

## Role and Significance of Atopy Patch Test

**Ružica Jurakić Tončić, Jasna Lipozenčić**

University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

**Corresponding author:**

Professor Jasna Lipozenčić, MD, PhD  
University Department of Dermatology and Venereology  
Zagreb University Hospital Center and School of Medicine  
Šalata 4  
HR-10000 Zagreb  
Croatia  
[jasna.lipozencic@zg.htnet.hr](mailto:jasna.lipozencic@zg.htnet.hr)

Received: September 7, 2009

Accepted: January 8, 2010

**SUMMARY** Atopic eczema/dermatitis syndrome (AEDS) is a chronic, intermittent, inflammatory, genetically predisposed skin disease characterized by severe pruritus and xerosis. AEDS is a common disorder in children with an increasing prevalence. A number of environmental factors have been implicated in the pathogenesis of AEDS. Atopy patch test (APT) is a patch test using type I allergens known to elicit IgE mediated reactions. Results are evaluated after 48 and 72 h. APT has been recognized as a useful diagnostic tool in the diagnosis of delayed type of reaction in AEDS since specific IgE (sIgE) and skin prick test (SPT) can be only correlated with early reactions. Standardized technique has been proposed by the European Task Force on Atopic Dermatitis. It consists of purified allergen preparation in petrolatum, applied in 12 mm diameter Finn chambers mounted on Scanpor tape to non-irritated, non-abraded, or tape-stripped skin on the upper back. Optimal results were obtained with petrolatum, in aeroallergen concentration over 5000 PNU. Food allergy takes place in the first years of life, while the role of aeroallergens becomes more significant in older children and adults. A common scenario is development of allergy to cow's milk early in life, usually accompanied by allergy to hen's egg and wheat. Up to 3 years of age, the child usually becomes tolerant to food and sensitization to one of multiple aeroallergens occurs. The children that will develop clinically relevant reactions to food may benefit from elimination diets. APT has been recognized as a diagnostic tool in food allergy evaluation, but its role remains controversial and double blind placebo controlled food challenge remains the gold standard. It has a role in the detection of gastrointestinal manifestations of allergy and in eosinophilic esophagitis. When the symptoms occur at air-exposed sites, the role of aeroallergens is possible. Today, the most commonly used aeroallergens are house dust mite, pollen and animal dander.

**KEY WORDS:** atopy patch test, atopic eczema/dermatitis syndrome, food allergy, aeroallergens, skin prick test

## INTRODUCTION

Atopic eczema/dermatitis syndrome (AEDS) is a chronic, intermittent, inflammatory, genetically predisposed skin disease characterized by severe pruritus and xerosis (1-5). AEDS is a common disorder in children and there is evidence of an increasing prevalence, which has doubled since the 1970s in the western world. First symptoms are usually not present at birth and they appear by the age of 3 months. AEDS affects 10%-12% of infants and according to some authors even up to 25% in some countries (3-6). Prevalence studies indicate large variability among countries, with a ratio between low and high prevalence. A large international study (ISAAC) included more than 190000 children from 56 countries and the prevalence ranged from 2% in Indian subcontinent and Iran to more than 22% in Sweden (7-10). There is an increasing number of patients with AEDS in adulthood with a prevalence of up to 1%-3% (11). In 80% of children, symptoms occur by the age of one year, and in 90% by the age of five years (12).

AEDS is part of the so-called atopic syndrome and is often associated with a family history of atopy and frequently predates the development of allergic rhinitis (AR) and/or asthma (AA) later in life (13-15). Atopy is an inherited predisposition that causes a tendency to suffer from one or more of the following 'atopic diseases': allergic asthma (AA), allergic rhino-conjunctivitis (AR) and AEDS. The diagnosis of 'atopy' is not based on a single distinctive clinical feature or laboratory test, but rather results from a combination of patient and family history and clinical findings. Recently, a new definition of atopy restricted to IgE production has been proposed and is defined as personal or familial tendency to produce antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as AA, AR or atopic dermatitis (16).

Clinical phenotype is the result of a combination of genetics, specific environmental factors and individual immune characteristics (13,17,18). The diagnosis is based on the presence of characteristic clinical features (1,19-22). Diagnostic criteria given by Hanifin and Rajka still have advantage over the UK Working Party's diagnostic criteria (1,21). The disease severity is usually scored by the SCORAD scoring system (2). Distribution of lesions depends on the age of the patient, and the most disabling symptom is severe pruritus that can be responsible for insomnia.

Patients with AEDS frequently have elevated levels of IgE and the disease severity is usually in correlation with the level of IgE (23,24). The role of IgE is to facilitate allergen presentation to T cells *via* its binding to Fc receptors on Langerhans cells (25,26). It is still unclear whether IgE sensitization has a central role in the pathogenesis of AEDS, represents an epiphenomenon of the disease activity, or is just a cofactor for promoting certain gene-environment interactions (27). Although atopy is clearly associated with AEDS, a group of authors have published a paper stating that up to two thirds of AEDS patients are not atopic (27). The latest nomenclature of AEDS differentiates two forms of the disease. The more common form is the extrinsic type which is IgE dependent. The intrinsic type is characterized by the lack of specific IgE and negative immediate skin reactions to environmental allergens and food (11,28-30). It is interesting to mention that the European multi-center study showed that 7% of patients with the 'intrinsic type' of AEDS had positive atopy patch test (APT) (31). The same results with positive APT to *Dermatophagoides* are reported by Seidenari *et al.* and Manzini *et al.* (32-34). Ingordo *et al.* report that 8 of 12 patients with 'intrinsic' AEDS reacted to partially purified whole-mite preparation (35).

A number of environmental factors have been implicated in the pathogenesis of AEDS. Food and aeroallergens are the most relevant allergens in AEDS (19). Food allergies are found predominantly early in life, most commonly during the first few years. The prevalence of food allergy in children with AEDS varies from 40% to 80% (3,36-38). The risk of relevant food allergy increases with the severity of symptoms and this subpopulation of children will benefit from elimination diets (6,36). The common scenario is the loss of allergy to food, milk in particular, until the age of three years. Allergy to aeroallergens usually develops after infancy, first to house dust mite (HDM) and animal epithelium, and later to pollen. Sensitization to food (egg white, cow's milk and wheat) in infants is usually associated with the appearance of IgE to inhalants later in life (39,40).

The incidence of contact sensitization among AEDS patients is similar to that in non-atopic population (41,42). The most common contact allergens in atopic adults are nickel, latex, fragrance mix and balsam of Peru (41,42).

Atopy patch test involves epicutaneous application of type I allergens known to elicit IgE-mediated reaction, followed by evaluation of

eczematous skin reaction after 48 and 72 h (19). The first experimental study on patch test with aeroallergens was published in 1937 by Rostenberg and Sultzberger, and in 1982 by Mitchell *et al.* (43,44). The first study dealing with food dates from 1989 (45), and after that several authors have reported results in APT with foods (6,46-50).

The value of APT seems to be highest in children less than 2 years of age (6). There is a problem concerning the age and the fact that foods are studied in younger individuals, whereas aeroallergens are studied in older children and adults (19).

When biopsy is performed from allergen-induced eczematous APT site, allergen specific T cells are cloned (51,52). The TH2 cytokine pattern is initially present and after 48h TH1 pattern is predominant (51,53). An early influx of inflammatory dendritic epidermal cells into lesional skin has been demonstrated (54). When allergen is captured by IgE molecules, it binds to IgE receptor on Langerhans cells. Antigen presentation results in specific T cell reaction which is responsible for eczematous reaction observed clinically (25). T cells are responsible for the reaction occurring in lesional skin in AEDS and also in the skin in APT, and macroscopic and microscopic similarities indicate that APT is a valid model for inflammation found in AEDS (25,55,56). APT represents a T-lymphocyte-mediated allergen specific response (55,56).

Literature data indicate that positive APT reactions can occur in 15%-90% of AEDS patients, depending on the methodology used in testing (19,57,58). Healthy individuals as well as patients with respiratory atopy without a history of eczema have negative APT or react to HDM with lower frequency and intensity compared with AEDS patients (33,58).

Ronchetti *et al.* found positive APT with food in 4%-11% and with aeroallergens in 4%-30% of an unselected children population, depending on allergen tested (59), and these results are in conflict to other study results (60,61).

According to the literature, APT with food was positive in 89% of children whose SPT was negative (46). Also, a group of authors found no correlation between positive APT and SPT for food, but found an association of APT and SPT with aeroallergens (59). The possible explanation could be that aeroallergens have a pathomechanism involving IgE, while the reaction to food often involves other immune mechanisms (59). Skin biopsies in positive APT with food provided evidence for all four Coombs and Gell reactions (59).

Various APT techniques have been described in the literature. In order to enhance the penetration of the allergen into the skin, skin abrasion, tape-stripping and sodium lauryl sulfate application were used (60-66). Some authors perform stripping before allergen application in water solutions which are not occlusive; others use vaseline in order to have good penetration into the skin (58,60,64). Aeroallergens were tested with several vehicles, but optimal results were obtained with petrolatum (60). Today, APT is performed on non-lesional, untreated skin in remission (31,60,67). The European Task Force on Atopic Dermatitis (ETFAD) has developed a standardized APT technique. It consists of purified allergen preparation in petrolatum, applied in 12 mm diameter Finn chambers mounted on Scanpor tape to non-irritated, non-abraded, or tape-stripped skin on the upper back (31,68,69). The test is read after 48 and 72 h and the reading key is the appearance of erythema, and the number and distribution pattern of the papules (69).

Usage of aeroallergen concentrations over 5.000 PNU (protein nitrogen units)/g in petrolatum allows for testing on clinically uninvolved skin without potentially irritating tape-stripping (60,70). Various concentrations of allergens are described in the literature, ranging from 1 x SPT (10,000 AU/mL) to 1,000 x SPT (60,64,71). Van Voorst Vader *et al.* conclude that the optimal allergen concentration should be 500 x SPT with exposure time of 48 h (64). Langeveld-Wildschut *et al.* conclude that concentration should be equal to 10,000 AU/mL (1 x SPT) and according to their results increasing the allergen concentration to up to 1,000,000 AU/mL (10 x SPT) did not significantly influence the number of positive results (72). Darsow *et al.* noticed significant increase in positivity of APT results with a concentration of 10,000 compared to 1000 PNU/g (60). Darsow *et al.* found that optimal test concentrations were 5,000 PNU/g for grass pollen and 7,000 PNU/g for *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and cat dander (71). The authors from Poland also studied the impact of allergen concentration and found that 0.1 x SPT was too low, while 10 x SPT concentration had significantly more positive reactions than 1 x SPT (58). They also observed that some patients had reactions after 24 hours, some after 48 hours, and one patient had reaction after 24 hours, but not after 48 hours. Some other authors observed a similar phenomenon (64,72).

Commercial preparations for APT are available in a concentration of 200 IR/g (index of

reactivity) of aeroallergens in petrolatum. The potency of 100 IR/g was designed as the strength of allergenic extract that elicited a geometric mean wheal diameter of 7 mm in SPT in patients sensitive to the corresponding allergen (19).

APT for food is still not well standardized and most of the studies performed APT with cow's milk, hen's egg and wheat. It is generally preferred to use fresh food rather than commercial extracts in testing. Niggemann *et al.* used one drop of fresh cow's milk containing 3.5% fat, whisked hen's egg and wheat dissolved in water (1 g/10 mL) and put on filter paper (37).

Heine *et al.* published a proposal for standardized interpretation of APT in children with AEDS and suspected food allergy (73). According to them, skin induration and papule formation were the most useful positive predictors for food allergy, especially if both features were present at the same time. Extensive induration beyond the margins of the Finn chamber was also found to be highly specific. The cut-off number of the papules on the skin was seven. A combination of skin induration and at least seven papules was 100% specific and predictive for food allergy. Moderate erythema was highly specific, but less reliable. Moderate erythema as a solitary finding is not sufficient as a criterion for APT positivity. Single skin sign such as skin induration, papules or moderate erythema alone were 47%-88% predictive; however, a combination of two signs was 86-100% predictive. The presence of all three signs is 100% specific and predictive (73).

Specificity and sensitivity of APT greatly depends on the allergen tested and the age of the patient (74). APT with cow's milk was more sensitive in children (median age, 13 months) with late reactions (45%) than in those with early (27%) and combined reactions (36%). For hen's egg, APT was less sensitive for late (17%) than for early (45%) or combined reactions (32%). Wheat sensitivity was higher in late (29%) than in early (22%) reactions and highest in combined reactions (50%) (74). Higher numbers for sensitivity and specificity of APT with fresh food have been reported by Niggemann *et al.* and Roehr *et al.*, who used provocation outcomes to compare APT with fresh food and commercial products (3,31,75). There was great concern regarding the accuracy and reliability of APT in children less than 2 years old (6,76-78), but recent study results have confirmed that APT significantly increases the possibility of early detection of food allergy in small children (6,46,74,76-81).

The frequency of positive APT in children over 24 months decreases, which could be due to acquisition of food tolerance or thicker skin in older child, resulting in less antigen penetrating the skin (6,79). According to literature data, the specificity of APT depends on the age of the patient (74,79). For hen's egg, the highest specificity was found in children aged 1-3 years, while specificity for cow's milk, wheat and soy increased with age, reaching 100% for cow's milk in children older than 2 years, and for wheat and soy in children older than 6 years (74). APT with food is most often found positive in children aged 6 months to 7 years (82). According to some authors, APT with food can be performed in children aged up to 12 years (73).

Certain aeroallergens were tested in a multi-center study for diagnostic sensitivity and specificity (31). Sensitivity analysis suggested that for some allergens a concentration over 200 IR/g may be necessary to demonstrate sensitization (31). The problem with aeroallergens is that there is no gold standard provocation test (31). On the contrary, results from APT with food can be comparable to the results of double-blind placebo-controlled food challenge (DBPCFC) which is considered to be the gold standard in determining food allergy. Bindslev-Jensen *et al.* published a position paper on standardization of food challenges in patients with immediate reactions to food, but it is known that some patients with AEDS can have only delayed type of reactions (83-90). Specific IgE and APT can be false positive, resulting in low positive predictive values (84). Due to poor reliability of specific IgE and APT results, DBPCFC is still considered as gold standard for the appropriate diagnosis of food allergy (84-90).

Only few studies tackled reproducibility of ATP with food and inhalant allergens (91,92). Tests with aeroallergens were invariably reproducible. The reason for difference in reproducibility of testing with food and aeroallergens is still unknown (91).

There are several pitfalls for APT, such as irritative skin reactions with similar appearance to IgE mediated reaction and non-IgE mediated reaction (74,87). Patients with AEDS are prone to skin irritation and might therefore show more false-positive results (74). Variations can occur due to differences in food processing and preparation, route of exposure and because of the role of augmenting factors lowering the threshold value for clinical reaction (87). Variations can occur because of the differences in the allergen (whole mite vs. mite extracts), allergen concentration, vehicle, skin

condition at the time of testing, site of testing and reading time (60,69,92-95). In a multicenter European study, reactions to allergen-carrying test substances were also observed (31).

Patients with AEDS can have two different patterns of allergic response to allergens, i.e. IgE mediated and cell mediated (88,96). Therefore, APT can give positive skin test results in patients with negative SPT or sIgE (96). The outcome of APT can be only partially predicted by specific IgE or SPT results (96).

Papers have been recently published on the modulation of APT and SPT by pretreatment with topical immunomodulators. Pimecrolimus cream had a potential to suppress the development of lesions induced by aeroallergens (97), whereas pretreatment with tacrolimus 0.1% ointment did not inhibit the APT reaction in patients with atopic dermatitis (98).

## FOOD ALLERGY

Allergy to food in general can present with gastrointestinal, respiratory and various skin symptoms (4,99-104). The role of food allergy in AEDS has been the biggest controversy in dermatology, but today there is unquestionable evidence that it has an important role in the pathogenesis of AEDS (103,104). Food allergy typically affects infants and young children (103-105). When the treatment with topical corticosteroids and emollients is not effective in a young child with AEDS, it is advisable to rule out or confirm food allergy, especially to cow's milk (46,104-106). The proportion of food allergy in children with AEDS has been reported to be 40% to 80% (38, 73-74, 90, 107).

Identification of the offending allergen is important in the management of AEDS, since unnecessary elimination of certain food can be harmful to the child's health (105). Allergy to food depends on the child's age, eating tradition of the family and country, but most often milk, eggs, soy, wheat, nuts, tree nuts and fish are involved (74). Breastfed infants can also become sensitized to food through the mother's milk (6,106-111). It has been shown that severe eczema can be worsened by ingestion of certain food in older children and adults as well, and this is particularly true for 'pollen-associated' foods (99). In theory, all food containing proteins can be the cause of allergy. A food-allergen library has been formed and comprises well-characterized authentic natural and recombinant allergens (112).

Reactions to foods in AEDS can present as non-eczematous reactions, isolated eczematous reactions or a combination of these two (99). Non-eczematous reactions include cutaneous symptoms such as pruritus, urticaria, rashes and/or non-cutaneous gastrointestinal or respiratory symptoms as well as anaphylaxis (99). Eczematous reactions to food are also called late or delayed reactions, and can appear isolated or in combination with other symptoms. Reactions to food can implicate IgE (immediate) or T cells (late phase) mediated immune reactions (88,96).

Immediate reactions to food are manifested by skin symptoms (pruritus, erythema, urticaria or macular and morbilliform rash), gastrointestinal symptoms (nausea, vomiting, abdominal cramps, diarrhea) and respiratory symptoms (nasal congestion, rhinorrhea, wheezing) (101,104). SPT has been used for decades in determination of food allergy (113). There is clear relationship between positive SPT and immediate reaction and between positive APT and delayed reactions (6,37,46,50,80,81,114-116). However, a positive SPT result to food does not prove the role of a specific allergen in the pathogenesis of AEDS (6). Delayed reactions are more commonly found in AEDS with positivity in APT (36,114). According to one study, only 11% of children with AEDS have isolated immediate reaction to food, while 49% have delayed type of reaction (82). After oral food challenge, 50% of children with AEDS that reacted to food showed both immediate and delayed type of reaction and 15% of children had worsening of eczema only (84).

Those patients that exhibit late reactions have higher levels of IL-2, IFN and TNF- $\alpha$ , confirming the role of T lymphocytes. T cells obviously play an important role in food-sensitive AEDS and it was shown in several recent studies (52,55,117,118). Sütas *et al.* found lower serum IL-10 concentrations in subjects with late onset reactions, and it is well known that IL-10 is an inhibitory cytokine (117). Positive SPT/sIgE as markers of immediate onset reactions are usually found in children younger than 3 years, while the prevalence of delayed-onset reactions are higher in children over 3 years of age (101,114).

APT has been recognized as a diagnostic tool in food allergy evaluation, however, its role remains controversial (46,73,119-121). APT with food is not standardized and there are different methods of preparing test materials, thus producing controversial results (19). APTs with cow's milk, hen's egg and wheat are most commonly

used (6). Several commercial freeze-dried food extracts are now available, but their diagnostic accuracy is still largely undefined (102). Canani *et al.* studied diagnostic accuracy of APT in children with food allergy-related gastrointestinal symptoms and used in parallel fresh food and freeze-dried purified food protein extracts contained in a commercial kit. Commercial extracts were provided in 20% protein concentration in a vaseline mixture, while APTs with fresh food were performed using one drop of 3.5% fat milk, soybean milk, whisked hen's egg (egg white and yolk), and wheat powder dissolved in water at a concentration of 1 g/10 mL (102). So far, there is no standardization of test materials and there is a need to define whether there is a difference between fresh food and freeze-dried products (6). Fresh food is preferred over commercial extracts, although some authors found no difference between commercial milk and egg allergens and fresh food preparations (102). In other studies, better concordance with oral challenge test (6,122), as well as higher specificity and sensitivity were detected when APT was performed with unprocessed food (3,37).

The work-up algorithm for children with AEDS and suspected food allergy starts with detailed history and medical examination. It is recommended to proceed with SPT or determination of specific IgE antibodies (36). A combination of SPT and APT can enhance the accuracy of diagnosis of specific food allergies (78,123,124). In some studies, APT showed best specificity and its predictive capacity can be further improved by combining it with sIgE determination and SPT, although data from some studies could not confirm it (125). In some patients, oral food challenge could become unnecessary by combining these three methods (3,74,86).

The skin application food test (SAFT) is a reliable and child friendly alternative to SPT, especially for children less than 3 years old (36,126). SAFT is performed on the unabraded volar aspects of the lower or upper arm using medium (8 mm) Finn-chambers on Scanpor. Results are read after 10, 20 and 30 minutes (36,126). It investigates IgE-mediated acute contact urticaria induced by application of the allergen to the skin. It is more child friendly due to needle avoidance (76). However, Hansen *et al.* have reported severe systemic reactions in SAFT with eggs (3/10), argued reproducibility, and pointed to discordant findings in half of the patients (76). Devillers *et al.* have pointed out their view regarding positive SAFT reaction and stated that all patients with positive SAFT reaction

would have positive APT if the allergen would be left on the skin long enough. Their proposition is to change the name of SAFT to immediate-type APT reaction (36).

DBPCFC has been the gold standard in the diagnosis of food hypersensitivity for the last few decades (3,73,83,126-137). The classic procedure is based on repeat food administration for some hours and observation during the next 48 hours. However, oral challenge test carries the risk of anaphylaxis and sometimes there are difficulties in the interpretation of delayed type of reaction (132-134). Isolauri and Turjanmaa performed DBPCFC and repeat open food challenges (OFC) with cow's milk and confirmed that open challenge test with close follow up could be appropriate in clinical practice (46).

SPT has been used for decades to prove or exclude sensitization to allergens, but the specificity of prick testing is controversial. A group of authors defined skin weal diameters in SPT to egg, milk and peanut above which open oral food challenges were positive (100% specificity) (78,113,122). Quantification of sIgE to hen's egg and cow's milk has been suggested, and relationship was found between the sIgE levels and oral challenge threshold (121,138-141). Recent studies have shown that a combination of quantification of sIgE (or SPT) and APT could significantly improve the diagnostic accuracy when food allergy is suspected (3,138-141). Saarinen *et al.* compared the value of sIgE, APT, SPT and oral challenge, and could not find the test or a combination of tests that could be compared to oral challenge (125).

During the first year of life, cow's milk allergy is responsible for allergy in 2%-7% of children, and the majority of these children have gastrointestinal symptoms such as gastroesophageal reflux, colics, diarrhea, constipation, failure to thrive, or blood in stools (120). Reaginic antibodies are the cause of just one part of these reactions and therefore SPT or determination of sIgE has poor sensitivity (142). Current data on APT indicate 79% sensitivity and 91% specificity in infants with gastrointestinal symptoms without skin involvement (120). APT has a considerably higher sensitivity than SPT, which is consistent with the predominant delayed type of allergy. Therefore, APT is very useful for detection of cow's milk allergy (120).

Majamaa *et al.* tested 143 children with AEDS up to 2 years of age, and 50% of them were positive in oral challenge test to cow's milk. The authors found 26% of infants to have positive milk-specific IgE, only 14% of cases were positive for

milk in SPT, and APT was positive in 44% of children whose allergy to milk was confirmed by DBPCFC (80).

The authors from Turkey combined APT and SPT for cow's milk allergy and reported 100% sensitivity, 50% specificity, 100% negative predictive value and 76% positive predictive value and concluded that APT with SPT could be a useful combination to exclude cow's milk allergy in children with allergic manifestations. They conclude that DBPCFCs are still obligatory in the presence of positive tests (143).

There is an association of the disease severity and degree of sensitization in children with hypersensitivity to cow's milk and hen's egg. Moreover, sensitization to egg, and to a lesser extent to cow's milk, indicates worse outcome in terms of persistence and severity of the disease (144).

The authors from Poland performed APT, SPT and oral food challenge (OFC) in children with suspected milk-related AEDS (101). Children were divided into two groups, i.e. younger than 3 years and older than 3 years. Among positive reactions in OFC, 8.8% of children had an immediate type of reaction and the others had delayed type of reaction to milk (101). All children with immediate reactions were younger than 3 years. The delayed type of reactions included skin, respiratory and gastrointestinal symptoms (101). The authors also found that specificity of APT was higher in older children (101). Some other study results confirmed the significance and accuracy of APT for diagnosing allergy to cow's milk in all age groups (74,78,80,82,143).

In the majority of cases, children acquire tolerance to cow's milk by the age of three years, but IgE-mediated hypersensitivity to cow's milk often persists to school age and is a risk factor for other atopic diseases. Non-IgE hypersensitivity to milk is considered to be a more benign condition and the child usually develops tolerance (125,144-148). About 80% of children will 'lose' their reactivity to milk over 1 to 3 years, developing multiple food allergies with AR and AA (101). Some studies indicated multiple food sensitizations for cow's milk and cereals (149). Cereal challenge was positive in 73% of children with cow's milk allergy (149).

Osterballe *et al.* studied diagnostic accuracy of APT in the diagnosis of hypersensitivity to cow's milk and hen's egg in children 3 years of age and concluded that APT could not predict hypersensitivity in this population (121).

Egg allergy is one of the most common allergies

in children. In children with AEDS it can present as itching in the mouth/throat, rhinitis, conjunctivitis, asthma, urticaria, vomiting, diarrhea and anaphylaxis (76,121,148). Sensitization to hen's egg is considered to be the strongest predictor of AEDS persistence after childhood (13,144). Isolated delayed reactions (symptoms appearing more than 2 h of ingestion) have been reported by some authors, but Hansen *et al.* did not record this type of reaction to egg (76). Among cases of clinically positive allergy to egg with immediate reaction, 40%-60% of children had positive reaction in APT (142). The authors conclude that this test is not relevant because of the positive reactions in egg tolerant children. No advantage of APT or SAFT in determination of egg allergy was found due to the lack of reproducibility. Also, APT and SAFT can cause systemic reactions, and therefore were not superior to SPT (76). Therefore, DBPCFC/OFC remains the gold standard for egg allergy.

APT has a significant role in determining delayed type allergy to wheat. Sensitization to cereals is much more common than it was believed before (101). In case of wheat allergy, patch testing with cereals will significantly increase the probability of early detection of cereal allergy in infants with AEDS (99-101). There are speculations that positivity to cereals in SPT may in fact reflect grass pollen allergy (99-101). The group of patients with cereal allergy can develop cross reactions to pollen later in life. Stromberg *et al.* and Turjanmaa *et al.* found that APT was earlier positive than SPT in small children, especially with cereals (6,19). Children with food allergy and AEDS can be sensitized to more than one allergen and multiple sensitizations have been observed, such as for cereals and cow's milk (6,50). Järvinen *et al.* found that 73% of patients with cow's milk allergy had positive cereal challenge (149).

The prevalence of food allergy to peanuts is increasing in Western countries (123,150-152). The mean age at onset is 2 to 3 years (152). The prevalence is around 1/150 and is probably underestimated. Peanuts can be contained in vegetable oils used for baking products and pastries and are frequently ingested as hidden allergens (153). The onset of symptoms is usually abrupt and a very small amount of allergen is sufficient to induce severe reaction. Determination of sIgE and SPT are routinely performed for detection of peanut allergy (123,135,148). However, SPT results are in poor correlation with delayed type reactions. Combined SPT and APT can represent a useful integration to standard testing modalities used for the diagnosis

of peanut allergy (123). SPT reactivity was more frequently observed in patients above 12 years, whereas APT was more often positive in children under 6 years (123). APT for peanuts was more sensitive than SPT, particularly in children under 12 years of age (123). By measuring the levels of sIgE to peanuts, it is possible to identify a subset of patients that will very likely experience clinical reaction (138,139).

APT is also a useful diagnostic tool in patients with food-allergy-related gastrointestinal symptoms and the accuracy of the test is higher when fresh foodstuff is used (102). Food hypersensitivity in gastrointestinal tract can involve IgE mediated, T cell mediated or combined reactions. IgE mediated reactions are found in oral allergy syndrome (pollen-food allergy syndrome) and gastrointestinal anaphylaxis. T cell mediated gastrointestinal reactions include food protein induced enterocolitis, proctocolitis and enteropathy and celiac disease. Mixed T cell and IgE mediated gastrointestinal type of reactions are found in allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis (103,104). Eosinophilic esophagitis and gastroenteritis are most frequently seen during infancy through adolescence and typically present with symptoms of gastroesophageal reflux (103,104). Eosinophilic gastritis can occur at any age and it might present as pyloric stenosis with outlet obstruction and postprandial, projectile emesis. Weight loss and failure to thrive are hallmarks of this disorder (103,104).

Eosinophilic esophagitis has an increasing incidence in the USA and Australia (102,154-157). The symptoms are similar to those in gastroesophageal reflux, but do not respond to aggressive treatment with medications used for gastroesophageal reflux. A combination of SPT and APT can help decide on the correct diets that will result in resolution of symptoms and normalization on esophageal biopsies in more than 95% of patients (155-157).

Many children grow out of their food allergy, especially to milk and egg, but they often remain allergic to nuts and fish during their life (82). So, 26% of children become tolerant to the specific food in the first year and another 11% in the second year of diet. Saarinen *et al.* published a paper on the clinical course and prognosis of cow's milk allergy, and found the IgE mediated cow's milk allergy to often persist to school age (125).

## ALLERGY TO AEROALLERGENS

In general, APT positivity with food and aeroallergens is less frequently found in older individuals (32,33,79,119). The possible explanation could be that the skin of children is thinner and allergens can more easily penetrate and generate the reaction (19,158). The prevalence of allergy to inhalants is higher in children over 3 years of age (101). A common scenario is the loss of allergy to food, especially milk until the age of three, and development of allergy to multiple inhalants (101,119).

If an adult patient develops symptoms on air-exposed surfaces, the eliciting role of aeroallergens is possible, especially if the patient has no symptoms in the areas covered by clothes (42,159). So, 15% to 70% of patients with AEDS have positive APT and it is observed that there is a high frequency of positive APT in patients with eczematous lesions at air-exposed skin (159-164). The role of sensitization to aeroallergens is more relevant in older children and adults (42).

APT may be helpful in case of suspicion of aeroallergen allergy (58,93). Positive aeroallergen APT results are observed in the majority of patients and can thus be regarded as an additional diagnostic criterion in AEDS (160). The most common aeroallergens used in APT are house dust mite, animal dander and grass. Other aeroallergens used are trees (birch), weed pollen, moulds and cockroach (58,59,162). The degree of sensitization to aeroallergens is directly associated with the severity of AEDS (164). When performing APT with aeroallergens, both petrolatum and aqueous solution of the allergen can be used, but petrolatum is preferred (165).

The usefulness of APT for aeroallergens has not yet been determined (93). The authors from Singapore found correlation of APT for house dust mite with RAST, while the results for cat fur correlated with SPT (93). APT proved efficient in the detection of pollen and house dust mite allergy (3,31,159,166,167). APT results showed significant concordances with the history, SPT and RAST for *D. pteronyssinus*, cat dander and grass pollen (67,68,93,160). According to the authors, optimal test concentrations are 5,000 PNU/g for grass pollen and 7,000 PNU/g for *D. pteronyssinus* and cat dander (60,71). APT had a higher specificity (69% to 92%, depending on the allergen) with regard to clinical relevance of allergen as compared with SPT (44% to 53%) and RAST (42% to 64%) (31,71).



One of the most common aeroallergens is house dust mite and sensitization to house dust mite should be considered when symptoms occur at uncovered skin (63,65-67,163,168,169). House dust mite is considered to be an important aggravating factor in AEDS patients, especially during childhood and adolescence (32,168-176). Children that have persistent AEDS are exposed to higher environmental levels of house dust mite allergens and there is an association between positivity to aeroallergens and the severity of AEDS (164,172). The most important pathogens in Central Europe are *D. pteronyssinus* and *D. farinae* (Derp and Derf). Their allergens are derived from their excretion (Derp1 and Derf1) and from the body of the mite (Derp2, Derf2). Swedish authors found that 56% of atopic patients were sensitized to house dust mite (173). There is a correlation between mite concentration in bed mattress and floor of the room with the severity of symptoms. One person leaves from 0.5-1 g of epithelium during one week, which is sufficient for feeding of thousands of mites over few months (11). Measures of mite elimination result in symptom relief (174,175). There is evidence that later development of respiratory allergy might be partially avoided by house dust mite avoidance (174).

Although positive responses to mite patch tests are also observed in subjects without AEDS, their frequency and intensity are significantly lower compared to AEDS patients (33,61). Deleuran *et al.* report that irritant reactions to Derp1 and Derp2 are more commonly found when testing is done with extracts (173). Some authors suggest that allergy may not be the only mechanism involved in APT positivity to house dust mite (93,173). If mite extracts are used on testing, this could contribute to better immunoallergologic characterization of patients with AEDS and respiratory allergy (32). Italian authors confirmed the high value of APT in patients with mite-induced AEDS and respiratory allergy, and have suggested that its routine use might improve the diagnosis of respiratory allergy to house dust mite (176). According to their results, APT was more frequently positive than SPT (176).

The yeast *Malassezia furfur* (*M. furfur*) is part of normal cutaneous flora, but is also one of the triggering factors in AEDS. *M. furfur* can elicit an eczematous reaction in sensitized atopic patient and could be an important trigger (177,178). The *M. furfur* patch test could be of diagnostic value in this group of patients (177). There are published data on the correlation of positive APT to *M. furfur*

with TH2-like peripheral blood mononuclear cells response (178). *M. furfur* recombinant proteins for APT are available (178).

Animal epithelium is another common aeroallergen, and sensitization is characteristic for pet owners, veterinarians and laboratory workers (42). Cat epithelium allergen named Fel d 1 is present for long time in living places after the animal has been removed, therefore, clinical improvement cannot be expected immediately (169,179).

Pollen is also one of the allergens that can cause eczematous reactions (180). The possible role of sensitization to pollen should be considered if the flares occur seasonally (180). It is the most problematic aeroallergen to avoid (42,180). These patients are advised not to take part in outdoor activities and personal hygiene is particularly important (42). Patients carry pollen on themselves and it is very advisable to wash exposed areas of the body (daily hair wash) (42).

## CONCLUSIONS

Atopy patch test (APT) includes epicutaneous application of type I allergens known to elicit IgE mediated reaction, followed by evaluation of eczematous skin reaction after 48 and 72 h. Current data show obvious relationship between AEDS and food allergy. Food allergy is observed early in life and most of the children outgrow it until the age of three. Food allergy can manifest as eczematous reactions, non-eczematous reactions or their combination. Eczematous reactions are also called late or delayed reactions to food and have T cell reactions implicated in the pathogenesis. Determination of T-cell mediated reaction by APT could have more relevance than demonstration of IgE mediated sensitization. APT is a good model for T cell mediated hypersensitivity reactions. There is clear correlation between positive APT and delayed type, and between positive SPT and immediate type of reactions to food. Correlation of APT with clinical symptoms and OFC test has shown significance, pointing to the good accuracy of this diagnostic test. The number of positive APT reactions decreases after 2 years of age, probably due to thicker skin or as the result of induction of tolerance to the allergen. The test specificity is higher in older children.

APT for aeroallergens is also very useful, especially if the patient develops symptoms on air exposed areas. Positive aeroallergen APT results are observed in the majority of patients and can thus be regarded as an additional diagnostic

criterion in AEDS. The most common aeroallergens used in APT are house dust mite, animal dander and grass, trees (birch), weed pollen, moulds and cockroach.

The European Task Force on Atopic Dermatitis (ETFAD) has developed a standardized technique for APT. It consists of purified allergen preparation in petrolatum, applied in 12 mm diameter Finn chambers mounted on Scanpor tape to non-irritated, non-abraded, or tape-stripped skin on the upper back. There is no standardization of test materials and there is a need to define whether there is difference between fresh food and commercial extracts. Some authors prefer fresh food because of better concordance with OFC test. It is recommended to use concentration for aeroallergens over 5,000 PNU, and for some allergens concentrations should be even higher. Standardized interpretation of the test has been proposed. The test is read after 48 and 72 hours and the reading key is the appearance of erythema, number and distribution pattern of the papules.

The results of APT depend on technical variables (allergen concentration, size of the chamber, occlusion time and site of application), and personal characteristics of the person tested, such as age and previous skin condition. Differences among different authors and study results derive from the fact that authors use different vehicles, allergen concentration, Finn chambers size, different preparation of tested allergens (fresh food or commercial, whole mite vs. extracts). There also are intra- and inter-observer variations during analysis of APT results. Atopic patients are prone to irritative skin reactions and this could be the cause of false-positive reactions. The sensitivity and specificity of the test greatly depend on the allergen tested and the age of the patient.

APT is not proposed as a single screening test in patients with AEDS. It should be used in addition to SPT and detection of sIgE. Results usually have to be confirmed by performing DBPCFC in order to prove reaction to food. Due to poor reliability of specific IgE and APT results, DBPCFC is still regarded as the gold standard for an accurate diagnosis of food allergy. Specific IgE and APT can be false-positive, resulting in low positive predictive values. Although in theory a combination of SPT and ATP may seem promising, there are conflicting results recently published in the literature on the clinical value of the combination.

So far, atopy patch test remains a useful tool in the hands of experienced clinician, who will

skillfully combine these results with clinical appearance, sIgE determination, SPT and sometimes, if necessary, with oral challenges. None of these diagnostic tools has the power alone, but the combination enables better insight and understanding the nature of the atopic dermatitis/eczema syndrome.

## References

1. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980;92:44-7.
2. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993;186:23-31.
3. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:548-53.
4. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
5. Hanifin JM. Epidemiology of atopic dermatitis. *Monogr Allergy* 1987;21:116-31.
6. Strömberg L. Diagnostic accuracy of the atopy patch test and skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002;91:1044.
7. Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995;25:815-9.
8. Naldi L, Parazzini F, Gallus S; GISED Study Centres. Prevalence of atopic dermatitis in Italian schoolchildren: factors affecting its variation. *Acta Derm Venereol* 2009;89:122-5.
9. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, *et al*. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in childhood. *J Allergy Clin Immunol* 1999;103:125-38.
10. UCB Institute of Allergy: European Allergy White Paper. Allergic disease as a public health problem. Braine-l'Alleud, Belgium; 1997. pp.14-47.

11. Fölster-Holst R, Pape M, Buss YL, Christophers E, Weichenthal M. Low prevalence of the intrinsic form of atopic dermatitis among adult patients. *Allergy* 2006;61:629-32.
12. Queille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood. I. Initial analysis of 250 parameters. *Acta Derm Venereol Suppl (Stockh)* 1985;114:87-92.
13. Pajno GB, Peroni DG, Barberio G, Pietrobelli A, Boner AL. Predictive features for persistence of atopic dermatitis in children. *Pediatr Allergy Immunol* 2003;14:292-5.
14. Musgrove K, Morgan J. Infantile eczema. A long term follow up study. *Br J Dermatol* 1976;95:362-5.
15. Morren MA, Przybilla B, Bamelis M, Heykants B, Reynaers A, Degreef M. Atopic dermatitis: triggering factors. *J Am Acad Dermatol* 1994;313:467.
16. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, *et al.* Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
17. Wollenberg A, Bieber T. Atopic dermatitis from the genes to skin lesions. *Allergy* 2000;55:205-13.
18. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis, pathophysiology, epidemiology, diagnosis and management. *J Allergy Clin Immunol* 1999;103:717-28.
19. Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. EAACI/GA2LEN Position paper: Present status of the atopy patch test. *Allergy* 2006;61:1377-84.
20. Bos JD, van Leent EJ, Sillevis Smitt JH. The millennium criteria for diagnosis of atopic dermatitis. *Exp Dermatol* 1998;7:132-8.
21. De D, Kanwar AJ, Handa S. Comparative efficacy of Hanifin and Rajka's criteria and the UK Working Party's diagnostic criteria in diagnosis of atopic dermatitis in hospital setting in North India. *J Acad Dermatol Venereol* 2006;20:853-9.
22. Brenninkmeijer EE, Schram ME, Leeftang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008;158:754-65.
23. Laske N, Niggemann B. Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr Allergy Immunol* 2004;15:86-8.
24. Joishy M, Alfaham M, Tuthill D. Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr Allergy Immunol* 2005;16:283.
25. Wistokat-Wülfing A, Schmidt P, Darsow U, Ring J, Kapp A, Werfel T. Atopy patch test reactions are associated with T-lymphocyte mediated allergen-specific immune responses in atopic dermatitis. *Clin Exp Allergy* 1999;29:513-21.
26. Maurer D, Ebner C, Reininger B, Fiebiger E, Kraft D, Kinet JP, Stingl G. The high affinity IgE receptor mediates IgE-dependent allergen presentation. *J Immunol* 1995;154:6285-90.
27. Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis. *J Allergy Clin Immunol* 2004;114:150-8.
28. Wüthrich B, Schmid-Grendelmeier P. The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ('extrinsic') and the non-allergic ('intrinsic') AEDS. *J Invest Allergol Clin Immunol* 2003;131:1-5.
29. Ott H, Stanzel S, Ocklenburg C, Merk HF, Baron JM, Lehmann S. Total serum IgE as a parameter to differentiate between intrinsic and extrinsic atopic dermatitis in children. *Acta Derm Venereol (Stockh)* 2009;89:257-61.
30. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wüthrich B. Epidemiology, clinical features, and immunology of the 'intrinsic'(non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 2001;56:841-9.
31. Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wüthrich B, *et al.* The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004;59:1318-25.
32. Seidenari S, Manzini BM, Danese P, Giannetti A. Positive patch test to whole mite culture and purified mite extracts in patients with atopic dermatitis, asthma and rhinitis. *Ann Allergy* 1992;69:201-6.

33. Seidenari S, Giusti F, Pellacani G, Bertoni L. Frequency and intensity of responses to mite patch tests are lower in nonatopic subjects with respect to patients with atopic dermatitis. *Allergy* 2003;58:426-9.
34. Manzini BM, Motolese A, Donini M, Seidenari S. Contact allergy to dermatophagoides in atopic dermatitis patients and healthy subjects. *Contact Dermatitis* 1995;33:243-6.
35. Ingordo V, D'Andria G, D'Andria C, Tortora A. Results of atopy patch tests with house dust mites in adults with 'intrinsic' and 'extrinsic' atopic dermatitis. *J Eur Acad Dermatol Venereol* 2002;16:450-4.
36. Devillers AC, de Waard-van der Spek FB, Mulder PG, Oranje AP. Delayed- and immediate-type reactions in the atopy patch test with food allergens in young children with atopic dermatitis. *Pediatr Allergy Immunol* 2009;20:53-8.
37. Niggemann B, Reibel S, Wahn U. The atopy-patch test (APT) – a useful tool for diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;55:281-5.
38. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988;113:447-51.
39. Sigurs N, Hattevig G, Kjellman B, Kjellman NI, Nilsson L, Björkstén B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;94:757-63.
40. Ingordo V, D'Andria G, D'Andria C. Adult-onset atopic dermatitis in a patch test population. *Dermatology* 2003;206:197-203.
41. Akhavan A, Cohen SR. The relationship between atopic dermatitis and contact dermatitis. *Clin Dermatol* 2003;21:158-62.
42. Pónyai G, Hidvégi B, Németh I, Sas A, Temesvári E, Kárpáti S. Contact and aeroallergens in adulthood atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008;22:1346.
43. Rostenberg A, Sulzberger MD. Some results of patch tests. *Arch Dermatol* 1937;35:433-54.
44. Mitchell E, Chapman M, Pope F, Crow J, Jouhal S, Platts-Mills T. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;1:127-30.
45. Breneman JC, Sweeney M, Robert A. Patch test demonstrating immune (antibody and cell-mediated) reactions to foods. *Ann Allergy* 1989;62:461-9.
46. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
47. Räsänen L, Lehto M, Reunala T. Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance. *Clin Exp Allergy* 1992;22:385-90.
48. Räsänen L, Lehto M, Turjanmaa K, Savolainen J, Reunala T. Allergy to ingested cereals in atopic children. *Allergy* 1994;49:871-6.
49. Turjanmaa K. The role of atopy patch tests in diagnosis of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2005;5:425-8.
50. Kekki OM, Turjanmaa K, Isolauri E. Differences in skin-prick and patch test reactivity are related to the heterogeneity of atopic eczema in infants. *Allergy* 1997;52:755-9.
51. van Reijssen FC, Bruijnzeel-Koomen CA, Kalthoff FS, Maggi E, Romagnani S, Westland JK. Skin-derived aeroallergen-specific T-cell clones of Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992;90:184-93.
52. Johansson C, Ahlberg N, Andersson A, Lundberg L, Karlsson MA, Scheynius A, *et al.* Elevated peripheral allergen-specific T cell response is crucial for a positive atopy patch test reaction. *Int Arch Allergy Immunol* 2009;150:51-8.
53. Thepen T, Langeveld-Wildschut EG, Bihari IC, van Wichen DF, van Reijssen FC, Mudde GC. Biphasic response against aeroallergen in atopic dermatitis showing a switch from initial TH2 response to TH1 response *in situ*: an immunocytochemical study. *J Allergy Clin Immunol* 1996;97:828-37.
54. Sager N, Feldmann A, Schilling G, Kreitsch P, Neumann C. House-dust mite-specific T cells in the skin of subjects with atopic dermatitis: frequency and lymphokine profile in the allergen patch test. *J Allergy Clin Immunol* 1992;89:801-10.
55. Langeveld-Wildschut EG, Bruijnzeel PLB, Mudde GC, Versluis C, Van Ieperen-Van Dijk AG, Bihari IC, *et al.* Clinical and immunologic variables in skin of patients with atopic

- eczema and either positive or negative atopy patch test reactions. *J Allergy Clin Immunol* 2000;105:1008-16.
56. Kerschenlohr K, Decard S, Przybilla B, Wollenberg A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol* 2003;111:869-74.
  57. Langeland T, Braathen LB, Borch M. Studies of atopy patch test. *Acta Derm Venereol Suppl (Stockh)* 1989;144:105-9.
  58. Czarnecka-Operacz M, Bator-Wegner M, Silny W. Atopy patch test reaction to airborne allergens. *Acta Dermatovenerol Croat* 2005;13:3-16.
  59. Ronchetti R, Jesenak M, Trubacova D, Pohanka V, Villa MP. Epidemiology of atopy patch tests with food and inhalant allergens in an unselected population of children. *Pediatr Allergy Immunol* 2008;19:599-604.
  60. Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentrations – an approach to standardization. *J Allergy Clin Immunol* 1995;95:677-84.
  61. Ingordo V, Dalle Nogare R, Colecchia B, D'Andria C. Is the atopy patch test with house dust mites specific for atopic dermatitis? *Dermatology* 2004;209:276-83.
  62. Gondo A, Saeki N, Tokuda Y. Challenge reactions in atopic dermatitis after percutaneous entry of mite antigen. *Br J Dermatol* 1986;115:485-93.
  63. Norris PG, Schofield O, Camp RD. A study of the role of house dust mite in atopic dermatitis. *Br J Dermatol* 1988;118:435-40.
  64. van Voorst Vader PC, Lier JG, Woest TE, Coenraads PJ, Nater JP. Patch test with house dust mite antigens in atopic dermatitis patients: methodological problems. *Acta Derm Venereol* 1991;71:301-5.
  65. Bruynzeel-Koomen CA, Van Wichen DF, Spry CJ, Venge P, Bruynzeel PL. Active participation of eosinophils in patch test reaction to inhalant allergens in patients with atopic dermatitis. *Br J Dermatol* 1988;118:229-38.
  66. Tanaka Y, Anan S, Yoshida H. Immunohistochemical studies in mite antigen-induced patch test sites in atopic dermatitis. *J Dermatol Sci* 1990;1:361-8.
  67. Ring J, Darsow U, Gfesser M, Vieluf D. The 'atopy patch test' with aeroallergens in atopic eczema. *Int Arch Allergy Immunol* 1997;113:379-83.
  68. Darsow U, Ring J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000;25:544-51.
  69. Kerschenlohr K, Darsow U, Burgdorf WH, Ring J, Wollenberg A. Lessons from atopy patch testing in atopic dermatitis. *Curr Allergy Asthma Rep* 2004;4:285-9.
  70. Darsow U, Abeck D, Ring J. Allergie und atopisches Ekzem: Zur Bedeutung des "Atopie-Patch-Tests". *Hautarzt* 1997;48:528-35.
  71. Darsow U, Vieluf D, Ring J. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double blind multicenter study. Atopy Patch Test Study Group. *J Am Acad Dermatol* 1999;40:187-93.
  72. Langeveld-Wildschut EG, van Marion AM, Thepen T, Mudde GC, Bruijnzeel PL. Evaluation of variables influencing the outcome of the atopy patch test. *J Allergy Clin Immunol* 1995;96:66-73.
  73. Heine RG, Verstege A, Mehl A, Staden U, Rolinck-Werninghaus C, Niggemann B. Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatr Allergy Immunol* 2006;17:213-7.
  74. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K, *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006;118:923-9.
  75. Niggemann B, Wahn U, Sampson HA. Proposals for standardization of oral food challenge tests in infants and adolescents. *Pediatr Allergy Immunol* 1994;5:11-3.
  76. Hansen TK, Høst A, Bindslev-Jensen C. An evaluation of the diagnostic value of different skin tests with egg in clinically egg-allergic children having atopic dermatitis. *Pediatr Allergy Immunol* 2004;15:428-34.
  77. Niggemann B. The role of atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis. *Pediatr Allergy Immunol* 2001;12:37-40.
  78. Vanto T, Juntunen-Backman K, Kalimo K, Klemola T, Koivikko A, Koskinen P, *et al.* The

- patch test, skin prick test and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants. *Allergy* 1999;54:837-42.
79. Perackis K, Celik-Bilgili S, Staden U, Mehl A, Niggemann B. Influence of age on the outcome of the atopy patch test with food in children with atopic dermatitis. *J Allergy Clin Immunol* 2003;112:625-7.
  80. Majamaa H, Moisiö P, Holm K, Kautiainen H, Turjanmaa K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:346-51.
  81. Majamaa H, Moisiö P, Holm K, Turjanmaa K. Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:851-6.
  82. Rokaite R, Labanauskas L, Vaideliene L. Role of the skin patch test in diagnosing food allergy in children with atopic dermatitis. *Medicina (Kaunas)* 2004;40:1081-7.
  83. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, *et al.* Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004;59:690-7.
  84. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D, *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;34:817-24.
  85. Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2004;4:379-85.
  86. Niggemann B, Rolinck-Werninghaus C, Mehl A, Binder C, Ziegert M, Beyer K. Controlled oral food challenges in children – when indicated, when superfluous? *Allergy* 2005;60:865-70.
  87. Niggemann B, Beyer K. Diagnostic pitfalls in food allergy in children. *Allergy* 2005;60:104-7.
  88. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:8-13.
  89. Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM, *et al.* Atopic dermatitis and food hypersensitivity reactions. *J Pediatr* 1998;132:132-6.
  90. Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled, food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999;29:91.
  91. Ronchetti R, Jesenak M, Barberi S, Ronchetti F, Rennerova Z, Trubacova D, *et al.* Reproducibility of atopy patch tests with food and inhalant allergens. *J Biol Regul Homeost Agents* 2008;22:27-33.
  92. Heinemann C, Schliemann-Willers S, Keltner D, Metzner U, Kluge K, Wigger-Alberti W, *et al.* The atopy patch test – reproducibility and comparison of different evaluation methods. *Allergy* 2002;57:641-5.
  93. Goon A, Leow YH, Chan YH, Ng SK, Goh CL. Atopy patch testing with aeroallergens in patients with atopic dermatitis and controls in Singapore. *Clin Exp Dermatol* 2005;30:627-31.
  94. de Bruin-Weller MS, Knol EF, Bruijnzeel-Koomen CA. Atopy patch testing – a diagnostic tool? *Allergy* 1999;54:784-91.
  95. Rancé F. What is the optimal occlusion time for the atopy patch test in the diagnosis of food allergies in children with atopic dermatitis? *Pediatr Allergy Immunol* 2004;15:93-6.
  96. Fuiano N, Incorvaia C, Prodam F, Procaccini DA, Bona G. Relationship between the atopy patch test and clinical expression of the disease in children with atopic eczema/dermatitis syndrome and respiratory symptoms. *Ann Allergy Asthma Immunol* 2008;101:174-8.
  97. Weissenbacher S, Traidl-Hoffmann C, Eyerich K, Katzer K, Braeutigam M, Loeffler H. Modulation of atopy patch test and skin prick test by pretreatment with 1% pimecrolimus cream. *Int Arch Allergy Immunol* 2006;140:239-44.
  98. Oldhoff JM, Knol EF, Laaper-Ertmann M, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Modulation of atopy patch test: tacrolimus 0.1% compared with triamcinolone acetone 0.1%. *Allergy* 2006;61:622-8.
  99. Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rancé F, Turjanmaa K, *et al.* Eczematous reactions to food in atopic eczema: a position paper of the EAACI and GA2LEN. *Allergy* 2007;62:723-8.
  100. Jesenak M, Rennerova Z, Babusikova E, Havlicekova Z, Jakusova L, Villa MP, *et al.*

- Food allergens and respiratory symptoms. *J Physiol Pharmacol* 2008;59:311-20.
101. Cudowska B, Kaczmarski M. Atopy patch test in the diagnosis of food allergy in children with atopic eczema dermatitis syndrome. *Rocz Akad Med Białymst* 2005;50:261-7.
102. Canani RB, Ruotolo S, Auricchio L, Caldore M, Porcaro F, Manguso F, *et al.* Diagnostic accuracy of the atopy patch test in children with food allergy-related gastrointestinal symptoms. *Allergy* 2007;62:738-43.
103. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113:805-19.
104. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. *Clin Dermatol* 2003;21:183-92.
105. Jesenák M, Bánovcin P. Atopy patch test in diagnosis of food allergy in children with atopic dermatitis. *Acta Medica (Hradec Kralove)* 2006;49:199-201.
106. Kaczmarski M. Clinical forms of cow milk protein intolerance in children. *Pol Tyg Lek* 1989;44:81-5.
107. de Boissieu D, Dupont C. Patch tests in the diagnosis of food allergies in the nursing infant. *Eur Ann Allergy Clin Immunol* 2003;35:150-2.
108. Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. *Acta Paediatr* 1999;88:7-12.
109. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow up at age 7 years in a prospective randomized study of combined maternal and infant food allergy avoidance. *J Allergy Clin Immunol* 1995;95:1179-90.
110. Kilshaw PJ, Cant AJ. The passage of maternal dietary proteins in human breast milk. *Int Arch Allergy Appl Immunol* 1984;75:8-15.
111. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 1991;118:520-5.
112. Hoffmann-Sommergruber K, Mills EN, Vieths S. Coordinated and standardized production, purification and characterization of natural and recombinant food allergens to establish a food allergen library. *Mol Nutr Food Res* 2008;52:59-65.
113. Eigenmann P, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1999;10:186-91.
114. Cocco R, Solé D. Patch test in the diagnosis of food allergy. *Allergol Immunopathol (Madr)* 2009;37:205-7.
115. Zeiger RS. Atopy in infancy and early childhood: natural history and role of skin testing. *J Allergy Clin Immunol* 1985;75:633-9.
116. 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;74:26-33.
117. Sütas Y, Kekki OM, Isolauri E. Late onset reactions to oral food challenge are linked to low serum interleukin-10 concentrations in patients with atopic dermatitis and food allergy. *Clin Exp Allergy* 2000;30:1121-8.
118. Langeveld-Wildschut EG, Thepen T, Bihari IC, van Reijssen FC, de Vries IJ, Bruijnzeel PL, *et al.* Evaluation of the atopy patch test and the cutaneous late-phase reaction as relevant models for the study of the allergic inflammation in patients with atopic eczema. *J Allergy Clin Immunol* 1996;98:1019-27.
119. Brenninkmeijer EE, Legierse CM, Sillevius Smitt JH, Last BF, Grootenhius MA, Bos JD. The course of life of patients with childhood atopic dermatitis. *Pediatr Dermatol* 2009;26:14-22.
120. De Boissieu D, Waguët JC, Dupont C. The atopy patch test for detection of cow's milk allergy with digestive symptoms. *J Pediatr* 2003;142:203-5.
121. Osterballe M, Andresen KE, Binslev-Jensen C. The diagnostic accuracy of the atopy patch test in diagnosing hypersensitivity to cow's milk and hen's egg in unselected children with and without atopic dermatitis. *J Am Acad Dermatol* 2004;51:556-62.
122. Rancé F, Juchet A, Brémont F, Dutau G. Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy* 1997;52:1031-5.
123. Seidenari S, Giusti F, Bertoni L, Mantovani L. Combined skin prick and patch testing enhances identification of peanut-allergic patients with atopic dermatitis. *Allergy* 2003;58:495-9.

124. Beyer K, Teuber SS. Food allergy diagnostics: scientific and unproven procedures. *Curr Opin Allergy Clin Immunol* 2005;5:261-6.
125. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005;116:869-75.
126. de Waard-van der Spek FB, Elst EF, Mulder PG, Munte K, Devillers AC, Oranje AP. Diagnostic tests in children with atopic dermatitis and food allergy. *Allergy* 1998;53:1087-91.
127. Wüthrich B. Food allergy, food intolerance or functional disorder? *Praxis (Bern)* 1994;98:375-87.
128. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 1976;58:500-15.
129. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999;10:226-34.
130. Muraro MA. Diagnosis of food allergy: the oral provocation test. *Pediatr Allergy Immunol* 2001;12:31-6.
131. Sicherer S, Morrow EH, Sampson HA. Dose-response in double-blind, placebo controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2000;105:582-6.
132. Reibel S, Röhr C, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. What safety measures need to be undertaken in oral food challenges in children? *Allergy* 2000;55:940-4.
133. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
134. Asero R, Fernandez-Rivas M, Knulst AC, Bruijnzeel-Koomen CA. Double-blind, placebo-controlled food challenge in adults in everyday clinical practice: a reappraisal of their limitations and real indications. *Curr Opin Allergy Clin Immunol* 2009 May 28. [Epub ahead of print]
135. Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for food allergen challenges in young children: a comparison of *in vitro* with *in vivo* tests. *Clin Exp Allergy* 2001;31:1031-5.
136. Rancé F, Deschildre A, Villard-Truc F, Gomez SA, Paty E, Santos C, *et al.* Oral food challenge in children: an expert review. *Eur Ann Allergy Clin Immunol* 2009;41:35-49.
137. Bahna SL. Food challenge procedure: optimal choices for clinical practice. *Allergy Asthma Proc* 2007;28:640-6.
138. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
139. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
140. Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.
141. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? *J Allergy Clin Immunol* 2003;112:196-201.
142. Hill DJ, Duke AM, Hosking CS, Hudson IL. Clinical manifestations of cow's milk allergy in childhood. II The diagnostic value of skin tests and RAST. *Clin Allergy* 1988;18:481-90.
143. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Sackesen C, Kalayci O. Evaluation of utility of atopy patch testing, skin prick testing, and total and specific IgE assays in the diagnosis of cow's milk allergy. *Ann Allergy Asthma Immunol* 2005;94:553-60.
144. Wolkerstorfer A, Wahn U, Kjellman NI, Diepgen TL, De Longueville M, Oranje AP. Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC Study Group. *Clin Exp Allergy* 2002;32:70-3.
145. Host A, Halken S. A prospective study of cow's milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990;45:587-96.
146. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
147. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-



- blind placebo controlled food challenges. *J Pediatr* 1990;117:561-7.
148. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-6.
149. Järvinen KM, Turpeinen M, Suomalainen H. Concurrent cereal allergy in children with cow's milk allergy manifested with atopic dermatitis. *Clin Exp Allergy* 2003;33:1060-6.
150. Pucar F, Kagan R, Lim H, Clarke AE. Peanut challenge: a retrospective study of 140 patients. *Clin Exp Allergy* 2001;31:40-6.
151. Sicherer SH. Clinical update on peanut allergy. *Ann Allergy Asthma Immunol* 2002;88:350-61.
152. Hourihane JOB, Kliburn SA, Nordlee JA, Hefle SL, Taylor SL, Warner JO. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 1997;100:596-600.
153. Schäppi GF, Konrad V, Imhof D, Etter R, Wüthrich B. Hidden peanut allergens detected in various foods: findings and legal measures. *Allergy* 2001;56:1216-20.
154. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363-8.
155. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeaao E, *et al.* Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198-206.
156. Gupte AR, Draganov PV. Eosinophilic esophagitis. *World J Gastroenterol* 2009;15:17-24.
157. Asaa'ad A. Eosinophilic gastrointestinal disorders. *Allergy Asthma Proc* 2009;30:17-22.
158. Boralevi F, Hubiche T, Léauté-Labrèze C, Saubusse E, Fayon M, Roul S, *et al.* Epicutaneous aeroallergen sensitization in atopic dermatitis infants – determining the role of epidermal barrier impairment. *Allergy* 2008;63:205-10.
159. Darsow U, Vieluf D, Ring J. The atopy patch test: an increased rate of reactivity in patients who have an air-exposed pattern of atopic eczema. *Br J Dermatol* 1996;135:182-6.
160. Samochocki Z, Owczarek W, Rujna P, Raczyńska A. Hypersensitivity to aeroallergens in adult patients with atopic dermatitis develops due to the different immunological mechanisms. *Eur J Dermatol* 2007;17:520-4.
161. Samochocki Z, Owczarek W, Zabielski S. Can atopy patch tests with aeroallergens be an additional diagnostic criterion for atopic dermatitis? *Eur J Dermatol* 2006;16:151-4.
162. Whitmore SE, Sherertz EF, Belsito DV, Maibach HI, Nethercott JR. Aeroallergen patch testing for patients presenting to contact dermatitis clinics. *J Am Acad Dermatol* 1996;35:700-4.
163. Werfel T, Kapp A. Environmental and other major provocation factors in atopic dermatitis. *Allergy* 1998;53:731-9.
164. Schäfer T, Heinrich J, Wjst M, Adam H, Ring J, Wichmann HE. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999;104:1280-4.
165. Oldhoff JM, Bihari IC, Knol EF, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Atopy patch test in patients with atopic eczema/dermatitis syndrome: comparison of petrolatum and aqueous solution as a vehicle. *Allergy* 2004;59:451-6.
166. Bruijnzeel PL, Kuijper PH, Kapp A, Warringa RA, Betz S, Bruijnzeel-Koomen CA. The involvement of eosinophils in the patch test reaction to aeroallergens in atopic dermatitis: its relevance for the pathogenesis of atopic dermatitis. *Clin Exp Allergy* 1993;23:97-109.
167. Gordon S. Allergy skin tests for inhalants and foods. Comparison of methods in common use. *Otolaryngol Clin North Am* 1998;31:35-53.
168. Holm L, Vanttage-Hamsteen M, Ohman S, Scheynius A. Sensitization to allergens of house dust mite in adults with atopic dermatitis in a cold temperate region. *Allergy* 1999;54:708-15.
169. Fischer S, Ring J, Abeck D. Atopic eczema. Spectrum of provocation factors and possibilities for their effective reduction and elimination. *Hautarzt* 2003;54:914-24.
170. Harving H, Korsgaard J, Dahl R, Beck HI, Bjerring P. House dust mites and atopic dermatitis. A case-control study on the sig-

- nificance of house dust mites as etiologic allergens in atopic dermatitis. *Ann Allergy* 1990;65:25-31.
171. Beltrani V, Hanifin J. Atopic dermatitis, house dust mites and patch testing. *Am J Contact Dermatitis* 2002;13:80-2.
172. Huang JL, Chen CC, Kuo ML, Hsieh KH. Exposure to high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: a 3 year follow-up. *Pediatr Allergy Immunol* 2001;12:11-6.
173. Deleuran M, Ellingsen AR, Paludan K, Schou C, Thestrup-Pedersen K. Purified Der p1 and p2 patch tests in patients with atopic dermatitis: evidence for both allergenicity and proteolytic irritancy. *Acta Derm Venereol* 1998;78:241-3.
174. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfibre fibres on mite sensitization. *J Allergy Clin Immunol* 1998;101:28-32.
175. Kubota Y, Imayama S, Hori Y. Reduction of environmental mites improved atopic dermatitis with positive mite-patch tests. *J Dermatol* 1992;19:177-80.
176. Fuiano N, Incorvaia C. Value of skin prick test and atopy patch test in mite-induced respiratory allergy and/or atopic eczema/dermatitis syndrome. *Minerva Pediatr* 2004;56:537-40.
177. Tengvall Linder M, Johansson C, Scheynius A, Wahlgren C. Positive atopy patch test reactions to *Pityrosporum orbiculare* in atopic dermatitis patients. *Clin Exp Allergy* 2000;30:122-31.
178. Johansson C, Eshaghi H, Linder MT, Jakobson E, Scheynius A. Positive atopy patch test reaction to *Malassezia furfur* in atopic dermatitis correlates with a T-helper-2-like peripheral blood mononuclear cell response. *J Invest Dermatol* 2002;118:1044-51.
179. de Meer G, Toelle BG, Ng K, Tovey E, Marks GB. Presence of timing of cat ownership by age 18 and the effect on atopy and asthma at age 28. *J Allergy Clin Immunol* 2004;113:433-8.
180. Eyerich K, Huss-Marp J, Darsow U, Wollenberg A, Foerster S, Ring J, *et al.* Pollen grains induce a rapid and biphasic eczematous immune response in atopic eczema patients. *Int Arch Allergy Immunol* 2008;145:213-23.

Njegovane ruke, usprkos rada u kućanstvu  
sa **NIVEA-CREME**

Ako morate kao laborantica ili liječnica mnogo baratati sa toplom i hladnom vodom, možete imati dobro njegovane ruke. Najbolje je da natarete lice i ruke temeljito navečer sa Nivea-Creme. Vi možete to učiniti i tokom dana, jer ona prodire potpuno u kožu, bez da ostavi sjaj na površini. Koža Vam postaje usljed toga otporna i mekana poput baršuna. Nivea-Creme podaje Vam ovu nježnu put, kojoj se mi toliko divimo kod mladeži.

Razlikuje se od luksuznih krema:  
Nivea-Creme: najveći učinak, a kraj toga jeftina.

JUGOSL. P. BEIERSDORF & Co. d. s. o. j.  
MARIBOR

Nivea-Creme: Din 5.00 — 22.00.

Cared hand inspite of homework with Nivea cream; year 1934.  
(From the collections of Mr. Zlatko Puntijar)