British Journal of Nutrition (2010), **103**, 1699–1701
doi:10.1017/S0007114509993813

Invited Commentary

Early peanut exposure: poison or panacea?

(First published online 26 January 2010)

Peanut allergy remains a significant public health concern, crossing continents and socio-economic boundaries. The dietary and social restrictions pertaining to the label of peanut allergy can severely impair the quality of life of both children and their parents[1]. While peanut desensitisation is being trialled in the UK and USA, at present the mainstay of treatment is strict peanut avoidance. However, dietary indiscretion and inadvertent exposures are relatively common, particularly among teenagers. Rarely this can result in severe anaphylaxis or death triggered by minute traces of peanut allergen[2].

The role of primary prevention in preventing immunological sensitisation has been a matter of debate for the past 40 years. In 1998, the UK Government's Chief Medical Officer's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) recommended that peanut ingestion should be avoided during pregnancy and lactation in families where there was an increased risk of atopy[3]. In addition, it was suggested that children at risk of developing allergies should not be exposed to peanut products before 3 years of age. There was never any strong evidence backing these proposals but a feeling within the scientific community that early exposure to peanut allergens may predispose a child to the development of peanut allergy. This guidance was not restricted to the UK but also circulated by US and Australian Paediatric Societies. However, within the past 10 years there has been a paradigm shift and clinicians are being to question the efficacy of peanut avoidance in primary prevention. Initially there were anecdotal reports from communities where peanut ingestion was high. These populations had an extremely low incidence of peanut allergy. This has been followed by a recent formal study of Jewish children in Israel where early peanut exposure is associated with an approximate 10-fold lower incidence of peanut allergy compared with their UK Jewish counterparts[4].

The systematic review by Thompson *et al.* [5] in this issue set out to evaluate the current literature examining early life exposure to peanut allergen and the subsequent development of peanut sensitisation and/or allergy[5]. Their conclusions suggest a dearth of reliable evidence investigating the role of early peanut exposure on the development of peanut sensitisation and allergy. Even between studies there was no consensus and more data are required before firm conclusions can be drawn and official guidance proffered. The Learning Early About Peanut Allergy (LEAP) study, an investigation into the role of early peanut exposure in atopic children is due to report within the next few years[6] and these results are awaited with anticipation. In the meantime, we are left to conjecture how early allergen exposure promotes or abrogates the development of peanut sensitisation.

Food allergy, a notable first step on the 'allergic march', often begins within the first year of life. There is a great deal of controversy regarding the timing of allergen sensitisation with conflicting evidence suggesting transplacental *v.* exclusively postnatal priming. Elaborating on this is fundamental to the design of primary prevention strategies. Peanut-specific IgE, unlike IgE to other food and aeroallergens, has not been identified in cord blood[7], and thus sensitisation is believed to occur during or after the postnatal period. In animal studies at least, there are critical factors such as dose, route and timing of allergen delivery and the presence or absence of adjuvant factors which have been demonstrated to affect the bias of the adaptive immune response towards preferential IgE production. At present it is believed that there is a bell-shaped curve underpinning the relationship between allergen dose during pregnancy and early infancy, and the development of clinical sensitisation. Thus, at very low doses of allergen the threshold for sensitisation is not achieved and the adaptive immune system remains naive to the presence of the allergen. As the allergen dose is raised, sensitisation occurs via Th2-dependent mechanisms with the consequent development of clinical manifestations. However, at high levels of allergen exposure, immunological tolerance prevails, Th2-type cytokine production is switched off and the child is protected from IgE-mediated sequelae. An observational study of egg intake during pregnancy in relation to allergic outcomes in the infants by 6 months of age has supported the concept of a bell-shaped curve and related this to the level of IgG antibody transported from mother to fetus, across the placenta during the second half of gestation[8]. The efficacy of immunotherapy is thought in part to be due to the production of protective IgG antibodies and there is some limited clinical evidence supporting its role in primary prophylaxis. The offspring born to women who continued rye grass immunotherapy through pregnancy, compared with contemporaneous controls with rye grass allergy, had less rye grass allergy even up to 12 years of age[9]. This is supported by murine studies showing that egg immunisation during pregnancy reduces the susceptibility of offspring to egg sensitisation[10]. However, not all studies have supported this concept as no difference was demonstrated in the development of asthma/rhinitis or skin prick test positivity to pollen allergens, between offspring whose mothers received immunotherapy compared with sibling controls[11]. Postnatally the early use of immunotherapy in the evolution of atopic disease

NS British Journal of Nutrition

where patients had a single specific allergy reduced the risk of an increase in the number of specific allergies[12–14], and pollen immunotherapy has delayed or prevented the march from rhinitis alone to asthma[15,16]. Further work is needed to clarify the potential role of immunotherapy in primary and secondary allergy prevention.

Most peanut allergy occurs in the absence of preceding peanut ingestion. As such, sensitisation is believed to occur via non-oral routes of exposure such as via the skin and/or respiratory tract. In the skin, application of creams containing peanut oil has been shown to increase the risk of peanut allergy approximately 6-fold[7]. It has also been recently established that peanut allergy is greatest in households having a high median peanut consumption, suggesting that environmental non-oral routes of peanut exposure are important for sensitisation[17]. The recently described genetic mutations in the filaggrin gene are associated with an increased risk of eczema, allergic rhinitis and allergen-induced sensitisation[18]. This gene affects skin barrier function and mutations are likely to impair function and allow allergen to penetrate the epithelial barrier leading to immunological sensitisation. The role of the filaggrin gene in the development of food allergy and particularly peanut sensitisation remains to be addressed.

Unfortunately, part of the problem in interpreting large-scale studies of primary prevention in peanut allergy is that they often only examine sensitisation by means of peanut-specific IgE or skin prick test positivity, which is not synonymous with disease. This is due to ethical and logistical concerns of conducting oral peanut challenge. The relationship between sensitisation and clinical reactivity to peanuts is complex, with both false positive and negative associations. This may be attributed to such factors as local IgE production, the inflammatory milieu within the tissues and the allergen content of the materials used in allergy tests. Thus an individual can be skin prick test negative whilst still displaying physical manifestations of peanut allergen on oral exposure. The converse is also true that children with large skin prick tests to peanut allergy can show immunological tolerance. Oleosins are a family of small proteins which contain a unique hydrophobic domain and act as emulsifiers for the storage of lipid in seeds. Isoforms of peanut oleosins have been identified[19]. Falsely negative skin prick tests could be due to the lack of oleosins in commercially available extracts or the fact that their epitopes may be buried in the inner membrane and thus not recognised by cellular-associated IgE. The importance of oleosins is highlighted by their greater bioavailability in foods with a high fat content. A challenge study showed that peanut-containing food with a high fat content augmented the allergic reaction following ingestion[20]. Until studies are conducted which assess both sensitisation and allergic disease there will continue to be conflicting views about the relative value of specific allergen exposure strategies for primary and secondary prevention.

Acknowledgements

E. M. M. has no conflicts of interest. J. O. W. receives bursaries and travel expenses for delivering lectures and serving on scientific advisory boards for Novartis, Merck, UCB Pharma, Allergy therapeutics, Danone, Airsonette and Unilever, and receives research grants from Danone, Airsonette and Lincoln Medical. J. O. W. is a member of the Advisory Committee for Novel Foods and Processes of the Food Standards Agency and until July 2009 was a trustee of the Anaphylaxis Campaign.

Eleanor M. Minshall
John O. Warner

Department of Paediatric Allergy
Imperial College Healthcare NHS Trust and
Imperial College, London W2 1NY, UK
email Eleanor.minshall@imperial.nhs.uk

References

1. King RM, Knibb RC & Hourihane JO (2009) Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy* **64**, 461–468.
2. Hourihane JO, Kilburn SA, Dean P, *et al.* (1997) Clinical characteristics of peanut allergy. *Clin Exp Allergy* **27**, 634–639.
3. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (1998) Statement on peanut allergy. http://archive.food.gov.uk/dept_health/archive/cot/peanut.htm
4. Du Toit G, Katz Y, Sasieni P, *et al.* (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* **122**, 984–991.
5. Thompson RL, Miles LM, Lunn J, *et al.* (2010) Peanut sensitisation and allergy: influence of early life exposure to peanuts. *Br J Nutr* **103**, 1278–1286.
6. Anonymous (2009) Learning Early About Peanut Allergy (LEAP). http://www.leapstudy.co.uk
7. Lack G, Fox D, Northstone K, *et al.* (2003) Factors associated with the development of peanut allergy in childhood. *N Engl J Med* **348**, 977–985.
8. Vance GH, Grimshaw KE, Briggs R, *et al.* (2004) Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. *Clin Exp Allergy* **34**, 1855–1861.
9. Glovsky MM, Ghekiere L & Rejzek E (1991) Effect of maternal immunotherapy on immediate skin test reactivity, specific rye I IgG and IgE antibody, and total IgE of the children. *Ann Allergy* **67**, 21–24.
10. Melkild I, Groeng EC, Leikvold RB, *et al.* (2002) Maternal allergen immunization during pregnancy in a mouse model reduces adult allergy-related antibody responses in the offspring. *Clin Exp Allergy* **32**, 1370–1376.
11. Settipane RA, Chafee FH & Settipane GA (1988) Pollen immunotherapy during pregnancy: long-term follow-up of offsprings. *Allergy Proc* **9**, 555–561.
12. Des Roches A, Paradis L, Menardo JL, *et al.* (1997) Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* **99**, 450–453.
13. Pajno GB, Barberio G, De Luca F, *et al.* (2001) Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* **31**, 1392–1397.

British Journal of Nutrition

14. Purello-D'Ambrosio F, Gangemi S, Merendino RA, *et al.* (2001) Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* **31**, 1295–1302.
15. Möller C, Dreborg S, Ferdousi HA, *et al.* (2002) Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* **109**, 251–256.
16. Niggemann B, Jacobsen L, Dreborg S, *et al.* (2006) Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* **61**, 855–859.
17. Fox AT, Sasieni P, Du Toit G, *et al.* (2009) Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* **123**, 417–423.
18. Weidinger S, O'Sullivan M, Illig T, *et al.* (2008) Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* **121**, 1203–1209.
19. Pons L, Chery C, Romano A, *et al.* (2002) The 18 kDa peanut oleosin is a candidate allergen for IgE-mediated reactions to peanuts. *Allergy* **57**, Suppl. 72, 88–93.
20. Grimshaw KE, King RM, Nordlee JA, *et al.* (2003) Presentation of allergen in different food preparations affects the nature of the allergic reaction – a case series. *Clin Exp Allergy* **33**, 1581–1585.

British Journal of Nutrition