthermore, our results showed that the polyclonal increase of IgE synthesis was closely associated only with D.f.-specific IgE levels, but not with moth-specific ones. Since both D.f.-and moth-specific IgE levels can considerably contribute to the elevation of total serum IgE level, it is unlikely that total serum IgE level influences the clonal proliferation of IgE B cells. From these, it is supposed that the polyclonal increase of IgE synthesis associated with total serum IgE reflects the non-specific activation of IgE B cells occurring as a result of a continuous antigenic stimulation by house dust mite.

Marsh *et al.* have suggested that total serum IgE levels are under a genetic regulation [4]. An action of the gene is speculated to control the clonal expansion of IgE B cells [19]. It is of great importance to investigate this genetical problem. However, we cannot argue this problem from our present RAST study.

Turner *et al.* [7] have reported in the epidemiologic study in the Highlands of New Guinea that no significant difference in the incidence of *Ascaris*-specific IgE antibodies can be found between mite-sensitive asthmatics and insensitive non-asthmatics. This indicates that the house dust mite sensitivity does not influence the IgE production to the *Ascaris* antigen which exhibits a much more potent allergenic activity than the house dust mite. On the other hand, in Japan, where helminth infection is not present, some potent allergen overwhelming the mite has not been demonstrated and even if moth has a strong allergenicity similar to mite, the sensitization to moth is limited to the summer season only [20]. Under these conditions, it seems likely that IgE antibody production to a wide variety of allergens is highly dependent upon the mite sensitivity.

The allergenic situation differs considerably from one geographical environment to another. It is therefore interesting whether similar results are shown in other dominant allergens, *D. pteronyssinus* in U.K. or grass pollen in the western U.S.

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