

Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance

A. T. Clark and P. W. Ewan

Department of Allergy and Clinical Immunology, Addenbrooke's Hospital, University of Cambridge Clinical School, Cambridge, UK

Summary

Background Peanut and tree nut allergy are common, increasing in prevalence and the commonest food cause of anaphylaxis. In the USA, 7.8% are sensitized (have nut-specific IgE), but not all those sensitized are allergic. Lack of data makes interpretation of tests for nut-specific IgE difficult.

Objectives This is the first study to investigate the clinical significance of test results for peanut and tree nut allergy in allergic or tolerant patients. Findings are related to the severity of the allergy.

Method An observational study of 1000 children and adults allergic to at least one nut. History of reactions (severity graded) or tolerance to up to five nuts was obtained and skin prick test (SPT)/serum-specific IgE (CAP) performed.

Results There was no correlation between SPT size and graded severity of worst reaction for all nuts combined or for peanut, hazelnut, almond and walnut. For CAP, there was no correlation for all nuts. Where patients tolerated a nut, 43% had positive SPT of 3–7 mm and 3% $\geq$ 8 mm. For CAP, 35% were positive (0.35–14.99 kU/L) and 5% $\geq$ 15 kU/L. In SPT range 3–7 mm, 54% were allergic and 46% were tolerant. There was poor concordance between SPT and CAP (66%). Of patients with a clear nut-allergic history, only 0.5% had negative SPT, but 22% negative CAP.

Conclusions Magnitude of SPT or CAP does not predict clinical severity, with no difference between minor urticaria and anaphylaxis. SPT is more reliable than CAP in confirming allergy. Forty-six per cent of those tolerant to a nut have positive tests $\geq$ 3 mm (sensitized but not allergic). One cannot predict clinical reactivity from results in a wide 'grey area' of SPT 3–7 mm; 22% of negative CAPs are falsely reassuring and 40% of positive CAPs are misleading. This emphasizes the importance of the history. Understanding this is essential for accurate diagnosis. Patients with SPT $\geq$ 8 mm and CAP $\geq$ 15 kU/L were rarely tolerant so these levels are almost always (in $\geq$ 95%) diagnostic.

Keywords allergy, anaphylaxis, diagnosis, food, nut

Submitted 13 May 2002; revised 31 October 2002; accepted 25 November 2002

Introduction

Peanut and nut allergy are common and the incidence is rising. In 1994, 0.5% of 4-year-olds in the UK had peanut allergy and 1.3% were sensitized (i.e. had specific IgE antibody) to nuts [1]. Since then the sensitization rate has risen to 3.2% in children in the UK [2] and 7.8% of adults and children in the USA [3]. The incidence of clinical allergy to nuts in the UK has trebled to 1.5% [2]. In the UK, 1 : 3500 people suffer anaphylaxis arising in community annually, though this is assumed to be an underestimate [4]. Peanut allergy is the commonest cause of fatal and near-fatal reactions to food [5]. This creates anxiety about accurate diagnosis and management.

Peanut is a member of the legume family, only distantly related to tree nuts. However, for simplicity throughout this

paper we will use the term 'nuts' to mean both peanut and tree nuts.

Investigations for detection of specific IgE are either skin prick tests (SPT) or serological assays, such as CAP (CAP-System FEIA). Whereas the allergist would rely on SPTs, the CAP is usually the only available test for general practitioners, paediatricians and physicians.

The presence of specific IgE antibody (sensitization) is not the same as clinical allergy. For inhalant allergens, only about 40% of those with positive tests have allergy symptoms [6], but there is lack of data on the significance of peanut or nut IgE antibodies, so interpretation of tests for nut allergy is difficult [7–9]. Further, about 60% of children with nut allergy have atopic eczema [10, 11], increasing the likelihood of positive tests for specific IgE.

Although '100% diagnostic SPT values' (SPT $\geq$ 8 mm) and '95% positive predictive CAP values' (15 kU/L – upper end of class 3) have recently been proposed for peanut allergy by Sporik [12] and Sampson [13], i.e. an upper cut-off level above which allergy is predicted, this accounts for a minority of results and there are no data to show clinical correlation across the

Correspondence: P. W. Ewan, Department of Allergy and Clinical Immunology, Box 40, Addenbrooke's Hospital, University of Cambridge Clinical School, Hills Road, Cambridge CB2 2QQ, UK.
E-mail: pamela.ewan@addenbrookes.nhs.uk

entire range. Further, there are no data for tree nuts. This means that history is essential for interpretation of results below these levels, and without this many patients are falsely labelled as clinically allergic. An additional difficulty is interpretation of tests where no history is available, e.g. details are not known or in children such as siblings of nut-allergic children who have never eaten nuts. The aim of this study is to clarify interpretation of tests used in peanut and nut allergy, relating different levels to allergy or tolerance for different nuts. This is the first study to interpret results across the entire range and has focused on a large population. We have analysed results of both SPT and CAP to up to five nuts in 1000 patients allergic to at least one nut, with an unequivocal history of either allergy or tolerance to particular nuts. The significance of SPT and CAP results is presented in relation to the allergy and tolerance and severity of allergy. The correlation between SPT and CAP was also examined. This information will aid practising physicians to interpret these tests.

Patients and methods

This was a cross-sectional observational study over a 7-year period of patients referred to a specialist Allergy Clinic. One thousand patients with a typical history of an acute allergic reaction to a nut, confirmed by a positive SPT and/or CAP were included. A typical history means acute onset of one or more of the following features: urticaria, angio-oedema, pruritis of the oro-pharyngeal mucosa, laryngeal oedema, asthma, abdominal pain and/or vomiting, lightheadedness, fainting or collapse occurring immediately or soon after ingestion of a food known to contain a nut (Table 1). Equivocal cases, either on clinical grounds or if a food was not known with certainty to contain nut, were excluded. Full details of the clinical spectrum are published elsewhere [11].

Subjects

Age distribution of the subjects was: 0–5 years, 365 (36%); 6–10 years, 219 (22%); 11–17 years, 142 (14%); > 17 years, 276 (28%). The ratio of males to females was 1 : 1.

Details of the nut which caused the most severe reaction (referred to as the 'index reaction') and amount eaten were obtained and the severity graded (Table 1) [11]. It was determined for each patient whether they had reacted to other nuts, tolerated these, or had never ingested them.

A total of 4106 SPT were performed for up to five nuts in 1000 patients using a standard technique (single headed lancet, Medipoint, Mineda, NY, USA) and widely used extracts of peanut, Brazil nut, almond, hazelnut, walnut extracts, positive (histamine 10 mg/mL) and negative controls (saline), supplied by ALK Abelló (Hørsholm, Denmark). Weal diameter was measured in mm. Irregular shapes were recorded as the mean of two perpendicular diameters.

Blood was drawn at the same time and specific IgE to peanut, Brazil nut, almond, hazelnut and walnut was estimated using the CAP method (Pharmacia, Peapack, NJ, USA). A total of 900 nut CAP assays were performed in 223 patients. Results are expressed in kU/L and grouped into classes 0–6 (negative to very high). CAP assays were performed in a regional immunology laboratory which participates in a national quality control scheme.

Statistics

Group medians were compared by Mann–Whitney *U*-test using StatView (Abacus Concepts, Inc., Berkley, CA, USA); a value of $P < 0.05$ was considered significant.

Results

Peanut was responsible for the majority of index reactions (Table 2). The severity of index reactions caused by peanut, Brazil nut and hazelnut is shown in Table 3.

Does the size of SPT or level of CAP indicate clinical severity?

Taking reactions to all five nuts there was no correlation between severity (grades 1–5) and SPT diameter (Fig. 1). This was true when peanut was considered alone, but for Brazil nut alone there was an increase in SPT diameter only when severe reactions (grade 5; median 14 mm) were compared to mild–moderate reactions (grade 1–4; median 10 mm; $P = 0.0005$). There was a similar but non-significant trend for almond and hazelnut.

In order to correct for the influence of amount of allergen ingested on severity grade, a further analysis was performed excluding patients who had reacted to only traces of, or contact with, nut. This made no difference to the findings either for all nuts combined or individual nuts. Although exact quantification of the amount of nut ingested was not possible, this allowed us to identify a group who had eaten at least one nut.

Table 1. Classification of the most severe (index) reaction and number of patients

Reaction grade	Clinical features (the most severe feature experienced)*	Number of patients (%)
1. Mild	Localized erythema/urticaria angio-oedema/oral pruritis only	215 (23)
2. Mild	Generalized erythema/urticaria/angio-oedema	96 (10)
3. Mild	1. or 2. plus gastrointestinal symptoms/rhinoconjunctivitis only	182 (19)
4. Moderate	Mild laryngeal oedema (voice change/tightening of throat)/mild asthma	379 (40)
5. Severe	Marked dyspnoea/hypotensive symptoms (light-headedness/collapse/loss of consciousness)	73 (8)

*For grades 3, 4 and 5, patients will also have experienced symptoms in grade 1, 2 or 3.

Table 2. Frequency of nuts which caused the most severe reaction in allergic individuals

	Allergic		Tolerant*	
	<i>n</i>	%	<i>n</i>	%
Peanut	589	58	196	24
Brazil nut	162	16	60	21
Hazelnut	63	6	127	41
Almond	34	3	210	55
Walnut	30	3	94	43
Cashew	29	3		
Pecan	8	1		
Type of nut mixed or unknown	101	10		

*Frequency of nuts tolerated by individuals who are allergic to one other type of nut.

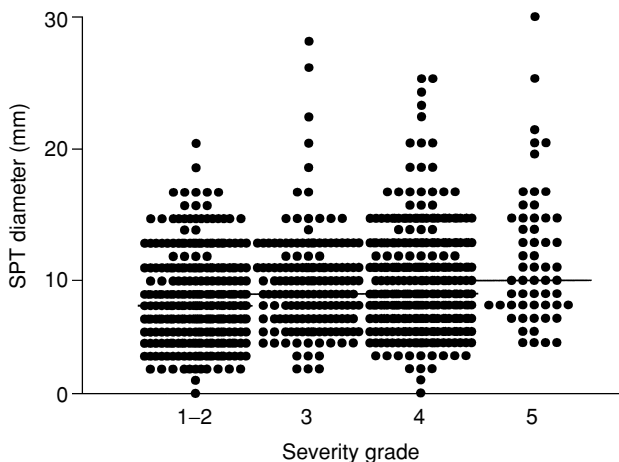


Fig. 1. Skin prick test (SPT) diameter for either peanut, Brazil nut, almond, hazelnut or walnut in 885 patients, whichever caused the index (most severe) reaction. Severity of reaction was graded 1–5, where 1 was mild (local urticaria) and 5 was severe (anaphylaxis; see Table 1). Bar = median.

Taking the nut that caused the most severe reaction (history positive and test positive) there was no correlation between the CAP level and severity grade (Fig. 2).

What is the profile of results in allergic patients?

Of subjects allergic to any nut, 99.5% had SPT ≥ 2 mm to the nut which caused the index reaction; 98% had SPT ≥ 3 mm (Fig. 3) and 91.6% SPT > 4 mm. However, taking the nut that caused the most severe reaction, 22% with positive SPT to that nut had negative CAP and only 30% had CAP ≥ 15 kU/L (upper end class 3).

What is the profile in tolerant patients?

When we examined results for all nuts which were tolerated by nut-allergic patients, we found: (i) clinical information – of patients known to be allergic to at least one nut, 21–55% tolerated another type of nut (Table 2). Peanut and Brazil nut were the least well tolerated (24% and 21%); (ii) SPT – only 3% had a strongly positive SPT (≥ 8 mm; Fig. 4). For individual nuts: peanut 4%, Brazil 7%, almond 3%, hazelnut 2%, walnut 1% had SPT ≥ 8 mm. For Brazil nut, 3% of tolerant patients had SPT ≥ 9 mm; only 54% had a negative SPT (0–3 mm); 43% had

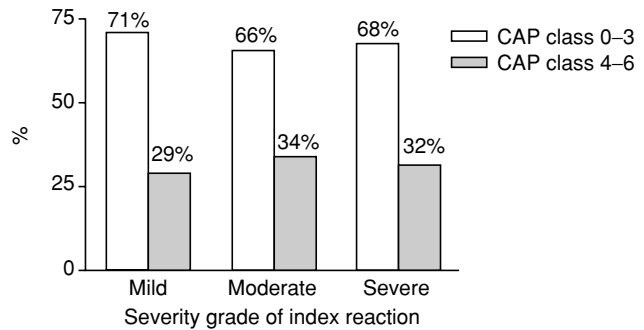


Fig. 2. Distribution of CAP result grouped into low (class 0–3) or high (class 4–6) in most severe (index) reactions of different clinical severity for all five nuts (mild = grade 1–3, moderate = grade 4, severe = grade 5; see Table 1).

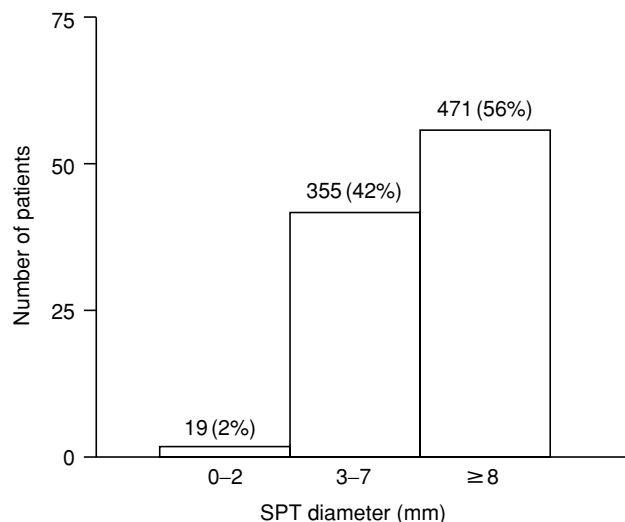


Fig. 3. Distribution of skin prick test (SPT) result for nuts which caused the most severe (index) reaction in allergic individuals.

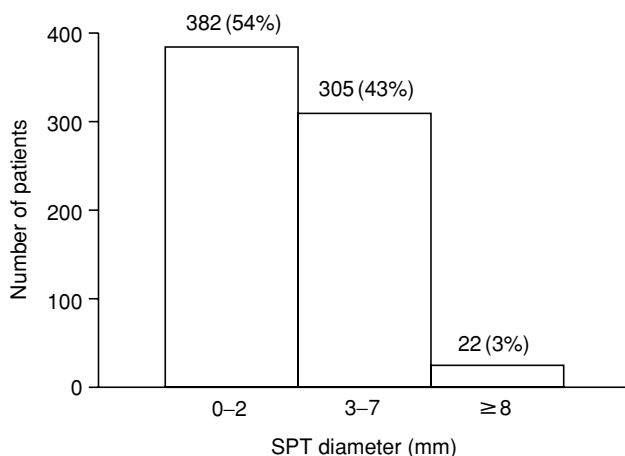


Fig. 4. Distribution of skin prick test (SPT) diameter for tolerated nuts in patients with allergy to other nuts.

positive SPT in the range 3–7 mm and (iii) CAP results in the same group showed that only 5% had CAP ≥ 15 kU/L, 60% had a negative CAP (class 0) and 35% had a positive in the range (0.35–14.99 kU/L or class 1 to upper-end class 3).

Table 3. Clinical severity distribution percentage (*n*) in each group (10)

Severity grade	Peanut	Brazil nut	Hazelnut
1–3	61% (361)	32% (51)	43% (27)
4	24% (200)	60% (97)	51% (32)
5	5% (32)	8% (14)	6% (4)

Table 4. Comparison between SPT diameter and CAP result of nut-allergic subjects for all nuts, regardless of clinical information

	CAP	
	≥ 0.35 kU/L	< 0.35 kU/L
SPT ≥ 3 mm	39	24
< 3 mm	12	25

Table 5. Comparison between SPT and CAP result for nut, where it caused the most severe (index) reaction (a, *n* = 180; b, *n* = 12)

	CAP	
	≥ 0.35 kU/L	< 0.35 kU/L
a) All nuts		
SPT ≥ 3 mm	77	19
< 3 mm	4	0
b) Walnuts		
SPT ≥ 3 mm	25	0
< 3 mm	75	0

What is the meaning of SPT in the range 3–7 mm?

Of 660 patients with SPT 3–7 mm, 355 (54%) were allergic and 305 (46%) tolerant to that nut.

What is the correlation between SPT and CAP?

Taking a cut-off of ≥ 3 mm for SPT and ≥ 0.35 kU/L for CAP and testing for all nuts independent of clinical information there was concordance between SPT and CAP of 64% (Table 4). A positive SPT and negative CAP largely accounted for discordance. The same pattern was found when results for individual nuts (peanut, Brazil nut, almond and hazelnut) were examined.

When only data relating to nuts which caused the most severe reaction in each individual (i.e. excluding milder reactions to other nuts) were analysed, concordance improved to 77%, the majority of discordance being due to false negative CAP (Table 5a). The data were similar when results for individual nuts were analysed, except for walnut (Table 5b).

This clinical information was very robust, usually being available in great detail as this was the presenting problem.

Discussion

SPT and CAP should be used in practice to confirm clinical allergy in patients with a history suggestive of a type I

hypersensitivity reaction. In isolation they only show the presence of specific IgE (sensitization), but commonly this is not appreciated. A positive test without a good history or no history can lead to misdiagnosis. The aim of this study is to provide information to allow better interpretation of tests for nut specific IgE. The gold standard to confirm food allergy would be double-blind, placebo-controlled food challenges (DBPCFC); this would only be possible in a study of a small number of patients. Studies where the diagnosis is not confirmed by DBPCFC may be biased by including some non-allergic patients. We have taken a different approach, which is to use a very large sample size and only include patients with a clearcut history after definite nut ingestion, assessed by experienced allergists. The latter reduces the likelihood of inclusion of non-nut-allergic patients, and the former reduces the impact of this. It was not our intention to estimate positive or negative predictive values of SPT/CAP which would require 10 000 DBPCFCs for this study (i.e. several nuts per subject, each with placebo).

It may be argued that, in some patients, allergy may have resolved. This is mitigated by the fact that 72% of our sample were children with a short interval (usually a few months) from last reaction to time of study.

There may be interoperator variation but this should be small, as the majority of SPTs were performed by one specialist allergy nurse and two experienced allergists using a standardized technique and identical skin test solutions and lancets.

Clinical data are required to interpret test results

Our data show that in a large population with defined peanut and nut allergy, 46% of patients were sensitized to other nuts but could tolerate these. This new and important finding emphasizes that these tests cannot be interpreted in isolation and that a detailed clinical history is essential. Up to 55% of patients allergic to one nut were able to tolerate another type of nut.

CAPs are usually the only investigation available to non-allergists; however, our data show that, for nut allergy, 22% of negative CAPs are falsely reassuring and 40% of positive CAPs are misleading. It is important to understand this in order to interpret these tests correctly.

SPT and CAP as predictors of clinical severity

Allergic reactions to nuts cover a wide spectrum from mild to severe, and assessment is complicated by the amount ingested [11]. The severity of previous reactions taken in the context of the amount ingested and the presence and severity of asthma are variables commonly used to estimate sensitivity and to plan treatment for emergency reactions [11]. However, it is known that nut allergy may resolve [14] or occasionally become more severe [15, 16] so a reliable laboratory marker of severity is desirable. High milk-specific CAP levels are associated with more severe and persistent cow's milk allergy [17]. We found that neither SPT size nor CAP value can predict the severity of clinical reactivity to nuts even when the amount eaten is taken into account. The same median SPT size was found in patients with a few perioral wheals as in those with life-threatening anaphylaxis. However, we have shown for the first time that, in Brazil nut allergy, patients with the most severe reactions had larger SPT wheals, and a larger proportion of Brazil

nut-allergic patients had severe reactions compared to peanuts (Table 3). These findings raise the possibility that Brazil nut allergy may be more severe. Brazil nut was the second commonest cause of nut allergy (Table 2) confirming findings of our earlier series in the UK [10].

SPT size/CAP value for allergy diagnosis

Is there a test value which confirms clinical allergy? We have identified a SPT cut-off level of ≥ 8 mm for confirmation of peanut allergy. This confirms the study of Sporik [12], but in a much larger sample and in a clinic setting as faced by practising physicians, without recourse to challenge tests. We extend this to provide the first diagnostic levels for Brazil, almond, hazelnut and walnut. We found that only 3% of subjects tolerating any nut had SPT diameter ≥ 8 mm (≥ 9 mm for Brazil nut). Sampson [13] proposed children with CAP ≥ 15 kU/L to peanut had a positive predictive value (ppv) of 95% for a positive challenge. The ppv depends on the prevalence of the condition in the population [18] and so it may not be appropriate to extend this observation more generally to patients seen in a typical allergy clinic. However, our results confirm this is a useful cut-off in such a setting and extend it to include tree nuts, as only 5% of adults and children who tolerated any nut had CAP values > 15 kU/L. CAP results above this value therefore indicate an individual is likely to react if exposed.

What is the 'grey area' where patients may be either allergic or tolerant? Results from many tolerant ($n = 305$) and allergic ($n = 355$) individuals lie in a 'grey area' beneath these values, but still positive, where one could not be certain of their significance (SPT 3–7 mm or CAP 0.35–14.99 kU/L; Figs 3 and 4). It is important to recognize that this is an area of overlap between allergy and tolerance. In a recent paper, Hill et al. lowered their threshold for the '100% diagnostic SPT level' for peanut allergy from ≥ 8 mm [12] to > 4 mm [19], i.e. within our 'grey area' without showing the reasoning for this. Our data, showing that 32% of subjects tolerating a nut had SPT ≥ 4 mm, disagree with this cut-off.

Acknowledgement

Dr Clark was supported by a grant from the Food Standards Agency, UK.

References

- 1 Tariq SM, Stevens M, Matthews S, Ridout S, Twisleton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *Br Med J* 1996; 313:514–7.
- 2 Grundy J, Bateman B, Gant C, Matthews SM, Dean T, Arshad H. Rising prevalence of allergy to peanut in children: Data from sequential cohorts. *J Allergy Clin Immunol* 2002; 110:784–9.
- 3 Chiu L, Sampson HA, Sicherer SH. Estimation of the sensitisation rate to peanut by prick skin test in the general population. *J Allergy Clin Immunol* 2001; 107:S192.
- 4 Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *Quart J Med* 1996; 89:859–64.
- 5 Yunginger JW, Sweeney KG, Sturner WQ et al. Fatal food-induced anaphylaxis. *JAMA* 1988; 260:1450–2.
- 6 Haatela T, Bjorksten F, Heiskala M, Suoniemi I. Skin prick test reactivity to common allergens in Finnish adolescents. *Allergy* 1980; 35:425.
- 7 Menardo JL, Bousquet J, Rodiere M, Astruc J, Michel FB. Skin test reactivity in infancy. *J Allergy Clin Immunol* 1985; 75:646.
- 8 Skassa-Brociek W, Manderscheid JC, Michel FB, Bousquet J. Skin test reactivity to histamine from infancy to old age. *J Allergy Clin Immunol* 1987; 80:711.
- 9 Freidhoff LR, Meyers DA, Marsh DG. A genetic-epidemiologic study of human immune responsiveness to allergens in an industrial population. *J Allergy Clin Immunol* 1984; 73:490.
- 10 Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients. new features and associations. *Br Med J* 1996; 312:1074–8.
- 11 Ewan P, Clark A. Long-term prospective observational study of the outcome of a management plan in patients with peanut and nut allergy referred to a regional allergy centre. *Lancet* 2001; 357:111–5.
- 12 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.
- 13 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.
- 14 Hourihane JOB, Warner JO, Roberts SA. Resolution of peanut allergy: a case-control study. *Br Med J* 1998; 316:1271.
- 15 Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83:900–4.
- 16 Sicherer SH, Burks WA, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998; 102:e6.
- 17 Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cow's milk allergy in children: immunological outcome over 2 years. *Clin Exp Allergy* 1993; 23:124–31.
- 18 Roberts G, Lack G. Food allergy: getting more out of your skin prick tests. *Clin Exp Allergy* 2000; 30:1495.
- 19 Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for food allergen challenges in young children: comparison of *in vitro* with *in vivo* tests. *Clin Exp Allergy* 2001; 31:1031–5.