

Institution: University of Aberdeen

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Maternal allergen exposure during pregnancy and childhood allergy: changing UK Public Health policy

1. Summary of the impact

Research by the University of Aberdeen has helped deliver a turnaround in the medical advice given to pregnant women in the UK regarding the consumption of peanuts. Previous Department of Health advice was for pregnant women with a personal or family history of allergic disease to avoid eating peanuts in order to prevent allergy in their offspring. However, the Aberdeen research into neonatal immune responses demonstrated that laboratory responses of cord blood mononuclear cells exposed to allergens *in vitro* were unrelated to antenatal allergen exposure. The findings and resulting change in health advice attracted wide international attention.

Therefore this research has had impact in: health and welfare by changing dietary guidelines, increasing public awareness of a health risk public behaviour and influencing decisions and care practices by a health service.

2. Underpinning research

Asthma and allergic diseases such as atopic dermatitis, allergic rhinitis and food allergies are closely associated inflammatory conditions that share a common immunological aetiology. These conditions are major public health concerns in affluent westernised countries because of their high prevalence - approximately 39% of children and 30% of adults in the UK have one or more of these conditions - and financial impact on healthcare systems. It is increasingly evident that antenatal and early life factors influence the development of asthma and allergic disease.

In 1997/8, Anthony Seaton, Professor of Environmental and Occupational Medicine at the University of Aberdeen since 1988 (retired 2003); and Dr Graham Devereux, Clinical Senior Registrar and (since 2005) University of Aberdeen Clinical Senior Lecturer/Honorary Consultant Physician, (subsequently promoted to Professor), established a birth cohort study to investigate associations between maternal diet during pregnancy and childhood asthma and allergic disease. To provide mechanistic insight into detected associations, the Aberdeen researchers conducted a study of cord blood mononuclear cells (CBMC), funded by a personal fellowship awarded in open competition to Dr Devereux.

Cord blood mononuclear cells (CBMC) can be extracted from neonatal umbilical cord blood and, if cultured, will proliferate after exposure to allergens. Previously it was almost universally accepted that these responses were a consequence of fetal exposure to, and immune sensitisation by, maternally sourced allergens and increased the likelihood of childhood allergic disease. This finding was believed to be pertinent to the development of food allergy, particularly peanut allergy, which had increased in prevalence in previous decades, from being a rarity to approximately 2% of children in 2000.

The aim of the fellowship was to identify antenatal influences on CBMC responses [1]. A novel method was developed to quantify CBMC proliferative and cytokine responses after stimulation with allergens [2]. Using the control antigen keyhole limpet haemocyanin (from the west coast of Chile), it became clear that CBMC were responding to antigens to which pregnant women in the UK could not have been exposed.

This unexpected finding was followed up by an investigation of the association between CBMC responses and foetal allergen exposure. A method was developed to determine whether the

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CBMC were responding to allergens for the first time, or had been stimulated previously, using the CD45 antigen expressed on the surface of Th-cells (specifically the CD45 isoform of the cells responding after allergen stimulation were determined) [3]. This approach is well-established in adults; unsensitized cells express the CD45RA^{high} isoform while previously sensitized cells express the CD45RO^{high} isoform. Using this method for the first time in neonatal Th-cells, the Aberdeen researchers demonstrated that CBMC proliferative responses to stimulation with timothy grass allergen are split equally between infants with CBMC responses mediated by Th-cells that express CD45RA^{high} and infants with CBMC responses mediated by Th-cells that express the CD45RO^{high} isoform [3].

It was concluded that timothy grass allergen-specific foetal Th-cells can be sensitised *in utero*, but that this priming does not occur in all individuals even if their CBMC respond to the allergen *in vitro*.

These outcomes contradicted the widely held view at the time that CBMC responses were a direct consequence of foetal immune sensitisation. Therefore the experimental basis for concluding that *in utero* exposure to maternally sourced peanut allergen sensitised the foetal immune system leading to peanut allergy in later life was no longer tenable.

3. References to the research

Peer reviewed publications:

[1] Devereux G, Barker RN, Seaton A. (2002). Ante-natal determinants of neonatal immune responses to allergens. *Clin Exp Allergy*, 32: 43-50. (Citations= 204).

(This research represented the first demonstration that cord blood mononuclear cell responses were associated with recognised and putative risk factors for asthma and allergy e.g. birth order, maternal smoking, maternal diet).

[2] Devereux G, Hall AM, Barker RN. (2000). Measurement of T-helper cytokines secreted by cord blood mononuclear cells in response to allergens. *J Immunological Methods*, 234: 13-22. (Citations =36).

(This work described the development and validation of a sensitive novel cellELISA technique to quantify the secretion of cytokines by cord blood mononuclear cells).

[3] Devereux G, Seaton A, Barker RN. (2001). *In utero* sensitisation of allergen specific T-helper cells. *Clin Exp Allergy*, 31: 1686-1695. (Citations= 64).

(These studies described for the first time that cord blood mononuclear cell responses are not a reliable indicator of antenatal allergen exposure and immunological sensitisation, contradicting this widely held belief).

Underpinning grants:

SHERT/Mrs J Baxter Fellowship 1547: *The in utero environment, neonatal T-helper cell differentiation and the development of childhood atopy*. 1998-2000. £90,000 awarded to Dr Graham Devereux.

Grampian University NHS Trust Endowment Grant: *The in utero environment, neonatal T-helper cell differentiation and the development of childhood atopy*. 1999-2000. £4,500 awarded to Dr Graham Devereux.

4. Details of the impact

The research in Aberdeen and subsequent collaborative work has directly impacted on public health and wellbeing, with documented changes to dietary guidelines issued by the UK Department

of Health to pregnant women regarding potential health risks. Existing Department of Health advice for pregnant women with a personal or family history of allergic disease was to avoid eating peanuts to reduce the risk of their children developing a peanut allergy. This advice was guided by responses seen in immune system cells cultured and exposed to allergens in the laboratory.

In 2008, the British Nutrition Foundation published a review undertaken on behalf of the Food Standards Agency. Devereux was part of the team compiling the review, which was tasked with systematically reviewing literature relating to early life peanut exposure and subsequent peanut allergy [a, b]. The review of human studies, and of narrative expert-led reviews of animal and CBMC studies (including the Aberdeen ones) demonstrated the lack of clear evidence to link either maternal exposure, or the timing of introduction of peanuts in the diets of children, to the subsequent development of sensitisation or allergy to peanuts. This work thus called into question the then UK Department of Health advice offered to expectant and breast-feeding mothers regarding peanut consumption [c].

The Committee on Toxicity (COT, an independent scientific committee that advises government departments) subsequently decided to review its 1998 statement that recommended pregnant women with a personal or family history of allergic disease should avoid eating peanuts during pregnancy and whilst breastfeeding [c]. As one of three experts in the area, Devereux was invited to contribute to the 2009 review, which included epidemiological and trial data, as well as a review of evidence, (including the Aberdeen research) that *in vitro* CBMC responses could occur in the absence of maternal allergen exposure. The overall conclusion of the COT review was that the available evidence suggested neither an adverse or beneficial effect of maternal peanut consumption during pregnancy and lactation on the development of peanut allergy in children [d]. The COT conclusions were accepted by the Department of Health and issued as revised advice to pregnant mothers in 2009. It was then incorporated into the advice literature provided to all pregnant women in the UK (approximately 600-700,000 expectant mothers every year) [e,f]. The new advice states that as the research has shown that there is no clear evidence to say whether eating peanuts during pregnancy affects the chances of a baby developing a peanut allergy, pregnant women can eat peanuts as part of a balanced diet as long as they are not allergic to them or advised otherwise by a health professional. The same advice has been offered to breastfeeding mothers.

Devereux has shared his research with a wide international audience, presenting to a number of conferences and organisations. These include the December 2008 Netherlands Asthma Foundation Annual Scientific Meeting in Amersfoort, the XXII European Congress of Perinatal Medicine in Granada in May 2010, and the European Science Foundation European Medical Research Councils (EMRC) Forward Look 'Gene Environment Interaction in Chronic Disease' in Barcelona in October 2010. He also presented the data to the British Nutrition Foundation taskforce for Nutrition and Development: short- and long-term consequences on health, in May 2013.

Therefore the claimed impact as defined by REF is that: the research by Dr Devereux and colleagues and subsequent collaborative work has directly impacted on public health and well-being with documented changes to dietary guidelines issued by the Department of Health to pregnant women to inform them of a health risk and change behaviour. Decisions by a health service have therefore been informed by research, public behaviour has changed, health care training guidelines have changed; public awareness of a health risk has changed; dietary guidelines have changed; professionals have used this research in conducting their work.

5. Sources to corroborate the impact

[a] British Nutrition Foundation. Systematic review of literature on early life patterns of exposure to, and avoidance of, food allergens and later development of sensitisation and clinical food allergy, with particular reference to peanut allergy.

http://www.foodbase.org.uk//admintools/reportdocuments/439-1-774_T07052_Final_main_report-June_2008_-_as_accepted-_with_footnote.pdf

(Report to FSA presenting the results of a systematic review conducted by the British Nutrition Foundation on behalf of the Food Standards Agency at the request of the COT. Researcher from Aberdeen's role acknowledged in authorship, along with highlighted research that is described and cited on page 100 and referenced on page 102.)

[b] Thompson RL, Miles LM, Lunn J, Devereux G, Dearman RJ, Strid J, Buttriss JL. (2010). Peanut sensitisation and allergy: influence of early life exposure to peanuts. *Br J Nutr*, 103: 1278-86.

(Publication presenting the results of a systematic review conducted by the British Nutrition Foundation on behalf of the Food Standards Agency at the request of the COT. Dr Devereux's role acknowledged in authorship, along with highlighted research.)

[c] Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Peanut Allergy. London: Department of Health; 1998. <http://cot.food.gov.uk/pdfs/cotpeanutall.pdf>

(Original 1998 COT advice that pregnant women carrying a fetus at high risk of allergic disease should avoid consuming peanuts during pregnancy.)

[d] Committee on Toxicity of Chemical in Food, Consumer Products and the Environment (2009). Statement on the review of the 1998 COT recommendations on peanut avoidance.

<http://cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf>

(2009 COT review of 1998 COT recommendations. Dr Devereux's role in COT review acknowledged on page 1 and role in British Nutrition Foundation systematic review containing original research acknowledged on page 7.)

[e] Revised Government advice on consumption of peanut allergy during pregnancy, breastfeeding, and early life and development of peanut allergy (2009).

http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/Healthcare/Children/Maternity/Maternalandinfantnutrition/DH_104490

(Revised Department of Health advice to pregnant women that they no longer need to avoid eating peanuts during pregnancy.)

[f] NHS Choices, Foods to avoid during pregnancy. <http://www.nhs.uk/conditions/pregnancy-and-baby/pages/foods-to-avoid-pregnant.aspx>

(NHS information to pregnant women on foods during pregnancy, which highlights the change in advice on peanuts.)