Institution: King's College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Studies on childhood peanut allergy reverse the guidelines to avoid peanuts in infancy

1. Summary of the impact

King's College London (KCL) research has revealed that children who eat peanuts in infancy have a lower risk of peanut allergy than those who do not. This finding, and the associated research, has had significant national and international impact, as it led to a marked change in UK, European and American guidelines, such that they no longer discourage the introduction of peanuts to the infant diet. High profile coverage in scientific, government and lay press has widely disseminated this information.

An additional impact of the work was the development of the KCL Allergy Academy. This has become a large educational programme which each year reaches more than 1000 healthcare practitioners, plus patients and parents.

2. Underpinning research

Peanut allergy is common and can be fatal: Peanut allergy (PA) affects 1–2% of children and results in profound health and lifestyle challenges. It is most commonly found in atopic children, those who are prone to allergic reactions. And it often persists into adulthood, which is an ongoing problem because peanuts are found in many food products. Unlike food intolerances, an allergy to a food such as peanuts involves the immune system; this can be stimulated by tiny or trace amounts of peanuts in predisposed children. An initial exposure to peanuts results in the production of IgE antibodies. Subsequent exposure leads to production of histamines and other compounds that cause the symptoms of allergy, such as itching and inflammation. Allergic reactions to peanuts can be severe and life threatening.

KCL lab builds on strong foundations of research into peanut allergy: The 1998 guidelines in the UK and North America recommended that mothers avoid peanuts during pregnancy and lactation and infants avoid peanut consumption. Despite this, the prevalence of PA has continued to increase in these countries. In 2003, Professor Gideon Lack's research at Imperial College London defined PA in a large birth cohort of 15,000 children in the *Avon Longitudinal Study of Parents and Children* (ALSPAC study). It was found that maternal consumption of peanut during pregnancy and lactation, and infant consumption of peanut, were not risk factors for the development of PA. Professor Lack moved to KCL in May 2006 where he investigated what factors may actually cause PA or protect against PA.

KCL research shows consumption of peanuts in infancy is associated with low rates of peanut allergy: The possibility of inducing tolerance to peanuts when eaten (oral tolerance) was explored in a KCL study that compared the prevalence of PA in Jewish children in the UK and Israel. Both groups shared a common ancestral background (which meant that any differences found were likely to be due to nurture, not nature). It was shown that PA was 10-fold more prevalent in UK children than in Israeli children. Paradoxically, Israeli infants consume large quantities of peanuts in the first year of life, whereas UK children avoid peanuts (1).

Environmental exposure is linked to peanut allergy: Eczema in the first 6 months of life, especially severe eczema, and the application to skin of creams containing peanut oil are important independent risk factors involved in the development of PA. KCL research has shown, in a large case-controlled study, that high household exposure to peanut in the environment is associated with PA (2); this supports the hypothesis that sensitisation to peanut occurs by exposure via the skin, especially via inflamed or broken skin. Maternal peanut consumption during pregnancy and breastfeeding, and infant peanut consumption, were not linked to the development of PA. Although children exposed to high levels of environmental peanut had a high risk of developing PA, they appeared to be protected against developing PA if they had eaten peanuts in the first year of life (2).

Molecular basis of peanut allergy: Filaggrin is a skin protein molecule that helps maintain a two way barrier against water loss from the skin and against the entry of allergens through the skin. Mutations in filaggrin that disrupt its function, so called loss-of-function mutations, are carried by up to 10% of

people. In research involving multiple cohorts, the largest of which was provided by Professor Lack's group at KCL, loss-of-function mutations in filaggrin were shown to be associated with PA (3).
Immune response to peanut allergens is driven by route of exposure: KCL research has revealed that allergic sensitisation through the skin, in people with a peanut allergy, is associated with a skin-homing type of immune cell (the CLA+ T cell). By contrast, in peanut-tolerant people, a gut-homing type of T cell (the α4β7+ T cell) produces the main response to peanut. This provides further evidence that exposure to allergens through the gut induces tolerance (4).

Defining the parameters of oral tolerance to peanuts: The KCL findings have directly led to the creation of the Learning Early About Peanut Allergy (LEAP) study, which is now in its sixth year. This is the first large-scale randomised controlled trial, where 640 high-risk infants were randomly assigned to groups which either consumed peanuts or avoided peanuts in the first year of life. In addition, the Enquiring About Tolerance (EAT) study is also looking at the early introduction of allergenic foods, including peanuts, in over 1300 participants. Emerging data from the LEAP study show that a substantial proportion of the children enrolled at 4–11 months of age had significant IgE levels to peanut, despite never having eaten peanuts (5). Furthermore levels of biologically active peanut protein in household dust is related to a family's peanut consumption (6).

3. References to the research

1. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, Fox AT, Turcanu V, Amir T, Zadik-Mnuhin G, Cohen A, Livne I, **Lack** G. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol.* 2008;122:984–91.
2. Fox AT, Sasieni P, du Toit G, Syed H, **Lack** G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol.* 2009;123:417–23.
3. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, Northstone K, Henderson J, Alizadehfar R, Ben-Shoshan M, Morgan K, Roberts G, Masthoff LJ, Pasmans SG, van den Akker PC, Wijmenga C, Hourihane JO, Palmer CN, **Lack** G, Clarke A, Hull PR, Irvine AD, McLean WH. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol.* 2011;127:661–7.
4. Chan SM, Turcanu V, Stephens AC, Fox AT, Grieve AP, **Lack** G. Cutaneous lymphocyte antigen and α4β7 T-lymphocyte responses are associated with peanut allergy and tolerance in children. *Allergy*. 2012;67:336–42.
5. Du Toit G, Roberts G, Sayre PH, Plaut M, Bahnson HT, Mitchell H, Radulovic S, Chan S, Fox A, Turcanu V, **Lack** G; Learning Early About Peanut Allergy (LEAP) Study Team. Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol.* 2013;131:135–43.e12.
6. Brough HA, Santos AF, Makinson K, Penagos M, Stephens AC, Douiri A, Fox AT, Du Toit G, Turcanu V, **Lack** G. Peanut protein in household dust is related to household peanut consumption and is biologically active. *J Allergy Clin Immunol.* 2013; 132:630-8.

4. Details of the impact

Impact on public policy – a change in the guidelines: The current thinking on peanut allergy and the appropriate timing and route of exposure of peanuts to infants has been directly influenced by the KCL research. The House of Lords Science and Technology Committee and the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) incorporated the KCL research into a change in the recommendations. In a COT report published in 2008 (7), the work on the association of PA with the use of peanut oil-based skin products and high household environmental exposure to peanut was extensively quoted as evidence that the route of relevant exposure in developing PA was not likely to be oral. Overall, the KCL findings provided supporting evidence to change the recommendations and no longer restrict maternal consumption during pregnancy or breast feeding or restrict peanut consumption in infancy. COT stated: *"The shift in the balance of evidence since 1998 is such that the Committee believes that the previous precautionary advice to avoid peanut consumption during pregnancy, breast feeding and infancy, where there is atopy or atopic disease in family members, is no longer appropriate."* (7)

In parallel, the American Academy of Pediatrics (AAP) also reversed its policy in 2008 (8), citing Professor Lack's research on the association of low incidence of PA with infant peanut consumption as contributing evidence. This report concluded that: "*although solid foods should not be introduced before 4–6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease, regardless of whether infants are fed cow milk protein formula or human milk. This includes the introduction of foods that are considered to be highly allergic, such as fish, eggs and foods containing peanut protein".* (8)

Furthermore, the KCL work on the prevalence of PA in the UK and Israel was recognised in the 2009 Government Office for Science review of this work (9): *"The findings call into serious question the 1998 DH advice to mothers.…The reviewers were impressed by the whole approach and commented that the commissioning, execution and follow-up to this work were of the highest standard.… The ideas underpinning this work were innovative and at the forefront of the field"*. Furthermore, one reviewer commented that the *"recommendations and conclusions illustrate reflection by the research team about the meanings of their findings for policy/practice."* (9)

The European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines of March 2013 cite the KCL UK-Israel study (ref 1) and state that "...the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after the age of 4 months" (10). The International Collaboration in Asthma & Allergy with the American Academy of Allergy, Asthma & Immunology, European Academy of Allergy and Clinical Immunology, World Allergy Organization, and American College of Allergy, Asthma, and Immunology also cites our work supporting the concept that early dietary introduction of allergenic foods such as peanut in infants' diet may prevent the development of food allergies (11).

Exposure in the scientific and medical press: Scientists have also been influenced by the findings of the KCL research. An expert panel review on the diagnosis and management of allergy in the USA highlighted the KCL research showing that early sensitisation to foods such as peanuts is independently associated with inflamed skin (dermatitis) and household consumption of peanut (12). The attention of many scientists and clinicians is focused on the role of the first definitive clinical trials, such as KCL's LEAP and EAT, in defining the critical timing of oral exposure to allergens such as peanut (13).

Specialist organisations take the new advice on board: Organisations that support people with severe allergies have been proactive in spreading the word. For example, websites such as that of the Anaphylaxis Campaign provide clear explanations of the various findings from KCL's scientific papers on peanut allergy (14). Similarly, Food Allergy Research & Education (FARE) which works on behalf of the 15 million Americans with food allergies has detailed the KCL research on its website (15).

Influence on clinical practice: The influence of the new guidelines is clear, with examples ranging from the Food Standards Agency's testing of the impact of the new advice (16) to clinicians changing their practice (17). Another consequence of the KCL research was the creation of the KCL Allergy Academy in 2008. This runs multiple study days annually, in various areas of allergy, often involving other partners such as the Academy for Paediatric Gastroenterology at Great Ormond Street. More than 1000 healthcare professionals participate each year, and the KCL Allergy Academy attracts income of £286,000 per year from industry (18).

Dissemination to the general public through the UK and American press: The implications of the KCL research has been extensively reported and well received in the UK press and media. At least ten newspaper reports and the BBC Radio 4's Women's Hour have positively covered the KCL research and the LEAP trial, a selection of which is referenced here (19). Similarly, the American press have also highlighted the worldwide impact of the KCL findings (e.g. 20).

5. Sources to corroborate the impact

Impact on public policy – a change in the guidelines

7. Committee on Toxicity 2008 statement on the "Review of the 1998 COT Recommendations on

Peanut Avoidance". http://cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf
See sections: 42, 44, 48, 56, 57, 68ii, 69, 71, 72

8. The 2008 American Academy of Pediatrics policy revision: Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. http://pediatrics.aappublications.org/content/121/1/183.full
Government Office for Science Review, 16 April 2009. See Project 5
9. http://www.bis.gov.uk/assets/goscience/docs/science-review-fsa/214-09-sc-b-a6-annex-6.doc
10. European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy and Anaphylaxis Guidelines, March 2013. Cites ref 1. http://www.eaaci.org/attachments/EAACI-Food%20Allergy%20Primary%20Prevention.pdf
11. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G, Sampson HA. ICON: food allergy. *J Allergy Clin Immunol.* 2012;129:906-20.

Exposure in the scientific and medical press

12. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel, Oct 2010 http://www.jacionline.org/article/S0091-6749(10)01566-6/fulltext#appseca2 See section 3.5
13. Kessler R. Food: Picky Eaters. *Nature*. 2011;479:S8–9. Discusses LEAP and EAT studies. http://www.nature.com/nature/journal/v479/n7374_supp/full/479S8a.html

Specialist organisations take the new advice on board

14. Anaphylaxis Campaign http://www.anaphylaxis.org.uk/what-is-anaphylaxis/knowledgebase/peanut-allergy-research-into-skin-contact?page=9
15. Food Allergy Research & Education (formerly Food Allergy Initiative and Food Allergy & Anaphylaxis Network) http://www.foodallergy.org/document.doc?id=194

Influence on clinical practice

16. Testing of Draft Revised Government Advice on Peanut Consumption During Early Life http://www.food.gov.uk/multimedia/pdfs/peanutadvice09.pdf
17. What changed my practice: http://thischangedmypractice.com/pediatric-allergy/
18. KCL Allergy Academy: http://www.allergyacademy.org/home

Dissemination to the general public

UK press

19. Advice not to feed peanuts to babies may be behind soaring levels of food allergies, The Telegraph, 25 Oct 2008 http://www.telegraph.co.uk/health/3255865/Advice-not-to-feed-peanuts-to-babies-may-be-behind-soaring-levels-of-food-allergies.html
The Times Allergy Supplement, 2 June 2011 http://np.netpublicator.com/?id=n66771779 (p.10)
BBC Radio 4 – Woman's Hour Programme, 8 Sept 2011
http://www.bbc.co.uk/programmes/p00k9xp7

American press

20. Early Life Peanut Consumption Might Prevent Allergy, ABC News, 15 Nov 2008
http://abcnews.go.com/Health/Healthday/story?id=6259804&page=1
Can peanut allergies be cured…by eating peanuts? Time, 1 March 2010
http://www.time.com/time/health/article/0,8599,1968474,00.html
The Peanut puzzle, The New Yorker, 7 Feb 2011 http://jeromegroopman.com/ny-articles/PeanutPuzzle-0207-2011.pdf