

REVIEW

Peanut allergy — current status and future challenges

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The reasons why peanut allergy is such an important area of research and clinical service development are clear cut: it starts early in life, is usually severe and does not resolve [1–4]. Accidental exposure to peanut is common (in effect unavoidable) [3,4]. The incidence of peanut allergy has apparently doubled in the last 10 years [5]. It now affects $\approx 1\%$ of British pre-school children [6]. Peanut accounts for the majority of food-related anaphylactic fatalities [7,8] and for between 24% and 30% of all cases of anaphylaxis in the community (i.e. excluding intravenous drugs and anaesthetics given in hospitals) [9]. Peanut allergy is a frightening diagnosis for families to be given.

It is apparent that despite the perceived general increase in the incidence and prevalence of allergy and atopy over the last 30 years [10], the issue of peanut allergy has received very little attention in Britain until recently. There have been exciting developments in both clinical and fundamental aspects of this almost uniquely severe food allergy. This review aims to summarize aspects of clinical and scientific progress in the field in the last few years. These new findings will be placed in the context of established features of peanut allergy, addressing the subject as a whole, rather than as a digest of recent developments.

Sensitization to peanut happens early in life

Seventy-three per cent of peanut allergic subjects are from atopic families and nearly all ($>95\%$) demonstrate some other manifestations of atopy [1–3]. In America it is practically impossible not to consume peanut butter early in life. Zeiger's studies following a control group (normal diets) and a study group (parents having been advised to avoid, among other foods, nuts and peanuts) of American children at high risk of atopy show that all the control group and 80% of the study group had eaten peanuts by their second birthday [11]. A similar picture is apparent in Britain, with 23 out of 24 nut allergics that presented under the age of 2, being allergic to peanuts, which accounted for all cases who were allergic to a nut by the age of 1 [1].

Peanut is a cheap and tasty food. The relative cheapness

of peanut in an easily usable form (peanut butter) makes it an attractive proposition for parents preparing snacks for themselves and their young children. Of the tree nuts only hazel is available in a spreadable form (analogous to peanut butter) and therefore they constitute only a small part of children's diets. Tree nuts themselves are more expensive and are rarely introduced to children's diets before 4 or 5 years of age due to the risks of inhalation. This later introduction, outside the 'sensitization window', and less frequent consumption may account for the relative infrequency of tree nut allergy compared with peanut allergy.

Sensitization to peanut occurs early in life. Eighty per cent of British peanut allergic subjects reacted to their first known exposure to peanuts [3]. This occult sensitization is more common in younger British peanut allergic people, see Fig. 1 [2]. In a French study of 54 newborn infants (less than 11 days) and 71 babies aged between 17 days and 4 months old, 8% of both groups had positive SPTs to peanut, implying sensitization *in utero* or soon after birth [12]. IgE does not traverse the placenta. Antigens other than peanut have been shown to be capable of causing the fetus to react with production of antigen specific IgE, detectable in cord blood [13]. We have identified a circumstantial link between the self-reported increased consumption of peanuts by pregnant and breast-feeding mothers (implying sensitization transplacentally or via breast milk) and a definite decrease in age of onset of peanut allergy over the last 10 years, see Fig. 2 [2]. Peanut proteins can be found in breast milk for several hours after the mother has eaten peanuts [14] and, anecdotally, we are aware of cases of infants reacting adversely to breast feeds after maternal consumption of peanut.

The role of peanut oils in sensitization has been raised by other groups, implicating peanut oil-based vitamin preparations [15] and infant milk formulae [16]. Topical application of creams and lotions containing peanut oils has been suggested as causing sensitization [17–19]. Commercially available peanut oils do not contain detectable amounts of peanut protein (see later) but it is possible that the levels of peanut protein that are required to sensitize an individual are below the limits of detection of current bioassays. Children with damaged skin (eczema) may be particularly sensitive to topically applied medications containing potentially

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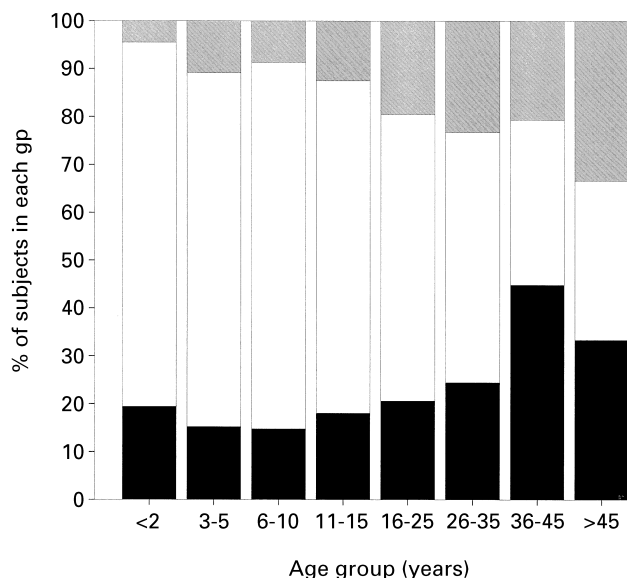


Fig. 1. Peanuts eaten safely before episode causing first allergic reaction. Peanuts eaten before ■, Don't know; □, No; ■, Yes. Kruskal–Wallis 1 way ANOVA $P < 0.0001$. * data from reference 2.

allergenic components (not just peanut oils). In the absence of data many pharmaceutical and cosmetic companies have chosen to remove peanut oil from topical preparations [20,21]. The role of different routes of exposure to peanut and its timing in the sensitizing process may be an exciting

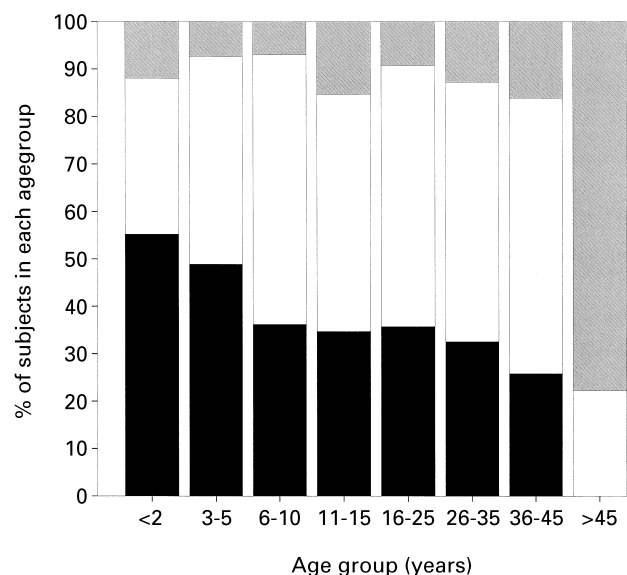


Fig. 2. Association of current age of peanut allergic subjects ($n=622$) and reported maternal consumption of peanut while pregnant or breast-feeding. Mother ate peanuts** ■, Missing/not know; □, No; ■, Yes. Kruskal–Wallis 1 way ANOVA $P = 0.001$ * data from reference 2; ** >once/week while pregnant/breast-feeding.

area for further research, with results applicable to other forms of atopy.

Such evidence as exists suggests that peanut allergic children are usually born into atopic families and that there are no significant nutritional consequences to the mother of avoiding peanuts while pregnant or breast-feeding. We have developed a policy of practical advice that it may be prudent for pregnant women who are atopic, have an atopic partner or have atopic children to avoid peanuts during pregnancy and lactation. This obviously includes a lot of women, and considering 27% of peanut allergics do not have an atopic parent [2], it may be that all mothers, atopic and non-atopic alike, should avoid peanuts. For women with adequately varied diets avoiding peanuts while pregnant or breast-feeding is unlikely to compromise their nutrition, whereas, in the long-term, the adverse consequences of maternal peanut consumption may be considerable for the child.

Clinical features of peanut allergy

The clinical reaction to peanut is very stereotyped, and is identical in nature, if not severity to reactions to other foods. By and large, if the cluster of typical symptoms is absent [22], the diagnosis of peanut allergy is unlikely.

Provoking dose

Symptoms can occur on minimal contact with peanut, even through intact skin [3]. The risks to children with abnormal integuments such as children with eczema are probably higher. The minimum oral dose that has provoked reactions in double-blind placebo-controlled food challenges (DBPCFC) with other foods is between 100 and 500 mg of protein [23–25]. We have DBPCFC evidence (submitted) that peanut allergics react objectively to oral doses of peanut protein (2–5 mg) that are at least an order of magnitude lower than those reported previously. There have been a few case reports (not supported by appropriate challenge studies) of allergic reactions to the smell of peanut [26,27], but it is probably more likely that many reactions to the smell of peanut are a psychological aversion and a method of self-defence against true allergic contact than allergic reactions actually mediated by small volatile proteins. That is not to say that extremely sensitive patients would not react to the smell of peanuts and this problem needs to be taken seriously especially in enclosed spaces and those such as aeroplanes that recycle air supply. Jones *et al.* found low amounts of peanut protein in air filters of aeroplanes after a 6 month period of flying [28].

Accidental exposure

After the first reaction to a deliberate dose by an unknowing

parent, reactions are usually to accidental exposures. These are remarkably frequent. Half of a large group of British patients reported a reaction in the previous year [3]; this is similar to American experience [4]. Most fatal reactions take place in a situation in which the affected subject or his parent has no control over the preparation of the offending meal, i.e. in restaurants [7,8]. Most fatally affected individuals have eaten and reacted to the implicated food before and are trying to avoid it. There may be a dose–effect or they may have delayed the administration, or may not have had available, appropriate rescue medication, such as epinephrine [7].

Severity of peanut allergy and assessment of clinical risk

An almost unique feature of peanut allergy is the high frequency of severe reactions, even on first exposure. Forty per cent of first reactions involve wheeze, which we consider to be a severe symptom [3]. Peanut accounts for half of all food-related episodes of anaphylaxis and for most food-related anaphylactic deaths [7–9]. The severe nature of peanut allergy is also shown by the fact that double-blind challenge to prove peanut allergy is usually either unnecessary due to the classic nature of the reaction or is precluded by the severe nature of the reaction. In American centres which have traditionally used formal challenges to confirm the diagnosis of food allergy nearly half of peanut allergic patients were not challenged due to the severe nature of the reported reaction. This exclusion of half the patients [18 out of 34] contrasts with five out of 90 egg allergic patients and three out of 32 milk allergic patients [29].

It is clear that the majority of peanut allergics do not suffer successively worsening reactions with each exposure. A minority, however, may suffer a severe, or fatal, reaction, having previously been affected only mildly. There is no method of identifying people at such risk. The best indicator of risk of a severe reaction is a history of a similar reaction on a previous exposure [7]. Therefore, at least 40% of sufferers are at such a risk, even after just one exposure [3].

A history of current asthma was shown in a case–series to be associated with a fatal outcome after exposure to allergenic foods [7]. In British peanut allergic subjects, there is a significant association between a history of current asthma and increasing severity of the reported reaction to peanut, see Table 1 [3]. More than 60% of subjects report current asthma [2] and it therefore appears that, even in the absence of a history of a severe reaction, the majority of subjects are at risk of a severe reaction on subsequent exposure. Furthermore, a moderate reaction (such as laryngeal oedema, generalized urticaria or angioedema) to a tiny dose suggests that a larger dose may cause a worse reaction, particularly if there are coincident exacerbating factors such as alcohol

Table 1. Association of a history of asthma and severity of most recent reaction to peanut [adapted from reference 3]

Reaction*	History of asthma	No history of asthma	Total
Mild	45	47	92
Moderate	103	65	168
Severe	187	78	265
Total	335	190	525†

χ^2 (2 df) = 14.69, $P = 0.0021$. * Mild—local urticaria or oedema, rhinitis; moderate — generalized urticaria or angioedema, laryngeal oedema; severe — wheeze, collapse, hypotension. † Excluding 85 subjects with only one reaction to date and 12 missing data.

consumption or delay of self medication [7,8]. All peanut allergic people should be provided with and trained in the use of rescue therapy, unless there are consistent features that suggest the risk is low [30]. In our clinical practice (unpublished data) the numbers of such low risk subjects is less than 5% of all peanut allergic children seen.

Peanut allergy persists indefinitely

Peanut allergy is considered to be a life-long problem [4]. Considering its clinical severity and increasingly early onset, this diagnosis is extremely disappointing for affected families, in contrast to the other common allergies of childhood to (eggs and cow's milk) which often remit. SPTS can remain positive for many years after last exposure and long periods of avoidance (11 years in one case) may not lead to tolerance [4]. The basis of persistence of peanut allergy despite successful avoidance of obvious exposures is uncertain. We have unpublished data that show increased T-cell proliferative responses to crude peanut protein are not affected by the interval since last reaction to peanut. This may be due to frequent up-regulation by subclinical exposure to very low doses in foods thought not to contain peanuts or to persistence of memory T cells [31].

Exciting developments (unpublished) in epitope mapping of other food allergens suggests that resolution or persistence of food allergy may depend on the configuration (linear or conformational) of individual T cell and IgE epitopes (Sampson, HA. pers. comm.)

Clinical evaluation of peanut allergy

Individuals with histories suggestive of peanut allergy should be evaluated in centres that are equipped to undertake SPT and serum specific IgE measurements and have facilities for food challenges as simpler tests may not be definitive. A

negative SPT is highly predictive of the absence of peanut allergy, but up to 30% of positive SPTs are found in subjects who are tolerant of peanut on challenge [32]. The size of SPT weal may suggest which SPT positive subjects are tolerant [33] but it cannot be used as a substitute for peanut challenge in the confirmation or rebuttal of a history of reactivity to peanut.

Not every subject needs a food challenge. Most have clear-cut histories of recent reactions and have positive SPTs and RAST. Outside research settings challenge can be reserved for those who have unusual histories, results that contradict the history and those who may have become tolerant (suggested by uneventful exposure to peanut). Another group of children that may need challenge are those about to enter school. Mothers can control a pre-school child's diet with relative confidence and sending the child to school is even more traumatic than normal for the parents of food allergic children. Some children with a reaction early in life may have become tolerant by the age of 5 years and precautions regarding exposure to peanut and rescue strategies may be unnecessary. It is a reasonable opportunity to challenge such children before school entry because if they are still allergic they are likely to remain so. If they are no longer allergic a great burden is lifted from the family and the school. Challenge of such children is not absolutely indicated but many families are keen to see if the child remains allergic, even when SPT and RAST are positive.

Food safety

Accidental exposures to peanut have been fatal [8]. In many cases inadvertent exposure to peanut can be discovered by simple direct enquiry or detective work. In less stringently observed reactions, an obvious source of peanut protein is not determined. It has been shown on several occasions that the heating of peanuts and peanut products do not decrease the allergenicity of the product [34–37]. The safety or lack of safety of finished and processed peanut products has been addressed in two studies, assessing the issues of accidental exposure to hidden peanut antigens [35,36].

Nordlee *et al.* tested 19 different peanut products and peanut oils by RAST inhibition (prevention of binding of serum IgE from peanut allergic individuals). These products included peanut flour, peanut butter, peanut oil and peanut butter flavoured crisps. Peanut oil and hydrolysed peanut protein were shown not to contain peanut allergen and whole peanut flour was shown to contain very small amounts. The other products significantly inhibited IgE binding — suggesting high levels of allergenicity [35].

Keating *et al.* studied the industrial safety of catering equipment. This work involved sampling both food processing materials and finished peanut containing foods including M&M chocolates. They also studied virgin vegetable oil and vegetable oil that has been used to roast peanuts. They

were able to show that peanut protein was retrievable from deliberately spiked foods but not however, from the oil before use to roast peanuts [36]. Catering and food industries must be aware of the risks of tiny amounts of peanut protein. Labelling a food 'may contain nuts' is an inadequate response to the public's need for information and better quality control.

Peanut oils

Oils of other nuts and seeds are deliberately left relatively unrefined in order to enhance the flavour of foods to which they are added. These crude or so-called 'gourmet' oils include walnut, brazil, hazel, almond and sesame seed oil. It has long been known that sesame seed oil is a hazard to sesame allergic individuals [38,39]. The gourmet oils have recently been shown to contain appreciable amounts of protein, in contrast to refined peanut oil [40]. Crude peanut oil has been shown to contain enough aqueous peanut protein to bind IgE from peanut allergics. In contrast, no aqueous protein was detectable in refined peanut oil, using the same bioassay [41].

Refined peanut oil is sold in Britain as 'generic' vegetable oil, whereas crude peanut oil is only sold to the general public in the form of 'gourmet oils' which make it clearly identifiable. A voluntary code of practice has been introduced by British vegetable oil producers to ensure any crude oil they supply to food manufacturers is clearly identified. It is hoped that the food manufacturers and retailers will support and extend this code of practice to labelling foods containing crude oil which comprises less than 5% of the 6000 tons of peanut oil produced in Britain each year (J. Hancock, Anglia Oils, pers. comm.).

We have recently confirmed, using a large numbers of subjects, the findings of previous studies showing that refined peanut oil is safe for most peanut allergic subjects, including subjects who are severely affected [22]. Combining our 60 subjects with four reported by Bock and Atkins [4] and 10 by Taylor *et al.* [42] it is 97.75% likely that the chances of refined peanut oil causing a reaction are less than 5%: $(1 - (0.95)^{74} = 0.9775)$ [43]. This is a compelling statistic, especially when compared to the rate of reaction to crude oil (10% of subjects) that we found in the first reported challenge of subjects with crude oil [22]. It remains to be seen if lipid soluble or micellar proteins in oils may have a role in sensitization, but they do not appear to be implicated in subsequent allergic reactions.

Crossreactivity

Crossreactivity with legumes

Allergenic crossreactivity has been shown between inhalant and food allergens [44,45] and also between pistachio and

mangos and cashews [46,47]. Peanut (*Arachis hypogea*) is a legume, not a nut. Reactivity between the serum of peanut allergic subjects and 11 different legumes has been demonstrated *in vitro* [48] but there is little evidence of significant *in vivo* reactivity to legumes. Twenty-two of 32 DBPCFC proven peanut allergics were SPT positive to pea or soy (15 positive to pea, 17 to soy, 10 positive to both) but only one was DBPCFC positive to soy and only one other was DBPCFC positive to pea, with less severe reactions than to peanut itself [4]. Only one of 43 (2.3%) British peanut allergic children reported soy allergy and had a positive soy SPT. Four others (10%) had positive soy SPTs without clinical evidence of soy allergy [2].

The major storage proteins of legumes are globulins, subdivided into legumins and vicillins [49]. The two major peanut allergens, Ara h 1 and Ara h 2 are heat-stable vicillin proteins [50–52]. There are significant areas of homology between Ara h 1 and soy vicillins at the carboxy terminal portion of the amino acid chains, but these areas do not appear to be significantly involved in the binding of IgE [53]. Burk's group have shown that the major areas of difference between Ara h 1 and soy lie in the N-terminal portion. They have speculated that the N-terminal may be the location of significant linear IgE epitopes and that the absence of N-terminal homology accounts for the low frequency of coexistent peanut and soy allergy, despite the frequency of positive SPTs to soy, presumably mediated by carboxy terminal epitopes [54].

Crossreactivity with tree nuts or coexisting peanut and tree nut allergy?

Reactivity to tree nuts is a serious problem for peanut allergic people. It is unclear whether this is due to genuine crossreactivity or the coexistence of separate allergies in widely atopic individuals. Five of 12 brazil allergics were also allergic to peanut [55] and only 28 of 47 peanut allergics were allergic only to peanuts [1]. In our series of 60 adult peanut allergics 40 (66%) reported allergy to tree nuts but 50 (83%) had a positive SPT to one or more tree nuts [22]. The relative frequency of allergy to individual tree nuts in peanut allergics reflects the relative frequency of their consumption by the general population with almond, hazel and brazil nuts implicated far more commonly than pecan, cashew and pistachio.

Studies of T-cell reactions to peanut

CD4⁺ T cells are activated by engagement of T-cell receptors by peptide fragments presented by antigen presenting cells in a complex with HLA class II molecules. T cells are central to the control of the cellular immune response and also the regulation of IgE expression. Many

aero-allergen studies have shown associations between T-cell proliferation and levels of total IgE in blood. In the area of peanut allergy however, there have been relatively few studies of the role of T cells.

Dorion *et al.* showed interferon gamma production in a group of nine peanut allergics was significantly lower than that from two control groups (six atopics and six non-atopics). The levels of this interferon gamma production in response to stimulation with a single antigenic protein Ara h 2 correlated inversely with serum levels of anti-Ara h 2 IgE [31]. T-cell clones from the blood of peanut and nut allergic individuals demonstrated high levels of interleukin-4 and low levels of interferon gamma, consistent with a TH₂ like profile. There was also restriction of T-cell response by HLA DR and DP class II molecules [56]. In a case-control study and using T-cell clones from an individual peanut allergic subject de Jong confirmed a TH₂ phenotype [57]. In addition to these findings, Dorion and Leung showed that there is relative restriction of the T-cell receptor repertoire with the expansion of the Vβ₂ genotype in peanut allergics [58].

These studies of T-cell responses in peanut allergy point towards HLA Class II restriction of the immune response to peanut, antigen specificity and confirmation of the TH₁/TH₂ paradigm. On their own these factors do not account the unique severity of peanut allergy. Other factors such as epitope configuration may be involved.

Peanut allergy — current status and future prospects

Peanut is the most common cause of food related anaphylaxis and food related anaphylactic deaths [7–9]. Peanut allergy manifests early in life and is becoming more common. The diagnosis is usually easy on clinical history. In the hands of experienced clinicians, using tried and tested protocols in appropriately equipped facilities, formal challenge with peanut is a safe and reasonable part of the evaluation of people reporting peanut allergy.

The relative contributions of *in utero* or postnatal sensitization are uncertain. Factors that determine whether or not peanut allergy remits are unknown. The fact that, if children are still allergic by the age of 8 years, 80% will remain allergic into adulthood means peanut allergy is a very gloomy diagnosis to pass on to families. The underlying cellular mechanisms of the persistence of peanut allergy and the exaggerated response on exposure to peanuts have not been studied in depth but will surely yield exciting results in the next few years. The combination of such exciting fundamental research with further purification and cloning of major peanut allergens may lead to the development of strategies of peptide immunotherapy and desensitization.

In the medium term management of peanut allergy will continue as at present. The keys will remain early

identification of the increasing numbers of subjects, usually children, at risk and prudent dietary advice regarding food preparation at home by subjects and their parents. Increased awareness of food allergies by restaurants and caterers must continue to be a focus of concerted pressure from hospital and community medical services. All reasonable steps must be taken to eliminate or at least minimize the risk of exposure of peanut allergic subjects to peanut in day care facilities and schools. The appropriate provision of epinephrine and education of subjects and their carers in its use in the event of reactions will remain the benchmark by which the care of peanut allergic subjects will be judged for several years to come.

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