

Contact allergy: Another occupational risk to *Tetranychus urticae*

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Background: *Tetranychus urticae* is a phytophagous, macroscopic mite ubiquitous to warm climates, which causes occupational allergic symptoms in farm workers.

Objective: This study was designed to investigate the cause and mechanisms of an otherwise "undetermined" recurrent and occupational dermatitis on the hands of farm workers and to obtain a better diagnostic profile of the urticaria that many farm workers who are allergic to *T. urticae* experience.

Methods: Fifty-six farm workers with occupational cutaneous and/or respiratory symptoms and 10 healthy farm workers underwent in vivo and in vitro diagnostic trials by skin prick testing, serum-specific IgE determination, and three different types of epicutaneous tests.

Results: Four of the 10 patients with recurrent dermatitis had a positive IgE reaction to *T. urticae*, and five of the 10 had a positive patch test response. The percentage of positive patch test responses between subjects with positive *T. urticae* IgE and those with negative *T. urticae* IgE was similar. The diagnostic trial allowed the diagnosis of immune-mediated contact dermatitis in seven of the 10 patients with recurrent occupational dermatitis on the hands. The result of the epicutaneous open test on healthy skin with no history of eczema was positive in almost all patients with IgE to *T. urticae* and episodes of occupational urticaria.

Conclusions: Urticaria frequently occurring in farm workers allergic to *T. urticae* is an allergic contact urticaria. *T. urticae* is also directly responsible for recurrent dermatitis, caused by a different immune-mediated mechanism, in farm workers. (*J Allergy Clin Immunol* 1996; 98:732-8.)

Key words: *Tetranychus urticae*, contact urticaria, allergic contact dermatitis, protein contact dermatitis, patch test, open test, allergy

We recently described a seasonal occupational syndrome in 46 farm workers, which featured acute rhinitis coupled mostly with bronchial asthma, urticaria, or asthma and urticaria. Thirty-six patients had an IgE-mediated allergy to proteins from *Tetranychus urticae* (TU), a 0.4 to 1.0 mm mite ubiquitous to warm climates, commonly known as "red spider."¹ The urticaria was present exclusively on the healthy and uncovered skin and

Abbreviations used

ACD:	Allergic contact dermatitis
CU:	Contact urticaria
OCCS:	Overlapping contact cutaneous syndrome
PCD:	Protein contact dermatitis
SPT:	Skin prick test
TU:	<i>Tetranychus urticae</i>
TUWBE:	<i>Tetranychus urticae</i> whole body extract

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resembled the clinical picture of contact urticaria (CU).²

In the realm of cutaneous contact pathologic conditions caused by foreign protein, CU, protein contact dermatitis (PCD),^{3,4} and the classic allergic contact dermatitis (ACD)⁵ have different, well-defined characteristics and disease mechanisms. Moreover, contact dermatitis, char-

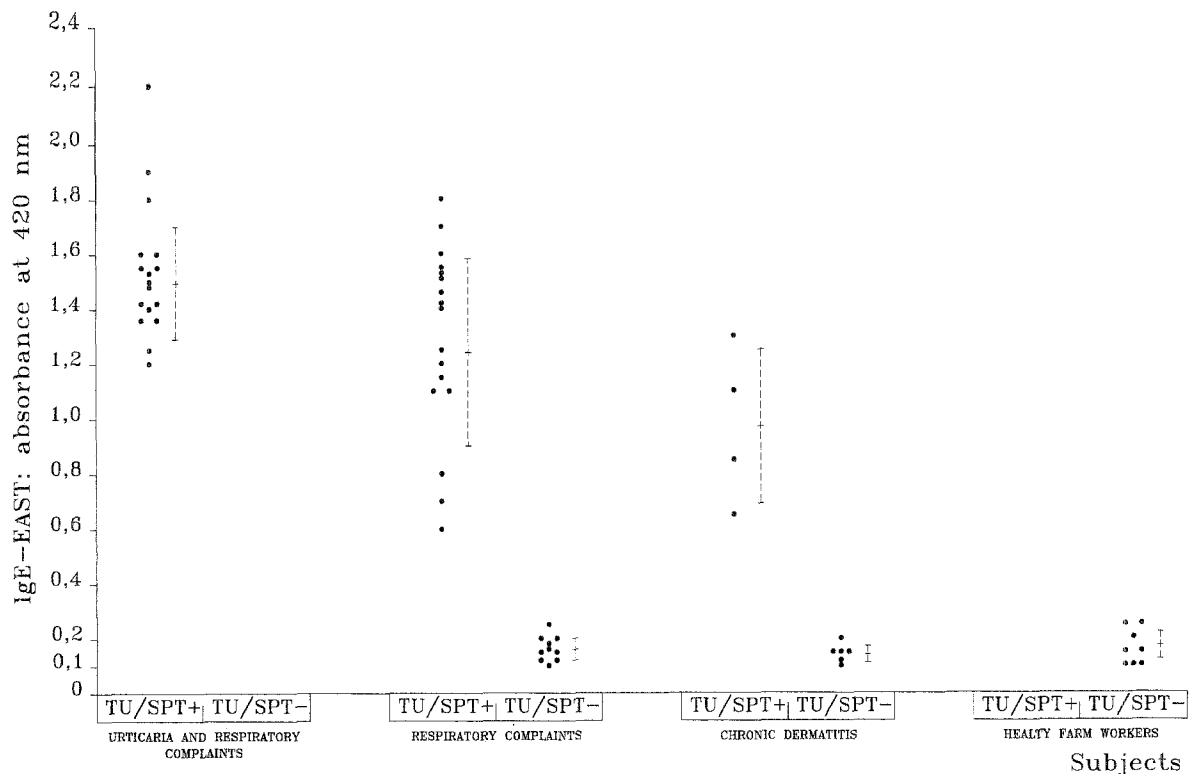


FIG. 1. TU-specific IgE serum levels (enzyme allergosorbent test) grouped by clinical history of TU sensitivity and results of SPTs with TU. *Dashed lines* represent standard deviation of the mean. *EAST*, Enzyme allergosorbent test.

acterized by overlapping urticaria-like and eczematous symptoms and governed by a different disease mechanism in the same individual, could also be caused by cutaneous exposure to normally inhaled allergens.⁶⁻¹³ Finally, it is worth noting that similar reactions have also been reported in other patients with no history of skin disease.¹⁴

Over the last 18 months, we have observed 10 farm workers with a recurrent seasonal and occupational dermatitis on the hands, the cause of which remained undetermined after standard patch tests (International Contact Dermatitis Research Group haptens), used in series with specific professional haptens (e.g., oil resins, pesticides), were performed. In the attempt to define the cause and mechanisms of this occupational dermatitis, we investigated the possible occurrence of TU-induced disease.

Consequently, each subject underwent skin prick tests (SPTs), serum IgE determination, and three different types of epicutaneous tests with a TU whole body extract (TUWBE) prepared in our laboratory.¹ The 46 farm workers examined in our first study were also included in the trial in order to define their urticaria more accurately.

METHODS

Patients and control subjects

Ten farm workers (4 women; average age, 32.2 years) had a history of at least 2 years of recurrent dermatitis on the hands, characterized by alternate periods of partial or total remission during the winter and spring and a worsening in the summer and autumn. Most patients (7 of 10) complained of frequent wheals (urticaria-like) and/or microvesiculated (acute eczematous) eruptions, with both local itching and flare, while working in the open with uncovered hands.

Six patients cited a family history of probable atopic disease, but only two had experienced rhinitis during childhood and gastrointestinal intolerance to eggs until the age of 6 years.

Two groups of farm workers had been previously examined for job-related acute urticaria with rhinitis complaints. One group consisted of 17 subjects with urticaria and respiratory complaints who were allergic to TU, as determined by positive SPT and IgE results; the other group consisted of 29 subjects with respiratory complaints, most of whom were allergic to TU also determined by positive SPT and IgE results.¹

Ten healthy farm workers, of the same age as the patients, served as control subjects. These subjects had no family history or other indication of atopic disease, but they all had job experience and exposure comparable to that of the patients.

TABLE I. TU epicutaneous test findings in healthy farm workers and in those with a job-related illness

Type of job-related disease and presence/absence of TU IgE	Urticaria-inducing open test		Acute eczema-inducing open test		Finn-chamber patch test	
	Positive	Negative	Positive	Negative	Positive	Negative
Recurrent dermatitis (<i>n</i> = 10)						
TU IgE ⁺ (<i>n</i> = 4)	3	1	3	1	2	2
TU IgE ⁻ (<i>n</i> = 6)	2	4	—	6	3	3
Urticaria and respiratory complaints (<i>n</i> = 17)						
TU IgE ⁺ (<i>n</i> = 17)	16	1	ND		6	11
TU IgE ⁻ (<i>n</i> = 0)	—	—	ND		—	—
Respiratory complaints (<i>n</i> = 29)						
TU IgE ⁺ (<i>n</i> = 19)	1	18	ND		6	13
TU IgE ⁻ (<i>n</i> = 10)	—	10	ND		1	9
Healthy farm workers (<i>n</i> = 10)						
TU IgE ⁺ (<i>n</i> = 0)	—	—	ND		—	—
TU IgE ⁻ (<i>n</i> = 10)	—	10	ND		—	10

Subjects were chosen on the basis of presence/absence of TU IgE.

ND, Not done.

TABLE II. TU patch test results in 56 subjects with and without TU-specific IgE

Patch test result	Total	IgE ⁺ subjects	IgE ⁻ subjects
Positive	18	14*	4*
Negative	38	26	12
Total	56	40	16

**p* = NS.

Patients and healthy subjects volunteered for the study, which was approved by the Ethical Committee of Naples Second University Medical School.

SPT and serum IgE assay

Both the patients and the control subjects had an SPT with TUVBE and an assay for serum TU IgE as previously described.¹ The drop of TUVBE was removed immediately from the intact skin surrounding the skin puncture to prevent a possible spontaneous absorption of the allergen.

Epicutaneous tests

On each occasion an amount of lyophilized TUVBE, prepared in our laboratory, was dissolved in sufficient distilled water to obtain a final concentration of between 5 and 6 mg/ml. The suspension was continuously shaken until all the epicutaneous tests were completed. Each test consisted of 0.15 ml of suspension absorbed by a filter paper disk.

The epicutaneous tests performed are as follows. The Finn-chamber patch test^{15,16} was applied to the healthy skin on the back. It was removed 72 hours later and read within 1 to 2 hours to allow the dermatitis-eczema local reaction.¹⁴ The urticaria-inducing open test with absorbed

TABLE III. Urticaria-inducing open test results in 56 subjects with or without TU-specific IgE

Test result	Total	IgE ⁺ subjects	IgE ⁻ subjects
Positive	22	20*	2*
Negative	34	20	14
Total	56	40	16

**p* = 0.02 (TU IgE⁺ > TU IgE⁻).

paper disk was applied to the healthy skin on the anterior forearm of subjects with no prior dermatitis in that area. It was removed after 20 minutes, and the urticaria-like skin reaction was read within 15 to 20 minutes.² The acute eczema-inducing open test with absorbed paper disk was only applied to the healthy skin on the hands of the 10 farm workers with occupational recurrent dermatitis and a history of this symptom in that area. The disk was removed after 30 minutes, and the acute eczematous local reaction was read within 20 minutes.^{3,4}

Epicutaneous test results as a tool to define an operative working diagnosis

Finn-chamber patch test. When a positive response to the Finn-chamber patch test was observed in patients and there was no response in the control subjects,¹⁶ we made a diagnosis of ACD induced by mites in patients with dermatitis and a diagnosis of delayed hypersensitivity to mites in patients with no history of recurrent dermatitis.^{5,14,17}

Urticaria-inducing open test. A positive response to the urticaria-inducing open test in patients with recurrent occupational dermatitis or urticaria was sufficient to establish a diagnosis of CU or allergic CU in the presence of IgE antibodies to mites.²

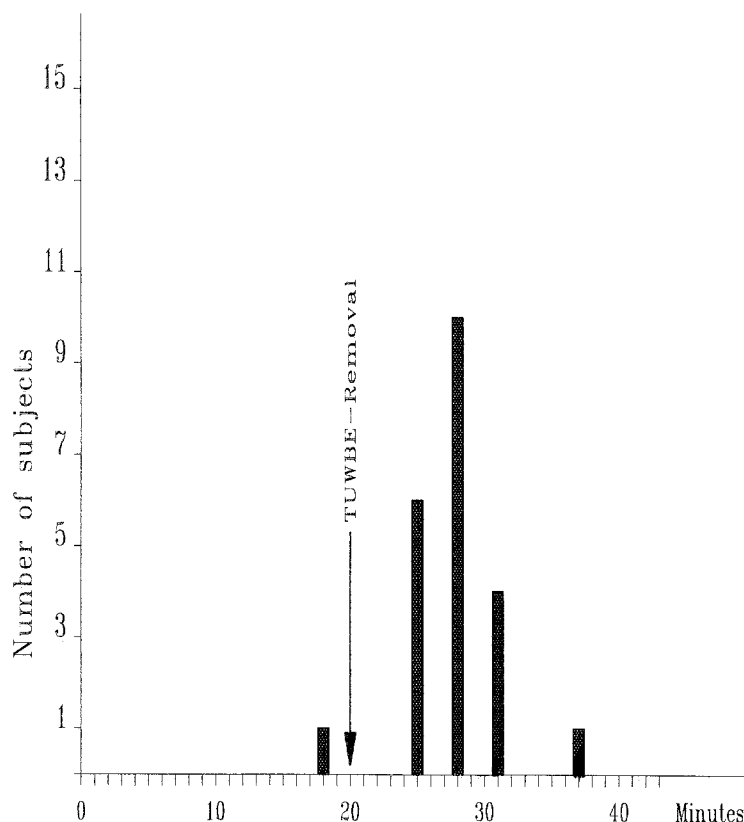


FIG. 2. Onset of the skin response during the "urticaria-inducing" open test compared with removal of TUVBE-absorbed paper disk.

Acute eczema-inducing open test. A positive response to the acute eczema-inducing open test with micro-vesiculated eruption and flare and the presence of concomitant TU IgE was sufficient to make the diagnosis of protein contact dermatitis^{3,4} in patients with job-related recurrent dermatitis.

Associated positive responses to different epicutaneous tests. The results of different epicutaneous tests confirm the existence of combined immune-mediated mechanisms at the skin level.^{6,9} We would like to define this phenomenon as an immune-mediated, overlapping contact cutaneous syndrome (OCCS) in our patients with recurrent, overlapping urticaria-like and eczematous skin lesions. The same phenomenon, observed in subjects without related clinical cutaneous symptoms, showed a simple activation of different immunologic mechanisms but no skin disease.

Associated negative responses for different epicutaneous tests. When all the epicutaneous test results were negative¹⁶ in patients with job-related recurrent, dermatitis,¹⁸ a diagnosis of irritating contact dermatitis was made.¹⁹

Statistics

The differences in the results of each epicutaneous test among subjects with different TU-induced patho-

logic conditions or between subjects with positive IgE antibodies to TU and those with negative IgE antibodies to TU were evaluated by the chi square test. Data are presented as means $\pm$ SD. Differences at a *p* value of less than 0.05 were considered significant.

RESULTS

SPT with TUVBE and IgE assay

Four of the 10 patients with job-related dermatitis on the hands had positive IgE antibodies to TU. This never occurred in the control subjects. All the patients with positive SPT responses to TU had a TU-specific serum IgE concentration at 2 standard deviations above the mean value of control subjects; no significant statistical differences in serum TU IgE were found among the patients who were not reactive to SPTs with TU and the control group (Fig. 1).

Epicutaneous tests

A summary of the results of epicutaneous tests is shown in Table I.

TABLE IV. Skin prick test, epicutaneous test, and operative working diagnoses in 10 farm workers with job-related recurrent dermatitis on the hands

Patient No.	TU IgE	Urticaria-inducing open test	Acute eczema-inducing open test	Finn-chamber patch test	Operative working diagnoses
1	+	I, E, W	I, E, MVE	+	OCCS (CU, PCD, ACD)
2	+	I, E, W	I, E, MVE	+	OCCS (CU, PCD, ACD)
3	+	I, E, W	—	—	CU
4	+	—	I, E, MVE	—	PCD
5	—	I, E, W	—	+	OCCS (CU, ACD)
6	—	—	—	—	ICD
7	—	—	—	+	ACD
8	—	—	—	—	ICD
9	—	—	—	—	ICD
10	—	I, E, W	—	+	OCCS (CU, ACD)

I, Itching; E, erythema; W, wheal; MVE, microvesiculated eruptions; ICD, irritating contact dermatitis.

Finn-chamber patch test

Results of the patch test with TU were positive in 18 of the 56 patients examined. There was no difference in percentage of response to the patch test between patients with positive IgE antibodies to TU and those with negative IgE antibodies to TU (Table II). Patch test results were negative in the control subjects. The patches, used with different concentrations of material, caused no direct irritation. The highest rate of positive patch test results was observed in patients with job-related dermatitis (50%), but a still relevant number of positive patch test results also occurred in subjects with both urticaria and allergic respiratory complaints (35.2%) and in subjects with only respiratory complaints (24.1%).

Urticaria-inducing open test

Results of the urticaria-inducing open test were positive in 22 patients (39.3%) and negative in the control subjects. The percentage of positive test results was significantly higher in subjects with positive IgE antibodies to TU than in those without IgE antibodies to TU (Table III). Test results were positive, as expected, in almost all the subjects with positive IgE antibodies to TU and occupational urticaria (16 of 17), also in a significantly lower number of subjects with occupational dermatitis ($p = 0.02$), and finally, in one patient alone among those with only respiratory complaints.

Except for the one patient with positive IgE antibodies to TU and occupational respiratory complaints, a positive urticaria inducing open test

result always correlated with the clinical findings of urticaria (16 subjects) or job-related urticaria-like flaring of dermatitis on the hands (5 subjects).

The patients who had a positive test result showed the onset of a skin response in a mean of 7.6 ± 3.5 minutes after removal of the TUWBE-absorbed paper disk. A point worth noting is that one patient with urticaria showed the onset of a skin response 2 minutes before the removal of TUWBE (Fig. 2).

Acute eczema-inducing open test

Results of the acute eczema-inducing open test were positive in three of the 10 patients with recurrent dermatitis; positivity was always coupled with TU IgE, and the clinical finding of dermatitis was coupled with seasonal job-related worsening, characterized by skin lesions resembling acute eczema.

Operative working diagnosis

With the test results for a diagnostic profile, the operative working diagnosis of immune-mediated OCCS caused by TU was confirmed in four of the 10 patients with job-related recurrent dermatitis. In the same group TU-induced isolated CU, PCD, and ACD occurred in only three subjects; whereas the persistently negative epicutaneous test results allowed the diagnosis of irritating contact dermatitis to be made in only three subjects (Table IV).

The positive results from the urticaria-inducing open test confirmed the diagnosis of allergic CU in almost all subjects who were allergic to TU and

had job-related urticaria and respiratory complaints (16 of 17). One subject alone, among the patients with positive IgE antibodies to TU and job-related respiratory disease, exhibited a slow-forming itchy wheal, despite the absence of a clinical history of urticaria. Of 13 subjects who had no related dermatitis, whether allergic to TU or not, the seven subjects with only job-related respiratory complaints and the six subjects with job-related, urticaria-associated respiratory complaints showed mild eczematous cutaneous reactions to the Finn-chamber patch test as a simple expression of an activated mechanism of delayed hypersensitivity (type IV).

DISCUSSION

Contact urticaria occurs on healthy skin after contact with rapidly penetrating substances² and can be caused by IgE-mediated or non-immune-mediated mechanisms. In the case of allergic CU the reaction often extends beyond direct local contact and is associated with eczematous skin lesions in 50% of patients. This disease, when induced by a single mechanism as shown with the "urticaria-inducing" open test, is a well-defined syndrome.^{2, 6, 20} The data from this study are useful in demonstrating that the occupational urticaria recurring in subjects allergic to TU is an allergic CU and that TU-induced allergic respiratory symptoms are provoked by direct contact of the allergen with respiratory mucosa. Clinically, recurrent CU may be the first sign in the future development of contact dermatitis, whether immune-mediated or not, in a locus minoris resistentiae, or vice versa.

In the case of PCD it has been clearly shown that recurrent and immediate, acute eczematous cutaneous reactions are implicated in persistent skin lesions of the hands, which occur in subjects with IgE antibodies to frequently handled food allergens,³⁻⁴ and that the histologic pattern of these types of immediate dermatitis is similar to classic ACD,³⁻⁴ demonstrating an immediate and delayed contact dermatitis.²⁰ When PCD has a single disease mechanism, shown by the concurrent positivity of the specific IgE and of the relevant acute eczema-inducing open test result, it is also a well-defined syndrome. However, the chronic types of contact dermatitis with overlapping urticaria-like and eczematous clinical features, which have been described as being induced by the cutaneous contact of various agents and governed by different, disease-associated mechanisms,^{6-9, 14} are undefined syndromes that can be defined as types of OCCS.

In four of the seven patients with job-related recurrent dermatitis caused by TU through different immune mechanisms, the diagnosis of OCCS is justified by the contemporary effects of two or more immune pathologic mechanisms and by the concurrent urticaria-like and eczematous symptoms, even if both the clinical and diagnostic overlaps may be induced exclusively by a TU IgE-mediated mechanism. In fact, the presence of IgE on the surface of Langerhans cells in the skin of patients with recurrent dermatitis is regarded as a fundamental link between exposure to an aeroallergen and the worsening of related eczematous lesions.²¹⁻²⁵ Although similar links are possible in most of our patients with TU IgE, we found no significant difference in the percentage of positive patch test results between patients with positive IgE antibodies to TU and those with negative IgE antibodies to TU with either recurrent dermatitis or with only respiratory complaints. An IgE-independent immunopathologic mechanism is probably also involved in the patients with TU-induced allergic CU but no recurrent dermatitis, in whom we found a TU-induced delayed hypersensitivity but a lack of correlation between both the TU IgE and urticaria-inducing open test results and the patch test results.

Finally, the delayed hypersensitivity to TU found in one of the 10 patients with only occupational respiratory complaints was demonstrated to be IgE-independent because there was no detectable TU IgE.

We suggest that the extensive use of epicutaneous tests coupled with an IgE assay would be useful when job-related allergens, such as TU, are implicated in a well-defined category of subjects with a high risk of sensitivity. Moreover, a correct interpretation of the follow-up of those intriguing subjects who have positive patch test results but no dermatitis could lead to a greater clinical understanding, beyond the etiology, of cutaneous contact skin disease and its primary prevention.

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REFERENCES

1. Astarita C, Franzese A, Scala G, Sproviero S, Raucci G. Farm workers' occupational allergy to *Tetranychus urticae*: clinical and immunological aspects. *Allergy* 1994;49:466-71.
2. Maibach HI, Johnson HI. Contact urticaria syndrome. *Arch Dermatol* 1975;111:726-30.
3. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976;2:28-42.

4. Hjorth N, Roed-Petersen J. Allergic contact dermatitis in veterinary surgeons. *Contact Dermatitis* 1980;6:27-9.
5. Sauder DN. Allergic contact dermatitis. In: Thiers BH, Dobson RL, editors. *Pathogenesis of skin disease*. New York: Churchill Livingstone, 1986:3-13.
6. von Krogh G, Maibach HI. The contact urticaria syndrome. *Semin Dermatol* 1982;1:59-66.
7. Boonk WJ, Ketel WJ, van. Skin testing in chronic urticaria. *Dermatologica* 1981;163:151-9.
8. Krook G. Occupational dermatitis from *Latuca sativa* (lettuce) and *Cichorium* (endive). Simultaneous occurrence of immediate and delayed allergy as a cause of contact dermatitis. *Contact Dermatitis* 1977;3:27-36.
9. Campolmi P, Lombardi P, Lotti T, Sertoli A. Immediate and delayed sensitization to garlic. *Contact Dermatitis* 1982;8:352-3.
10. Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TAE. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;1:27-30.
11. Platts-Mills TAE, Mitchell EB, Rowntree S, Chapman MD, Wilkins SR. The role of dust mite allergens in atopic dermatitis. *Clin Exp Dermatol* 1983;8:233-47.
12. Reitamo S, Visa K, Kaonen K, Käykö K, Stubb S, Salo OP. Eczematous reactions in atopic patients caused by epicutaneous testing with inhalant allergens. *Br J Dermatol* 1986;114:303-9.
13. Adinoff AD, Tellez P, Clark RAF. Atopic dermatitis and aeroallergen contact sensitivity. *J Allergy Clin Immunol* 1988;81:736-42.
14. Seidenari S, Manzini BM, Danese P, Giannetti A. Positive patch tests to whole mite culture and purified mite extracts in patients with atopic dermatitis. *Ann Allergy* 1992;69:201-6.
15. Lahti A, Hannuskela M. Hypersensitivity to apple and carrot can be reliably detected with fresh material. *Allergy* 1978;33:143-8.
16. Adams RM, Fischer T. Diagnostic patch testing. In: Adams RM, editor. *Occupational skin disease*. 2nd ed. Philadelphia: Saunders, 1990:240.
17. Coombs RAA, Gell PHG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PHG, Coombs RAA, Lackman PJ, editors. *Clinical aspects of immunology*. 3rd ed. Oxford: Blackwell Scientific Publications, 1975:761-82.
18. Mathias CGT. Contact dermatitis and workers' compensation: criteria for establishing occupation causation and aggravation. *J Am Acad Dermatol* 1989;20:842-8.
19. Adams RM. Occupational dermatoses and disorders due to chemical agents. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors. *Dermatology in general medicine*. 4th ed. New York: McGraw Hill, 1993:1767-83.
20. von Krogh G, Maibach HI. The contact urticaria syndrome and associated disease entities. In: Moschella SL, Hurley HJ, editors. *Dermatology*. Philadelphia: WB Saunders, 1982:323-33.
21. Bruijnzeel-Koomen C, Van Mwichen DF, Toonstra J, Berrens L, Bruijnzeel TLB. The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Dermatol Res* 1986; 78:199-205.
22. Barker JNWN, Alegre VA, Mc Donald DM. Surface-bound immunoglobulin E on antigen-presenting cells in cutaneous tissue of atopic dermatitis. *J Invest Dermatol* 1988;90:117-21.
23. De Groot AC, Young E. The role of contact allergy to aeroallergens in atopic dermatitis. *Contact Dermatitis* 1989;21:209-14.
24. Bieber T, Bruijnzeel-Koomen C. La cellule de Langerhans dans la physiopathologie de la dermatite atopique. *Ann Dermatol Venerol* 1990;117:185-93.
25. Mudde GC, Hansel TT, Vonreijssen FC, Osterhoff BF, Bruijnzeel-Koomen CAMF. IgE an immunoglobulin specialized in antigen capture. *Immunol Today* 1990;11: 440-3.