

REVIEW

How a non-allergist survives an allergy clinic

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This article is the result of six years of sudden, traumatic immersion therapy in the world of food allergy, following an innocent remark in 1996 from my then clinical director at Queen Mary's Children's Hospital, St Helier (Wrythe Lane, Surrey SM5 1AA), saying: "We really do not have much allergy service for children in this hospital. Why don't you start an allergy clinic?", and me, as a naïve relatively new consultant, agreeing. This has been added to by also doing the Paediatric Allergy Clinic at the Royal Brompton Hospital, with Professor Stephen Durham.

Initially we started with 48 bottles but ended up actually using only 30 (see Appendix). For phlebotomy for RAST testing, I would recommend using EMLA local anaesthetic cream only, as the incidence of urticaria with Ametop, especially in the presence of skin atopy, is unacceptable.

The clinic was arranged so that 5–6 new patients came at the beginning, starting at 1 00 pm, of whom half on average would require blood investigations or skin testing; EMLA cream would be applied, and they would be sent away for one hour. Follow ups would be seen in the interim, the new patients would then return, be bled, then counselled, and the whole cycle would then repeat itself.

The term food allergy implies an immune, usually IgE mediated, rapid response, usually within two hours.³ In theory, a response can be delayed for up to 24 hours, although this occurs in only a very small minority of cases and is a manifestation of type IV delayed hypersensitivity. These responses need to be distinguished from food intolerance, which is not immune mediated and usually caused by a direct caustic or toxic effect; for example, the perioral erythema in toddlers caused by tomatoes, citrus fruits, or spicy snacks is classical. Partial or complete lactase deficiency following, for example, rotavirus gastroenteritis, will cause only gastrointestinal symptoms. Gastrointestinal symptoms alone are an unusual manifestation of food allergy. Food aversion, a universal feature of all young children, must be distinguished from food allergy and is never confirmed on food challenge—generally because they refuse it! Hyperactivity (the child usually sitting entirely calmly in the chair) is often ascribed to sugars, E numbers, etc, which may or may not be true, but is definitely not food allergy.

There are very few formally trained paediatric allergists in the UK. Therefore allergy, and particularly food allergy, will find its way into all paediatric disciplines and especially in the orbit of the general paediatricians. Once it becomes known that one is prepared to see children with food allergy, then I can assure you, you will be deluged. A monthly clinic rapidly turned into a fortnightly clinic with a 45 week waiting list despite seeing 12 new and 10 follow up patients per clinic. This deluge of patients is borne out by survey data¹ showing that in adults (in High Wycombe!) 18–20% *believed* they were food allergic, despite only 1.4% actually being shown to be so on blinded food challenges. This belief among adults² inevitably permeates its way to their children. There is therefore the danger that one can be caught up in this maelstrom of belief that allergy underlies all known symptoms, and a healthy degree of scepticism is required to survive such a clinic.

HOW MIGHT SUCH A CLINIC BE ARRANGED?

The DGH allergy clinic consisted of myself (there was essentially no registrar) and a paediatric dietician. Don't contemplate such a clinic without one. They are invaluable, especially in infant diets ensuring adequate protein, vitamin, and mineral intakes; weaning strategies in the face of food allergies; hidden ingredients in foods, such as whey milk in sausages and egg-glaze on pastry; concepts of E numbers; knowledge of cross reactivities between agents such as latex and bananas, kiwi, papaya (see below); and greater contact with the food industry over changes in well known product recipes. The history, as in all things paediatric, is everything, but should specific skin tests be required, then following training, myself, the dietician, and the clinic nurse would all be able to perform them. We had skin testing bottles from ALK, together with the lancets, cotton wools, and swabs.

THE CONSULTATION

We used a home-made proforma history sheet which had a skin testing chart on the back. The proforma concentrates of course on the presenting complaint and its history, especially what was going on in the minutes or hours before the event occurred and how certain or vague these antecedents are. If the child was at a party or restaurant, one is always on vague territory and investigations under these circumstances become more likely, especially if the event was not witnessed by the parents. The time interval between the antecedents and the event is important; the longer it is, the less likely they are to be related. It is said that isolated gastrointestinal symptoms in the absence of anything else are most unlikely to be due to an immediate hypersensitivity reaction. The dosage of the alleged food is important; a minute dosage

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nearly touched or brought towards the lips, producing a florid reaction, is clearly more worrisome than a large dose, producing a vague reaction some hours later. Coexisting symptoms such as asthma are very important (see below in relation to provision of an EpiPen). Current or past symptoms of hay fever, and animal contacts leading to symptoms or eczema are helpful. Maternal food cravings during pregnancy, infant feeding methods, use of nipple creams, timing of weaning, and foods used in weaning, are potentially relevant. A family history of similar issues should be sought: if positive, it increases the likelihood of the patient also being food allergic.

It is worth going through specific check lists of foods a child does tolerate. The vast majority of food allergies in children are in the order of likelihood: milk, eggs, peanuts and tree nuts, fish, shellfish, and tree fruits; it is therefore worth specifically making sure that all the other categories apart from the one in the history are in fact tolerated. I always ask if the child snores, as the answer is yes and loudly in about 10%. It is the common situation that apart from this acute event the children are otherwise completely well. Clinical examination is often completely unrewarding apart from examination of the skin for eczema, a linear crease across the nose for perennial rhinitis, and a respiratory examination plus spirometry for those with any pre-existing asthma type symptoms.

"I came for my child to have allergy testing, not to have a history taken"

This above statement has been said to me with a distressing amount of frequency in clinic. Parents arrive with the conviction that their child has food allergy and all that is required is blood or skin tests. Bearing in mind that the nearest to a gold standard for the diagnosis of food allergy is a formal food challenge (see below), it is important to review the reliability of skin testing and blood measurements of food specific IgEs (RASTs).

Table 1 is taken from Sampson and Ho's data on 494, double blind, placebo controlled food challenges on 196 children compared with their respective skin test results.⁴ The positive predictive values of skin testing were moderately good but their negative predictive values were better. This study was carried out on a highly selected population. If these results were applied to a community setting with a 10% prevalence rate (some six times higher than the known UK prevalence rate) the value of skin testing in predicting symptoms on food challenge was very poor; however, no reaction to a skin test highly predicted a symptom free food challenge. Thus the principal use of skin testing is to disprove food allergy and *not* to show it.

This pattern is similar for blood, food specific RAST tests, and in Sampson and Albergo's study⁵ from 1984 in 40 children with eczema, a negative RAST highly predicted a symptom free food challenge but a positive RAST was a poor

predictor of a positive food challenge, even in these atopic eczematous children (see table 2).

So which to use, if any? Skin test are quick and comparatively cheap. They are not easy to perform in the under 6s but it certainly can be done. Attention to detail is very important (see table 3). Comparatively few bottles are needed for the great majority of patients, but a huge number are required for everyone, and the life span is a year. Very rarely, and not to my knowledge recorded in children, SPTs for peanuts have led to anaphylaxis requiring adrenaline. RASTs are expensive (€30 per allergen) and take at least a week, and often four weeks before results are available.

"Are food challenges infallible?"

The double blind, placebo controlled, food challenge is the current gold standard investigation for food allergy. In reality, double blind food challenges are very difficult and laborious to carry out except in a research setting, and most food challenges in the clinical setting are unblinded. Recently however, it was reported⁶ that 5/195 children symptom free on a double blind challenge had symptoms the following day on open feeding. Whether this is a quantitative effect or a repriming of the immune system is unclear.⁷ Table 4 gives some practical details.

"I think my baby is allergic to milk and the health visitor/GP/friend/magazine suggested I try soya milk"

The title scenario is extremely common and milk allergy is by far the commonest childhood food allergy, with a recently defined incidence in a Danish longitudinal study of 2.2% by age 1 year,⁸ though up to 15% has been claimed. The formal diagnostic criteria of milk allergy are: (a) the *definite* disappearance of symptoms after each *two* eliminations of cows' milk or cows' milk products; (b) the recurrence of *identical symptoms* after one challenge (double blind in older cases); and (c) exclusion of lactose intolerance and coincidental infection, especially likely with a mono-symptomatic gastrointestinal symptom. If an infant is shown to be allergic to cows' milk, it is very important that other animal milks (goats, sheep, buffalo, etc) are not used as a substitute and that soya milk is not used either. Cross reactivity between the milk proteins of cows, sheep, and goats is common. It was until recently received wisdom that 17–50% of cows' milk allergic infants were also allergic to soya; however, a recent prospective study⁹ quantifying this shows the risk to be substantial but not 50%. Klemola *et al* followed 170 infants with proven cows' milk allergy randomised to receive either soya or extensively hydrolysed formula. If either substitute formula was suspected of causing a reaction, a double blind, placebo controlled food challenge was performed; in addition, soya antibodies were measured in all infants at age 1 and 2 years. Ten per cent had a confirmed reaction to soya compared with 2% to extensively hydrolysed formula. The

Table 1 Comparison of 494 double blind, placebo controlled, food challenges with skin testing (positive = >3 mm) on 196 children

	Egg	Milk	Peanut	Soya	Wheat	Fish
Numbers +/-	90/34	53/53	20/21	29/78	19/65	11/7
Predictive value from study population						
PPV	85	66	55	35	35	77
NPV	90	93	75	84	94	80
Predictive value based on hypothetical population with 10% food allergy prevalence						
PPV	17	2	15	12	15	30
NPV	99	100	99	97	98	99

PPV, positive predictive value of >3 mm skin test correctly predicting symptoms on food challenge; NPV, negative predictive value of a skin test <3 mm correctly predicting no symptoms on blind food challenge. Adapted from Sampson and Ho.⁴

Table 2 Comparison of the predictive values of a positive or negative blood, food specific RAST to a blinded food challenge in 40 children with eczema

	Egg	Milk	Peanut	Soya	Wheat	Fish
PPV	57	27	44	20	18	33
NPV	82	93	100	95	94	94

Adapted from Sampson and Albergo.⁵

reaction rate to soya was 25% if the infant was less than 6 months old and 5% if the child was over 6 months old. However, 5% is still twice the extensively hydrolysed milk rate, and I still strongly recommend using extensively hydrolysed formula despite the foul taste (Neocate, Nutramigen, and Pregestemil are examples). Most importantly, from the Avon longitudinal study, soya milk usage raises the risk of subsequent peanut allergy by a factor of 2.6 (1.3 to 5.2).¹⁰

"My child has egg allergy which makes cooking for them extremely difficult"

Not having any eggs in the diet of a toddler is just as problematic as avoiding milk. Loprofin egg replacer, a starch based product, is an acceptable alternative in baking cakes, though add extra moisture when using Loprofin (chef's tip!).

"Can my child with egg allergy have the MMR or influenza vaccine?"

A definite yes to the MMR. Sampson's group studied 54 children¹¹ known to be allergic to eggs, some very severely. All received the MMR vaccine (the measles component is grown on chick embryo fibroblasts), even the 3/17 who had a positive reaction to MMR on skin testing. None had an immediate or delayed reaction. MMR vaccine and allergy in general has been recently reviewed.¹² Children with egg allergy should *not* have influenza vaccinations.

"My child had this speck of peanut butter for the very first time and he got this florid skin rash"

The fear of peanut and tree nut allergy is the most pervasive in the food allergy clinic. It is worth noting from the risk of death section below that deaths under age 13 years from peanut allergy are virtually unknown. It needs to be remembered that: (a) peanuts are from the bean family; (b) their common, but not universal cross reactivity with tree nuts, remains a mechanistic mystery; and (c) the incidence does appear to be increasing, perhaps due to the great availability of nuts and its use in spreads and processed foods, and it is partly inherited especially maternally.¹³ Peanuts have many other euphemistic names (table 5) and were used in a number of topical medical preparations, particularly nipple cream (for example Kamillosan), before 1995. An Isle of Wight prospective cohort study¹⁴ showed that by age 4 years, the clinical incidence is 6/1536 for peanuts and 2/1536 for tree nuts. Sex incidence appears equal and the median age at first reaction is 11 months. It is recommended

that nut allergy sufferers avoid vegetable oils and groundnut oil, but the risk of such refined oils is very low.¹⁵

"Will their next reaction be worse?"

In the UK, 567 children and adults, following an initial reaction were given verbal and written advice about management of their condition.¹⁶ Following this, 3/567 individuals, all adults >26 years, had a severe second reaction compared with 12% who had had a severe reaction on their initial presentation. No child during the follow up period had a severe reaction. However, in the USA, 83% followed for a median of six years had on average one accidental reaction per three years, of which 37% were defined as potentially life threatening.¹⁷ Intuitively by repeated exposure, this may prime the immune system and increase the ferocity of the immunological response, but this does not appear to occur in practice.

"Can they die?"

A very careful study of paediatric food allergy related deaths was published in this journal recently.¹⁸ This reviewed retrospectively, the five deaths that occurred between 1990 and 1998, and prospectively, those that occurred between 1998 and 2000. The exhaustive methodology ensured that all deaths were ascertained. Of the eight deaths between 1990 and 2000, four were due to milk, two peanut, one egg, and one mixed; there was no peanut death in any child under 13 years old. The problem of milk allergic death being the most common is that milk allergy tends to be most prominent in children under 1 year of age. However, to put this in context, the UK <16 years population is 13 million and the death rate from food allergy from the data cited above is 0.006 per 100 000 per year (95% confidence interval 0.002 to 0.01). From the Department of Transport website, the risk of being a <16 year old pedestrian death is 1.7 per 100 000 per year; that is, children are 283 times more likely to die as a pedestrian than from food allergies.

What was certainly noticed is that the risk of the more severe food allergy reactions were greater in those who had concurrent asthma independent of their food allergy.¹⁸ This is important when treatment options are considered.

"Will they grow out of it?"

The answer is: for milk and eggs, almost certainly; and for peanuts, possibly. It is estimated that 92% of children are tolerant of milk and dairy products by the age of 5,⁸ and eggs by the age of 8, in those who were previously allergic. The mechanism by which this may occur is not known for certain,

Table 3 Practice points for skin prick testing

- The child must have had no antihistamines for 24 hours (oral steroids have little effect on SPTs)
- Do not perform in the presence of severe eczema—it is cruel and could lead to severe responses
- Always include a negative and a positive (histamine) control
- Use sterile lancets on the inner (palmar) forearm or back (very unusual), drawn through the allergen liquid so as *not* to draw blood
- One lancet and one cotton wool ball per allergen
- Number them and record the allergen on paper as you go along as you will have forgotten the order by the end
- Always have an adrenaline EpiPen available
- Dermographism is demonstrable from the negative control producing a response
- Positivity is defined as 2 mm greater than negative control or equal or greater than positive control, but these are arbitrary

Table 4 Practical details for food challenges

(a)	Always conducted in hospital as a day case with easy access to resuscitation equipment and adrenaline—the one time you don't have it available ...
(b)	No antihistamines for previous 24 hours
(c)	Can only test one allergen per day
(d)	An intravenous cannula <i>must</i> be inserted before starting
(e)	Usually 30 minute stages: food on skin, left for 1 minute, then wiped off, then touch corner of lip, then eat 0.5 gram (1 ml), then 5 grams (5 ml), then 15 grams (15 ml), then 50 grams (50 ml), all 30 minutes apart. After last stage wait 60 minutes, then home if no adverse response. Total time about 5 hours
(f)	Isolated nausea is rarely an allergy; more usually dislike of food + stress
(g)	If needing to challenge the following day with different food, then Heplok cannula and send them home with it in overnight (no baths/showers), to return in the morning

but may relate to their maturing guts becoming less permeable to absorption of intact proteins. Figure 1 shows a linear epitope, namely a string of amino acids next to each other, producing an antibody response, compared with a conformational epitope—that is, amino acids from neighbouring loops of a protein, which taken together generate an antibody response. This second can only be produced when the protein is intact. One can therefore see why there can be grades of milk and egg allergy; for example, many children can tolerate eggs in cake but not as raw egg in chocolate mousse. This is because the egg has been heated to a higher temperature, and the egg protein partly denatured. Similarly some children tolerate UHT but not pasteurised milk.

How to reintroduce the foods depends on the severity of the previous reactions. If after 6–9 months of a milk diet all is well and the previous reactions had only been skin manifestations, then I reintroduce milk at home by suggesting that per 250 ml of extensively hydrolysed formula, one substitutes 25 ml with cows' milk (formula or doorstep, depending on age), increasing by 25 ml every two days, so that after a fortnight one is on complete cows' milk. There are two benefits: first, so that the cows' milk is not rejected on the grounds of taste and it is confused by the family as allergy; and second, the risk of a severe response is very small. If the child has had prior systemic reactions to milk, such as wheezing, stridor, or hypotension, a formal milk challenge in hospital is required. For eggs, again for those with milder reactions, on follow up it is often found that the child has inadvertently eaten cake and tolerated it; one can then consider the gradual introduction of a small amount of hard boiled then soft boiled eggs, etc. For those with prior systemic reactions a hospital based challenge is required.

Peanut allergy, hitherto regarded as a life long condition is not so; Hourahane and colleagues showed that 18% (22/230) of children became tolerant of peanuts some 3–5 years after their initial reaction, especially if the first reaction occurred at <2 years of age and the skin test at around age 8 years was <6 mm.¹⁹ At about 8 or 9 years of age or 3–5 years after the previous reaction when children are becoming a bit more independent, I skin test them, and if <6 mm I arrange a hospital based formal food challenge. A recent study on the use of a non-aggregating IgE antibody shows considerable promise in minimising responses to accidental ingestions.²⁰

Table 5 Euphemisms for peanuts

Groundnuts
Monkey nuts
Arachis oil
Marzipan
Goober
Goober pea

“My 14 year old, when she eats peaches, develops a tingling and itchiness in her mouth”

This is the oral allergy syndrome and appears “never” to involve a systemic reaction. It involves tree fruits, namely peaches, apricots, cherries, plums, apples, pears, etc. The symptoms are comparatively mild and rarely occur before age 12 years. Some patients are so keen to eat fruit that they pre-treat themselves with antihistamines beforehand. As with milk and egg, denaturing the protein will reduce the symptoms. So, for example, long life apple juice, cooked apple puree, or even microwaving an apple may reduce the symptoms. It is worth remembering that the reaction to kiwi fruit is now probably the most important and potentially dangerous of reactions to fruit.

“Sometimes when my child has had a meal and runs about afterwards, they develop a rash and wheezing”

This is a manifestation of exercise induced allergy. The mechanism is unknown. It also tends to occur in adolescents rather than children, with a female to male preponderance. There are often other atopic features in the history, such as hay fever and eczema, and the symptoms must occur within four hours of eating for such a diagnosis to be considered.

“Will my child react to other things that we won't know about in the future?”

The risk that having one food allergy increases the risk of others in this instance relates to the presumed genetic closeness of related foods. Apart from peanuts and tree nuts, there are three other characteristic groups:

- Latex/banana/kiwi/coconut/avocado/papaya
- Birch pollen/apple/hazelnut/celery/pear/carrot
- Mugwort/hazelnut/celery.

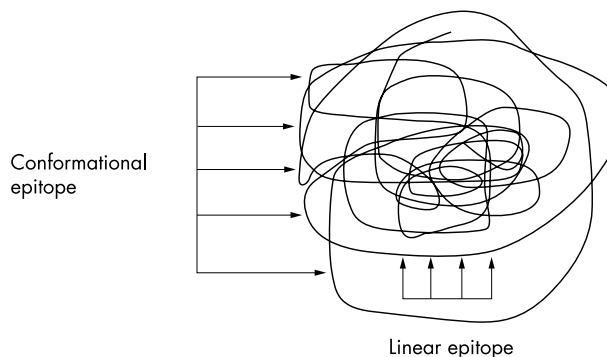


Figure 1 A schematic difference between a conformational and a linear epitope. Antibodies to a conformational epitope will not cause allergy if the protein is denatured, while those to a linear epitope will.

Reaction to one does not automatically mean reaction to all in a group, but the history should be sought, remembering that not all balloons have latex in them. I have never seen a mugwort/celery/hazelnut cross reaction in children. How carrots and celery are related to apples and hazelnuts defies my sense of reasoning, but then again the dolphin's closest relative is the cow.

"Will my child need an adrenaline injection device, for example, EpiPen or AnaPen?"

This is undoubtedly the most tortuous aspect of the consultation. There is no consensus on this matter, therefore one has to tread an uneasy path between laissez-faire and paranoia. What is undoubtedly unacceptable is the provision of an adrenaline device to someone and for them to turn up in an allergy clinic never having been taught how, and under what circumstances, to use it. Broadly, adrenaline injection devices should be provided for those who have what might be termed an "inside the body reaction", mainly choking, wheezing, and fainting. I personally do not include vomiting in this scenario. I do include an itchy throat, except as part of the oral allergy syndrome. The giving of written as well as verbal instructions to the parents and the school is valuable. I err on the side on giving a device in those who have pre-existing asthma or wheezing and in those in which the initial reaction dosage was exceedingly small. In the USA they would contend that *all* children who have had *any* reaction to peanuts should have an adrenaline injection device prescribed,²¹ though this is not currently my practice. I estimate that approximately one third of my new patients walk out with adrenaline injection devices. Nowadays, nearly all schools now have at least one child with a device in their school and have been taught their use; state schools have a nut free policy for their catering—which is not guaranteed. However, the school nurses and teachers must be trained if your child happens to be the first in the school with an injection device. This is where the community paediatric nurses and paediatricians are very helpful. For preschool children I normally prescribe one for home, one for carrying around, and one if they regularly stay with grandparents, where in my experience most unexpected reactions occur. For school children, I prescribe one for school, one for home, and one spare. I emphasise that it must be carried on their person at all times, as it is the unexpected reaction that tends to cause the problem. These scenarios can loosely be lumped as parties, restaurants, and holidays and it is at these times when control over the diet is at its weakest. Whether all adrenaline devices should be in duplicate, in case of technical failure is contentious, but I do not make this a routine practice. For children >8 years of age an adrenaline inhaler such as Primatene Misthaler, 10 puffs sublingually or into the cheek (*not* inhaled), is useful, as anecdotal evidence suggests that prompt use of the adrenaline inhaler in children virtually eliminates the need for an EpiPen. However, I continue to always recommend having both available.

"Does food allergy cause autism?"

No.

"My child is very hyperactive. Is this due to food allergy?"

Certain foods possess stimulants to which children may be more or less sensitive; for example, chocolate, mature cheese, cola drinks, tea, coffee, etc. Double blind studies on the effects of tartrazine shows that it has either no effect,²² a very subtle effect that parents didn't recognise,²³ or a dose dependent easily recognised effect on behaviour.²⁴ Whatever effect there is or isn't, it is a non-allergic one.

SUMMARY

The nature of personal practice is that it is personal. The evidence base for allergy management is not zero but is by no means complete. The message I want to put across is that, like everything else in paediatrics, the history is everything, and currently, available investigations for allergy require careful interpretation as they can be positively misleading. Sensible advice, plus the availability of a skilled paediatric dietician, means that an allergy clinic can become almost enjoyable.

ACKNOWLEDGEMENTS

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For further reading for insomniacs, I would suggest:

Holgate ST, Church MK, Lichtenstein LM, eds. *Allergy*, 2nd edn. London: Mosby, 2001.

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Websites:

www.eaaci.net is the home page for the European Academy of Allergy and Clinical Immunology, where after clicking on resources, there is a list of their recent consensus papers on various subjects. www.anaphylaxis.org.uk is the site of the anaphylaxis campaign, with among other items, a very useful list of warnings about foods found to have been cross contaminated with nuts as an example.

There are no conflicts of interest to declare

APPENDIX

Table A1 lists suggested bottles for skin prick testing—a personal choice as there is a virtually infinite choice.

Table A1 Suggested bottles for skin prick testing

Negative control*
Positive control*
House dust mite*
Cat*
Grass*
Aspergillus fumigatus*
Milk
Boiled milk
Egg white
Egg yolk
Peanut
Brazil nut
Almond
Cashew
Walnut
Hazelnut
Chocolate
Soya
Dog
Cat (see above)
Hamster
Horse
Mice
Wool
Strawberry
Kiwi
Peach
Apple
Mixed trees
6 grass (see above)
Birch pollen
Rapeseed
Cod
Salmon
Tuna
Mussel
Prawn
Crab
Meats†

*A standard six for the diagnosis of atopy.

† I've used these very rarely.

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