

Personal experience in the diagnostic procedures in children with atopic dermatitis and food allergy

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Atopic dermatitis (AD), a major health concern in children, is characterized by a multifactorial pathogenesis in which a significant role is played by foods, especially in infants (1). In addition, both diagnosis and treatment are difficult since the much in vogue diagnostic items, SPT and RAST yield varying results in terms of sensitivity, specificity, predicted positive and negative values (2-5). The diagnosis of FA-related AD relies on controlled challenge test.

However, recent studies have focused on the unpredictable hazards following food challenge tests in term of immediate reactions (6). It has also been shown (7) that late reactions are frequent and that they can develop even several days after the challenge test.

Aim of the present study was to evaluate in children with AD: 1) the prevalence of immediate and late reactions following challenge tests; 2) the sensitivity, specificity and predictive positive and negative values of SPT and RAST as regards both immediate and late reactions; 3) the prevalence of late reactions not preceded by immediate symptoms after challenge tests.

PATIENTS AND METHODS

Seventy-nine children (46 males and 33 females), ranging in age from 6 mo to 10 yr (median age 24 mo), and fulfilling the criteria of Hanifin & Rajka (8) for the diagnosis of AD were included in the study.

In all children prick tests were made with lactalbumin, casein, egg-white and wheat (Lofarma, Milano, Italy) on the volar surface of the

forearm and the reaction was read at 20 min. In some cases, additional food antigens were used, as suggested by case history. A negative control with glycerosaline solution and a positive one with histamine (0.1 mg) were made.

The prick tests were considered positive as follows: + when the wheal was the half of the histamine wheal; ++ when the wheal was equal to the histamine wheal; +++ when the wheal was two-fold the histamine wheal; ++++ when the wheal was more than two-fold the histamine wheal.

Total serum IgE levels were determined using Phadebas IgE PRIST® test (Pharmacia, Uppsala, Sweden). Specific IgE to food allergens were measured by the Phadebas RAST® method (Pharmacia, Uppsala, Sweden). First class RAST was considered positive.

Informed consent was obtained from the parents of each child.

Symptom scores and effect of elimination diet

The severity of AD lesions was assessed before and after the elimination diet using a semi-quantitative score as previously described (10).

Study design

Independently from SPT and RAST results, the children followed a CM- and egg-free diet for a 4-6 wk period. In some cases, on the basis

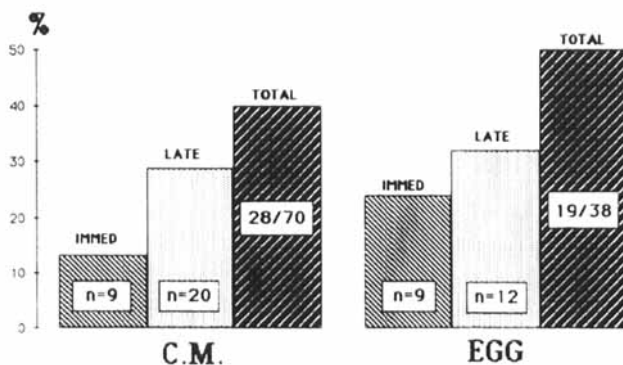


Fig. 1. Reactions (immediate and late) after the challenge test with cow's milk and/or egg.

of case history, and previous SPT or RAST results also fish, wheat or soya were excluded.

Parents were required to discontinue all topical corticosteroids during the trial, antihistamine for 7 days, and all beta-agonists for 12 h before the provocation test.

Food challenge test

At the end of the 4–6 wk period, 113 open challenge tests were performed in the hospital under observation and with emergency equipment at hand. In 23 of them the challenge test was done for both CM and egg. Seventy children were tested with CM, 38 with egg and 5 with other foods. CM or egg were administered as follows: a drop of CM (or of emulsified raw egg) was put upon the inner border of the lower lip, and a further 5 ml of CM (or 1 ml of emulsified raw egg) were given after 5 min. 100 ml of CM or half-boiled egg were given after 30 min. The reactions were defined as immediate if the first symptoms occurred within 4 h of ingesting the food antigen, and delayed if the first symptoms occurred after 4 h. If any symptoms secondary to the challenge test were observed, the challenge test in the hospital was terminated. After the last administration of the tested food the children were watched for at least 4 h and then discharged. Parents were instructed to continue to give the tested food at home (150 ml of CM twice a day or one boiled egg-a-day) and to record any reaction and report it at the following visit 7 and 15 days later.

The following formulas: $V = (sP) / [sP + (1-f)(1-p)]$ for positive and $g = f(1-P) / [f(1-P) + (1-sP)]$ for negative predictive accuracies were employed V = positive predictive accuracy, g = negative predictive accuracy, s = sensitivity, f = specificity, P = prevalence.

RESULTS

Before the elimination diet the children had a severity score (arithmetic mean) of 20 and after the elimination diet there was a significant drop up to 4 ($P = 0.001$).

SPT and RAST

SPT were positive in 54/70 children (77%), subjected to CM-challenge test and in 30/38 (79%) to egg-challenge test. RAST was positive in 27/70 (39%) CM- and in 15/38 (39%) of egg-challenge tests.

The children in the present study had a median value of total IgE of 50 IU/ml (range 5–1000 IU/ml). Total IgE levels were higher than 2 SD in 51/79 children (65%).

Challenge tests

A total of 113 food challenge tests were performed (70 with CM, 38 with egg and 5 with other foods). In the 108 children who underwent the challenge test with CM and/or egg

47/108 (44%) were positive. Only one child exhibited a severe anaphylactic reaction to CM requiring emergency therapy. 23/79 children were subjected to both challenge tests (CM and egg). Of these, 3 children showed positivity of both tests, 9 were positive only for CM, 5 were positive only for egg, and 6 were negative for either test.

Symptoms induced by food challenge test (Fig. 1)

Twenty-eight out of 70 CM-challenge tests (40%) were considered positive. 9/70 challenge tests (13%) elicited immediate, and 20/70 (29%) delayed reactions. Only one patient out of 38 (1.4%) had either immediate, or delayed

symptoms. 19/38 egg-challenge tests (50%) were considered positive. 9/38 children (24%) experienced immediate, and 12/38 (23%) delayed reactions. 2/38 patients (5%) had either immediate, or delayed symptoms.

The symptoms induced by food challenge test are summarized in Tables 1 and 2. The following symptoms occurred only immediately: lip edema in 4 cases (8.5%), pharyngeal pruritus in 1 case (2.1%) and shock in 1 case (2.1%). The remaining symptoms were either immediate or delayed: AD worsening in 26 cases (53.3%) (1 immediate and 25 late), pruritus in 24 cases (51.1%) (5 immediate and 19 late), rush/erythema in 21 cases (44.6%) (8 immediate and 13 late), urticaria in 9 cases (19.1%) (7 immediate and 2 late), asthma in 6 cases (17%) (3 immediate and 3 late), rhinitis in 5 cases

Table 1

Symptoms occurring after challenge test with cow's milk in children with AD, according to skin test score and RAST class

Subject n.	Age (mo)	Immediate reactions	Late reactions	SPT score	RAST class
95	20	Wo-AD, PR, URT, ER, DI, AS		2	4
66	36	URT, LO		3	2
59	48	URT		1	0
25	20	PR, ER, SH		4	0
131	21	PR, ER		3	4
31	15	ER, AS		3	2
82	8	ER		2	0
65	36	ER	Wo-AD	0	0
50	6.5	AS		1	1
116	23		AS	1	1
109	27		PR	3	0
92	56		PR, ER	2	1
33	30		URT, ER	4	1
56	18		Wo-AD	1	3
97	19		Wo-AD	2	0
88	11		Wo-AD	1	0
78	41		Wo-AD	2	0
69	27		Wo-AD	1	3
83	39		Wo-AD, PR	3	0
5	21		Wo-AD, PR	1	0
98	12		Wo-AD, PR	1	0
4	30		Wo-AD, PR, AS	4	2
96	15		Wo-AD, PR, ER	2	0
19	22		Wo-AD, PR, ER	2	2
84	10		Wo-AD, PR, ER	2	0
125	23		Wo-AD, PR, ER	0	0
32	66		Wo-AD, PR, ER	2	2
74	38		Wo-AD, PR, ER	0	0

Wo-AD = worsening atopic dermatitis; PR = pruritus; URT = urticaria; ER = erythema; LO = lip edema; DI = diarrhea; AS = asthma; SH = shock.

Table 2

Symptoms occurring after challenge test with egg in children with AD, according to skin test score and RAST class					
Subject n.	Age (mo)	Immediate reactions	Late reactions	SPT score	RAST class
72	18	URT, RH		3	4
58	8	URT, RH		1	0
62	14	URT, LO	Wo-AD	1	2
57	36	URT	URT	1	2
47	34	PR, RH		3	2
71	8	PR, LO, RH, ER		2	1
87	88	PhP		4	1
63	18	LO		1	2
18	29	ER		2	0
60	16		DIA, RH	3	4
28	16		PR, ER	3	3
79	34		Wo-AD	1	0
64	41		Wo-AD	0	0
114	20		Wo-AD, PR	3	0
130	24		Wo-AD, PR, AS	3	3
108	126		Wo-AD, PR, ER	2	1
53	20		Wo-AD, PR, ER	2	2
105	15		Wo-AD, PR, ER	2	0
73	37		Wo-AD, PR, ER	3	0

Wo-AD = worsening atopic dermatitis; PR = pruritus; URT = urticaria; ER = erythema; LO = lip edema; DI = diarrhea; AS = asthma; SH = schok.

(10.6%) (4 immediate and 1 late), diarrhea in 2 cases (4.2%) (1 immediate and 1 late).

Reliability of diagnostic tests
(Tables 3 and 4)

SPT sensitivity for CM was 0.89 both for immediate and 0.85 total reactions (immediate + late) after challenge test. RAST sensitivity for CM was 56% for immediate and 45% for total reactions. SPT sensitivity for egg was 100% for immediate and 95% for total reactions after

challenge test. RAST sensitivity for egg was 78% for immediate and 61% for total reactions.

SPT specificity for CM was 25% for immediate and 30% for total reactions after challenge test. RAST specificity for CM was 64% for immediate and 66% for total reactions. SPT specificity for egg was 27% for immediate and 38% for total reactions after challenge test. RAST specificity for egg was 74% for immediate and 83% for total reactions.

SPT predictive positive value for CM was 14% for immediate and 44% for total reactions

Table 3

Sensitivity, specificity and predictive accuracy of SPT and RAST to cow's milk (CM) and egg in children with AD (immediate reactions)

	Predictive accuracy							
	Sensitivity		Specificity		Positive		Negative	
	SPT	RAST	SPT	RAST	SPT	RAST	SPT	RAST
CM	89	56	25	64	15	19	93	91
Egg	100	78	27	74	30	48	100	91

after challenge test. RAST predictive positive value for CM was 20% for immediate and 48% for total reactions. SPT predictive positive value for egg was 32% for immediate and 64% for total reactions after challenge test. RAST predictive positive value for egg was 50% for immediate and 79% for total reactions.

SPT predictive negative value for CM was 93% for immediate and 80% for total reactions after challenge test. RAST predictive positive value for CM was 90% for immediate and 63% for total reactions. SPT predictive negative value for egg was 100% for immediate and 86% for total reactions after challenge test. RAST predictive positive value for CM was 91% for immediate and 68% for total reactions (Tables 3 and 4).

Figs. 2 and 3 show the sensitivity and the specificity of SPT and RAST as regards the immediate (Fig. 2) and late (Fig. 3) reactions after challenge test with CM. Fig. 4 and 5 show positive and negative predictive values of SPT and RAST as regards the immediate (Fig. 4) and total (Fig. 4) reactions after challenge test with CM. In both cases the values are shown according to the SPT score or RAST class variation considered as positive. Increasing the positivity, sensitivity increases but specificity worsens (Figs. 2 and 3) while predictive positive and negative values remain unchanged (Figs. 4 and 5).

Onset of late reactions

Fig. 6 shows the onset of late reactions after challenge test with cow's milk or egg. It is of note that all late reactions to egg developed

within the 5th day, whereas the majority of late reactions occurring after challenge test with cow's milk developed up to the 15th day.

New symptoms after challenge test

In 3 CM-challenge tests (2 immediate and 1 late reaction) asthma developed for the first time. In 1 egg-challenge erythema, pruritus and cough developed also for the first time.

DISCUSSION

In this study, 24-mo-old (median) infants with AD were evaluated for clinical food hypersensitivity by open food challenge tests, which were positive in 44% of cases. Only CM and egg were challenged since according to previous studies by us (11) these are the most common offending foods in Italian children. This data is similar to that of Sampson & McCaskill (12), who have demonstrated that in the typical American diet 6 foods accounted for 86% of the positive responses, egg accounting for 42% of these responses. Excluding from the 6 foods peanuts, soya and fish which are rarely included in a typical Mediterranean diet for young children, CM and egg would account for about 80% of the positive responses.

Eighteen children experienced immediate reactions after an elimination-provocation test as follows: 9 after CM and 9 after egg administration. No child had previously had such reactions after ingestion of tested foods. Therefore food challenges should always be done in a clinical setting with emergency equipment at hand.

Table 4

Sensitivity, specificity and predictive accuracy of SPT and RAST to cow's milk (CM) and egg in children with AD (immediate + late reactions)

	Predictive accuracy							
	Sensitivity		Specificity		Positive		Negative	
	SPT	RAST	SPT	RAST	SPT	RAST	SPT	RAST
Milk	85	44	30	66	46	46	79	63
Egg	95	61	38	83	60	56	88	55

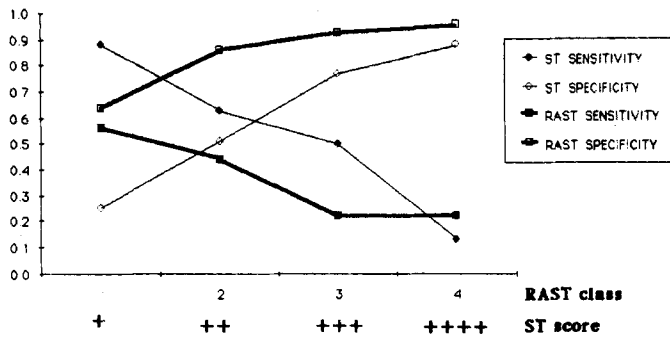


Fig. 2. Cow's milk sensitivity and specificity of skin tests and RAST according to skin test score or RAST class in children with immediate reactions to cow's milk challenge test.

In 4 children on elimination diets reported by David (13), anaphylactic shock occurred after the reintroduction of foods previously eliminated. Many of these immediate reactions may be a consequence of release of mediators: pruritus (direct mechanism), rush and erythema (vasodilation), edema and rhinorrhea (increase of vascular permeability). Pruritus in turn induces an increase of vasodilation and of vascular permeability. This agrees with the results of Sampson & Jolie (14) as to histamine release after food challenge tests. Although histamine was the only mediator they tested, it is possible that additional mediators released by mast cells are involved. However, since histamine is rapidly cleared in the portal and renal circulation, only a fraction of the histamine released by gut-associated mast-cells would reach peripheral sites. It is therefore likely that the histamine so released in a sensitized patient may facilitate

the entrance of a greater amount of antigen by inducing a local anaphylaxis. These antigens reach cutaneous mast cells very rapidly, thus inducing a further mediator release. As originally demonstrated by Engman et al. (15), the release of various mast cell mediators, including histamine, can provoke severe pruritus, secondary scratching, and subsequent development of eczematous skin lesions.

It is likely that a possible mechanism for exacerbation of AD includes second-phase leukotriene release from neutrophils and eosinophils, basophil recruitment or IC deposition in the skin (16-18).

Considering sensitivity, specificity, and positive and negative predictive accuracy of SPT and RAST of both CM and egg as regards immediate and total reactions (Table 3 and see (6)). SPT sensitivity is high (0.88 for CM and 1.00 for egg for immediate reactions and 0.88

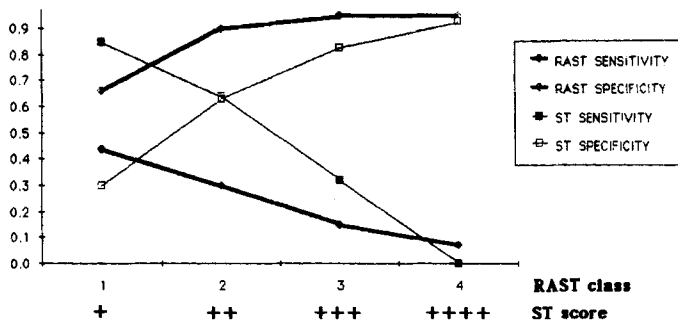


Fig. 3. Cow's milk sensitivity and specificity of skin tests and RAST according to skin test score or RAST class in the children who experienced a positive cow's milk challenge test (immediate and/or late reactions to cow's milk challenge test).

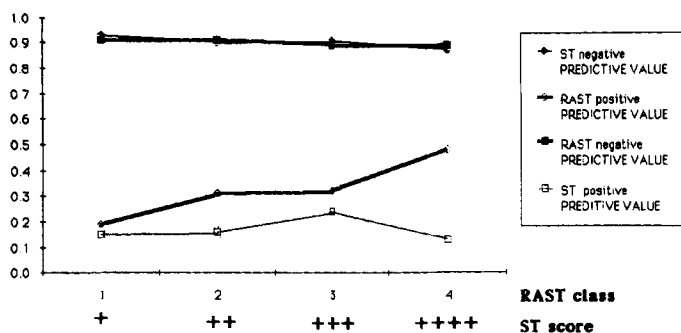


Fig. 4. Positive and negative predictive values of skin tests and RAST according to skin test score or RAST class in the children who experienced a positive cow's milk challenge test (immediate reactions to cow's milk challenge test).

for CM and 0.95 for egg for total reactions). However, specificity is low (0.25 for CM and 0.27 for egg for immediate reactions and 0.30 for CM and 0.38 for egg for total reactions). In addition, the SPT positive predictive values are low (0.15 for CM and 0.30 for egg for immediate reactions and 0.46 for CM and 0.60 for egg for total reactions). Since history is unreliable, especially as regards the immediate reactions predictivity, challenge tests in children with positive SPT should always be done with caution.

The SPT high negative predictive accuracy (0.93 for CM and 1.00 for egg) permits us to exclude immediate reactions following the challenge test.

RAST sensitivity is lower than that of SPT. RAST specificity is better than SPT; however,

neither can be utilized at the clinical level. In addition RAST negative predictive accuracy is lower than that of SPT and consequently scarcely useful for food allergy diagnosis. Its use should be limited to those cases in whom antihistaminic administration cannot be discontinued or dermographism is remarkable or lichenification fails to allow SPT evaluation.

Our data tally well with previous data (2, 17-19) only as regards SPT negative predictive accuracy. For the other parameters investigated, our values are lower than those reported by others (2, 17-19). Accordingly RAST positive predictive value (18, 20-21) is not confirmed by our data.

Another important point to be stressed is the period of time between the start of the challenge test and the onset of symptoms. In agreement

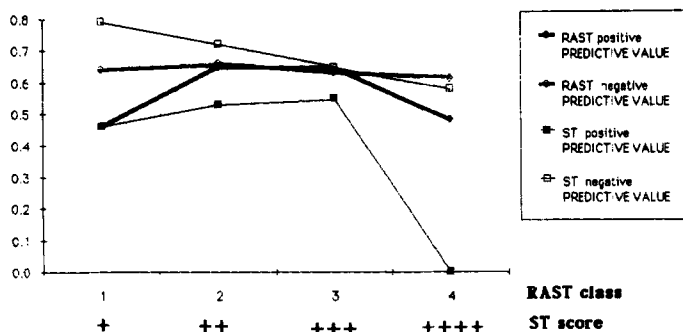


Fig. 5. Positive and negative predictive values for skin tests and RAST according to skin test score or RAST class in the children who experienced a positive cow's milk challenge test (immediate and/or late reactions to cow's milk challenge test).

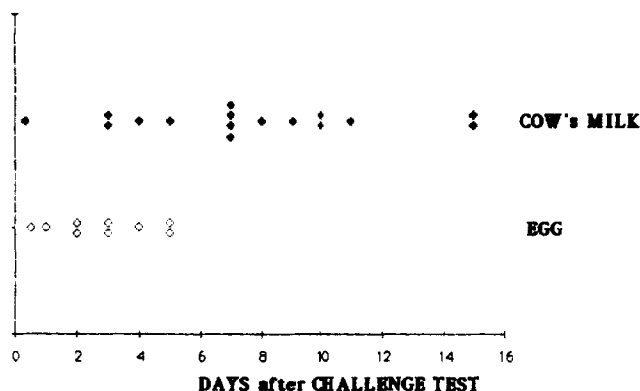


Fig. 6. Onset of late reactions (days) after challenge test with cow's milk or egg.

with Hill et al. (22), in some children the reactions were noted even several days from the first administration of the offending food.

These late reactions could be related to a spectrum of factors different from food antigens (e.g. dust mites, infections, emotions, etc.) which can only be ascertained with difficulty. However, these children again on elimination diets improve and worsen when a new food challenge test is performed.

Other factors may play a role: a) increasing amount of food administered by parents at home, b) association with other food items which can influence the absorption rate of the offending food (23).

In disagreement with the data of Sampson (24), most late reactions observed by us were not preceded by immediate reactions. We would like to emphasize that the only possible explanation is the very high total IgE values found by Sampson et al. in highly selected child populations (12, 25) (up to 45000 IU/ml with a median value of 4100 IU (12) and 8463 (25), while the children of the present study had a median value of total IgE of 50 IU/ml (range 5-1000 IU/ml)).

We can also speculate that the large-scale use of topical corticosteroids by the patients studied by Sampson et al. (12) could have in some way prevented the development of late reactions. It is well known that corticosteroids inhibit late phase reactions after challenge test with the specific allergen in allergic asthma (24). We

would like to stress that corticosteroids were not allowed to the children during the present study.

In conclusion we would like to stress the following points: 1) Immediate reactions following food challenge tests are frequent even in children who have never experienced them previously; 2) Case history is usually unreliable since the reactions can occur despite the negative history; 3) Since immediate reactions can be severe, appropriate emergency equipment and personnel should be at hand; 4) SPT can predict these reactions only rarely, whereas SPT is useful in excluding them due to their high negative predictive value; 5) Sensitivity and specificity of RAST are low as regards immediate and late reactions. The positive and negative predictive values are lower than those of SPT, which are easily and quickly performed and have lower cost; 6) The challenge test appears to be the only way to diagnose FA. In addition, a positive challenge test permits us to eliminate a food, and a negative one allows reintroduction, eliminating the risk of nutritional deficiencies and psychological disturbances which can follow restricted diets. The absence of immediate reactions does not exclude the possible onset of late reactions. Since these reactions may occur even several days after challenge tests the child should be followed during this period of time before issuing a definitive diagnosis.

REFERENCES

1. Benincori, N., Picarazzi, A., Tacconi, L., et al.: Dermattite atopica ed allergia alimentare nel bambino. Valutazione dei parametri clinici ed allergologici e dei risultati delle diete di eliminazione e dei test di provocazione in 96 casi. *Aggiorn Pediatr* 36, 129-135, 1985.
2. Sampson, H. A. & Albergo, R. A.: Comparison of results of skin test, RAST, and double blind, placebo-controlled food challenge in children with atopic dermatitis. *J. Allergy Clin. Immunol.* 74, 26-33, 1984.
3. Aas, K. & Johansson, S. G. O.: The RAST in the in vitro diagnosis of multiple reaginic allergy. *J. Allergy Clin. Immunol.* 48, 134-142, 1971.
4. Hoffmann, D. R. & Haddad, Z. H.: Diagnosis of IgE mediated reactions to food antigen by radioimmunoassay. *J. Allergy Clin. Immunol.* 54, 151, 1974.
5. Chua, Y. Y., Bremner, K., Llobet, J. L., Kokubu, H. L. & Collins Williams, C.: Diagnosis of food allergy by the radioallergosorbent test. *J. Allergy Clin. Immunol.* 58, 477-482, 1976.
6. Van Asperen, P. P., Kemps, A. S., Mellis, C. M., et al.: Immediate hypersensitivity reactions on the first known exposure to the food. *Arch. Dis. Child.* 58, 253-256, 1983.
7. Hill, D. J., Duke, A. M., Hosking, C. S. & Hudson, I. L.: Clinical manifestation of cow's milk allergy in childhood. 2: The diagnostic value of Skin Test and RAST. *Clin. Allergy* 18, 481-490, 1988.
8. Hanifin, J. M. & Rajka, G.: Diagnostic features of atopic dermatitis. *Acta Dermatovenereol. (Suppl.)* 92, 44-47, 1980.
9. Bock, S. A., Buckley, J., Holst, A. & May, C. D.: Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin. Allergy* 7, 375-383, 1977.
10. Businco, L., Benincori, N. & Cantani, A.: Clinical and immunological aspects of atopic dermatitis. A review and update. In Businco, L. (ed.): *Advances in Pediatric Allergy*. Amsterdam: Excerpta Medica, 195-236, 1983.
11. Meglio, P., Farinella, F., Giampietro, P. G., Cantani, A. & Businco, L.: Immediate reactions following challenge test in children with atopic dermatitis. *Allergic Immunol.* 20, 57-62, 1988.
12. Sampson, H. A. & McCaskill, R. N.: Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J. Pediatr.* 107, 669-675, 1985.
13. David, T. J.: Anaphylactic shock during elimination diets for severe atopic eczema. *Arch. Dis. Child.* 59, 983-986, 1984.
14. Sampson, H. A. & Jolie, P. L.: Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N. Engl. J. Med.* 311, 372-376, 1984.
15. Engman, M. F., Weiss, R. S. & Engman, M. F., Jr.: Eczema and environment. *Med. Clin. North Am.* 20, 651-663, 1936.
16. Leiferman, K. M., Ackerman, S. J., Sampson, H. A., et al.: Dermal deposition of eosinophilic granule major basic protein in atopic dermatitis: comparison with onchocerciasis. *N. Engl. J. Med.* 313, 282-285, 1985.
17. Sampson, H. A.: IgE mediated food intolerance. *J. Allergy Clin. Immunol.* 81, 495-504, 1988.
18. Bock, S. A., Remigio, L. K. & May, C. D.: Studies of hypersensitivity reactions to foods in infants and children. *J. Allergy Clin. Immunol.* 62, 327-334, 1978.
19. Dolovich, J., Hargreave, F. E., Chalmers, R., et al.: Late cutaneous allergic responses in isolated IgE-dependent reactions. *J. Allergy Clin. Immunol.* 52, 38-46, 1973.
20. Wraith, D. S., Merret, J., Roth, A., Yman, L. & Merret, T. S.: Recognition of food allergen patients and their allergen by RAST. *Clin. Allergy* 9, 25-36, 1979.
21. Johansson, S. G. O., Dannaeus, A. & Lilja, G.: The relevance of anti-food antibodies for the diagnosis of food allergy. *Ann. Allergy* 53, 665-672, 1984.
22. Hill, D. J., Duke, A. M., Hoskings, C. S. & Hudson, I. L.: Clinical manifestations of cow's milk allergy in childhood. II. The diagnostic value of skin tests and RAST. *Clin. Allergy* 18, 481-490, 1988.
23. Horowitz, M., Cook, D. J., Collings, P. J., et al.: The application of techniques using radionuclides to the study of gastric emptying. *Surg. Gynecol. Obstet.* 155, 737-744, 1982.
24. Sampson, H. A.: The role of food allergy and mediator release in atopic dermatitis. *J. Allergy Clin. Immunol.* 81, 635-645, 1988.
25. Sampson, H. A.: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J. Allergy Clin. Immunol.* 71, 473-480, 1983.