

EDITORIAL

Fetal and early-life origins of allergy

John O. Warner & Jill A. Warner

Imperial College London, London, UK

E-mail: j.o.warner@imperial.ac.uk



To cite this article: Warner JO, Warner JA. Fetal and early-life origins of allergy. *Pediatr Allergy Immunol* 2014; **25**: 7–8.

DOI:10.1111/pai.12201

In October 1990, the first issue of *Paediatric Allergy and Immunology* appeared under the editorship of Professor Bengt Björkstén. The very first review article was entitled 'Primary Sensitisation to Inhalant Allergens during Infancy.' It discussed the early postnatal period as a time of heightened risk for sensitization and heralded a major focus of the journal on the early-life origins of allergic disease (1). The second issue of the journal contained a paper from our research team on the concentration of exposure to allergens in early life in relation to subsequent sensitization, reinforcing the observations made by Holt and colleagues that early postnatal high allergen exposure increased the likelihood of sensitization (2).

An explicit aim of the journal was to enhance understanding of the immune mechanisms underlying the ontogeny of allergic disease with a view to identifying targets for intervention which might subsequently prevent the onset of allergy or alternatively be used as early intervention to interrupt the allergic march. Indeed the first issue, after we took over as editor in chief and managing editor in 1997 included a paper from the ETAC (Early Treatment of the Atopic Child) study group (3). The study was designed to demonstrate whether a pharmacotherapeutic approach could interrupt the 'March' from eczema to asthma. We were pleased to 'sign-out' from our editorship in 2010 with an issue which contained seven articles all focused on the early-life origins of allergic disease. This further elaborated on the imbalance in T helper 1 (TH1) and T helper 2 lymphocytes (TH2) and was followed by a number of studies identifying environmental factors in early life which modify outcomes (4).

This theme has continued under the current editorship of Professor Ulrich Wahn with the June 2013 issue that contained systematic reviews on the influence of the Mediterranean diet on asthma in children and microbial exposure on food allergy (5, 6).

We remain ever optimistic that we will identify effective strategies for allergy prevention. However, hitherto other than in animal models, most studies have merely identified associations between particular factors and subsequent allergy and allergic disease. Association is not synonymous with causation, and as indicated in an editorial by Ulrich Wahn, in some respects, our



Figure 1 A cartoon indicating that while early life interventions in murine models of allergy have been effective in modifying outcomes, hitherto human studies have been disappointing.

concepts and proposals have failed to transpose into effective interventions (7). Furthermore, it is now clear that influences on allergic sensitization are partially independent of those leading to allergic disease. While the ontogeny of allergic disease in murine models is relatively well characterized, the same is not true for humans. This is perhaps best illustrated by a figure we appended to the front cover of the February 2010 issue (Figure 1).

Epidemiology

Allergic conditions have increased in many countries worldwide over the last 30–40 yrs. This clearly cannot be explained by genetic mutation and has led to much research to identify environmental factors that could explain these changes (8). Migration studies have pointed to the early-life environment as being particularly critical to the expression of disease. First-generation adult immigrants from countries with a low prevalence of allergic disease to those with a higher prevalence retain a low risk of allergic disease, but when the children of

new immigrants are born in a higher prevalence country they have a much higher prevalence matching that of the indigenous population (9). While old studies suggested an association between breastfeeding and a reduced subsequent risk of allergic disease, more recent studies have been, from a pediatrician's perspective, immensely disappointing. There is currently inconclusive evidence of a protective effect of breastfeeding for eczema development and food allergy, while for asthma, there is a potential paradoxical effect (10). One could argue that postnatal environmental manipulation is shutting the door after the horse has bolted. This has led to more studies of antenatal events which constituted much of our research over the last 30 yrs.

Fetal origins

Pregnancy is in some respects a T helper 2 lymphocyte-mediated phenomenon. Under normal circumstances, the materno-fetal interface creates a TH2 and T regulatory environment by the generation of IL-4, 10, 13, and TGF-beta. These downregulate the maternal TH1 response against fetopaternal antigen which is an essential event to sustain pregnancy and enhance fetal growth. Failure to achieve this balance in both murine and human models results in early miscarriage or intrauterine growth restriction (11). The TH2-promoting cytokine milieu clearly impacts on the fetus, and there is good evidence of a TH2-biased immune response in the neonate (12) which in some circumstances may be irreversibly committed as a result of a range of factors including maternal and fetal genes, maternal allergy, nutrition, allergen and antibiotic exposure, and maternal gut microbiome (13). The latter is critical to the inoculum received by the neonate during a normal vaginal delivery. The rapid development of diversity of the gut microbiome in the infant

is likely to be a key factor switching the neonatal TH2-biased response to a more balanced pattern (14).

The future

It has become very clear that searching for a single explanation to explain the very high and increasing prevalence of allergic diseases is unlikely to provide definitive answers. There are complex interactions between genes and environment as for example shown in a study from Taiwan on environmental tobacco smoke exposure, gender, and interleukin-13 genetic polymorphisms (15). To identify multiple interacting events, it will be necessary to recruit vast pregnancy/birth longitudinal cohorts with monitoring of the mother and infant using genomics, proteomics, metabolomics, and microbiome in relation to environment. This will require the handling of massive databases with input from mathematicians and IT experts to conduct cluster analyses. Such approaches have been pejoratively described as fishing exercises, but are likely to be much more productive than employing pre-conceived hypothesis-driven research. The latter will, however, be required to substantiate associations identified from cluster analysis. This can then be followed by definitive intervention trials to prevent allergic disease.

To add further complexity to the situation, the new mantra, now that defining the human genome has accounted for only a small proportion of human diversity, is epigenetics. This elaborates on the way in which environmental factors, of which nutrition may be particularly critical, affect gene expression without directly changing the DNA sequence and thereby affect immune programming in early life. However, much still needs to be learned before there will be any chance of defining an effective intervention strategy, and we have no doubt that Paediatric Allergy and Immunology will be at the forefront in publishing this work (16).

Reference

- Holt PG, McMenamin C, Nelson D. Primary sensitisation to inhalant allergens during infancy. *Pediatr Allergy Immunol* 1990; **1**: 3–13.
- Warner JA, Little SA, Pollock I, Longbottom JL, Warner JO. The influence of exposure to house dust mite, cat, pollen and fungal allergens in the home on primary sensitisation in asthma. *Pediatr Allergy Immunol* 1990; **1**: 79–86.
- ETAC study group. Determinants of total and specific IgE in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1997; **8**: 177–84.
- Warner JO. In this issue. *Pediatr Allergy Immunol* 2010; **21**: 3–4.
- Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Piftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review meta-analysis. *Pediatr Allergy Immunol* 2013; **24**: 330–8.
- Marrs T, Bruce KD, Logan K, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 2013; **24**: 311–20.
- Wahn U. Considering 25 years of research on allergy prevention – have we let ourselves down? *Pediatr Allergy Immunol* 2013; **24**: 308–10.
- Burr ML, Wat D, Evans C, Dunstan FD, Doull IJ. British Thoracic Society Research Committee. Asthma prevalence in 1973, 1988 and 2003. *Thorax* 2006; **61**: 296–9.
- Wang H-Y, Wong GWK, Chen Y-Z, et al. Prevalence of asthma among Chinese adolescents living in Canada and in China. *Can Med Assoc J* 2008; **179**: 1133–42.
- Matheson NC, Allen KJ, Tang MLK. Understanding the evidence for and against the role of breastfeeding in allergy prevention. *Clin Exp Allergy* 2012; **42**: 827–51.
- Warner JO. The early life origins of asthma and related allergic disorders. *Arch Dis Child* 2004; **89**: 97–102.
- 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.
- Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med* 2012; **17**: 82–91.
- Bisgaard H, Li N, Bonnelykke K, Chawes BLK, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol* 2011; **128**: 646–52.
- Chen C-H, Lee YL, Wu M-H, et al. Environmental tobacco smoke and male sex modify the influence of IL13 genetic variants on cord blood IgE levels. *Pediatr Allergy Immunol* 2012; **23**: 456–63.
- Amarasekera M, Prescott SL, Palmer DJ. Nutrition in early life, immune programming and allergies: the role of epigenetics. *Asian Pac J Allergy Immunol* 2013; **31**: 175–82.