

Reactivity to IgE-dependent Histamine-Releasing Activity in Asthma or Rhinitis

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We investigated the relation between IgE reactive with histamine-releasing factor (HRF) and clinical status in patients with asthma or rhinitis. Sera were used to passively sensitize purified, lactic-acid treated basophils. IgE-independent HRF due to chemokines was removed from mononuclear cell supernatants with heparin-Sepharose. IgE-dependent HRF was determined by measuring the increase in histamine release between 1 min and 60 min, which was designated Δ HRF. HRF-reactive IgE was demonstrable in nine of 18 patients with allergic asthma, three of 19 patients with nonallergic asthma, five of 17 patients with allergic rhinitis, and none of 19 control patients. The presence of HRF-reactive IgE was associated with: (1) IgE to inhalant allergens; 40% of radioallergosorbent test (RAST)-positive individuals versus 8% of RAST-negative individuals were positive (OR = 7.8, $p < 0.005$); (2) bronchial sensitivity to histamine in all asthmatic patients (geometric mean PC₂₀: 1.50 versus 0.51 mg/ml; $p < 0.005$); and (3) bronchial sensitivity to histamine in allergic asthmatic patients (geometric mean PC₂₀: 1.27 versus 0.37 mg/ml, $p < 0.02$). These findings support the hypothesis that IgE-dependent HRF might contribute to the chronic allergic reaction. **Pasmans SGMA, Aalbers M, van der Veen MJ, Knol EF, van der Zee JS, Jansen HM, Aalberse RC. Reactivity to IgE-dependent histamine-releasing activity in asthma or rhinitis.**

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The reaction of an allergic patient to an allergen is characterized by an immediate response, occurring within 5 to 10 min and in some individuals followed by a late-phase response after 6 to 11 h (1, 2). The late phase of the allergic reaction correlates better with the disease severity of the patient (3). The pathogenesis of this late response is complex and not completely understood. After binding of the allergen to IgE on the surface of mast cells and/or basophils, these cells degranulate and release their mediators. These mediators cause the allergic symptoms of the acute response and attract inflammatory cells (neutrophils, eosinophils, lymphocytes, basophils, monocytes) into the affected site, and these cells are in turn primed or activated at the site of inflammation (late-phase response and chronic allergic inflammation) (1, 2).

Of cells expressing the high affinity receptor for IgE, the mast cell is the predominant source of mediators in the immediate allergic reaction, whereas basophils rather than mast cells release their mediators in the late phase (4). These data suggest that the basophil plays a role in the late phase of the allergic reaction (5). However, the stimulus for basophil activation in the allergic late-phase reaction and chronic allergic reaction is still unknown.

Histamine-releasing factors (HRFs) (6-10) are a heterogeneous group of proteins of 5 to 50 kDa, found in supernatants of different human cells. They induce histamine release from human basophils. Because both basophils and HRFs are present in this late reaction, HRFs are thought to be involved in the late response (6).

Part of the histamine release induced by HRF has been found to be due to chemokines. Monocyte chemoattractant protein-1 (MCP-1) is particularly thought to be important for the IgE-independent HRF histamine release in the cell supernatants described above (11-13). A reduction of 75 to 80% in histamine-releasing activity has been found after immunoabsorption of MCP-1; regulated on activation, normal T-cell expressed and secreted (RANTES); and interleukin-3 (IL-3) (14) in pooled HRF-MN supernatants.

Recently (15), we reported that supernatants of mononuclear cells contain a mixture of both IgE-independent and IgE-dependent HRF; the composition is qualitatively and quantitatively different in mononuclear supernatants of individual donors. The histamine release induced by the IgE-independent chemokines is already maximal after 1 min (11, 13, 16-19), whereas the histamine release induced by IgE-dependent activators (such as anti-IgE and allergen) is low at 1 min compared with the maximal response after 15 min (20). In mononuclear cell-derived supernatants (HRF-MN) that contain a high level of IgE-independent HRF, the IgE-dependent HRF is difficult to detect (13) and its clinical relevance difficult to evaluate. We therefore modified the assay method to measure the IgE-dependent HRF activity (13). We discriminated the IgE-dependent HRF in HRF-MN supernatants from the IgE-independent HRF by: (1) depleting most of the IgE-independent chemokine activity from the HRF-MN supernatants through its affinity to heparin-Sepharose; and (2)

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subtracting histamine release at 1 min from the histamine release response at 60 min.

In this study we investigated the correlation between the response to the IgE-dependent histamine release in HRF-MN and the disease status in patients with asthma and allergic rhinitis. By sensitizing basophils derived from nonallergic donors with serum IgE of the patients, we were able to avoid variation caused by (hypothetical) *in vivo* priming of the basophils. We investigated the presence of IgE reactive with HRF in four groups of subjects, respectively consisting of patients with allergic asthma, nonallergic asthma, and allergic rhinitis, and healthy control subjects.

METHODS

The study was performed after informed consent was obtained from the patients, and was approved by the local ethical committee.

Allergic asthma patients. Twenty-one patients with allergic asthma were selected from the outpatient Department of Pulmonology of the Academic Medical Center of Amsterdam (Table 1; patient group A). Asthma was diagnosed according to the criteria of the American Thoracic Society (21). Patients with asthma had a history of paroxysms of dyspnea, wheezing, and coughing. Patient selection was based on a low

histamine threshold ($PC_{20} \leq 8$ mg/ml), positive skin-prick test, and radioallergosorbent (RAST) positive to at least one inhalant allergen. All patients were in a stable phase of their disease. None of the patients had received immunotherapy. Three sera were excluded because they were found to sensitize basophils for histamine release induced by culture medium (presumably due to IgE antibodies to fetal calf serum [FCS] and/or streptokinase/streptodornase [SK/SD] present in this medium).

Nonallergic asthma patients. Twenty patients with nonallergic asthma were also selected from the outpatient Department of Pulmonology with a negative skin-prick test and RAST negative to a panel of common inhalant allergens (Table 1; patient group B). One serum was excluded because it was found to sensitize basophils for histamine release induced by culture medium.

Allergic rhinitis. Twenty patients with allergic rhinitis were selected from the outpatient Department of Otorhinolaryngology of the Academic Medical Center. Patients with allergic rhinitis had a history of sneezing, itching in the nose, and a running or blocked nose, but no history of current or past episodes of paroxysms of dyspnea, wheezing, and coughing (Table 2; patient group D). Patient selection was based on an allergic history, positive skin-prick test, and RAST positive to at least one inhalant allergen. All patients were in a stable phase of their disease. None of the patients had received immunotherapy. Three sera were excluded because they were found to sensitize basophils for histamine release induced by culture medium.

TABLE 1
CHARACTERISTICS OF PATIENTS WITH ALLERGIC ASTHMA AND NONALLERGIC ASTHMA

Patient No.	Basophil Donor	Age	Sex	S	FEV ₁ (% pred)	Rev FEV ₁ (%)	FEV ₁ /FVC (%)	PC ₂₀ (mg/ml)	ΔHRF (%)	TlgE (IU/ml)	RAST					
											G	B	M	C	D	*
Allergic asthma																
A6	A	34	M	1	69	ND	60	0.07	143	627	4	0	3	4	3	4
A10	A	43	M	0	73	11	69	3.97	5	12	0	0	2	0	0	2
A11	A	50	F	0	98	19	65	1.04	10	420	0	0	0	4	0	4
A12	A	45	F	1	62	18	57	1.15	5	49	0	0	0	1	0	1
A13	A	24	F	0	96	8	84	0.66	8	246	0	0	5	0	0	5
A14	A	38	F	1	68	4	76	0.25	25	112	0	0	3	4	2	4
A15	A	22	F	0	98	4	94	0.30	178	1,400	4	2	2	1	4	4
A16	A	41	F	1	106	5	82	4.90	3	14	0	0	1	0	0	1
A17	A	27	F	1	97	8	86	3.53	3	396	0	0	0	1	1	1
A18	A	45	F	0	91	13	67	0.20	0	8	0	0	2	0	0	2
A19	A	23	F	0	108	8	81	1.60	-3	117	0	0	0	1	0	1
A20	A	36	M	1	67	0	74	0.20	13	927	0	0	5	0	0	5
A21	B	29	F	0	117	5	77	1.20	69	466	2	0	0	4	4	4
A22	B	27	M	0	82	4	78	0.40	346	257	5	0	4	1	0	5
A24	B	41	M	1	72	3	70	0.50	-15	297	0	0	4	2	0	4
A25	B	24	M	0	68	5	83	0.90	15	911	0	0	4	2	0	4
A26	B	28	F	1	83	21	65	0.90	238	205	0	0	0	4	4	4
A27	B	43	M	1	88	33	51	0.32	38	362	0	0	0	5	5	5
Nonallergic asthma																
B9	A	38	F	1	80	14	69	2.90	5	45	0	0	0	0	0	0
B10	A	24	F	0	130	0	92	0.17	10	19	0	0	0	0	0	0
B11	A	33	F	0	113	3	76	1.31	23	7	0	0	0	0	0	0
B12	A	51	M	1	88	1	69	1.57	13	5	0	0	0	0	0	0
B13	A	33	F	1	105	ND	77	2.50	8	225	0	0	0	0	0	0
B14	A	21	F	0	118	6	96	0.86	8	63	0	0	0	0	0	0
B15	A	53	F	0	106	12	75	0.79	5	67	0	0	0	0	0	0
B16	A	30	F	0	66	9	68	3.60	5	209	0	0	0	0	0	0
B17	A	53	M	1	62	40	45	1.20	50	414	0	0	0	0	0	0
B18	A	33	F	1	100	11	80	3.74	5	6	0	0	0	0	0	0
B19	A	24	F	0	100	7	86	3.72	5	24	0	0	0	0	0	0
B20	A	56	F	1	61	-11	58	1.40	5	309	0	0	0	0	0	0
B21	B	48	M	1	57	16	42	1.10	0	51	0	0	0	0	0	0
B22	B	55	M	1	65	8	64	3.30	0	15	0	0	0	0	0	0
B23	B	42	F	0	85	1	81	1.90	8	104	0	0	0	0	0	0
B31	A	44	M	0	116	5	69	0.10	4	233	0	0	0	0	0	0
B32	A	33	F	1	86	1	68	3.10	4	34	0	0	0	0	0	0
B34	A	35	M	1	73	2	80	3.80	-2	137	0	0	0	0	0	0
B35	A	36	F	1	111	11	79	6.45	4	84	0	0	0	0	0	0

Definition of abbreviations: S = smoking; 0 = no; 1 = yes; rev FEV₁ = reversibility of FEV₁ with salbutamol; TlgE = total IgE; G = grass; B = birch pollen; M = house-dust mite; C = cat dander; D = dog dander; ND = not determined.

* Highest RAST score for panel of inhalant allergens.

Control group. Nineteen employees without a history of allergy or upper and lower airways diseases, and who were RAST-negative for a panel of common inhalant allergens, were selected from the Departments of Allergy and Pulmonology (Table 2; patient group C). Of the 19 control individuals, 13 were tested for bronchial histamine reactivity, which was normal ($PC_{20} > 8$ mg/ml) in all 13 tested individuals.

Positive control plasma: IgE+. MacDonald and colleagues have defined IgE derived from some allergic individuals that interacts with HRF as IgE+ in contrast to IgE-, which does not interact with HRF (6). One IgE+ serum (No. 163; total IgE = 2,600 IU/ml) derived from an individual with allergic asthma and a histamine threshold $PC_{20} \leq 8$ mg/ml was obtained from a donor to the Department of Plasmapheresis.

Cell Donors

Mononuclear cell donors. Three donors were selected from the Department of Plasmapheresis. All individuals were interviewed for an allergic history. In a RAST for inhalant allergens, two donors were negative and one was positive.

Basophil cell donors. Two donors were selected from the Department of Plasmapheresis. Both donors were RAST-negative for inhalant allergens and had a negative allergic history.

RAST and Total IgE Assay

The sera from all individuals were RAST tested with a panel of com-

mon inhalant allergens, and the total amount of IgE was measured as described previously (15, 22). The RAST was scored as follows: percentage binding of radioactivity between 0 and 2%: 0; 2 and 5%: 1; 5 and 10%: 2; 10 and 20%: 3; 20 and 40%: 4; and > 40%: 5. The highest scores in the RAST for each of the inhalant allergens tested are shown in Tables 1 and 2.

Skin-prick Test

Allergens for skin-prick tests were obtained from ALK (Copenhagen, Denmark). Skin-prick tests were performed with a panel of common inhalant allergens, as described by van der Zee and colleagues (15, 22).

Lung Function Tests

FEV₁ and FVC were measured with a calibrated, water-sealed spirometer, according to standardized guidelines (23). Bronchial hyperreactivity to histamine was determined by a 2-min tidal breathing method (24). The histamine threshold was defined as the interpolated concentration of histamine that caused a decrease in FEV₁ of 20% of the baseline value.

Histamine Release

Histamine release was performed as described previously (15). A stimulating polyclonal sheep anti-human IgE antiserum (100 ng/ml [15]) CLB, No. SH25P01; and house-dust mite extract (HDM, 1667 SQ/ml, ALK) were used to detect IgE-mediated histamine release. rMCP-1 (Pepro-Tech

TABLE 2
CHARACTERISTICS OF PATIENTS WITH ALLERGIC RHINITIS
AND OF THE HEALTHY CONTROL SUBJECTS

Patient No.	Basophil Donor	Age	Sex	ΔHRF (%)	TlgE (IU/ml)	RAST					*
						G	B	M	C	D	
Allergic rhinitis											
D9	A	43	M	10	69	0	0	4	0	0	4
D10	A	36	M	5	105	0	0	2	0	0	2
D11	A	23	M	10	62	0	0	4	0	0	4
D12	A	32	F	5	115	1	0	4	0	0	4
D13	A	28	F	8	78	0	0	2	0	0	2
D14	A	47	F	85	67	3	2	0	0	0	3
D15	A	35	M	5	826	2	0	2	0	0	2
D16	A	28	F	105	387	4	1	1	2	0	4
D17	A	27	M	23	209	0	0	3	0	0	3
D18	A	43	F	8	125	0	0	2	0	0	2
D20	A	16	M	5	86	0	0	3	0	0	3
D21	B	33	M	46	911	0	0	0	0	0	5
D22	B	29	M	23	71	0	0	0	4	0	4
D31	A	73	F	0	58	0	0	3	2	0	3
D32	A	33	M	-2	163	0	4	0	0	0	4
D34	A	50	F	2	98	0	4	0	0	0	4
D35	A	39	M	2	111	0	3	0	0	0	3
Controls											
C1	A	21	F	0	12	0	0	0	0	0	0
C2	A	29	F	0	29	0	0	0	0	0	0
C3	A	28	M	0	1	0	0	0	0	0	0
C4	A	28	M	4	16	0	0	0	0	0	0
C5	A	29	F	4	61	0	0	0	0	0	0
C6	A	33	F	2	45	0	0	0	0	0	0
C7	A	32	F	9	88	0	0	0	0	0	0
C8	A	28	F	2	42	0	0	0	0	0	0
C9	A	26	F	9	69	0	0	0	0	0	0
C10	A	40	M	6	26	0	0	0	0	0	0
C11	A	33	F	6	25	0	0	0	0	0	0
C12	A	29	M	4	23	0	0	0	0	0	0
C13	A	31	F	2	2	0	0	0	0	0	0
C14	A	38	F	0	48	0	0	0	0	0	0
C17	A	59	F	-2	0	0	0	0	0	0	0
C18	A	23	F	0	19	0	0	0	0	0	0
C19	A	45	M	4	241	0	0	0	0	0	0
C20	A	51	F	4	48	0	0	0	0	0	0
C21	A	30	F	2	18	0	0	0	0	0	0

Definition of abbreviations: S = smoking; 0 = no; 1 = yes; TlgE = total IgE; G = grass pollen; B = birch pollen; M = house-dust mite; C = cat dander; D = dog dander; ND = not determined.

* Highest RAST score for panel of inhalant allergens.

Inc., Rocky Hill, NJ) was used at concentrations of 10^{-7} M. The incubations with HRF-MN were performed in 350 μ l (250 μ l cell suspension and 100 μ l HRF-MN supernatant). Concentrated culture medium with SK/SD was tested as a negative control. The histamine release was stopped by diluting the cells in ice-cold phosphate-buffered saline (PBS). The results were not corrected for the spontaneous release. The spontaneous histamine release was below 10%.

Chemokine-depleted HRF-MN Supernatants

HRF-MN supernatants were prepared as described previously (15). Three HRF-MN supernatants that contained IgE-dependent HRF were pooled. Seventy-five milliliters of this pool was incubated with 3 g of heparin-Sepharose CL-6B (Pharmacia LKB Biotechnology AB, Uppsala, Sweden). After stirring overnight at 4° C, the supernatant was separated from the heparin-Sepharose on a filter. The depleted pool was concentrated three times by ultrafiltration using Amicon YM3 (3000 mw) membranes (Amivan Danvers, MA, Ireland) and named HRF-MN-hep.

Purified Basophils

Highly purified basophils were isolated and sensitized as described previously (15). We investigated the effect of stripping the IgE from purified basophils with lactic-acid buffer and of resensitization of the basophils (data not shown).

Detection of IgE-dependent Histamine Release in HRF-MN

We discriminated the IgE-dependent HRF in HRF-MN from the IgE-independent HRF by (1) depleting most of the IgE-independent chemokine activity from the HRF-MN supernatant with heparin-Sepharose; (2) subtracting the histamine release response at 1 min from the histamine release response at 60 min (the increase in histamine release between 1 min and 60 min in the lactic-acid treated cells that were not sensitized was < 10%); and (3) sensitizing lactic-acid treated basophils derived from a nonallergic donor with serum derived from the patients.

HRF Activity Expressed to Positive Control Serum: Δ HRF

The same IgE+ serum was used as a positive control serum in each of the three experiments. In experiments 1, 2, and 3, with basophil donors A, B, and A, respectively, the increases in histamine release between 1 and 60 min in response to HRF-MN-hep after sensitization with IgE+ were 40, 13, and 47%, respectively. For each patient serum, the increase between 1 and 60 min in histamine release in response to HRF-MN-hep was expressed as a percentage of the positive control IgE+ serum: Δ HRF.

Statistical Analysis

The cutoff value for Δ HRF was determined as the mean + 3 SD of the Δ HRF release found with sera derived from control individuals. Associations were determined with the chi-square test, and significant differences in geometric mean $\pm$ SEM values with Student's *t* test.

RESULTS

Comparing the Four Patient Groups

The histamine release response to chemokine-depleted mononuclear supernatant in the four study groups is shown in Figure 1. The results represent the increase in histamine release from 1 min to 60 min. Δ HRF is expressed as a percentage of the positive control serum. Using the control group (*n* = 19), we defined the cutoff value for being IgE+ (mean + 3 SD of Δ HRF) in this study at 12% of the positive control serum. All of the control subjects were below this value (Figure 1). In the patient groups, the numbers of sera with a Δ HRF histamine release of more than 12% were nine of 18 in the allergic asthma group, three of 19 in the nonallergic asthma group, and five of 17 in the allergic rhinitis group. The percentage of patients in the allergic asthma group with more than 12% Δ HRF histamine release differed significantly from that of the healthy control subjects (0%) (OR = 38.00, 1.98 to 730.54; *p* = 0.003). In the atopic patient groups (allergic asthma and allergic rhinitis), 40% of the individuals showed a Δ HRF histamine release of more than 12%.

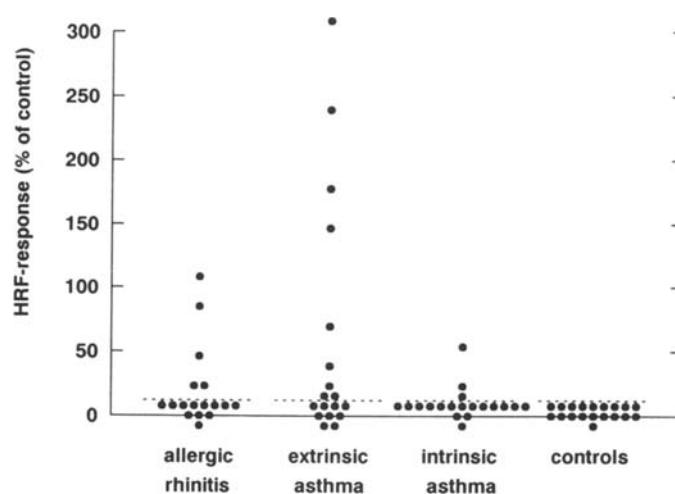


Figure 1. Histamine-release response to chemokine-depleted mononuclear supernatant in four patient groups. Results represent the increase in histamine release from 1 to 60 min. Δ HRF is expressed as percentage of the positive control serum.

This differed significantly from the nonallergic patient groups (nonallergic asthma and healthy controls), in which 8% of the individuals showed more than 12% Δ HRF histamine release (OR = 7.77, 2.00 to 30.29; *p* = 0.003). No significant differences were found in comparing the other patient groups with one another.

Association Between Δ HRF Histamine Release Response and the Different Parameters of Atopy

The Δ HRF histamine release response (*n* = 73) was significantly associated with: (1) the total IgE level (cutoff value 200 IU/ml): OR = 11.04, 3.17 to 38.41, *p* < 0.001; (2) the highest score in the RAST for inhalant allergens (cutoff value > 2): OR = 19.10, 4.66 to 78.24, *p* < 0.001; and (3) a positive RAST for grass pollen (cutoff value > 2): OR = 49.72, 2.58 to 958.75, *p* < 0.001; cat dander (cutoff value > 2): OR = 30.00, 3.28 to 274.52, *p* < 0.001; and dog dander (cutoff value > 2): OR = 49.72, 2.58 to 958.75, *p* < 0.001. The association between Δ HRF and IgE to house-dust mite (OR = 3.82, 1.07 to 13.62, *p* = 0.07) or birch pollen (OR = 0.44, 0.02 to 8.88, *p* = 0.96) was not significant.

Correlations in the Asthma Groups

In patients with asthma, the association between the bronchial histamine threshold and reactivity to HRF differed significantly (IgE+, geometric mean PC₂₀ = 0.51 mg/ml, 0.39 to 0.68; versus IgE-, geometric mean PC₂₀ = 1.50 mg/ml, 1.21 to 1.88; *p* for difference = 0.004; Figure 2). The association was also significantly different in patients with allergic asthma (IgE+, geometric mean PC₂₀ = 0.37 mg/ml, 0.27 to 0.50; versus IgE-, geometric mean PC₂₀ = 1.27 mg/ml, 0.89 to 1.81; *p* for difference = 0.017).

In the asthma groups, IgE+ was not significantly associated with age, sex, being a smoker, the percentage of reversibility of FEV₁ with salbutamol, percentage FEV₁ of predicted FEV₁, or the FEV₁/FVC ratio.

DISCUSSION

MacDonald and colleagues (6) postulated that IgE-dependent HRF is a lectin-like agent that interacts only in a subset of allergic individuals because of differences in glycosylation of IgE. Recently, an IgE-dependent HRF was identified by this group

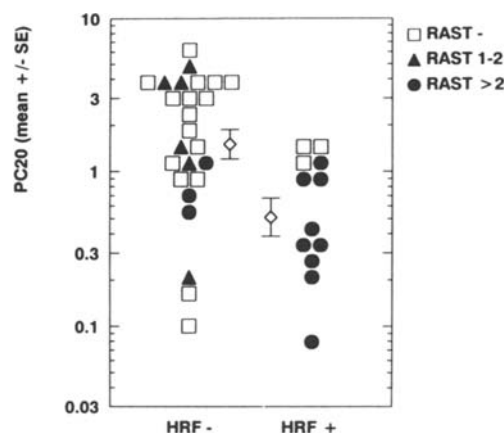


Figure 2. Comparison between HRF-positive sera (IgE+) and HRF-negative sera (IgE-) with PC₂₀ histamine (mg/ml) in asthmatic patients (allergic and nonallergic). The patients are subdivided according to sera that were RAST-negative for inhalant allergens in nonallergic asthma patients (open squares); sera that were RAST-positive for inhalant allergens in allergic asthma patients (closed triangles ≤ 2 in the RAST); and sera that were RAST-positive for inhalant allergens in allergic asthma patients (closed circles > 2 in the RAST). The open diamonds represent the geometric mean of the bronchial histamine threshold for the IgE- and IgE+ sera.

as p21 (25). An alternative explanation for the histamine release induced by IgE-dependent HRF would involve IgE antibodies to (an) autoallergen(s) released from human cells (15, 26).

Looking at the responsiveness to HRFs (which probably contained both IgE-dependent and IgE-independent HRF), the results reported by different investigators are contradictory. Some investigators have reported that only basophils derived from a subset of allergic individuals, and not from nonallergic individuals, respond to HRF. This response has been reported to correlate with the atopic status of the basophil donor (27–30) and with disease severity, and to depend on the presence of IgE+ (6, 31) on the surface of the basophils. Others, however, have found that basophils derived from both allergic and nonallergic individuals respond to HRF, although allergic individuals showed a higher extent of HRF-induced histamine release (32, 33); this response did not correlate with disease severity (33). Some of these investigators also described this response to HRF as being IgE+ mediated (33). The sensitization in the present study of lactic acid-treated basophils derived from two nonallergic donors with sera derived from different patients excludes *in vivo* priming of the basophils and the variability caused by using basophils from every patient. The only variable in the method we used was the patient serum.

A disadvantage of the serum-based bioassay as a test system is the possible involvement of serum factor(s) that modify IgE-dependent histamine release. However, both the spontaneous histamine release and the anti-IgE-mediated histamine release were comparable upon sensitization with the IgE+ and IgE- sera used in our study (data not shown).

The low prevalence of IgE+ status in the RAST-negative asthmatic patients suggests that IgE-dependent HRF is not an important factor in nonallergic asthma, confirming results obtained by others, who used platelet supernatants as an HRF source (28–30).

In all asthma groups, the geometric mean PC₂₀ for histamine was significantly different for the IgE+ and IgE- patients. We did not measure the PC₂₀ for histamine in the allergic rhinitis group. The association between IgE+ status and a low PC₂₀ for

histamine in asthma is not necessarily contradictory to the finding of IgE+ in patients with allergic rhinitis; a low PC₂₀ for histamine has been detected in some patients with allergic rhinitis without lower airway symptoms (34, 35).

Because both the cells that respond to IgE-dependent HRF and the inflammatory cells that produce HRF are present in the late-phase response and the chronic allergic reaction, our results support the hypothesis that IgE-dependent HRF contributes to the late-phase response and the chronic allergic reaction in a subpopulation of atopic patients. We conclude that in allergic rhinitis and allergic asthma, the response to IgE-dependent HRF is highly correlated with the atopic status of the patient. In all asthmatic patients and in allergic asthmatic patients, the presence of IgE+ is associated with a low histamine threshold (PC₂₀ for histamine: < 2 mg/ml).

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