

Assessment of the influence of irrelevant IgE on allergic sensitivity to two independent allergens

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Serum samples from 31 patients sensitive to both ragweed and rye grass were quantitated for IgE specific for ragweed antigen E (AgE) and rye grass group I (rye I) antigens employing the previously described radioallergosorbent test (RAST) elution technique. IgE anti-AgE ranged from 0.4 to 320 ng/ml and comprised 0.4% to 14.2% of total serum IgE. The same sera contained IgE anti-rye I ranging from 7.9 to 1,168 ng/ml, comprising 1.6% to 29.6% of total serum IgE. A new theoretical parameter (RF), representing the percent of total IgE-Fc receptors of target cells occupied by allergen-specific IgE, was calculated for each IgE specificity by using the determinations of allergen-specific IgE antibody, total serum IgE, and assuming an equilibrium constant for binding of IgE molecules to basophils of $10^9 M^{-1}$. This “% occupancy” parameter correlated with skin test titration, basophil cell sensitivity, and hay fever symptom scores as well as, but not better than, the absolute values of allergen-specific IgE. This finding suggests that in most atopic patients, the quantity of irrelevant IgE plays a relatively minor role in determining allergic sensitivity to a given allergen. The implications of this finding are discussed.

The radioallergosorbent test (RAST) has become widely used for detection of allergen-specific IgE in human sera.^{1, 2} We recently described an RAST elution technique which quantitates allergen-specific IgE in ng/ml terms.³ This technique allows direct quantitative comparison of specific IgE antibody with nonspecific or irrelevant IgE which may compete for target cell Fc ϵ receptors.

Numerous investigators have examined the correlation between RAST values for serum content of allergen-specific IgE and other allergic indices.⁴⁻⁷ Previous studies from our laboratories have shown significant correlations between IgE anti-ragweed determined by RAST and ragweed hay fever symptom

scores, skin test titration with ragweed extract, and leukocyte histamine release to ragweed extract.^{4, 5} However, in each case a significant portion of the variance remained unexplained by knowledge of the quantitative IgE anti-ragweed content alone.

It seems likely that nonspecific or irrelevant IgE competes equally on a molar basis with the specific IgE of interest for target cell receptor sites. We postulated that a parameter which accounts for this competition would correlate better than RAST values alone with other indices of allergic sensitivity. By measuring both total serum IgE and antigen-specific IgE for an individual serum and assuming a reasonable value for the equilibrium constant (K_D) for the Fc receptor-IgE interaction, we have derived such a parameter. This term which we designate RF reflects the amount of allergen-specific IgE bound to basophils and mast cells, taking into account the competition of specific and irrelevant IgE for target cell Fc ϵ receptors.

The present study extends our quantitation of allergen-specific IgE to two independent allergens in individual sera from 31 patients with seasonal rhinitis and examines the relationship of the RF parameter to other indices of allergic sensitivity in this group of patients.

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Supported by Grant AI 11936 from the National Institute of Health
Publication No. 320 from the O'Neill Research Laboratories,
Good Samaritan Hospital, 5601 Loch Raven Blvd., Baltimore,
Md. 21239.

Received for publication July 11, 1978.

Accepted for publication Aug. 11, 1978.

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*Recipient of MRC of Canada Fellowship Award.

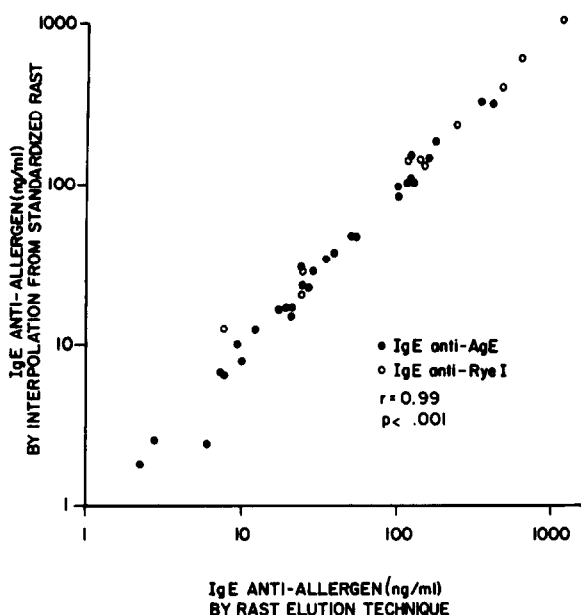


FIG. 1. Comparison of allergen-specific IgE determinations by the RAST elution technique (RET) and by interpolation from a RAST reference serum standardized by the RET.

MATERIALS AND METHODS

Patients

Patients were randomly selected from among those responding to an advertisement for volunteers having both spring and fall hay fever symptoms for a clinical study of immunotherapy for seasonal pollenosis. Data of their seasonal symptom scores and sensitivity to ragweed allergens by skin test titration, leukocyte histamine release, and RAST have been reported previously.⁵

Sera

Sera from these patients were taken in the spring before any of the patients had received immunotherapy. Some samples were pre-grass season; others were taken during the grass season. All were pre-ragweed season.

Antigens

Ragweed antigen E (AgE), research preparation No. 812-89-49, was obtained from the Research Resources Branch, National Institute of Allergy and Infectious Diseases, Bethesda, Md. It was deglycerinated by passage over a Sephadex G-25 column before being coupled to the Sepharose immunosorbent. Rye grass group I antigen (rye I) was generously supplied by Dr. David Marsh.

Allergosorbents

Sepharose-4B (Pharmacia Laboratories, Inc., Piscataway, N. J.) was used as sorbent for both the RAST and total IgE assays. Cyanogen bromide (Pierce Chemical, Rockford, Ill.) activation and coupling were performed as described previously.³

RAST elution technique

RAST elution technique has been described in detail previously.³ It consists of three procedures: (1) binding of antigen-specific IgE by the RAST allergosorbent, (2) elution of a calculable amount of the antigen-specific IgE by alkaline treatment (pH 9-11), and (3) measurement of the IgE eluted by a noncompetitive binding radioimmunoassay (direct radioimmunosorbent test [RIST]). Briefly, reaginic serum samples are incubated with antigen adsorbent for 4 hr and then washed three times. Triplicate samples, now containing (sorbent)-(antigen)-(IgE anti-antigen) complexes are then incubated with either pH 7.4 or pH 10-11 buffer for 1 hr, centrifuged, and the supernatant removed. After neutralization to pH 7.5, the supernatants were assayed for total IgE by the direct RIST. This pH treatment elutes a portion of the antigen-specific IgE bound to the sorbent. The sorbent is washed and then incubated for 20 hr with ¹²⁵I rabbit anti-IgE, washed four times, and the radioactivity counted. By comparing samples treated at alkaline pH with those sham-treated at pH 7.4, the fraction of the total antigen-specific IgE bound which was eluted by alkaline pH can be calculated. The absolute amount of IgE in the eluate is determined by a sensitive noncompetitive total IgE assay.⁸ By having determined the fraction of antigen-specific IgE eluted and the IgE content of these eluates and knowing the dilutional factors involved in the assay, the absolute amount of allergen-specific IgE bound can be calculated. To determine the absolute allergen-specific IgE of the serum sample, one must also determine the percent of allergen-specific IgE bound by the concentration of the allergosorbent used and include this factor in the calculations.

RESULTS

Quantitation of IgE by interpolation

The validity of the RAST elution technique for measuring IgE directed against single antigens has been shown previously for ragweed AgE and benzylpenicilloyl hapten.³ Of practical usefulness is the excellent correlation between antibody quantity calculated by the RAST elution technique and that obtained by interpolation from the standard curve of the reference serum whose allergen-specific IgE content had been determined by the RAST elution technique. This correlation for both antigen E and rye I in the 31 study sera is shown in Fig. 1. Interpolated potency estimates were therefore used to provide allergen-specific IgE content in ng/ml terms for purposes of this study.

Allergen-specific IgE values

Quantity of AgE-specific IgE (Table I) ranges from 0.4 ng/ml to 320.8 ng/ml with arithmetic and geometric means of 66.7 ng/ml and 20.2 ng/ml, respectively. The percent total IgE comprised by IgE anti-antigen E ranged from 0.4% to 14.2% (Fig. 2). IgE anti-rye I values ranged from 7.9 ng/ml to 1,168 ng/ml (Table I). Percent IgE anti-rye I of total IgE

TABLE I. Total IgE, allergen-specific IgE, and RF parameter for 31 study sera

Serum	Total IgE	IgE anti-AgE	RF	IgE anti-rye I	RF
	(ng/ml ± SEM)	(ng/ml ± SEM)		(ng/ml ± SEM)	
1	473.9 ± 20.1	39.0 ± 1.0	0.059	41.5 ± 0.5	0.063
2	397.0 ± 21.7	24.5 ± 2.4	0.042	43.4 ± 3.7	0.074
3	1,497 ± 108.2	142.9 ± 1.8	0.084	86.2 ± 8.2	0.051
4	2,212 ± 42.6	315.0 ± 17.2	0.131	239.7 ± 15.0	0.099
5	3,161 ± 21.1	154.1 ± 5.5	0.046	486.8 ± 36.3	0.145
6	1,013 ± 29.0	7.1 ± 0.5	0.005	189.6 ± 6.9	0.158
7	505.1 ± 9.5	34.7 ± 0.1	0.050	71.2 ± 2.3	0.103
8	739.7 ± 20.5	50.1 ± 4.3	0.054	188.4 ± 9.6	0.205
9	6,518	320.8 ± 29.6	0.047	1,168	0.047
10	644.0 ± 2.9	40.8 ± 4.0	0.049	33.5 ± 0.9	0.040
11	121.7 ± 5.8	13.2 ± 0.5	0.043	36.0 ± 2.8	0.119
12	1,310 ± 64.8	184.8 ± 5.1	0.123	153.5 ± 1.9	0.102
13	1,497 ± 13.0	27.0 ± 2.0	0.016	234.7 ± 3.8	0.140
14	2,398 ± 10.4	106.8 ± 1.4	0.041	38.7 ± 2.3	0.014
15	268.2 ± 10.4	10.0 ± 0.6	0.022	64.0 ± 1.6	0.142
16	169.5 ± 12.9	14.0 ± 0.9	0.040	20.5 ± 0.1	0.058
17	687.7 ± 3.2	26.9 ± 1.8	0.030	90.1 ± 4.5	0.103
18	1,401 ± 13.2	99.5 ± 0.1	0.062	103.8 ± 5.6	0.065
19	86.2 ± 0.9	0.4	0.001	13.6 ± 0.7	0.051
20	656.3 ± 38.7	24.2 ± 0.9	0.029	144.2 ± 3.6	0.136
21	6,147	157.5 ± 7.8	0.025	205.7 ± 11.0	0.032
22	168.8 ± 6.7	3.0 ± 0.3	0.008	7.9 ± 1.6	0.022
23	2,874 ± 113.9	17.0	0.005	45.6 ± 2.0	0.015
24	1,199 ± 113.1	4.7 ± 1.2	0.003	24.7 ± 1.4	0.018
25	4,144	207.3 ± 1.4	0.047	140.5 ± 7.5	0.032
26	253.4 ± 14.4	8.6 ± 0.5	0.019	54.5 ± 1.0	0.125
27	3,265 ± 13.8	13.3 ± 0.5	0.003	638.6 ± 27.4	0.185
28	73.6 ± 2.1	1.3	0.005	11.9 ± 0.3	0.046
29	1,128 ± 12.8	11.2 ± 0.9	0.008	121.2 ± 4.5	0.092
30	219.7 ± 1.1	2.4 ± 0.1	0.006	23.6 ± 0.2	0.058
31	604.4 ± 23.7	5.1 ± 0.0	0.006	84.6 ± 2.2	0.107
Arithmetic mean ± SEM	1,478 ± 301.0	66.7 ± 16.1	0.036 ± 0.006	155.0 ± 41.8	0.084 ± 0.009
Geometric mean	787.2	23.7	—	78.5	
Range	73.6-6,518	0.4-320.8	0.001-0.131	7.9-1,168	0.014-0.205

ranged from 1.6% to 29.6% (Fig. 2). The higher mean values of IgE anti-rye I compared with IgE anti-antigen E are in keeping with greater sensitivity to rye I by skin test titration, although by leukocyte histamine release these patients were on the average slightly more sensitive to antigen E.

Graphic representation of the IgE anti-AgE and IgE anti-rye I, plotted as a function of total IgE values, is seen in Figs. 3A and 3B. A significant correlation is seen between allergen-specific and total IgE values ($r = 0.75$ for AgE; $r = 0.78$ for rye I). No correlation exists between total IgE values and the percent of total directed against either antigen (Fig. 2). The

highest values obtained were 14.2% of total for AgE (Patient 4), 29.6% of total for rye I (Patient 9), and 40.5% for the sum of both allergens in an individual (Patient 9).

Correlation of allergen-specific IgE values with other allergic indices

Comparison of leukocyte histamine release by AgE and rye group I with serum IgE anti-AgE and IgE-anti-rye I values is shown in Figs. 4A and 4B. It can be seen that the sensitivity of an individual's basophils for release of histamine with the specific allergen correlates with the absolute values of the

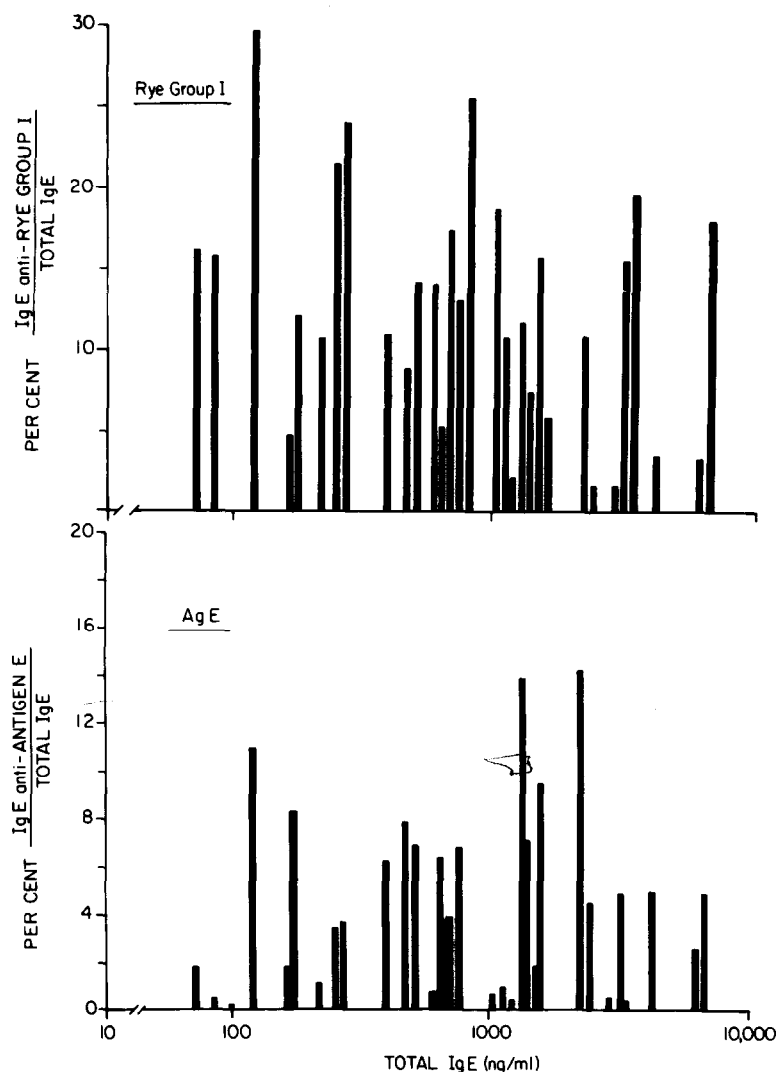


FIG. 2. Comparison of the percent of total IgE that is allergen-specific with the total IgE values in 31 sera. Percent allergen-specific IgE is not significantly correlated with total IgE for either rye group I or AgE.

allergen-specific IgE in the serum ($r_s = 0.70$ for AgE, $r_s = 0.47$ for rye I). Comparisons of leukocyte histamine release and independent AgE RAST analyses had been done previously on these sera⁵: a similar correlation coefficient ($r_s = 0.74$) was found. IgE anti-AgE values as determined by the RAST elution technique were also correlated with skin test titration values and fall hay fever symptom scores. As expected, these correlation coefficients were essentially identical to values previously obtained comparing arbitrary units from the RAST technique to these other indices of allergy.⁵ The determinations are seen in the first column of Table III. Correlation coefficients range between 0.61 and 0.79, suggesting that 35% to 65% of the variance remains unaccounted for by the allergen-specific IgE content alone.

Data for rye I allergen were limited to comparisons

of IgE anti-rye I with leukocyte histamine release (Fig. 4). Symptom scores during the grass pollination season did not correlate with IgE anti-rye I values. It has been reported previously that for this group of patients symptom scores during the grass season failed to correlate with leukocyte histamine release.¹¹ Since symptom scores also failed to correlate with the grass pollen counts, it was suggested that these scores did not represent symptomatology solely to grass allergens but also to other allergens present during the season examined.¹¹ Skin test titration determinations for rye group I allergen were performed two years following initiation of immunotherapy in this patient group. In 15 of the 31 patients who had received only placebo therapy and whose sensitivity might be expected to have remained relatively constant over this period, the allergen concentration producing a 2+

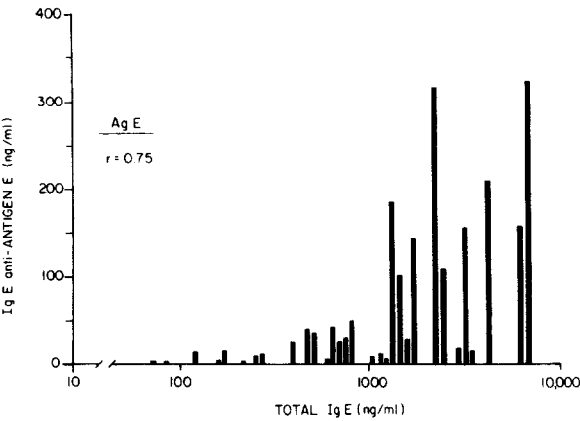


FIG. 3A. Comparison of allergen-specific IgE with total IgE values of the 31 sera tested for AgE.

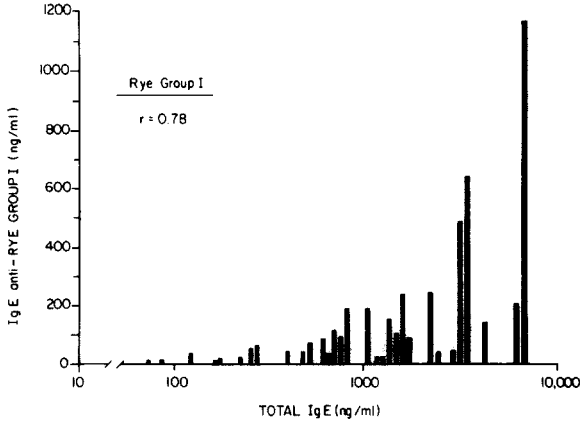


FIG. 3B. Comparison of allergen-specific IgE with total IgE values of the 31 sera tested for rye group I.

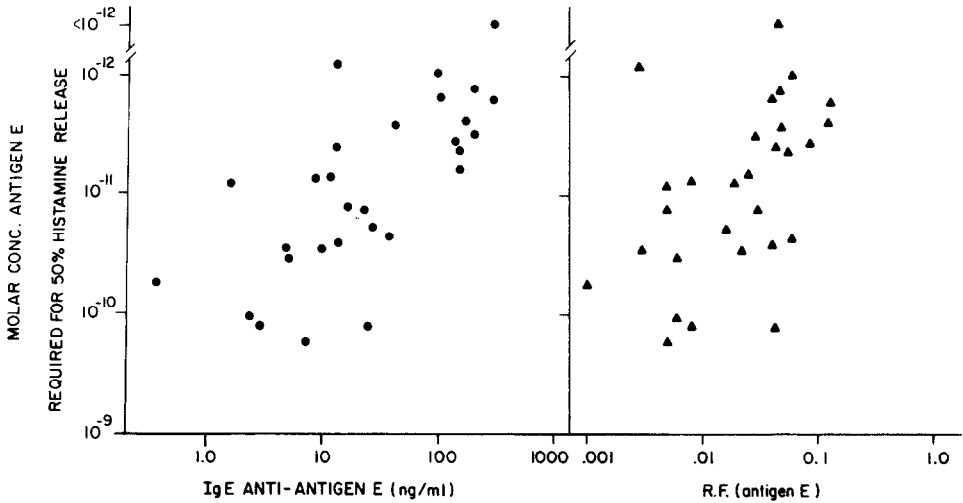


FIG. 4A. Correlations between leukocyte cell sensitivity and allergen-specific IgE for antigen E. The left panel shows absolute specific IgE levels; the right panel displays the RF value. Correlation coefficients are shown in Table III.

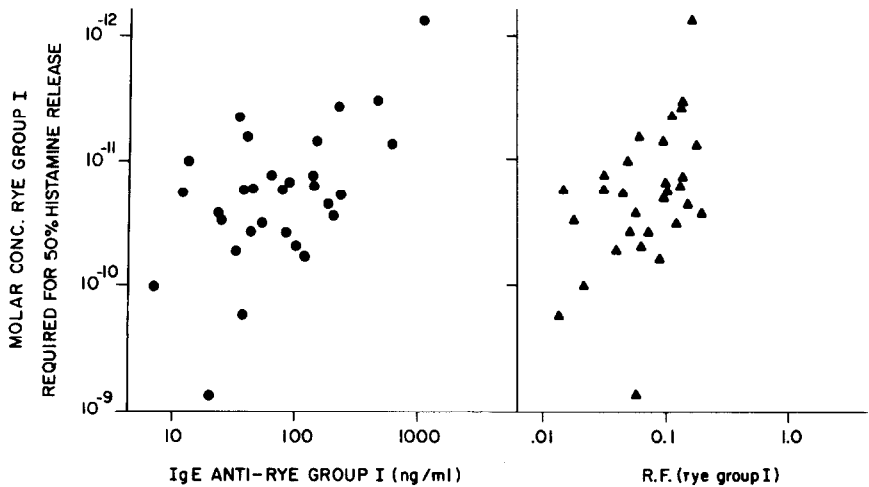


FIG. 4B. Correlations between leukocyte cell sensitivity and allergen-specific IgE for rye group 1. The left panel shows absolute specific IgE levels; the right panel displays the RF value. Correlation coefficients are shown in Table III.

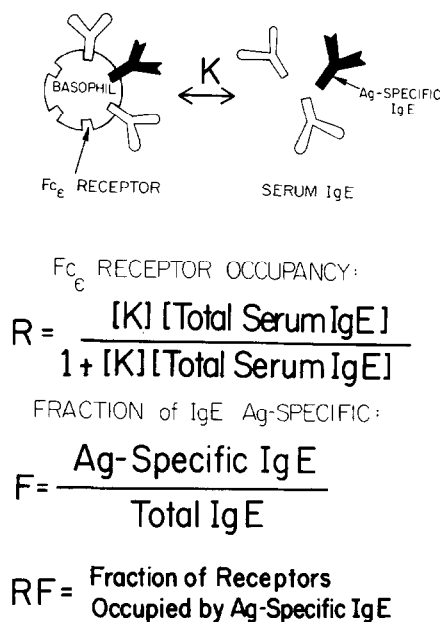


FIG. 5. Determination of the RF parameter, assuming the equilibrium constant (K) is the same for all IgE specificities.

skin reaction varied by less than tenfold; there was no significant correlation between these skin test mid-points and the IgE anti-rye I values.

Evaluation of RF parameter

Since one possible source of variation is the irrelevant or nonspecific IgE, we derived a parameter indicating the amount of antigen-specific IgE bound to basophils and mast cells, taking into account the competition of specific and irrelevant IgE for target cell Fc receptors. This consideration is schematically shown in Fig. 5. As verified by other investigators, an equilibrium is presumed to exist between circulating IgE in the serum and that fixed to basophils or mast cells. This equilibrium is influenced by the average affinity constant of the Fc receptor for IgE, labeled K . Work done by the Ishizakas has suggested that K values for human basophils lie between 10^8 and 10^{10} L/M.⁹ For our calculations we have assumed a K value of 10^9 L/M, but the conclusions reached are identical if one assumes any K between 10^8 and 10^{10} . Using the total serum IgE and the K values, one can calculate the fraction of basophil IgE-Fc receptors occupied by IgE molecules by the equation shown in Fig. 5, where R is the number of basophil receptors occupied by IgE and F is the fraction of total IgE which is specific for a given antigen. Thus, the product of R and F is the fraction of basophil receptors occupied by antigen-specific IgE.

An arbitrary example showing the effect of "irrelevant" IgE on the RF value is shown in Table II. Two

individuals with the same antigen-specific IgE (50 ng/ml) but differing by tenfold in total serum IgE have specific IgE antibody representing 0.05 and 0.5 of the total IgE. Because of the marked differences in serum IgE levels, the proportion of basophil IgE receptors occupied (R) differs considerably, and the fraction of those occupied receptors which can bind allergen-specific IgE (RF) differs by fourfold despite identical amounts of specific antibody and thus identical RAST titers.

Correlations of this new parameter (RF) with the other indices of allergic sensitivity are shown in Table III. Comparing correlation coefficients obtained with absolute values of IgE anti-AgE, it can be seen that, contrary to our expectations, there is no improvement in the level of correlation observed when the RF index was used in place of the absolute IgE antibody levels.

DISCUSSION

By utilizing the RAST elution technique, we are able to obtain considerable information that is not available from the traditional RAST assay. Since weight/volume estimates of allergen-specific IgE are determined, the percent of total IgE specific for a given allergen can be calculated. In the 31 patients studied, this percentage ranged from 0.4 to 14.2 for IgE anti-AgE; other sera we have subsequently tested have been as high as 38% of total IgE being specific for ragweed AgE. The percent of total IgE directed against rye I in the sera studied ranged from 1.6% to 29.6%. The sum of IgE directed against both allergens accounted for up to 40.5% of one individual's total serum IgE. Mean values for our patient group are lower than those reported by Gleich and Jacob¹² using a different method, but these investigators studied IgE against whole ragweed and mixed grass antigens rather than purified antigens. Our values for IgE anti-AgE are slightly lower but overlap with those of 15 patients reported by Zeiss and co-workers¹³ using still a different method.

An additional advantage of our technique over the commonly employed RAST assay is the capability of comparing the quantitative IgE response against different allergens in the same individual. Of the 31 patients studied, the mean response was greater for rye I than for AgE although many patients had higher levels of IgE anti-AgE than IgE anti-rye I. The greater anti-rye I content of the sera may reflect in part the fact that some sera were obtained during or shortly after the grass pollination season.

Using the absolute levels of allergen-specific IgE as determined by the RAST elution technique plus the total serum IgE values for individuals, one is able to

TABLE II. Illustrative example of the potential influence of "irrelevant" IgE on the putative receptor occupancy (RF) by allergen-specific IgE (see text)

Case	Total IgE (ng/ml)	Allergen-specific IgE (ng/ml)	F—Fraction (specific to total IgE)	R—Fractional Fc receptor occupancy at given IgE level	RF—Fractional Fc receptor occupancy by allergen-specific IgE
A	1,000	50	0.05	0.847	0.042
B	100	50	0.5	0.357	0.179

TABLE III. Correlation coefficients for indices of allergic sensitivity

	Ragweed antigen E		Rye grass group I	
	Serum IgE by RAST—IgE anti-AgE (ng/ml)	RF—Fractional receptor occupancy by IgE anti-AgE	Serum IgE by RAST—IgE anti-rye I (ng/ml)	RF—Fractional receptor occupancy by IgE anti-rye I
Leukocyte histamine release (molar conc. allergen for 50% release)	rs* = 0.70 (n = 29; p = <0.001)	rs = 0.58 (n = 29; p = <0.005)	rs = 0.47 (n = 30; p = <0.005)	rs = 0.46 (n = 30; p = <0.01)
Skin test titration (μ g/ml allergen required for 2+ skin response)	rs = 0.79 (n = 15; p = <0.01)	rs = 0.69 (n = 15; p = <0.005)	NA	NA
Symptom scores (average daily score during pollen season)	rs = 0.61 (n = 15; p = <0.01)	rs = 0.66 (n = 15; p = <0.005)	NA	NA

NA: not applicable; see text for explanation.

*rs: Spearman rank-order correlation coefficient.

determine the fraction of IgE-Fc ϵ receptors on target cells occupied by allergen-specific IgE, providing one assumes homogeneity of K ϵ among IgE molecules. This parameter (RF) was determined for each serum sample. The RF values showed significant positive correlation with leukocyte histamine release, skin test titration, and seasonal symptom scores (Table III). Contrary to our expectations, the RF values did not significantly improve the correlations one obtains using the allergen-specific IgE levels alone. Possible interpretations of this finding are: (1) The quantity of irrelevant IgE is of little importance in determining basophil and mast cell sensitivity to a specific allergen for most patients. (2) The implicit assumption that the average equilibrium constant for binding of IgE molecules to Fc ϵ receptors is equal for all IgE specificities is invalid; i.e., IgE of various specificities may have differing average binding constants for the Fc receptor. We do not favor this explanation, since significant Fc heterogeneity of immunoglobulin molecules has not been reported. (3) Intrinsic cellular factors independent of the IgE-trigger are of overriding importance in determining target cell sensitivity.

The competition of allergen-specific IgE and irrelevant IgE for target cell receptors has been dem-

onstrated in animals using passive cutaneous anaphylaxis (PCA) testing and in humans using the Prausnitz-Küstner (P-K) test. Significantly lower PCA titers are obtained when animals with high IgE levels induced by parasitic infestation are used for testing.¹⁴ In humans the P-K titer of a donor serum in different recipients was found to be inversely related to recipient serum IgE levels.¹⁵ Some clinical studies support the hypothesis that high IgE levels present in populations with parasitic disease may protect these persons from developing IgE-mediated allergic disease.^{16, 17} Of interest in the studies of IgE competition for mast cell receptor sites is the fact that the competing or irrelevant IgE must be allowed to react with the mast cells prior to incubation with the allergen-specific IgE-containing serum. Using a chopped human lung preparation, Godfrey and Gradidge¹⁸ examined a West African serum pool containing a high IgE level for its ability to inhibit histamine release caused by grass antigen after passive sensitization with a serum containing a low total IgE but significant IgE anti-grass. Pre-incubation of the lung tissue with the high IgE serum pool (IgE content 100 times that of the test serum) caused inhibition of subsequent sensitization with reaginic serum, but no inhibition was observed if

the high IgE serum was added at the same time or after the serum containing IgE anti-grass. This observation suggests it is very difficult to displace IgE already bound to mast cells and that saturation of unoccupied IgE Fc receptors with irrelevant IgE does not result in significant steric hindrance of the antigen-IgE interaction. The failure to abolish effective specific sensitization by adding to a reaginic serum a 100-fold excess of irrelevant IgE is compatible with the notion that very few specific IgE molecules bound to mast cells are required to sensitize the cell for subsequent mediator release.

Cellular factors influencing target cell sensitivity probably include biochemical differences which may affect the ease with which cells can be stimulated to release their mediators. Recent studies by Conroy, Adkinson, and Lichtenstein¹⁹ have clearly shown that in selected individuals with comparable amounts of IgE bound to their basophils as well as comparable amounts of total serum IgE, susceptibility to histamine release by anti-IgE stimulation varies markedly; conversely, individuals having the same percentage of histamine released by anti-IgE stimulation may have markedly different levels of serum as well as basophil-bound IgE. Thus it appears that certain intrinsic cellular "releasability factors" may be of considerable importance in determining the target cell sensitivity to specific allergens among allergic donors.

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