

Highly atopic children: Formation of IgE antibody to food protein, especially peanut

Barry Zimmerman, MD, FRCP(C), Susan Forsyth, BSc, and
Milton Gold, MD, FRCP(C) Toronto, Ontario, Canada

Highly atopic infants often form IgE antibodies toward multiple food protein in the first 2 years of life. They begin producing IgE antibody to inhalant allergens between the first and second year of life. We hypothesized that highly atopic children would be at significant risk of sensitization to peanut. We defined high atopy as serum IgE ≥ 10 times 1 SD from normal plus multiple positive RASTs. In this study we have characterized the immunologic status of 141 patients by measuring total serum IgE and specific IgE to several allergens, including peanut. These data demonstrated that, independent of clinical history, a positive RAST to peanut was more common in the highly atopic category compared to the low atopy category. Significantly more patients who were highly atopic and had a positive peanut RAST had a positive RAST for egg or milk compared to low atopic patients. More significantly, 33 of the patients had never knowingly received peanut, yet 21 (63.6%) had a positive RAST for peanut, whereas seven (21.2%) had a peanut antibody in the highest RAST category. All these seven patients were considered highly atopic according to the definition above, and three were younger than 2 years of age. These results suggest that highly atopic infants are at special risk for sensitization to peanut, even when they have never received peanut, and that characterization of immunologic sensitization to milk, egg, and peanut will identify the highly atopic infant. At present, it is not clear how these infants became sensitized, but they likely correspond to infants who have been reported as having a reaction to peanut on first known exposure. (J ALLERGY CLIN IMMUNOL 1989;83:764-70.)

We have described a relationship between degree of allergic sensitization (i.e., number of skin tests or RAST assays that are positive) and severity of asthma in both older and preschool children.^{1,2} We postulated that children inherit the tendency to asthma and that it is first expressed with viral infections. However, if they are also allergic to inhalant allergens, this adds a second mechanism for airway inflammation that aggravates the severity and persistence of the asthma. Since the generation of the late response appears to be a function of the degree of sensitization to an allergen³ and since sensitization to multiple allergens would create greater degrees of inflammation, it follows that more atopic children would be at the greatest risk for increased severity of asthma.¹ This suggests that the degree that the immune system is activated toward a facile production of IgE antibody to a broad

Abbreviation used

PRU: Phadebas RAST unit

range of allergens creates a risk factor for aggravation of diseases, such as asthma.^{1,2}

We reported that infants and children younger than 5 years of age, who have serum IgE at least 10 times the 1 SD from normal for age (more commonly, 20 to 50 times) and multiple positive RAST assays, also have B cells in their circulation that spontaneously produce cyclohexamide-inhibitable IgE when B cells are cultured in vitro. B cells that spontaneously produce IgE in vitro have been previously identified in the peripheral blood of highly atopic adults and result from continuous activation of the immune system toward IgE production. We have detected such cells in the circulation of infants as young as 1½ years of age.² These children appear to have an immune system that early in infancy is very activated toward IgE production. They generally produce IgE to multiple food proteins in the first year of life and then begin production of IgE to inhalant antigens early in life, that is, between the first and second year of age.² When

From the Hospital for Sick Children, Toronto, Ontario, Canada.

Received for publication Feb. 18, 1988.

Accepted for publication Sept. 17, 1988.

Reprint requests: Barry Zimmerman, MD, FRCP(C), Adverse Reaction Clinic Inc., 200 St. Clair Ave., W., Suite 414, Toronto, Ontario, Canada M4V 1R1.

these highly atopic children were first observed with asthma, it was more severe and required more constant medication, including steroids, compared to nonatopic and mildly atopic children.² A similar phenomenon was observed in children with atopic dermatitis in whom more severe dermatitis was associated with greater atopy (unpublished).

Peanut is known to be a strong allergen⁴⁻⁶ that creates persisting sensitization, even when peanut is avoided.⁷ We hypothesized that highly atopic infants would produce greater quantities of antibody to peanut than nonhighly atopic infants and that this might provide an indirect measure of the degree that the immune system is activated toward allergen recognition and IgE formation. One hundred forty-one children with a median age of 3.8 years (range 0.4 to 17 years) were questioned for a history of an immediate reaction to milk, egg, and peanut. Subsequently, serum IgE and RAST assays to 14 or more allergens were performed to characterize the children immunologically. In this study the presence of clinical sensitivity to peanut was not established by blind challenge, and IgE antibody to peanut was determined as a measure of immune activity rather than as a measure of clinical sensitivity.

MATERIAL AND METHODS

Patient population

All patients had been referred to the allergy-asthma clinic at the Hospital for Sick Children, Toronto, for a variety of clinical reasons, including reactions to foods. One hundred forty-one patients were questioned about a history of immediate reaction to milk, eggs, and peanuts, and the age of introduction of these foods. Immediate reaction was defined as a reaction occurring within 2 hours of ingestion of the food. Most reactions to peanut actually occurred within minutes of ingestion. Serum from each of these patients was assessed for total serum IgE and specific IgE antibody to three or more food allergens and 10 inhalant antigens by the RAST method.

Total serum IgE

Serum IgE was determined by a commercially available double-antibody radioimmunoassay (Pharmacia Ltd., Montreal, Canada). Patients' serum was incubated with ¹²⁵I-labeled human IgE and antibody to human IgE for 3 hours. Solid-phase antirabbit immunoglobulin was added, incubated for 30 minutes, and pelleted by centrifugation. Total IgE was determined from a reference curve provided with the kit. Age-related normal IgE values plus 1 SD were those provided by Pharmacia Ltd.

RAST and inhibitions

The RAST method used a commercially available system (Pharmacia Ltd.). Allergen disks were incubated with 50 μ l of patient serum for 3 hours at room temperature, washed

TABLE I. Patient characteristics

Total population	141
Mean age (yr)	4.7 $\pm$ 3.8
M/F	88/53
Clinical status (No.)	
Asthma	115 (81.6)
Eczema	98 (69.5)
Rhinitis	65 (46.1)
Animal allergy	63 (44.7)
Food allergy	86 (61.0)

Percent number in parentheses.

extensively with saline-Tween 20, and then incubated overnight with ¹²⁵I-labeled antihuman IgE. After the disks were again washed, the isotope bound was determined and compared with a reference curve coated with standard allergen provided by Pharmacia Ltd. Four samples of allergen of varying concentrations were used. These points may be expressed as a 1 to 4+ system or PRUs with 1+ equal to 0.35 PRU/ml; 2+, 0.7 PRU/ml; 3+, 3.5 PRU/ml; and 4+, 17.5 PRU/ml.

Samples that elicited counts above the top reference point were assigned as >17.5 PRU/ml. Positive and negative controls were included with each run. To express a significant level of IgE antibody, a PRU per milliliter level of 10 or higher was chosen. This point was midway in the 3+ range of the older 1 to 4+ quantitation.

For RAST-inhibition analysis, a dilution curve of the serum was created by incubating dilutions of the serum with the allergen disk of interest. A dilution that elicited 50% to 80% of maximal counts bound was chosen for the inhibition. Diluted patient serum was incubated with several concentrations of allergen (powdered milk or peanut extract generously provided by Pharmacia Ltd., Uppsala, Sweden) overnight at room temperature and then used in the standard RAST assay. Inhibitions were run in duplicate and always included a serum sample with no inhibitor added.

Statistical analysis

Data were analyzed by construction of two-by-two tables and subsequent chi-square analysis.

RESULTS

Clinical status of patients studied

Most patients studied (81.6%) had a history compatible with asthma, and almost 70% had a history of atopic dermatitis (Table I). A reaction occurring within 2 hours of eating any food was reported in 86 (61.0%) of the patients (Table I). A clinical reaction to peanut was reported in 53 of the 141 patients (37.6%), a reaction to egg in 55 (39%), and a reaction to milk in 48 of the patients (34%) (Table II). However, there were also 33 patients who had never received peanut (23.4%), 18 who had never received egg (12.8%), and one patient who had never received

TABLE II. Reactions reported to foods*

Reactions	Milk (48)		Egg (55)		Peanut (53)	
	No.	%	No.	%	No.	%
Urticaria/angioedema	22	51.2	36	69.2	43	81.1
Vomiting	26	60.5	16	30.8	7	13.2
Respiratory symptoms	8	18.6	7	13.5	16	30.2
Anaphylaxis	0	0	1	1.9	4	7.5
Other	7	16.3	4	7.7	1	1.9

*All reactions occurred within 2 hours of eating the food. Respiratory symptoms include lower airway symptoms (cough or wheeze) or upper airway (stridor or hoarseness). Anaphylaxis was a reaction that included airway symptoms, fall in blood pressure plus/minus changes in consciousness. All anaphylactic reactions required adrenaline, but no patient was intubated. Other reactions generally refer to rhinitis, diarrhea, or eczema.

TABLE III. Positive food RASTs in relation to history

Food	Clinical history	No.	RAST pos (%)	RAST* PRU ≥ 10 (%)	RAST PRU ≥ 17.5 (%)
Peanut	No reaction	55	14 (25.5)	1 (1.8)	1 (1.8)
	Pos reaction	53	49 (92.5)	34 (64.2)	20 (37.7)
	Never received	33	21 (63.6)	14 (42.4)	7 (21.2)
	Total	141	84 (59.6)	49 (34.8)	28 (19.9)
Egg	No reaction	68	16 (23.5)	3 (4.4)	1 (1.5)
	Pos reaction	55	43 (78.2)	14 (25.5)	5 (9.1)
	Never received	18	10 (55.6)	6 (33.3)	3 (16.7)
	Total	141	69 (48.9)	23 (16.3)	9 (6.4)
Milk	No reaction	92	23 (25.0)	0 (—)	0 (—)
	Pos reaction	48	35 (79.9)	15 (31.3)	9 (18.8)
	Never received	1	1 (—)	0 (—)	0 (—)
	Total	141	59 (41.8)	15 (10.6)	9 (6.4)

*pos, Positive. Phadebas RAST units were extrapolated from a 4-point reference curve (0.35 to 17.5 PRU/ml). If the sample bound more isotope than the highest reference point, it was expressed as >17.5 .

milk (Table III). The type of immediate reaction reported to each of the foods is recorded in Table II. Although urticaria and/or angioedema was the most common reaction overall (milk, 51.2%; egg, 69.2%; and peanut, 81.1%), this reaction was most common after peanut ingestion (peanut versus milk, $p < 0.005$). Vomiting was most common after ingestion of milk (milk versus peanut, $p < 0.001$). Respiratory complaints and anaphylaxis were most commonly reported with peanut and may reflect the greater tendency for peanut to be associated with systemic reactions.

RAST antibodies to peanut

In this series of patients, 59.6% of the 141 patients had a positive RAST to peanut (84 of 141), 48.9% had a positive RAST to egg (69 of 141), and 41.8% were milk RAST positive (59 of 141) (Table III). With each food, approximately 25% of individuals reporting no reactions to the foods had positive RASTs to these foods, indicating clinically irrelevant antibody (Table III).

However, when these RAST data were examined by PRU per milliliter, significantly more patients with a positive history of reaction to peanut had a PRU

TABLE IV. IgE antibody to peanut*

All patients	Serum IgE level								
	Highly atopic			Low atopic			Normal		
	No. 73	RAST pos 60	PRU ≥ 10 39	No. 38	RAST pos 16	PRU ≥ 10 9	No. 30	RAST pos 8	PRU ≥ 10 1
Never received	19	18	13	7	1	1	7	2	0
History positive	32	32	25	14	13	8	7	4	1
History negative	22	10	1	17	2	0	16	2	0

pos, Positive.
*Highly atopic was defined as serum IgE ≥ 10 times the normal plus 1 SD. Low atopic was serum IgE between 2 and 9.9 times the normal plus 1 SD, whereas normal IgE was serum IgE between 0 and 1.9 times normal plus 1 SD.

≥ 10 compared to patients with no history of reaction (34/53, 64.2% versus 1/55, 1.8%; $p < 0.001$) (Table III). More interestingly, 14 of 33 patients who had never received peanut (42.4%) also had positive RASTs to peanut with PRU ≥ 10 , and seven patients (21.2%) had PRU > 17.5 , which indicates isotope binding above the upper limit of this scale (Table III). A similar phenomenon was noted with a small group of patients who had never received egg (Table III). These data also demonstrated that patients with positive RASTs for peanut had higher levels of antibody to peanut than levels to milk or egg. Thus, 49 of 141 patients having a positive RAST to peanut had PRU ≥ 10 compared to 23 of 141 (16.3%) for egg ($p < 0.001$) or milk, 15 of 141 (10.6%), $p < 0.001$. The same difference in quantitation held for PRU > 17.5 , that is, the highest RAST category, where the number of patients positive to peanut was greater than to egg ($p < 0.001$) or milk ($p < 0.001$). This difference was confirmed by dilution analysis where it was found that antibody to milk or egg diluted out before antibody to peanut (data not presented).

Peanut sensitivity in relation to degree of atopy

The 141 patients were divided into three groups: highly atopic (serum IgE ratio ≥ 10 times 1 SD), low atopic (serum IgE ratio 2 to 9.9 times normal), or normal IgE (Table IV). Of the entire population of 141 patients, 73 were considered highly atopic, 38 were considered low atopic, and 30 patients had normal IgE. Of the highly atopic patients, 60 of 73 had a positive peanut RAST compared to 16 of 38 low atopic patients ($p < 0.001$) and eight of 30 patients in the normal IgE group ($p < 0.001$). In the group of patients who had never knowingly eaten peanut, significantly more patients in the highly atopic groups

had a positive RAST to peanut (i.e., 18/19, 94.7%, compared to 1/7, low atopic; $p < 0.001$) and 13 of the 19 patients had PRU ≥ 10 (72.2%, Table IV). Six of these 13 patients were younger than 2 years of age. Three of these infants had RAST positive to peanut in the highest class. Thus, although this group of highly atopic children had never knowingly eaten peanut, their RAST values were not different from the history-positive, highly atopic infants. The history-negative group were also instructive. More of the highly atopic patients had a positive RAST to peanut than patients in the low atopic or normal IgE groups ($p < 0.01$), indicating that many of the clinically irrelevant low-level positive RASTs to peanut were occurring in highly atopic children.

Association between positive peanut RAST and positive RASTs to egg and/or milk in highly atopic children

A high proportion of patients who had formed IgE to peanut also had a positive RAST to egg or milk. Significantly more highly atopic patients who had a positive RAST to peanut also had positive RASTs to milk or eggs compared to the low atopic patients (Table V).

Peanut RAST results in children younger than 2 years of age: Comparison of low to high atopic children

Of the 141 children studied, 33 (30%) were younger than 2 years of age. Of these children, eight were categorized as low atopic; that is, IgE was 2 to 9.9 times the normal plus 1 SD for age. A further 13 children were classed as high atopic (IgE was ≥ 10 times the normal plus 1 SD for age) (Table VI). Peanut RAST results are presented in Table VI and compared with results for egg, milk, and wheat, as well as cat

TABLE V. IgE antibody to egg or milk in patients with a positive peanut RAST*

	Highly atopic			Low atopic		
	No.	RAST pos (%)	PRU ≥ 10 (%)	No.	RAST pos (%)	PRU ≥ 10
Either egg/milk	60	50 (83.3)	25 (41.7)	16	7 (43.8)	0
Egg	60	48 (80.0)	24 (40.0)	16	7 (43.8)	0
Milk	60	41 (68.3)	12 (20.0)	16	4 (25.0)	0

pos, Positive.

*Of the 141 patients who had a positive RAST to peanut, 60 were highly atopic and 16 were low atopic (see Table IV for definition of highly atopic and low atopic).

TABLE VI. RAST results, including peanut in children younger than 2 years of age: low versus high atopic*

No.	Ratio	Age (yr)	IgE	Peanut	RAST results (PRU/ml)					
					PNT	EGG	MLK	WHE	CAT	ALT
1	2.2	1.1	29 (13)	NG	0	0	0	0	0	0
2	2.3	0.8	22 (10)	N	0	0	0	0	0	0
3	2.7	1.0	35 (13)	NG	0	0.6	0	0	0	0
4	2.9	0.4	21 (7.3)	NG	0	0	0	0	0	0
5	6.0	1.8	130 (23)	NG	0	1.5	16.0	0	0	ND
6	6.2	1.2	80 (13)	Y	4.8	3.0	0.4	0.4	0	0
7	6.2	1.5	143 (23)	Y	2.7	1.8	4.2	0.4	0	0
8	7.8	0.6	57 (7.3)	NG	9.8	2.5	0.9	0	0	0
9	12.3	1.3	160 (13)	Y	10.7	0	0	0	0	0
10	12.9	0.4	94 (7.3)	NG	0	0	14.5	0	0	0
11	15.4	1.4	200 (13)	NG	14.0	2.0	6.6	1.1	0	0
12	21.2	0.4	155 (7.3)	NG	2.7	11.7	5.4	0.7	0	0
13	22.7	1.3	295 (13)	Y	>17.5	11.5	>17.5	2.0	1.3	0
14	23.1	1.0	300 (13)	NG	2.1	11.7	13.5	0.7	0.9	0
15	26.2	1.3	340 (13)	NG	2.9	1.4	3.0	1.0	0	0
16	82.6	1.9	1900 (23)	Y	>17.5	3.0	3.0	1.7	0	ND
17	120.0	1.0	1560 (13)	NG	11.5	>17.5	>17.5	12.8	3.7	0
18	123.1	0.8	1600 (13)	NG	12.5	11.5	9.3	1.8	0	0
19	200.0	0.7	2000 (10)	NG	>17.5	>17.5	5.6	9.8	3.2	0.5
20	234.8	1.5	5400 (23)	NG	>17.5	>17.5	>17.5	13.3	7.5	1.2
21	300.0	1.0	3900 (13)	NG	>17.5	15.4	0.7	17.0	0	0

Low atopic, ratio of 2 to 9.9; high atopic, ratio ≥ 10.0 ; NG, peanut never received; N, peanut received with no history of reaction; Y, peanut received with history of immediate reaction; PNT, peanut; WHE, wheat; ALT, *Alternaria*.

*Ratio calculated as serum IgE: normal plus 1 SD for age. RAST results expressed in PRU per milliliter (see Material and Methods). Number in brackets is Pharmacia normal IgE in units per milliliter plus 1 SD for age.

and *Alternaria*. The patients are sorted by increasing ratios of serum IgE: normal plus 1 SD. Of these patients, 15 had never received peanut, and yet 10 of these patients had a positive peanut RAST. Six of these infants had a peanut RAST >10 PRU/ml, and three infants had values that were above the scale limit (i.e., >17.5 PRU/ml), despite never having been knowingly fed peanut. These patients were in the highly atopic category.

RAST-inhibition studies

To prove that the antibodies being detected to peanut in highly atopic patients who had never received peanut were specific antibodies, we performed RAST-inhibition assays (see Material and Methods). Serum from patient J. W. had a total IgE of 600 U/ml (normal plus 1 SD, 40) and positive RAST assays to milk (PRU, 15.5) and peanut (PRU, >17.5). That incubation of the serum with peanut but not milk inhi-

TABLE VII. RAST inhibitions*

Disk	Inhibitor	$\mu\text{g/ml}$	Counts bound (cpm)	% Inhibition
Peanut	Peanut	0	13,337	0
		1000	3,811	72.2
		200	3,782	72.5
		50	4,659	34.2
		10	10,646	20.4
Peanut	Milk	0	17,636	0
		1000	17,874	0
		200	17,456	1.0
		40	17,425	1.2
		8	16,479	6.6
Milk	Peanut	0	11,632	0
		1000	9,432	19.2
		200	10,417	10.6
	Milk	0	11,632	0
		1000	683	95.4
		200	1001	92.6

$$*\% \text{ Inhibition} = 100 \times \left(1 - \frac{\text{Total counts} + \text{inhibitor} - \text{background}}{\text{Total counts} + \text{no inhibitor} - \text{background}} \right)$$

bited the RAST assay to peanut in a concentration-dependent fashion while incubation with milk proteins failed to do so is presented in Table VII. By contrast, incubation of the serum with milk protein virtually completely eliminated the binding to the milk disk, whereas incubation of the serum with peanut protein only marginally influenced the binding to the milk disk.

DISCUSSION

In this study we have examined the formation of IgE antibody to peanut in 141 children using RAST assay for peanut. We were particularly interested in the level of antibody formed by young children whom we have termed highly atopic. We have arbitrarily defined high atopy as a serum IgE ≥ 10 times the normal plus 1 SD for age and multiple positive RAST assays because we have previously found that the B cells of such individuals, when they are cultured in vitro, spontaneously produce IgE, even in infancy.² Peanut is known to be a strong allergen⁴⁻⁶ capable of eliciting major reactions on first known exposure.⁸ The antibody to peanut tends to persist, and the clinical sensitivity to peanut also persists.^{7,9} We hypothesized that highly atopic young children, including infants, might be at special risk for sensitization to peanut because of the ease with which they form IgE antibody. The formation of IgE antibodies to multiple food protein, including peanut, might help to identify highly atopic infants prospectively to attempt modification of their future course.

In this study we examined the formation of IgE

antibody to peanut in 141 consecutive children who were first observed in the allergy and asthma clinics at the Hospital for Sick Children, Toronto. On the basis of their serum IgE, these children were divided into normal IgE groups, low atopic groups (serum IgE 2 to 9.9 times plus 1 SD for age), and high atopic groups (serum IgE ≥ 10 times plus 1 SD for age). We found that highly atopic children had significantly more positive RASTs to peanut compared to low atopic children (Table IV) and that this was independent of the clinical history. There was also a group of children who had never knowingly eaten peanut but had positive RASTs for peanut. Many of these children had RAST assays that were greater than the upper limit of the standard curve (i.e., >17.5 PRU); three of these children were infants. As in other studies,¹⁰ a high percentage of patients never having had a clinical reaction to peanut had a positive RAST to peanut (25.5%; Table III), but when the concentration of antibody to peanut was expressed in PRU per milliliter (see Material and Methods), patients with a history of positive reaction commonly had PRU ≥ 10 (34 of 53; 64.2%) compared to one of 55 nonreactors (1.8%; $p < 0.001$). In fact, these low-level positive RASTs to peanut, which usually had a PRU per milliliter value of <5 (data not presented) and which were not associated with a clinical reaction, usually occurred in highly atopic individuals (Table IV, negative peanut history: 22 patients with serum IgE ≥ 10 times normal of whom 10 or 58.8% had a positive peanut RAST compared to four of 33 nonhighly atopic patients, $p < 0.01$). Those data demonstrate that the

formation of IgE antibody to peanut is common in the highly atopic individual and most likely represents the ease with which their immune system responds to even trivial quantities of this strong allergen. Because these patients had high total serum IgE, it was necessary to prove that the antibody being detected was specific for peanut. Serum from a child who was reported to have had a reaction to milk and who had strongly positive RAST assays to milk and peanut, despite the absence of ingestion of peanut, was assessed by RAST inhibition with peanut or milk protein (Table VII). The antibodies proved to be inhibitable only by the appropriate antigen, confirming the specificity of the assays.

We concluded that children who are highly atopic, that is, those whose immune system produces IgE antibodies in a facile fashion, often become sensitized to peanut, even though peanut has been withheld from their diet. At present it is not clear how sensitization occurred in these children, but it presumably resulted from trivial amounts of peanut protein contaminating other foods or perhaps breast milk.^{8,11} Although cross-reactivity with other legumes remains a possibility, we rarely found high RAST positivity to soy in these children (data not presented), and the parents did not commonly report reactions to beans or peas. These data suggest that identification of IgE antibody to multiple food proteins, including peanut, when the infant has not received peanut, will identify the highly atopic individual.

Our data also support the conclusion that higher concentrations of antibody are formed to peanut compared to milk or egg. Children in the highly atopic category often produce IgE antibody to more than one food protein in infancy. Despite the facile formation of IgE to foods, the expression of clinical reactivity is not straight forward, and often on blind challenge, such children do not have clinical reactions.^{4, 7, 9, 10} We do not know whether the children we studied would have had clinical reactions to the food(s) at the time of study. However, the production of IgE antibody to multiple food proteins in infancy appears to be a hallmark of highly atopic infants who subsequently produce IgE antibody to inhalant allergens early in life. If such children are first observed with asthma, it often requires constant medication, including inhaled or oral prednisone.² These children usually have the risk factors identified with persisting asthma of childhood.¹²

We believe the highly atopic infant to be a special subset of children who need to be identified and studied separately from other atopic individuals. At present

we do not know the prevalence of such infants but would suggest that they can be detected within the first year of life. It appears likely that most studies on allergy prevention by breast feeding, and late introduction of milk or eggs would only contain a small number of such infants, and therefore, most studies would be focused on mildly atopic infants (even when both parents have a history of allergy) and would be focused on infants who may not be at high risk of significant allergy. By identifying highly atopic infants, the results of dietary manipulation for prevention of allergy and allergic diseases might be clarified.¹³ It appears likely that the high prevalence of such infants in our study is due to selection bias in the pattern of patients referred to our tertiary clinic. Such highly atopic infants are probably uncommon in an unselected population and therefore would go unnoticed in most epidemiologic studies.

REFERENCES

1. Zimmerman B, Feanny S, Reisman J, et al. Allergy in asthma. I. The dose relationship of allergy to severity of childhood asthma. *J ALLERGY CLIN IMMUNOL* 1988;81:63.
2. Zimmerman B, Chambers C, Forsyth S. Allergy in asthma. II. The highly atopic infant and chronic asthma. *J ALLERGY CLIN IMMUNOL* 1988;81:71.
3. Umamoto L, Poothill J, Dolovich J, Hargreave FE. Factors which influence late cutaneous allergic responses. *J ALLERGY CLIN IMMUNOL* 1976;58:60.
4. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J ALLERGY CLIN IMMUNOL* 1978;62:327.
5. Nordlee JA, Taylor SL, Jones RT, Yuninger JW. Allergenicity of various peanut products as determined by RAST inhibition. *J ALLERGY CLIN IMMUNOL* 1981;68:376.
6. Kemp AS, Mellin CM, Barnett D, Sharota E, Simpson J. Skin test, RAST, and clinical reactions to peanut in children. *Clin Allergy* 1985;15:73.
7. Bock SA. The natural history of food sensitivity. *J ALLERGY CLIN IMMUNOL* 1982;69:173.
8. Van Asperen PP, Kemp AS, Mellin CM. Immediate food hypersensitivity reactions on the first known exposure to the food. *Arch Dis Child* 1983;58:253.
9. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatrics* 1985; 107:669.
10. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1984;74:26.
11. Gerrard JW, Perelmutter. IgE-mediated allergy to peanut, cow's milk, and egg in children with special reference to maternal diet. *Ann Allergy* 1986;55:351.
12. Martin AJ, Landau LI, Phelan PD. Predicting the course of asthma in children. *Aust Paediatr J* 1982;18:84.
13. Zeiger RS, Heller S, Mellon M, et al. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J ALLERGY CLIN IMMUNOL* 1986;78:224.