

Review Article

Peanut allergy: A major public health issue

Warner JO. Peanut allergy: A major public health issue.
Pediatr Allergy Immunol 1999; 10: 14–20. © Munksgaard, 1999

J. O. Warner

University of Southampton/Southampton
General Hospital, Southampton, Hampshire,
UK

Key words: peanut allergen; peanut allergens;
peanut oils; primary sensitization; RAST; skin
prick tests

J. O. Warner, University of Southampton/
Southampton General Hospital, Southampton,
Hampshire, UK

Accepted 15 November 1998

Peanut allergy has become a major public health issue in many countries because it is relatively common, causes severe and sometimes fatal reactions, starts early in life, and rarely resolves. The problem has recently preoccupied even statutory Government agencies with the publication of official reports.

The UK Department of Health produced an expert committee report making recommendations on peanut avoidance in women during pregnancy and lactation, and in children up to at least 3 yr of age (1). Whilst the committee felt that evidence supporting a link between exposure to peanut allergen early in life and sensitization was inconclusive, it was 'unwise to discount' this possibility. Therefore, it was felt prudent to recommend avoidance for all pregnant and lactating women who were either atopic themselves or whose partner or children had atopic disease. The arbitrary lower age of 3 yr was suggested as the minimum to maintain avoidance in the resulting child. However, because peanut allergy nearly always occurs in individuals with associated clinical allergic disease (96%) (2), this recommendation was *not* extended to the non-atopic population. Clearly, prospective studies would be required to establish whether this recommendation is an appropriate public health measure. Such studies would take many years to complete but we publish a paper in this issue of *Pediatric Allergy and Immunology* from South Africa which supports the concept of *in utero*

sensitization to peanuts via maternal ingestion, utilizing data from a small case-control study (3).

There is also a need to rationalize food labeling legislation so that the all-too-frequent accidental exposures to peanut can be avoided (4, 5). Thus, the International Life Sciences Institute (Europe) produced a Food Allergy Expert Group report to establish scientifically based criteria for deciding which food constituents should always be labeled, irrespective of quantity (6). The list of food allergens inevitably included peanut, for which there is the largest evidence base to justify the recommendation. Also included are crustaceans, egg, fish, milk, sesame seed, soya bean, tree nuts (including almond), and wheat.

There has also been a remarkable proliferation of scientific papers published on peanut allergy in the last decade, which may well represent the increasing prevalence of the problem (7). However, most of the early reports came from the USA where peanut consumption, particularly in early life, first became popular (5, 8–10). One concern in relation to the apparent increase in peanut allergy has been the potential for the commonly utilized peanut oils to contribute to sensitization. In this issue of *Pediatric Allergy and Immunology* we publish a paper which suggests that peanut oils in vitamin preparations are probably not a concern in relation to primary sensitization (11).

This review highlights some of the key issues in relation to the health burden of peanut allergy.

Increasing prevalence

Over the last three decades there has been a remarkable increase in the prevalence of the atopic diseases asthma, eczema and hay fever, in many countries in the developed world. During the same period of time, there are no data that have accurately ascertained prevalence rates for peanut allergy, in any populations. Nevertheless, there is clearly a higher prevalence of peanut allergy in successive generations within families of peanut-allergic probands. Thus, the prevalence of peanut allergy has been shown to be 0.1% in grandparents, 0.6% in aunts and uncles, 1.6% in parents, and 6.9% in siblings. This would point to there having been a true increase in prevalence, which may be related to a general trend for increased prevalence of atopy, associated, of course, with increasing exposure to the allergens of peanut (7).

Peanut and peanut products were introduced into the European diet towards the end of World War II with the arrival of large numbers of American troops. Increasing Americanization of lifestyle and diet in Europe have resulted in peanuts being used evermore extensively. The average British consumption *per capita* in 1994 was 1.77 kg/person/yr. This is one-half of the intake of the average North American resident. Nevertheless, it is perhaps surprising that there has been less appreciation of an increasing problem in relation to peanut allergy compared with other atopic diseases unless it is only very recently that the problem has increased. There is an overwhelming anecdotal impression from clinical practice that acute, severe peanut allergy is presenting in much younger children than has been the case in the past, as well as now being manifest in larger numbers of older children and young adults. As we have evidence of more recent increasing use of peanut and peanut products at a progressively earlier age, this must focuss attention on early exposure as being important in relation to sensitization and subsequent manifestation of disease.

Genes and early sensitization

The role of genetic predisposition to allergy must not be ignored. There is a virtual absence of peanut allergy in populations in sub-equatorial Africa that have overall low rates of atopy but high consumption of peanut. Crushed peanuts are often introduced into the diet of Korean children from weaning (at $\approx$ 6 months of age) but peanut allergy is rare in Korea (K. S. Park, personal communication). Studies from France,

however, suggest that sensitization can occur exceedingly early. Hatahat et al. (12) skin prick tested 54 newborn infants, who were under 11 d of age, and 71 babies aged between 17 d and 4 months. In both groups, 8% had a positive test to peanut, implying sensitization in very early life and possibly even before birth. As immunoglobulin E (IgE) clearly does not cross the placenta, it is likely that the fetus and/or the newborn infant is exposed to peanut proteins, thus producing sensitization. This concept is supported by Frank et al. (3) who, in a case-control study, showed that peanut-allergic children's mothers had ingested more peanut during pregnancy, but not during lactation, than mothers of milk- or egg-allergic children. We have shown that this is the case on the basis of cord-blood peripheral mononuclear cell proliferative responses to allergens such as egg and milk (13). We have also established that this can occur in the middle of the second trimester of pregnancy, from 20 to 22 weeks of gestation onwards (14). Other groups have made similar observations, the most recent being in relation to milk proteins (15).

Food antigens can be retrieved from human breast milk. This has been known for many years (16). More recently, peanut allergens have been demonstrated in breast milk. De Bolt et al. studied nine nursing mothers who excluded legumes for 24 h before eating 90 g of roasted peanuts. Peak peanut allergen levels in breast milk occurred at varying times between 1 and 5 h after ingestion (17). Indeed from our own studies (7), we identified one child who reacted adversely to breast feeds after the mother ate peanuts. We have also identified an increased peanut consumption by pregnant and breast-feeding mothers whose children have later been shown to be peanut allergic. This is in keeping with the observation that 80% of British peanut-allergic people react on their first direct exposure to peanut (4). Furthermore, Zeiger's studies, which followed-up a control group and a study group of American children with hypoallergenic diets for the first 2 yr of life, showed that all infants in the control group and 80% of infants in the study group, despite parents having been advised to avoid nuts and peanuts, had eaten peanuts by their second birthday (8). In 23 of Ewan's 24 'nut'-allergic patients who presented under the age of 2 yr, the allergies were caused by peanuts. Peanuts accounted for all patients who were allergic to a 'nut' by the age of 1 yr. She concluded that sensitization to peanuts or nuts had occurred 'considerably earlier than the age at presentation' (2).

Route of sensitization

Whether this early age of onset of sensitization is caused by exposure *in utero* or occurs during lactation will be difficult to establish without further prospective longitudinal study, although the data from Frank et al. (3) would suggest that *in utero* exposure is more important. Clearly, there is concern that hidden exposure might occur in various foods. The role of vitamin D preparations containing peanut oil has been raised (18). This has also been suggested in relation to initiation of eczema in children fed on milk formulae containing peanut oils. A study of four infants with eczema suggested worsening on challenge with a peanut-containing milk formula (19). This was further investigated by Kull and colleagues. They concluded that peanut oil-based vitamin preparations have probably not increased sensitization rates, though there was an association with a wider range of symptoms following allergic responses to peanut (11).

There have also been concerns about possible topical exposure to peanut allergens via peanut oil-containing formulations (20–24). It is of particular concern that children who already have inflamed skin (i.e. those with eczema) might be particularly susceptible to sensitization by the topical route. There are a few topical preparations recommended for the treatment of eczema that have an *Arachis* oil base. Certainly this is an area that requires further investigation. In the interim, it would seem prudent to recommend that individuals with broken skin, and particularly those with the potential for atopy, should not use *Arachis* oil-containing preparations. Low-dose exposure to allergen in the skin may be more likely to induce an allergic type of response than the higher-dose exposure that occurs through the gut following allergen ingestion. Thus, recommendations about avoidance of topical preparations containing peanut oils does not necessarily imply that similar exposure through the gut will have the same effect (25).

Allergenicity of oils

The question of whether purified peanut oils are allergenic has now been appropriately addressed. Bock & Atkins gave up to 30 ml of refined peanut oil to four subjects who had previously reacted on double-blind challenge to peanut – none reacted to the oil (5). Taylor et al. studied 10 adult peanut allergics in a double-blind crossover study with peanut oil, using olive oil as a placebo. The peanut allergics ingested 1, 2 and 5 ml of encapsulated oils successively and none reacted.

The conclusion from this was that peanut oil is not allergenic in peanut-allergic individuals (26). Conversely, however, an assay of so-called cold pressed or crude peanut oils has identified antigenic proteins at a dose of 3.3 µg/ml. However, in the same study, no protein could be demonstrated in highly refined oils (27). Another group also failed to identify any peanut protein in refined peanut oils, although once peanut had been cooked in the oil, allergen could be detected (28). Our own study comprised 60 proven peanut-allergic subjects, over 50% of whom had severe reactions. No subject reacted to an ingestion of up to 16 ml of purified oil. Six subjects reacted to crude oil, although only two of these reactions were unequivocal in terms of being objective. The other four subjects only had subjective sensations. Even the two objective reactions were mild. Thus, statistically there is a 95% likelihood that peanut oil represents a risk to fewer than 5% of peanut allergics. Therefore it can be concluded that refined peanut oil is safe for those with peanut allergy and even crude oil is very unlikely to produce a severe reaction (29).

Whilst refined and crude oils need not be implicated as causing acute, severe or life-threatening reactions in individuals who are already allergic, it is not yet possible to exclude these oils in relation to having a role in primary sensitization. Nevertheless, it seems improbable that this is the case by the oral route, though this assertion remains unproven.

Prevalence and clinical features of peanut allergy

Peanut allergy is relatively common in children. Overall, food allergy affects up to 8% of pre-school children (30). Bock et al. found that 93% of positive double-blind placebo-controlled food challenges in children were caused by just eight foods, in order of frequency being: egg, peanut, milk, soy, tree nuts, shellfish, fish, and wheat (31). In a cohort of 4-yr-old children on the Isle of Wight, 1.3% were identified with skin test-positive reactions to peanut, although only six of the 13 so identified actually had a clinical history of an allergic reaction to peanut (32). This latter study perhaps gives the most recent and accurate assessment of the true prevalence of peanut allergy. Clearly it is impossible to establish whether the seven sensitized individuals had latent allergy or just true sensitivity without allergy.

Peanut allergy is considered to be a lifelong problem. Compared with milk and egg allergy, it rarely remits. Bock & Atkins reported the results of a follow-up of 32 children who had positive

double-blind placebo-controlled food challenges with peanut. Many suffered frequent accidental reactions, 50% within the previous year. Two to 10 yr later, skin prick tests (SPTs) were still positive in all the individuals (5). In our own study, 25% of peanut allergics reported having had a reaction in the previous 6 months and 50% in the previous year (4). The findings of these studies indicate that peanut allergy, once developed, nearly always persists and accidental exposures, despite attempts at avoidance, are common. However, these have been based on follow-up of established peanut allergy in older children. Whether the same is true of peanut allergy in infancy remains to be established. As is the case for egg and milk allergy, remission rates may be higher in infancy than in childhood (33).

Peanut is the commonest food to cause severe acute and sometimes life-threatening reactions. Indeed, it accounts for one-third of all severe food-related reactions (9). Features of the fatalities included associated asthma and a failure to use epinephrine. Most fatal reactions occurred outside the home environment.

Our own experience in 622 self-reported peanut allergic individuals was that only 19% had been knowingly exposed to peanut before the first documented reaction, implying a high frequency of occult sensitization. Severe symptoms were commoner in adults than in children but over 50% had moderate or severe reactions associated with wheezing or other breathing difficulty, cyanosis, and/or collapse. A common association with more severe reaction was abdominal pain, a feature not reported in previous studies. This is a symptom that was not apparent in individuals who had mild reactions, such as angio-edema and urticaria. Fifty per cent reacted merely to the touch of a peanut and 90% reacted to eating significantly less than one whole peanut.

Our study also demonstrated that 50% of individuals with more than one reaction felt that the severity was similar in successive exposures; 38% had worsening reactions; and only 2.5% had a decrease in severity. The adjuvantizing effect of exercise in exacerbating reactions was noted in 2.9% of individuals but an additional 0.8% reported amelioration of symptoms with exercise. Disappointingly, epinephrine in any form was carried by only 65% of individuals, and only 18 of 43 (41%) who had collapsed during a reaction had actually been given epinephrine as treatment. It was clear that acute reactions were under-treated, and sufferers had inadequate education and training in the use of rescue medication following diagnosis (4).

Associated allergies

Peanut is not a tree nut but a legume. *In vitro* studies in peanut allergics have shown extensive cross-reactivity with other legumes, such as soy, peas, beans, etc. (34). However, clinical studies suggest that *in vivo* cross-reactivity is rare (5). Many peanut-allergic patients report associated allergy to tree nuts. Given the taxonomic disparity between peanuts and tree nuts, cross-reactivity seems unlikely. It is perhaps more likely that this is an associated sensitivity. In our group of patients, 49% reported associated tree nut allergy. Conversely, five of 12 UK brazil nut allergics were also allergic to peanuts (35). Recently, a major brazil nut antigen known as 2S-albumin was transferred to soy beans transgenically. The 2S protein, being rich in methionine, was considered to be a useful way of enhancing the nutritional qualities of the soy beans. However, it was subsequently identified that the transgenic soy bean contained allergen that inhibited binding of brazil nut-specific IgE and caused positive SPTs in brazil nut-allergic individuals (36). This resulted in the withdrawal of the transgenic bean before it reached the food chain. However, it remains to be established whether or not associated tree nut allergy is a result of shared allergen protein sequences.

Dose-response relationships

As apparent from the previous sections of this report, accidental exposure to hidden peanut antigen in prepared food is common. Severe reactions have been reported from cross-contamination of kitchen utensils (10). The question of how much peanut can actually induce a reaction has not been properly studied. We recently conducted double-blind placebo-controlled food challenges in 14 peanut allergic subjects with doses of peanut ranging from 10 µg to 50 mg. An attempt was made to identify a threshold dose that produced a response. One subject had a severe reaction to 5 mg; four subjects had mild objective reactions to 2, 5 and 50 mg, respectively; four subjects had mild subjective reactions to 50 mg; and five of the subjects tolerated doses up to and including 50 mg. The nine individuals with positive reactions had short-lived subjective reactions to preceding doses before the objective response and, in two subjects, to doses as low as 100 µg. This indicates that the threshold dose varies widely but can occur at exceedingly low doses (37).

Objective evaluation of clinical history

In our studies, we have been able to make some estimates of the reliability of clinical evaluations in peanut-allergic individuals. The questionnaire-based diagnosis of peanut allergy in adults revealed a 13% false-positive rate based on subsequent SPTs and peanut challenge. The false-positive rate for questionnaire-based diagnosis in children was 14%, based primarily on SPTs and validated in a small percentage by subsequent challenge. The features associated with false positivity on history were neatly divided into two. Approximately 50% of the individuals reported unusual symptoms, often developing many hours after challenge. Where tested, these symptoms could sometimes not be replicated by formal challenge procedures. The remaining 50% were individuals who had mistakenly attributed an acute severe reaction to peanut. In some instances this was because of isolated tree nut rather than peanut allergy where a product from a nut mix had been ingested.

Evaluation of skin tests

The Isle of Wight 4-yr birth cohort follow-up data indicated that a significant percentage of individuals with positive SPTs may have sensitization without necessarily a history of clinical disease consequent upon exposure. There are no data to indicate the exact sensitization rate in the absence of symptomatic allergy. My own clinical experience would suggest that it may be fairly high, particularly in the asthmatic population. However, whether this represents latent allergy, which will subsequently show itself, remains to be seen by follow-up. Certainly this is the case for skin test positivity to grass pollens in adolescence (38). SPTs, provided they are carried out with appropriate allergen extracts with positive and negative controls, rarely give false-negative results. However, in a very recent paper investigating the value of SPTs in children with atopic dermatitis, two of 10 children with negative peanut tests had a positive food challenge test. The false-positive rate was higher, with nine of 25 children with positive skin tests not reacting on food challenge (39).

There is a moderate correlation between SPT wheal size and clinical severity. However, the clinical usefulness of this correlation is very limited owing to the large overlap between groups. Based on all the studies carried out in my group, the SPT was 96% sensitive and 77% specific (18, 29). Sporik & Hill have recently suggested that only 13% of subjects with small

SPT reactions (50% of the diameter of the reaction to 1 mg/ml histamine) react to relevant nut on food challenge compared to more than 85% of those with a SPT reaction of more than twice the diameter of the histamine control (40). More challenges with peanut would be needed to confirm or refute these findings.

IgE (total and specific)

Most, but not all, peanut-allergic children have raised serum total IgE levels (38). To my knowledge, there has been no study of sensitivity and specificity of IgE antibody measurements, whether by radio-allergo-sorbent test (RAST) or using newer techniques. My own anecdotal impression is that both specificity and sensitivity are lower with IgE antibody measurements than for skin prick testing. However, this has not been exhaustively investigated. As with skin prick testing, there is little correlation between the degree of positivity of the RAST and severity of clinical reaction in response to peanut.

Peanut allergens

It is important to be aware both from SPT and RAST that the extract of peanut used is crude, containing many proteins in variable quantities (depending on the company manufacturing the material) and, indeed, with some potential for variation from batch to batch. Currently there is no gold standard peanut antigen against which to test any materials. This is unlikely to be standardized until the major peanut allergenic proteins have been better characterized. By Western immunoblotting, we have shown that the larger the number of separated peanut proteins recognized by IgE from individual patients' sera, not unexpectedly, the higher their RAST. However, we also have some limited evidence that patients with IgE antibodies against a low-molecular-weight protein (of 7000 MW) were more likely to have severe disease. Further elaboration of these observations is required (41).

Our study, based on individual Western blots from 91 peanut-allergic individuals, clearly identified the two hitherto well-described major peanut allergens, Ara h I (63 000 MW) (42) and Ara h II (17 000 MW) (43). However, we have also identified two other major allergens of 15 000 and 51 000 MW with, in total, 19 separate proteins being recognized by IgE from some patients. Thus, a great deal more work is required to elaborate on the different important peanut proteins.

T-cell responses

Peripheral blood mononuclear cell proliferative responses to crude peanut extract are increased in peanut-allergic individuals compared with atopic or non-atopic controls. Furthermore, there are some differences in cytokine generation from the proliferating cells, suggesting that there is a T helper 2 (Th2)-predominant response to the peanut in allergic individuals (44, 45). There is no correlation between the degree of proliferative response of mononuclear cells and the clinical severity, SPT wheal size or peanut-specific IgE levels (46).

Immunogenetics

Few studies have investigated the immunogenetics of peanut allergy. In one, there was a selective expansion of T cells expressing V β ₂ (T-cell-receptor variable regions) (47), and in our own study there was some human leucocyte antigen (HLA) class 2 restriction: DRB1*08, DRB1*08-12, tyr 16, and DQB1*04 (48). We also have some information on immunogenetic analysis of the heavy chain variable regions of IgE from patients allergic to peanuts with a predominance of V_H1 gene families. The IgE V_H sequences were highly somatically mutated but there was clear evidence of clustering of amino acids, indicative of antigen selection, in only a minority. This suggests that there could be a super-antigen effect in peanut allergy (48).

Food challenge

In the final analysis, double-blind placebo-controlled food challenges are considered the gold standard in making a definitive diagnosis of peanut allergy (31). From the data presented above, it is apparent that in the majority of clinical situations, a good history and a positive SPT is probably all that is required. Where SPT sensitivity is dubious or negative, challenges are indicated. It has, however, also become apparent that even food challenges are not without problems. There is a marked disparity between the reported severity of reactions to peanut and the reactions observed under challenge conditions. As the latter is strictly controlled to avoid any adjuvantizing influences, this is perhaps not surprising. Nevertheless, this creates a possibility that some clinically relevant sensitivities might be missed under controlled-challenge conditions.

Conclusion

Much has been learned in recent years about the magnitude of the clinical problem of peanut allergy. The factors that contribute to the life-threatening nature of the condition in some individuals have not been identified. Furthermore, we still know little of the timing and nature of primary sensitization, although we believe that exposure early in life, perhaps even *in utero*, is important. Diagnostic procedures have been well evaluated. Management is based on avoidance, which often fails, and rescue treatment of accidental exposures based on the use of epinephrine. All too frequently, the relatively straightforward rules of management are not followed. Thus the overwhelming message is that more research and more education are urgently required.

References

1. COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT. Peanut Allergy. London: Department of Health, 1998. pp. 1–57.
2. EWAN PW. Clinical study of peanut and nut allergy in 62 consecutive patients: New features and associations. *BMJ* 1996; 312: 1074–8.
3. FRANK L, MARIAN A, VISSER M, WEINBERG E, POTTER PC. Exposure to peanuts *in utero* and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 1999; 10: 21–6.
4. HOURIHANE JO'B, KILBURN SA, DEAN TP, WARNER JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997; 27: 634–9.
5. BOCK SA, ATKINS FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83: 900–4.
6. BOUSQUET J, BJORKSTEN B, BRUNZEEL-KOSMEN CAFM, et al. Scientific criteria and the selection of allergenic foods for product labelling *Allergy* 1998; 53: 3–21 (supplement).
7. HOURIHANE JO'B, DEAN TP, WARNER JO. Peanut allergy in relation to heredity, maternal diet and other atopic diseases: Results of a questionnaire survey, skin prick testing and food challenges. *BMJ* 1996; 313: 518–21.
8. ZEIGER RS, HELLER L, MELLON MH, et al. Effect of combined maternal and infant food allergen avoidance on development of atopy in early infancy: A randomised study. *J Allergy Clin Immunol* 1989; 84: 72–89.
9. YUNGINGER JW, SWEENEY KG, STURNER WQ, et al. Fatal food induced anaphylaxis. *JAMA* 1988; 26: 1450–2.
10. SAMPSON HA, MENDELSON L, ROSEN JP. Fatal and near fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380–4.
11. KULL I, HALLNER E, LILJA G, ÖHMAN-JOHANSSON AC, ÖMAN H, WICKMAN M. Peanut oil in vitamin A and D preparations—reactions to skin test and manifestation of symptoms. *Pediatr Allergy Immunol* 1999; 10: 21–26.
12. HATAHAT R, KIRCH F, CANNY G, MONERET-VAUTRIN DA. Sensitization to peanut before four months based on 125 cases (English abstract). *Rev Fr Allergologie Immunol Clin* 1994; 34: 377–81.
13. WARNER JA, MILES EA, JONES AC, QUINT DJ, COLWELL

- BM, WARNER JO. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; 24: 423–30.
14. JONES AC, MILES EA, WARNER JO, COLWELL BM, BRYANT TN, WARNER JA. Fetal peripheral blood mononuclear cell proliferative responses to mitogenic and allergenic stimulæ during gestation. *Pediatr Allergy Immunol* 1996; 7: 109–16.
 15. SZEPPALUSI Z, NENTWICH I, GERSTMAYR M, et al. Prenatal allergen contact with milk proteins. *Clin Exp Allergy* 1997; 27: 28–35.
 16. WARNER JO. Food allergy in fully breast fed infants. *Clin Allergy* 1980; 10: 133–6.
 17. DE BOLT MFH, JOHANSEN KL, YUNGINGER JW. Secretion of peanut allergens in breast milk of nursing mothers (abstract). *J Allergy Clin Immunol* 1993; 93 (Suppl.): 342.
 18. DE MONTIS G, GENOBEL D, CHEMILLIER TSUONG M, DUPONT C. Sensitization to peanut and vitamin D oily preparations (Letter). *Lancet* 1993; 341: 1411.
 19. MONERET-VAUTRIN DA, HATAHAT R, KANNY G. Risks of milk formulas containing peanut oils contaminated with peanut allergens in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1994; 5: 84–8.
 20. LEVER LR. Creams and ointments containing peanut oil may lead to sensitization (Letter). *BMJ* 1996; 313: 299.
 21. JOYCE R, FROSH A. Baby massage oils could be a hazard (Letter). *BMJ* 1996; 313: 299.
 22. WEEKS R. Peanut oil in medications (Letter). *Lancet* 1996; 348: 759–60.
 23. MORRIS M, SMITH S. Allergy to peanut (Letter). *Lancet* 1996; 348: 1522.
 24. BARRIS N. Allergy to peanut (Letter). *Lancet* 1996; 348: 1522.
 25. JOOST VAN NEERVEN RJ, EBNER C, YSSEL H, KAPSENBERG ML, LAMB JR. T-cell responses to allergens: epitope specificity and clinical relevance. *Immunol Today* 1996; 17: 526–32.
 26. TAYLOR SL, BUSSE WW, SACHS MI, PARKER JL, YUNGINGER JW. Peanut oil is not allergenic to peanut sensitive individuals. *J Allergy Clin Immunol* 1981; 68: 372–5.
 27. HOFFMAN DR, COLLINS-WILLIAMS C. Cold pressed peanut oils may contain peanut allergen. *J Allergy Clin Immunol* 1994; 93: 801–2.
 28. KEATING MU, JONES RT, WORLEY NJ, SHIVELY CA, YUNGINGER JW. Immunoassay of peanut allergens in food processing materials and finished foods. *J Allergy Clin Immunol* 1990; 86: 41–4.
 29. HOURIHANE JO'B, BEDWANI SD, DEAN TP, WARNER JO. Randomised double blind, crossover food challenge study of allergenicity of peanut oils in peanut allergic individuals. *BMJ* 1997; 314: 1084–8.
 30. JAMES JM, SAMPSON HA. An overview of food hypersensitivity. *Pediatr Allergy Immunol* 1992; 3: 667–78.
 31. BOCK SA, SAMPSON HA, ATKINS FM, et al. Double blind placebo controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988; 82: 986–97.
 32. TARIQ SM, STEVENS M, MATTHEWS S, RIDOUT S, TWISELTON R, HIDE DW. Cohort study of peanut and tree nut sensitization by age of 4 years. *BMJ* 1996; 313: 514–7.
 33. HOURIHANE JO'B, ROBERTS SA, WARNER JO. Resolution of peanut allergy: A case control study. *BMJ* 1998; 316: 1271–5.
 34. BARNETT D, BONHAM B, HARDEN MEH. Allergenic cross-reactions among legume foods – an *in vitro* study. *J Allergy Clin Immunol* 1987; 79: 433–8.
 35. ARSHAD SH, MALMBERG E, KRAFF K, HIDE DW. Clinical and immunological characteristics of brazil nut allergy. *Clin Exp Allergy* 1991; 21: 373–6.
 36. NORDLEE JA, TAYLOR SL, TOWNSEND JA, THOMAS LA, BUSH RK. Identification of the brazil nut allergen in transgenic soy beans. *N Engl J Med* 1996; 334: 688–92.
 37. HOURIHANE JO'B, KILBURN SA, HEFLE S, NORDLEE J, TAYLOR S, WARNER JO. An evaluation of the sensitivity of peanut allergic subjects to very low doses of peanut protein: A randomised double blind placebo controlled food challenge study. *J Allergy Clin Immunol* 1997; 100: 596–600.
 38. HAGY GW, SETTIPANE GA. Prognosis of positive allergy skin tests in an asymptomatic population: a 3 year follow-up of colleague students. *J Allergy Clin Immunol* 1971; 48: 200–11.
 39. EIGENMANN PA, SAMPSON HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998; 9: 186–91.
 40. SPORIK R, HILL D. Allergy to peanuts, nuts and sesame seed in Australian children. (Letter). *BMJ* 1996; 313: 1477–8.
 41. CLARKE MCA, KILBURN SA, HOURIHANE J, et al. Serological characteristics of peanut allergy. *Clin Exp Allergy* 1998; 28: 1291–7.
 42. BURKES AW, WILLIAMS LW, HELM RM, et al. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. *J Allergy Clin Immunol* 1991; 88: 172–9.
 43. BURKES AW, WILLIAMS LW, CONNAUGHTON C, et al. Identification and characterisation of a second major peanut allergen, Ara h II, with use of sera of patients with atopic dermatitis and positive peanut challenges. *J Allergy Clin Immunol* 1992; 90: 962–9.
 44. DORIAN BJ, BURKES AW, HARBECK R, et al. The production of interferon gamma and response to major peanut allergen, Ara h II, correlates with serum levels of IgE anti-Ara h II. *J Allergy Clin Immunol* 1994; 93: 93–9.
 45. DE YONG EC, SPANHAAS S, MARTENS BPM, CAPSENBERG ML, PENNINKS AH, WIERENGA EA. Food allergen (peanuts) specific Th-2 clones generated from the peripheral blood of a patient with peanut allergy. *J Allergy Clin Immunol* 1996; 98: 73–81.
 46. HOURIHANE JO'B, CLARKE MCA, DEAN TP, WARNER JO. Peanut allergic subjects' peripheral blood mononuclear cell proliferative responses to crude peanut protein. *Clin Exp Allergy* 1998; 28: 163–8.
 47. DORIAN BJ, LEUNG Dym. Selective expansion of T cells expressing V β ₂ in peanut allergy. *Pediatr Allergy Immunol* 1995; 6: 95–7.
 48. HOWELL WM, TURNER SJ, HOURIHANE JO'B, DEAN TP, WARNER JO. HLA class 2 DRB1, DQB1, DPB1 genotypic associations with peanut allergy: Evidence from a family based and case control study. *Clin Exp Allergy* 1998; 28: 156–62.
 49. JANEZIC A, CHAPMAN C, SNOW R, et al. Immunogenetic analysis of the heavy chain variable regions of IgE from patients allergic to peanuts. *J Allergy Clin Immunol* 1998; 101: 391–6.