

Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests

U. Darsow and J. Ring

Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany

Summary

Aeroallergens and food allergens are relevant eliciting factors of atopic eczema. This article focuses on the methods used for diagnosis in patients with suspected allergy to airborne or dietary allergens and who are suffering from atopic eczema. In addition to classical tests of IgE-mediated hypersensitivity (intracutaneous or *in vitro* testing), the role of provocation procedures is described. For aeroallergens, the atopy patch test yields the most specific results with regard to clinical history as compared with classical methods. For food allergens and pseudoallergic reactions to additives, this holds true for the double-blind, placebo-controlled food challenge. The methods and their limitations are discussed from a practical point of view.

Introduction

The chronic inflammatory skin disease atopic eczema (atopic dermatitis) is characterized by recurrent intense pruritus and a typically age-related distribution and skin morphology. There is no specific marker for atopic eczema and the diagnosis is made by a combination of clinical features (the disease definition is reviewed elsewhere^{1–4}). 'Atopy' is defined as familial tendency to develop certain diseases (extrinsic bronchial asthma, allergic rhinoconjunctivitis and/or atopic eczema) on the basis of a hypersensitivity of skin and mucous membranes against environmental substances, associated with increased IgE production and/or altered nonspecific reactivity.^{5–6} The role of allergy in eliciting and maintaining the eczematous skin lesions is still controversial, which is due mainly to a lack of specificity of the classic tests for IgE-mediated hypersensitivity. Among the allergens found to be relevant in atopic eczema, aeroallergens and food allergens are the most important. Therapeutic consequences of diagnosis of an allergy are based upon avoidance strategies, which can be very expensive and distressing for the patient. Thus,

the relevance of (often multiple) IgE-mediated sensitizations in patients with atopic eczema for the treatment of the skin disease should be evaluated. This review focuses on the methodology used currently.

Atopy patch test with aeroallergens in patients with atopic eczema

It has long been known that environmental substances such as aeroallergens can produce flares in some patients with atopic eczema.⁷ An epicutaneous patch test with allergens known to elicit IgE-mediated reactions, and the evaluation of eczematous skin lesions (Atopy Patch Test, APT)^{8–10} is proposed as the diagnostic tool for characterizing this subgroup of patients. Patients with atopic eczema often have elevated serum levels of IgE,¹¹ which may correlate with severity of disease.^{12–14} In addition, aeroallergen avoidance, especially with regard to house dust mites, can result in marked improvement of skin lesions.^{15,16} The hypothesis is that Langerhans cells bind and present 'immediate type' allergens, which penetrate the impaired epidermal barrier in atopic eczema patients. This concept is derived from studies showing IgE and IgE-binding structures on the surface of epidermal Langerhans cells^{17–19} together with mite allergen.²⁰ Allergen-specific T cells have been cloned from APT

Correspondence: U. Darsow, Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Biedersteiner Straße 29, D-80802 München, Germany.

Table 1 Allergen-specific concordance of APT with skin prick test and RAST. *n* = 36 patients with atopic eczema.

Allergen	Skin prick test	RAST
<i>D. pter.</i>	0.53	0.69
Cat dander	0.50	0.67
Grass pollen	0.39	0.42

biopsies; these T cells showed a characteristic TH2 (T helper cell subpopulation) cytokine secretion pattern initially, whereas after 48 h a TH1 pattern was predominant.^{21,22} This same pattern is also found in chronic lesions of atopic eczema.

Several groups demonstrated that eczematous skin lesions can be induced in patients with atopic eczema by patch testing with aeroallergens.^{8–10,23–29} The earliest publications on patch testing of aeroallergens date from 1937,³⁰ the association of pollen allergy and hand dermatitis was published 1946.³¹ The step to patch testing of aeroallergens especially in patients with atopic eczema was first documented in 1982 by Mitchell *et al.*²⁸ Due to variations in the methods used, such as skin abrasion, tape stripping, and sodium lauryl sulphate application for the enhancement of allergen penetration, differing percentages (15–100%) of positive APT results were obtained. No clear-cut correlations with the skin prick test or specific IgE measurements could be obtained and the sensitivity and specificity of experimental APTs with regard to clinical history remained unclear. We performed several studies to standardize the methods of APT (vehicle, dose response, etc.) and to define the relationship with clinical covariates.

In a methodological trial 36 patients with atopic eczema, four patients with rhinoconjunctivitis only, and 10 healthy controls were epicutaneously tested with lyophilized allergens from house dust mite (*Dermatophagoides pteronyssinus*), cat dander, grass pollen mixture and vehicle controls.⁹ Petrolatum and hydrogel were used as vehicles, 1000 and 10 000 protein nitrogen units per gram (PNU/g) were the allergen concentrations for the first dose–response orientation. APT reactions were evaluated after 48 and 72 h, according to the International Contact Dermatitis Research Group rules for conventional contact allergy patch testing.³² Results were compared with skin prick test, total and specific serum IgE. In total, the reactions of 17 patients (47%) were graded as clear-cut positive ($\geq +$). Control sites remained negative, nonatopic volunteers and patients suffering from allergic rhinoconjunctivitis only presented no positive APT reactions. In 15 out of 23 patients, a higher rate of reaction was obtained with

higher allergen concentrations ($P = 0.0023$, Wilcoxon's matched-pairs-signed-rank test). Allergens in petrolatum elicited twice as many APT reactions as allergens in hydrogel vehicle. Thirty-six per cent of patients reacted to house dust mite, 22% to cat dander, and 16% to grass pollen. Of patients with *D. pter.*-positive APT 62% showed a corresponding positive skin prick test and 77% showed a corresponding elevated specific IgE. The allergen-specific concordance of APT and classic tests of IgE-mediated hypersensitivity are given in Table 1. High allergen-specific IgE in serum is not a prerequisite for a positive APT, as was also seen for the correlation with skin prick test; also, positivity of two tests in the same group of patients does not imply a direct link. On the other hand, in most APT-positive patients elevated specific IgE was found as compared with those with negative APT, thus a role for IgE in the reaction mechanism of APT is suggested. Further studies on APT were performed with petrolatum vehicle: a prospective dose-dependency study with four concentrations of the same three aeroallergens as above was performed in 57 patients with atopic eczema.³³ These patients were prospectively divided into two subgroups according to clinical features: group I ($n = 26$) patients had eczematous skin lesions predominantly on air-exposed areas not covered by clothing: hands, lower arms, head and neck area, ankles; group II ($n = 31$) patients were compared as a control group without a conspicuous distribution of skin lesions or with lesions only on the trunk. Allergen concentrations of 500, 3000, 5000, and 10 000 PNU/g in petrolatum were used. In this study, the percentage of patients with clear-cut positive reactions was significantly higher in group I patients with eczematous skin lesions of air-exposed areas (69%) as compared with group II patients (39%; $P = 0.02$, Fisher's exact test). In group I, the maximum reactivity was almost reached with 5000 PNU/g, the last concentration step doubling allergen concentration to 10 000 PNU/g increased APT reactivity by only 11%.

To date, no 'gold standard' of provocation for allergy diagnosis in atopic eczema exists. Thus, the history of allergen-specific exacerbation may be used as a parameter for clinical relevance. With regard to the clinically known phenomenon of 'summer eruption' of atopic eczema, the validity of the APT was investigated. Seventy-nine patients were tested with 10 000 PNU/g grass pollen allergen mixture in petrolatum and simultaneously with 10 mg dry, unprocessed pollen of *Dactylis glomerata* grass.³⁴ The APT results were again compared to history, skin prick tests and specific corresponding IgE and the eczema pattern. This study showed significantly higher frequencies of positive APT

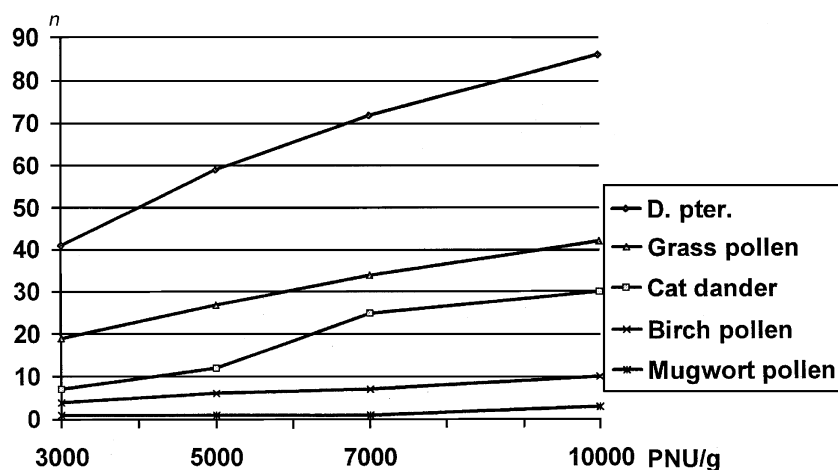


Figure 1 Dose-response of APT in 253 adult patients with atopic eczema (birch and mugwort pollen $n = 88$). APT reactivity (number of patients with positive reactions) increases with allergen dose. Most reactions were elicited by *D. pter.*

reactions (with both methods used) in patients with a corresponding history of exacerbation of skin lesions during the grass pollen season of the previous year, or in direct contact with grass (75% with positive APT). Patients without this prospectively obtained history (16% with positive APT; $P < 0.001$, Fisher's exact test) showed significantly lower APT reactivity. The skin prick test and specific IgE were correlated significantly with the APT using standardized allergen (10 000 PNU/g; $P < 0.001$, χ^2 test). Again, controls showed no APT reaction (both APT methods). For the first time, sensitivity and specificity of an APT procedure could be calculated with regard to a prospectively obtained patients history. Depending on the APT procedure, the sensitivity ascribed to history of exacerbations during the grass pollen season was 0.67–0.75, and the specificity was 0.84–0.90. The APT specificity exceeded the specificity of the classic tests of IgE-mediated hypersensitivity, which was 0.33 for the skin prick test and radioallergosorbent test (RAST). Conversely, the sensitivity of the classical method was higher (0.92 for RAST, and 1.0 for skin prick test). Cases in which unprocessed pollen led to eczematous lesions on nonpretreated skin of atopic eczema patients, and in

which there was good correlation to history, demonstrate that pollen may be involved in eczema flares in some patients and should be considered with regard to avoidance strategies.

The data from a recently published randomized, double-blind multicentre trial,³⁵ involving 253 adult patients and 30 children with atopic eczema, corroborated the previous results. Adults were tested with 3,000–10 000 PNU/g of *D. pter.*, cat dander, grass pollen, and (in two study centres only; $n = 88$) with birch and mugwort pollen. Methodology was similar to previous trials. In this study, 10–52% of patients reported previous eczema flares after contact with at least one of the allergens. The frequencies of clear-cut positive APT, skin prick tests and specific IgE detection are given in Table 2. APT results were correlated significantly with history, skin prick test, and specific corresponding IgE for *D. pter.*, cat dander, and grass pollen ($P < 0.001$, χ^2 test). Again, the specificity of APT was higher, depending on allergen, than with the skin prick test or specific IgE; however, the APT sensitivity ranged from 42 to 56%, whereas the skin prick test and specific IgE reached higher scores (Table 3). A dose-response curve for the APT could be obtained (Fig. 1). The optimal allergen doses are in the range 5000–7000 PNU/g.

Table 2 Skin prick test, specific IgE and APT in adult patients with atopic eczema.

Clear-cut positive results	Skin prick	RAST	APT (48 h)
<i>D. pter.</i> ($n = 253$)	59%	56%	34%
Cat dander ($n = 253$)	54%	49%	12%
Grass pollen ($n = 253$)	65%	75%	18%
Birch pollen ($n = 88$)	65%	65%	11%
Mugwort pollen ($n = 88$)	36%	53%	3%

One allergen, 22%; two allergens, 8%; three allergens, 5% (APT 48 h).

Table 3 APT Multicentre Study: sensitivity and specificity of different test systems in 253 patients with atopic eczema.

Test	Sensitivity*	Specificity*
Skin prick test	69–82%	44–53%
RAST	65–94%	42–64%
APT	42–56%	69–92%

*Allergen-dependent, referring to patient's history.

Table 4 Diagnostic dietary steps for oral provocation tests in patients with atopic eczema.

Step	Day	Food products
Adults		
1	1 + 2	Carbohydrates, cereals and vegetables
2	3 + 4	Milk and dairy products
3	5 + 6	Meat and spices
4	7 + 8	Poultry and eggs
5	9 + 10	Fish and seafood
6	11 + 12	Fruits (and nuts)
7	13 + 14	Food additives and colours
Children		
1	1 + 2	Cereals and vegetables
2	3 + 4	Cow's milk and dairy products
3	5 + 6	Hen's eggs

Atopic eczema and the role of food allergy and pseudo-allergy

A provocation of atopic eczema flares by foods has been reported repeatedly with the vast majority of cases seen in children^{36,37} and should be considered in the management of atopic eczema when there is a history of provocation by food or when conventional treatment measures are ineffective. Egg white, nuts, seafood and peanuts are the most frequently (80–90%) incriminated allergens; in children soy, cow's milk and wheat flour are also responsible. Whereas the IgE-mediated reactions are the most common ones, nonimmunological, pseudo-allergic reactions to food additives or citrus fruit can also provoke atopic eczema in some cases.^{36,37} A small quantity of unprocessed, high-molecular food proteins may be able to pass the bowel wall, thus eliciting a systemic or cutaneous reaction in sensitized patients with atopic eczema for whom an increased intestinal permeability is postulated. Resorbed food antigens may interact directly with specific IgE bound to Fc receptors on Langerhans cells and other immunologically relevant cell populations.³⁸ A decrease in the number of circulating eosinophils was detected after oral provocation and subsequent clinical reaction; in

addition, eosinophil cationic protein was increased in serum and stool samples from patients with positive oral provocation test reactions.³⁸ According to a study by Guillet and Guillet the presence of food allergy is indicative of a prognosis of severe atopic eczema and of associated respiratory atopy.³⁹ As therapy, only the relevant allergens should be avoided, whereas undirected extensive elimination diets are not indicated. The prophylactic effect of breast-feeding in the development of atopic eczema has been shown in an prospective study closely following healthy children from infancy over a period of 17 years.⁴⁰ Further recommendations in children at risk for atopic diseases suggest the avoidance of highly allergenic foods for the lactating mother during the first months of life due to priming the immune system of these genetically predisposed individuals;^{40,41} however, the long-term protective effect of hypoallergenic diet is controversial.

Diagnosis of food allergy in patients with atopic eczema

Sampson *et al.* described in several publications in the 1980s^{38,42,43} correlations of positive oral provocation tests (OPT) with skin prick test, specific IgE and elevated serum histamine levels in children with atopic eczema. In 63% of a group of 320 patients with extensive atopic eczema positive food challenges were reported, with skin symptoms in 75% of reactions. No population-based data are available on the frequency of these reactions, only selected patient groups have been investigated. Most studies on food influence on atopic eczema have been performed in infants and children. Sampson states a prevalence of 40% positive OPT in children with atopic eczema.⁴²

As in other allergic diseases, the allergy diagnosis is established in several steps. The personal history is of crucial importance for the diagnosis, but has a lower validity in atopic eczema than in other adverse food reactions.⁴² Hidden sources of allergen in processed foods have to be considered. Unfortunately, the most common food allergens – milk and egg – are frequently added to improve the integrity of other food products such as meatballs or pasta. Nuts may be added to flavour sauces and baked goods. Diet diaries are used as adjunct to history over a specified time period and may help to reveal unknown sources of food allergens.

Skin tests with native foods ('prick-prick-technique') may be more reliable than with commercially available, processed extracts in screening patients with suspected IgE-mediated food allergies. While negative skin prick tests – according to some authors – nearly exclude IgE-mediated allergy, positive tests do not prove relevant allergy. Of course, all variables influencing the outcome of a skin prick test must be considered.^{6,42} Intradermal

Table 5 APT reaction grading key (ETFAD consensus), 11 April 1997, and 30 June 1998.

–	Negative
?	Erythema only, questionable
+	Erythema, infiltration
++	Erythema, few papules (up to three)
+++	Erythema, papules from four to < many
++++	Erythema, many papules, or spreading papules
+++++	Erythema, (papules and) vesicles

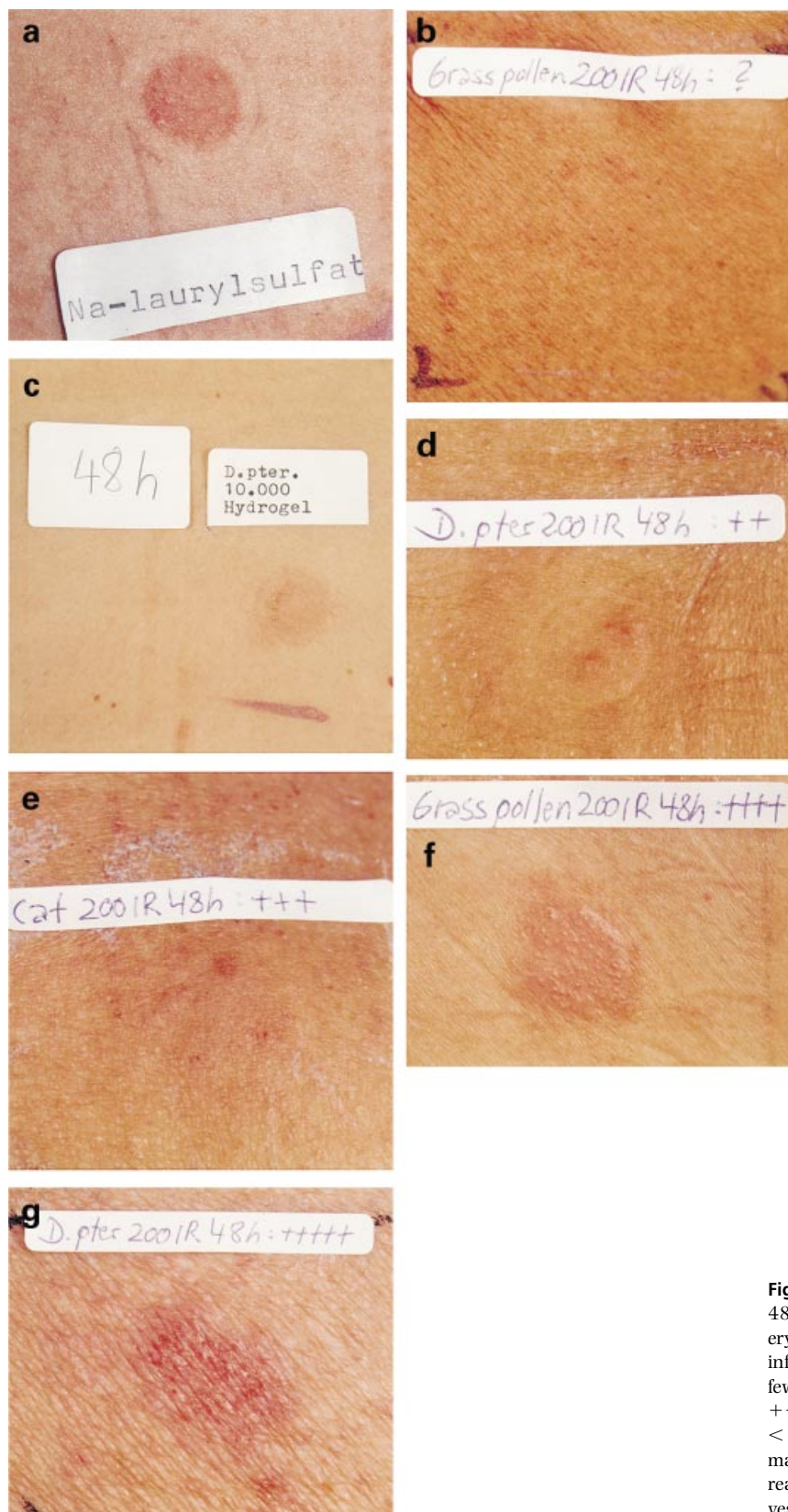


Figure 2 (a) Irritative patch test reaction, 48 h. (b) Questionable APT reaction: erythema only. (c) APT reaction +: erythema, infiltration. (d) APT reaction ++: erythema, few papules (up to three). (e) APT reaction +++: erythema, papules from four to < many. (f) APT reaction ++++: erythema, many papules, or spreading papules. (g) APT reaction +++++: erythema (papules and vesicles).

skin tests have no higher predictive value, but bear a higher risk of systemic reactions.

In the few studies carried out in adult patients, specific IgE to food allergens showed no good correlation with provocation test results.³⁸ However, it is the only method in patients with dermatographism, severe eczema or antihistamine medication and has its role in the general concept of allergy diagnosis.⁴² The predictive value of specific IgE determination to food allergens may be increased after the elimination of cross-reactivity to certain carbohydrate determinants in the RAST.⁴⁴ Further *in vitro* diagnostic methods (histamine release, lymphocyte proliferation, cytokines) and also food patch tests (so far unstandardized) are being researched.

Specific elimination diets may be initiated in the diagnosis of food-induced atopic eczema. As in other diseases triggered by food allergens, the OPT remains the 'gold standard' for the diagnosis.^{42,43} The value of open oral challenges is higher in patients with negative results than in patients with positive results. Preferably, the provocation is performed as double-blind placebo-controlled food challenge, e.g. with 'masked' (lyophilized) foods in coloured and flavoured neutral formulas after at least 1 week of corresponding elimination diet. Provocation tests require inpatient treatment under standardized conditions and trained personnel for treatment of anaphylactic reactions. The selection of tested foods depends on history and skin test or *in vitro* results. Our diagnostic diet schedule for adults and children is listed in Table 4 (modified from Ring⁶ and Przybilla & Ring³⁶). Every 1–2 days (depending upon the time interval between food intake and symptoms), new foods are introduced. For atopic eczema, early (within 1–2 h after provocation) and late reactions (2–24 h) can be distinguished. The latter may necessitate extended oral provocation protocols in some patients to avoid overlap of different food allergens. Repetitive scoring of eczema severity (e.g. with the SCORAD system) by the same investigator is recommended. Further details on food challenges and precautions in highly sensitized patients have been summarized.^{42,45} Additives in capsules may be tested in a placebo-controlled manner according to standardized protocols.⁶

Role of the APT in allergy diagnosis in patients with atopic eczema

The APT with aeroallergens may provide an important diagnostic tool, as shown in two patient subgroups. In patients with an air-exposed eczema distribution pattern, positive APT reactions occurred at lower allergen doses compared with other patients with atopic eczema. Patients

with an aeroallergen-specific history had significantly more positive APT reactions. The lower sensitivity but higher specificity of the APT compared with skin prick test or RAST favours the notion that the classical tests may have some value as screening tests, specificity may be added by the APT. As for bronchial asthma and rhinoconjunctivitis, the results of our studies sustain the concept of extrinsic/allergic vs. intrinsic/cryptogenetic atopic eczema with a heterogeneity of disease subgroups.⁴⁶ Questions remain open concerning the clinical relevance of positive APT results in patients with a negative history and negative skin prick tests or RAST, as no gold standard exists for the provocation of eczematous skin lesions in aeroallergen-triggered atopic eczema. These questions may be answered only by controlled studies using specific provocation and elimination procedures in patients with positive and negative APT results. The allergen specificity of the APT was underscored by the results of a study⁴⁷ on T-lymphocytes under specific stimulation with the allergens used in our multi-centre trial.³⁵ Some evidence for the practical relevance of positive APT reactions may be drawn from an early report on 18 patients by Clark and Adinoff.^{27,48} These authors described a positive APT reaction in combination with a detection of specific IgE antibodies in skin prick tests, strongly associated with aeroallergens identified in the patients' environments. The final scientific proof for the relevance of aeroallergens identified by positive APT reactions for the management of atopic eczema in the identified patients is still missing but appropriate allergen specific avoidance strategies^{49,50} are recommended in patients showing positive APT reactions. The diagnostic validity of APT in routine diagnosis of aeroallergen-triggered atopic eczema is investigated in further controlled studies. We are currently co-ordinating a European multi-centre study with biologically standardized APT extracts of the European Task Force on Atopic Dermatitis (ETFAD). Consensus meetings of most groups performing APT for clinical use in Europe were held on 11 April 1997, and 30 June 1998. One result of these meetings was a consensus APT reading key for describing the intensity of APT reactions (Table 5, Fig 2). The planned multi-centre trial also deals with the evaluation of food allergen patch testing. The APT is still not a routine method. With the ongoing standardization, a test for the clinical relevance of an aeroallergen sensitization that can be applied in the allergist's practice may evolve. The identified subgroup of patients may profit extraordinarily from allergen avoidance.

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