

Peanut Allergy

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KEYWORDS

- *Arachis hypogea* • Atopic disorders
- Oral induction of tolerance • Peanut

HISTORY OF PEANUT CULTIVATION

Peanut (*Arachis hypogea*) is a native South American legume that has been valued for many centuries. Peanut kernels have been found in Peruvian archaeological sites demonstrating organized agriculture 10,000 years ago.^{1,2} In contrast, the absence of peanuts from Greek and Roman remains and writings and pre-Columbian Old World records, strongly suggests that peanut was unknown to these early European civilizations. By the time the Conquistadores arrived in South America, the Incas felt that peanuts were “a luxury of the rich and curious (rather than) a food for the poor.”³ This high status of peanut in the South American diet contrasts with reports of customs on Hispaniola, Columbus's landfall in the New World. Fernandez (1535) noted “It [peanut] is a healthy food but it is not eaten by Christians unless they are unmarried males or children or slaves or common people. Its consumption among the Indians is very common.”⁴

Peanut cultivation spread with the conquest of Central and North America and was introduced to Africa as a food for slaves. Today it is a significant cash crop particularly in West Africa. Up to the nineteenth century, peanut was used in North America as a food for slaves, poor whites, and increasingly as food for animals. In our time, the largest producers of peanuts (India and China) grow peanuts largely for animal rather than human consumption. The growth of peanut as a cash crop occurred in North America on the back of 2 developments: the American Civil War and mechanization of vegetable oil production. Peanuts were grown extensively in the southern United States before the Civil War. Its use as an easily transportable high-energy food increased during the Civil War and spread to northern cities. It is difficult to say when peanut and peanut butter appeared in significant amounts in Europe. However, by the 1970s, peanut had become a common food in the United Kingdom, in both its nut and butter forms. The United States produces 8 billion kg per annum.⁵

Conflict of interest: I have helped develop a patented desktop calculator for predicting the outcome of food challenge but I have no personal financial stake in its commercialization.

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BOTANY AND BIOLOGY OF PEANUT AND PEANUT PROTEINS

Peanut is the fruit of the legume *Arachis hypogea*. It is also know as the goober nut or earth nut, and more commonly as a groundnut. The German for peanut is erdnusse (groundnut). It is called a groundnut because the seed pod initially appears on the branches of the plant and as it increases in weight the branch bends and the dependent pods become buried in the soil where they mature before harvesting. Peanut is a high protein food, 24% by weight and is therefore comparable with cheese, fish, and beef. Most of peanut's 49% fat content is unsaturated making it an attractive and stable source of oil for human consumption. Fiber levels are comparable with wholemeal bread (1.5 g/100 g).

Peanuts contain ~25% protein. The major peanut proteins to which most North American and northern European individuals develop an allergic reaction are Ara h1, Ara h 2 and Ara h3, respectively^{6,7} but in southern Europe Ara h 8 and Ara h 9 are more dominant (Table 1 for summary).⁸ The allergens in peanut have been studied intensively for more than 20 years, seeking to find a biochemical basis for the severity of peanut allergy and to explore whether protein modifications result in reduced allergenicity. Although neither aspiration has been fully satisfied much has been learned.

Efforts have been made to reduce the allergenicity of major peanut allergens, particularly Ara h 2, with in vitro studies showing significant reductions in IgE binding and in basophil histamine release.⁹ However, modification of peanut proteins may alter its botanic function and it does not address the broad diversity of allergenic proteins that exist in peanut plants, where elimination of one will probably not eliminate the allergenic potential of other proteins.

EPIDEMIOLOGY

Peanut allergy seems to develop early in life with most affected children in the United States and the United Kingdom developing symptoms before the age of 2 years.^{10,11}

Table 1 Botanic and immunologic profiles of major peanut allergens		
Protein	Molecular Weight and Botanic Function	Clinical Relevance
Ara h1	63.5 kDa, vicillin storage protein	Heat stable
Ara h 2	17.5 kDa, vicillin storage protein, trypsin inhibitor	Heat stable, more commonly associated with severe clinical reactions than other peanut proteins
Ara h 3/4	60 kDa, 11S globulin, seed storage protein	—
Ara h5	15 kDa, profilin	Commonly associated with cross-sensitization with other plant allergens but probably of little relevance to clinical reactivity
Ara h6	15 kDa 2S albumin	Moderate homology with Ara h 2. IgE to Ara h6 persists with time
Ara h8	16.9 kDa, Bet v1 homolog	Probably most significant as being responsible for cross-reactivity with birch pollen analogs
Ara h 9	Lipid transfer protein	Low prevalence of recognition in American and northern European populations, more commonly recognized in southern Europe

Data from Refs.^{6–8}

The age of exposure and age of first reaction to peanut have both decreased in recent years in the United States.¹¹

Family studies have shown that peanut allergy is more common in first-degree relatives of children with peanut allergy than in the general population.^{12–14} It remains uncertain if this can solely be explained by a shared genetic background^{15,16} or also reflects environmental factors that are shared in families.

The known international variation in peanut allergen recognition probably reflects alternative cooking and intercultural feeding practices that may increase or decrease peanut's *in vitro* allergenicity (**Fig. 1**).^{17–19} In addition, timing of its first introduction into the diet affects prevalence as clearly demonstrated when comparing peanut prevalence between genetically similar but geographically separate Jewish populations (Israel vs United Kingdom) with different feeding practices.²⁰

Serologic studies have shown that the diversity of IgE recognition of peanut proteins is more associated with clinical outcome than recognition of individual proteins^{21,22} although recognition of Ara h 2 is repeatedly shown to be associated with more severe (mostly respiratory) symptoms.⁷ It has also been shown that Ara h 2 sensitivity is more likely to be associated with reactivity in formal challenge than recognition of Ara h 8, which probably reflects Bet v1-related cross-reactivity.⁶ At the present time, the most useful predictors of persistence after the first 2 years of life are a maximum wheal size of >6 mm for the peanut skin prick test (SPT) or a peanut-specific IgE >3 kilounits of antibody (kUA)/L.²³

Cellular-based assays of T-cell recognition of peanut peptides, and of IgE and IgG, G₁ and IgG₄ diversity, tend to show that there is a diverse spectrum of reactivity with no particular pattern of antibody production that could easily predict severity in a way that is clinical useful.^{24–28} Combination scores that account for both dose and clinical reaction during food challenge have been associated with specific IgE levels^{27,29} but there remains the problem that reactivity in a formal food challenge is not strongly linked with reported reaction severity in community reactions (reactions in the field).²⁹

PEANUT ALLERGY IS A MARKER FOR OTHER ATOPIC DISORDERS

Individuals with peanut allergy are almost universally atopic in other ways, with rates of asthma, atopic dermatitis (AD), and rhinitis that are higher than the general population.



Fig. 1. Different cooking methods alter peanut's *in vitro* allergenicity in different ways. Boiling reduces IgE binding, roasting increases it. This woman in Keneba, Gambia, is dry roasting peanut kernels. (Courtesy of Dr Kerry Jones, Medical Research Council Laboratories, Keneba; with permission.)

In the United Kingdom, monoallergy to peanut is a rare finding, with less than 5% of cases showing no other sensitization.¹⁰ This can be a good clue to the diagnosis when meeting a new referral for evaluation. In addition, it has been known for 2 decades that asthma, particularly poorly controlled asthma, is associated with fatal outcome in food allergy, particularly peanut allergy,³⁰ and conversely that an existing diagnosis of peanut allergy is associated with worse respiratory outcomes in asthmatic children.^{31,32} Furthermore, children with peanut allergy who are clinically considered to have outgrown preexisting asthma continue to show increased levels of exhaled nitric oxide (eNO), implying persisting inflammation in the airway.³³ In view of these data, it is considered best practice to ensure optimal asthma control as a key part of managing peanut allergy (see later discussion). Similarly AD is a common clinical finding in children with peanut allergy. AD is considered the earliest marker of atopic predisposition.

Much higher odds of developing peanut allergy has been found if a mother (retrospectively recalled at 5–7 years) had applied skin creams containing peanut oil to infant skin.³⁴ Experimental work showed application of peanut to both intact and especially to abraded mouse skin caused migration of Langerhans cells out of the skin and to systemic sensitization, as measurable by increased serum peanut-specific IgE, and a T_H2 biased cytokine profile.³⁵

An interesting observational study from the United Kingdom has suggested that compared with control families (no food allergy) and families with a child at high risk for but not actually demonstrating peanut allergy (the index child had egg allergy), families with a child with peanut allergy were more likely to consume peanut and especially peanut butter in the home, with a dose-response relationship evident between nonoral exposure to peanut and having peanut allergy.³⁶

PREVALENCE OF PEANUT SENSITIZATION AND CONFIRMED ALLERGY

At present, there are estimates that up to 9% and 11% of North American and British children of 8 years or older^{6,37} and 8.9% of Australian infants of 12 months of age (K. Allen, personal communication, 2010) are sensitized to peanut although less than half of these children can be proved to be allergic to peanut by food challenge (see later discussion). In contrast the Early Prevention of Asthma and Allergy in Childhood (EPAAC) study found that in infants aged 1 to 2 years with moderate AD, sensitization to peanut could be found in more than 20% of children.³⁸ It is unclear whether this is primary sensitization or cross-reactive sensitization with birch pollen and other plant allergens that may have been encountered by the inhaled route before oral exposure to peanut.

Several studies suggest a steady increase in the prevalence of peanut allergy from the mid-1990s. For example, at 3 to 4 years of age, the Isle of Wight cohort born in 1989 had a 1.3% peanut sensitization prevalence and a 0.6% prevalence of actual clinical peanut allergy. No formal diagnostic challenges were performed.³⁹ Subsequent birth cohort studies from the Isle of Wight⁴⁰ and a cross-sectional 2-center study from the UK mainland showed the rate of peanut allergy (proved by challenge) had increased to 1.8% by 2005.⁴¹

Population-based studies that result in a gold standard diagnostic double-blind, placebo-controlled, food challenge are less common in the United States but self-reported surveys conducted by telephone in the United States have shown similar figures and a similar increase from 0.4% in 1997 to 1.4% in 2008.⁴² The 2005/2006 National Health and Nutrition Examination Survey study reported an estimate prevalence of peanut allergy of 1.3%.⁴³

PATTERNS OF CLINICAL REACTIVITY

The diagnosis of peanut allergy is simple to make in the presence of known exposure to peanuts and a stereotypical reaction (Table 2). Reactions typically start soon after exposure and it is usually possible to identify peanut in the food eaten^{10,11} Most reactions to peanut are benign and are survived. However, peanut is overwhelmingly and disproportionately represented in case series of severe and fatal outcomes, particularly in community-based retrospective surveys of deaths and severe allergic reactions.^{30,44,45} Methodologically there may be biased reporting of reactions when peanut is implicated compared with more unusual foods that are not recognized by emergency staff as allergens or foods that are considered more mundane such as milk and egg.

DIAGNOSIS OF PEANUT ALLERGY

As shown in Table 2 the features of a peanut allergic reaction are simple to distinguish as reactions are typical and are usually similar in individuals who have repeat reactions and in formal challenge settings. Observed variation in reactions with time⁴⁶ may be caused by the onset of asthma, dose variation, or extrinsic factors such as exercise, infection, and other cofactors.⁴⁷

Although the double-blind, placebo-controlled food challenge is considered the gold standard for diagnosis, it is logistically demanding and time consuming. Therefore, an open food challenge is acceptable in most settings, especially for young children. Most peanut challenges are well tolerated; most children (>90%) who react to the challenge do not need epinephrine, even with conservative criteria for intervention.^{48,49} Families respond favorably to food challenges, even when they result in a reaction.⁵⁰ Although a formal food challenge is not possible in all diagnostic settings, more than half of the individuals who undergo a food challenge do not react, even if their SPT or serum IgE level suggests the presence of a peanut allergy.^{6,51}

Several investigators have developed specific values for SPT (>6–8 mm in most reports) or peanut-specific serum IgE levels (>14–15 kUA/L) that would indicate a likely

Table 2 Clinical reactivity to peanut is stereotyped	
A Likely Case of Peanut Allergy	A Case Unlikely to be Caused by Peanut Allergy
First known exposure to peanut or previous known peanut allergy	Multiple previous episodes of safe consumption of peanut
Multiple allergic disorders Asthma AD Rhinitis Food allergies (especially egg allergy)	No other allergic disorders identified
Stereotyped reaction Rapid onset (minutes) Predominant cutaneous and respiratory symptoms Urticaria/angioedema Rhinoconjunctivitis Wheezing	Atypical reaction Slow onset (hours, even overnight) Headache/joint pains Nonurticarial skin rashes
Low (relative) dose of peanut consumed	High (relative) dose of peanut consumed
Peanut usually easily identifiable in implicated meal/snack	Peanut implicated in retrospect

positive reaction during an oral food challenge.⁵² Although these may be useful in deciding if a diagnostic challenge is necessary or can be postponed, they do not add greatly to the scenario of a carefully taken history that characterizes a reaction as likely to have been caused by peanut, with a positive SPT or specific IgE level that might be less than the decision point. In clinical practice, a typical history (see **Table 2**) and supportive tests mean a true diagnosis of peanut allergy is likely to be present in 85% of cases.¹⁰ Therefore it is not immediately and automatically necessary to challenge every child who presents with a history of reactivity to peanut. Research protocols may demand challenges but routine clinical practice is now more commonly using challenges to determine if peanut allergy has resolved. It is now possible to use more subtle assessments that combine the effects of known predictors of challenge outcome with others whose effect has been difficult to quantify, such as age and sex.⁵³

RESOLUTION AND RECURRENCE OF PEANUT ALLERGY

Bock and Atkins⁵⁴ famous paper in 1988 reported follow-up of 42 children with a positive double-blind, placebo-controlled food challenge. Four died and none of the survivors outgrew their sensitivity to peanut during follow-up. Our group's case-control study in the mid-1990s showed that peanut allergy could not be demonstrated in 20% of children with broadly similar reports of index reactions.⁵⁵ This group had not been established based on an initial double-blind, placebo-controlled food challenge but later studies, based on initial double-blind, placebo-controlled food challenge, found a near identical rate of resolution⁵⁶ and it is now well established that peanut allergy can resolve. Negative follow-up challenges are more likely in those with low SPT and specific IgE levels, so it is worth measuring these on an annual or biannual basis to assess the likelihood that the allergic reaction is subsiding.

Peanut allergy may recur. Eight percent of children who initially had a positive oral food challenge but with time became tolerant (as shown by negative challenge) could not tolerate peanut in their diet after discharge.⁵⁷ It is possible that a half-day or full-day challenge protocol may be too short for some individuals who might experience temporary hyposensitization and who then revert to a reactive state when reexposed to peanut at home. It is therefore recommended that after passing an oral food challenge, peanut should be eaten regularly (but how regularly is not known).⁵⁸ Children who cannot reintroduce peanuts after a challenge should be offered extended follow-up and reconsidered for further peanut challenge at a later date. Children who have passed a peanut challenge should remain under clinical review until peanut is back in the diet and family life no longer has to factor in the rigors of peanut avoidance. At this stage, epinephrine autoinjectors can be withdrawn if there is no other indication for their retention (usually other food allergies).

EFFORTS TO PREVENT PEANUT ALLERGY

When peanut allergy emerged as a significant health care condition in the early 1990s major research efforts were already underway to establish the efficacy of avoidance diets in preventing allergic disorders, mainly relating to the outcome of asthma. Regulatory and professional advice for pregnant and nursing mothers and their infants to avoid peanut was issued in the United Kingdom and the United States in the late 1990s.⁵⁹ Irrespective of the quality of the evidence base for this advice, it is clear the advice had no definite effect on sensitization or allergy rates. This might be because the advice was unclear or being ignored⁴¹ or that the general population or even merely the atopic population were not the correct target populations. The

American Academy of Pediatrics and the UK's Committee on Toxicity of Food both rescinded this advice in 2008 (although they did not specify what advice should be given instead).^{60,61} A recent report hints that the advice might have been correct if it had been more strictly limited to high-risk families. A prospective follow-up of young infants (mean age 9 months) with milk or egg allergy (therefore considered high risk for peanut allergy) has shown that more than a quarter of such infants have peanut-specific IgE levels higher than 5 kUA/L. These infants were 3 times more likely to have been born to mothers who had consumed peanut while pregnant or breastfeeding. The effect may have been stronger for consumption during pregnancy than during breastfeeding.⁶² This finding merits prospective replication to elucidate some way to identify and counsel women at risk of such an outcome in their offspring.

An intensive trial of early introduction of peanut into the diet of peanut-sensitized children is underway,⁶³ aiming to prevent peanut allergy.

CONSERVATIVE MANAGEMENT OF PEANUT ALLERGY

Peanut allergy can be fatal so the anxiety that peanut allergy causes can be considered useful if it elicits appropriate levels of caution. However, it is also known that families can react in extreme ways because of their fears of such a fatal outcome.⁶⁴ Many children with food allergies are home schooled in the United States,⁶⁵ although this is unusual elsewhere. One of the most important tools to manage food allergies, including a peanut allergy, is the engagement of an expert allergist. Comprehensive allergy care significantly reduces the rate of accidental exposure as well as severity progression.^{66,67}

Up to 50% of children with peanut allergy develop sensitization to tree nuts^{10,68} and they are more likely to develop sensitization to sesame than children with other food allergies.⁶⁹ For these reasons, planned review of sensitization to these and occasionally other food groups is good practice in children with peanut allergy. However, if such foods are already safely consumed testing is not required.

In some countries most children with peanut allergy get an epinephrine pen prescription, but in other countries a more cautious approach is taken. The practice in the United States of providing most if not all individuals with peanut allergy with an epinephrine pen is easily understood from a medicolegal perspective but can be criticized for being paternalistic and too conservative, or conversely too aggressive (in that most children with peanut allergy will never need them and the requirement to decide when to use them is a burden on caregivers, especially those who are not members of the index family). It is definitely expensive. More importantly, their prescription without parental training and support may cause additional anxiety.⁷⁰ However, our local experience suggests that proper education on the use of epinephrine kits decreases parental anxiety (>95% of respondents, A Dunngalvin, J Hourihane, unpublished data, 2009). There is a strong case, accepted by affected families, for other modalities of availability of epinephrine to be explored,⁷¹ analogous to the proliferation of automated external defibrillators in public facilities.

THERAPEUTIC OPTIONS FOR PEANUT ALLERGY

Conservative and supportive management remain the cornerstones of medical care for individuals with peanut allergy. Peanut allergy is now a well-characterized condition with some identifiable risk factors for persistence and resolution (SPT and peanut-specific IgE levels, allergen sensitization profile) and for severity (certainly asthma and possibly eNO status and Ara h 2 sensitization status). However, the medical goals of a cure or even an attenuation of severity of peanut allergy have been elusive.

Table 3
What are the unresolved issues regarding oral induction of tolerance to peanut?

Unknowns	Options	Reason	Comment
Who should be offered treatment?	Everyone Benign reactors Severe reactors	Progression of severity is uncertain To prevent progression To prevent fatality	Not logistically feasible This group is most likely to remit spontaneously Fatal reactions are rare but are feared by nearly all families Quality of life may improve significantly
How long to treat?	2–3 years	Early effects of peanut OIT reflect those of inhalant immunotherapy	No data yet for any duration of treatment
	5 years Indefinitely	Comparable with venom intolerance —	— Families may not want to stop
How can treatment success be measured?	SPT, peanut-specific IgE DBPCFC	Easily done in routine practice Not easily done in routine practice	May not change during treatment Reaction severity in DBPCFC not strongly associated with reaction severity in the field Not yet studied systematically in OIT trials
	Quality of life	Easy to measure	
Where to treat?	Research centers Allergy centers Private practice	Experience of peanut OIT Experience of immunotherapy Patient access	Not geographically accessible to most patients Resource issues, personnel, and financial Likely massive demand, but safety, governance and insurance/reimbursement issues
What peanut preparation to use?	Whole peanut Defatted peanut	Widely available Easily available	— Easy to vary dose, but may not be identical to whole peanut
	Modified dominant peanut allergens	Ara h2 modification attenuates reactivity in vitro and in animal studies	Other unmodified allergens may become more relevant in exposures after OIT
How to manage protocol violations	Missed doses Double doses Intercurrent life and health events	? drop a dose level ? continue or skip a dose Asthma, pregnancy new medications, and so forth	Early reports suggest not a major problem No data yet Viral illness has elicited breakthrough reactions during OIT No pregnancy data yet

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge.

Injection immunotherapy is not well tolerated⁷² and anti-IgE therapy has not translated into routine clinical practice after the promising early studies.⁷³ Trials are underway after promising animal studies of Chinese herbal remedies and peanut-based immunotherapy with bacterial vectors.^{74,75} The current cutting edge of peanut allergy research is oral induction of tolerance (OIT). Groups in the United States, the United Kingdom, Australia, and Germany are committed to large programs of research aiming to deliver what would be the most important development in this field to date.⁷⁶

Protocols are broadly similar and have been shared between some groups, indicating viability outside the developing centers.^{77–80} Entry criteria have not always been a formal double-blind, placebo-controlled food challenge and severe reactors were not always included in the first trials. Early data indicate that more than half of the subjects, but not all of them, complete induction and retain remission during the maintenance phase. Reactions to OIT, mostly minor upper airway symptoms, are more common during induction than during the maintenance. More severe symptoms, such as chest symptoms are only present in 1.7% of reactions during induction, and decrease to 0.2% during maintenance.^{78,79}

The first report of successful treatment was from the United Kingdom,⁸⁰ using a protocol developed at Duke University. In this first report 4 subjects were reported, 2 with a history of previous reactions to peanut and 2 without such a history but with peanut-specific IgE levels that would predict reactivity. All 4 subjects increased their threshold dose of defatted peanut flour by factors of between 48 and 478 times their threshold dose at entry.

Duke data suggest that the immunologic changes witnessed in peanut OIT reflect those seen in inhalant allergen immunotherapy, which can be discontinued after 3 to 5 years with persisting clinical efficacy for several years thereafter, which might suggest that peanut OIT treatment could be limited to a 3-year or 5-year time frame rather than continued indefinitely.⁷⁸ This remains unproved to date. Furthermore, although early data suggest that peanut OIT may have a place in the management of patients with peanut allergy, substantial issues remain to be addressed, including the feasibility of providing peanut OIT outside heavily resourced academic centers (Table 3). Although in an attempt to gain access to such therapies, patients from some countries (eg, Ireland) travel to other countries (United Kingdom), authorities in the United States have on more than one occasion advised that peanut OIT is not yet ready for routine clinical practice.⁸¹ It will take time for experience of peanut OIT to build up in centers outside the vanguard of this advance.

SUMMARY

Peanut allergy is now a well-characterized condition with high levels of medical, regulatory, and public awareness. Disease-modifying therapeutic options are emerging but the best approach has not yet been established. Families affected by peanut allergy are vulnerable to extreme anxiety around peanut allergy and physicians must recognize this undesirable consequence of the explosion of information about peanut allergy in the last 2 decades. Prudent and supportive medical advice, risk assessment, family education, and training in rescue medication use form the basis for the management of peanut allergy. The immunologic and biochemical information with which physicians can characterize patients with peanut allergy using routinely available in vivo and in vitro tests has improved and will continue to evolve. Meanwhile, sufficient data on the feasibility, effectiveness, and safety of peanut OIT are awaited. This therapy is not ready for prime time yet.

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