

Early origins of allergic disease: a review of processes and influences during early immune development

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Purpose of review

With the disturbing increase in allergic disease, there is a pressing need to determine the causes, pathogenesis and safe avenues for disease prevention. Although events in early life appear important, no causal pathways have been identified. This review examines new developments in the area of foetal and early postnatal immune maturation. It secondly addresses early predisposing influences and protective factors that may have a future role in allergy prevention.

Recent findings

New developments in the understanding of the ontogeny of allergen-specific immune responses in atopic infants are discussed, including the role of early type 1 and 2 immune responses, and how these are influenced by perinatal antigen presenting cell and T-cell immaturity. The controversial role of early dietary exposures including breastfeeding, food allergens, hydrolyzed formulae and other dietary factors including omega-3 fatty acids are discussed in the context of the most recent literature. Equally contentious, the role of early house dust and pet allergen exposure is discussed in light of new epidemiological studies and disappointing early results of multicentre allergen avoidance studies. Finally, a number of studies in animals and humans suggest that bacterial products can influence early immune development, providing a new potential therapeutic avenue for disease treatment and prevention.

Summary

Complex multifactorial genetic and environmental interactions make research in this area difficult and apparent associations with allergic disease may not be causal in nature. Many current targets for prevention, such as early allergen exposure and infant feeding practices, are proving to be ineffective and may not be directly implicated in rising rates of disease.

Keywords

ontogeny, cytokines, cord blood, infants, allergy, T-cells, antigen presenting cells, bacteria, breastfeeding, aeroallergens, food allergens

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Abbreviations

APC	antigen presenting cell
BCG	bacillus Calmette–Guerin
HDM	house dust mite
PUFA	polyunsaturated fatty acid

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Introduction

Events and exposures during early life can influence many aspects of development, and immunological effects may be contributing to the recent epidemic increase in allergic diseases. A better understanding of the mechanisms of allergy pathogenesis is essential in order to provide methods for safely modifying early immune development and preventing allergic disease. This review explores early immune maturation in light of the most recent publications in this area, as well as potential factors which may influence these processes, as candidates for disease prevention.

Ontogeny of early immune responses in pregnancy and early childhood

Because early immunological events influence subsequent patterns of immune development, these are now of key interest in understanding the pathogenesis of allergic diseases.

Early allergen-specific immune responses in atopic infants

The expression of type 2 responses to allergens is the hallmark of allergic disease at all ages. In allergic infants and children, stronger allergen-specific type 2 responses are also the main distinguishing immunological feature and may be evident within the first year of life. However, recent studies indicate that allergen-specific type 1 interferon- γ responses are not necessarily deficient and may actually be increased as compared with non-allergic children [1*,2*,3]. The origins of these apparently 'excessive' or inappropriate immune responses are unclear, but appear to be related to earlier events, possibly in foetal life. Other recent studies [4*], demonstrate that T-cells from allergic infants have higher expression of activation markers (such as CD25 and CD30), also indicating that they are intrinsically more 'responsive' to allergens.

Impaired type 1 immune function in early life

Neonatal type 1 interferon- γ responses are significantly attenuated compared with adults [5*], and many groups

have observed that newborns at high risk of allergy (parental disease) have a greater relative deficiency of interferon- γ responses than infants at low risk of allergy. This was observed again in a recent study [6], and further suggests that impaired type 1 immune function may contribute in some way to persistence of the type 2 responses which normally dominate in the neonatal period. As yet, there is no definitive proof of this.

This reduced capacity for type 1 responses to polyclonal stimulation is also seen in children who develop symptomatic allergy in childhood [2•], even though allergen-specific interferon- γ responses may not be reduced (as discussed above). The reason for stronger interferon- γ responses to allergens in individuals with otherwise reduced interferon- γ capacity is unclear and requires further investigation.

The significance of foetal responses to allergens

There is ongoing speculation about whether allergen-responsive foetal T-cells have been primed by allergen exposure *in vivo* or if these reflect some other poorly understood process. Only half of the allergen-responsive T-cells in cord blood have recently been shown to have the CD45RO+ 'memory' phenotype [7•], and it is not clear why the remaining responses are observed in 'naïve' cell populations [7•]. For many reasons it may be inappropriate to assume that neonatal CD4+CD45RO+ T-cells are equivalent to adult T-cells with the same memory markers [8]. Mechanisms of potential in-utero allergen exposure are also unconfirmed. Allergens have been measured in amniotic fluid, and there is also indirect evidence that allergens can cross the placenta [9]. However, the relevance to in-vivo immune development is unclear. Of note, there is no clear correlation between levels of maternal allergen exposure and the presence, magnitude or character of foetal immune responses to these allergens [10,11•,12]. This suggests that maternal allergen encounter in pregnancy may not have a major influence on infant immune development, although more studies are needed.

Predisposition for type 2 immune responses in the neonatal period

During pregnancy maternal responses are normally type 2 skewed, with similar effects in the neonate [5•] and the placenta [13•]. This appears to be the result of both pro-type 2 products from the placenta (progesterone, interleukins 10 and 4 and prostaglandin E2) and apparent immaturity of type 1 function at birth. The relationship between type 2 responses at birth and atopic risk or atopic outcomes has been unclear, with a number of studies showing conflicting reports. In most recent studies, atopic risk (maternal atopy) was associated with higher numbers of CD4+IL13+ cells in cord blood [14] and stronger neonatal interleukin-13 (type 2) responses

to milk allergen (β -lactoglobulin) [15•]. Atopic disease (at 1 year) has also been associated with higher neonatal polyclonal interleukin-13 responses [16] or increased numbers of CD4+IL13+ cells in cord blood [14]. However, at this stage none of these measures appears to be of any practical value in predicting disease development.

The role of antigen presenting cell immaturity in early immune development

Reduced capacity for type 1 responses during the perinatal period may be related to the reduced capacity of neonatal antigen presenting cells (APCs) to provide adequate pro-type 1 T-cell stimulation during activation, in the form of interleukin-12 and other cytokines [17•] (S. Prescott *et al.*, in preparation). Recent cross-sectional data indicate that the capacity of APCs to produce interleukin-12 is orders of magnitude lower in neonates than in adults, and may not approach adult levels until late childhood [18•]. It has been suggested that a relative absence of interleukin-12 favours the development of a default type-2 cytokine profile, although other factors are clearly involved. Accordingly, the principal APCs involved in activation of naïve T-cells (dendritic cells) are also less mature in neonates and have been observed to be intrinsically programmed against type 1 responses [17•].

However, while reduced neonatal interleukin-12 capacity is related to the type 2 skewed allergen-specific responses observed in the neonate (S. Prescott *et al.*, in preparation), there is currently no conclusive evidence that high risk infants have more immature APC interleukin-12 signalling to account for relatively weaker type 1 responses. Although one recent study [19•] suggested that interleukin-12 responses to allergens are lower in neonates with a family history of allergic disease, other studies showed no differences in the capacity of high risk neonates to mount interleukin-12 responses to bacterial lipopolysaccharide (S. Prescott *et al.*, in preparation).

The role of perinatal T-cell immaturity in early immune development

An observed lack of correlation between interleukin-12 and interferon- γ responses in the neonate (S. Prescott *et al.*, in preparation) could also indicate that neonatal T-cells are less responsive to interleukin-12. Functional differences in the capacity of T-cells to respond to interleukin-12 and other pro-type 1 signals from APCs may occur in atopic or high risk infants. Although there is one report that neonates at high risk of atopy [20•] have reduced T-cell expression of the interleukin-12 receptor (IL-12R β 1) further studies are required to establish if T-cells of high risk infants are less responsive to T-helper type 1-trophic signals.

Differences in interferon- γ gene regulation in the neonate also indicate that neonatal T-cells are intrinsically different from mature adult T-cells. White *et al.* [21••] recently reported that neonatal expression of interferon- γ is inhibited by hyper-methylation of interferon- γ promoter CpG sites. It is not yet clear how variations in perinatal type 1 gene methylation status relate to the risk of subsequent allergic disease. The regulation of type 2 cytokine gene transcription has not been investigated in the neonatal period, although there are some preliminary studies in adults [22•]. It was recently observed that 'type 2' CD8+ T-cells (rather than CD4+ T-cells) are the main source of interleukin-13 in the neonate [5]. The possible immunoregulatory role of these and other cells still remains to be determined.

Exposures in early life: associations with early immune development and allergic disease

With the disturbing increase in allergic disease, there has been a pressing need to identify perinatal exposures that can be readily modified to reduce the risk of subsequent disease (reviewed by Liu [23]). While many potential in-utero and perinatal exposures have been associated with allergic disease and asthma [24••] the significance of these and potential causal pathways are unclear. Many of the targets for prevention, such as modifying early allergen exposure and infant feeding practices, may not actually be directly implicated in the increase in disease. In fact, recent findings challenge existing notions that early allergen avoidance and breastfeeding prevent allergic disease, as discussed further below.

Breastfeeding

Although breastfeeding is recommended in most centres as part of early strategies for allergy prevention, recent studies challenge this practice. The most recent of these [25••] found that New Zealand children born in the 1970s were more likely to develop subsequent allergic disease and sensitization at 13 years if they were breast fed ($n=504$) than if they were formula fed ($n=533$). A number of other recent studies support this association, including a German investigation [26•] which also found that a longer duration of breastfeeding increased the risk of atopic eczema dermatitis syndrome. Reports from both North America [27•] and Europe [28] also document an increased risk of asthma in breastfed children whose mothers were asthmatic, compared with those without maternal asthma, raising further questions about possible mechanisms.

These latest reports occur within a literature of fairly mixed findings, and are in apparent conflict with the most recent meta-analysis [29••] which found that exclusive breastfeeding in the first months of life was associated with reduced rates of subsequent asthma (OR

0.70; 95% CI 0.60–0.81). This systematic review, which included 12 prospective studies (8183 infants), found that the protective effect was greater in studies of high risk (HR) children (OR 0.52) than in studies of a combined population (OR 0.73). Since then, there have also been a number of reports suggesting a protective relationship between breastfeeding and allergic disease [30], including one that found that this relationship was independent of maternal asthma [31••]. Of particular interest, several of the studies that showed breastfeeding protected from early transient wheeze found the opposite relationship with persistent wheeze [27•,32]. While effects on 'transient wheeze' may be due to protection from infection this does not appear to explain all of the effect [33].

The practice of breastfeeding could influence infant immune development directly through 'immunological' properties and microbiological influences, but also indirectly by delaying exposure to other more allergenic proteins, such as cows' milk proteins and other antigenic formulations. Thus exclusive breastfeeding may have different effects on the developing immune system than if breastfed infants also receive other formulations, even if infrequently. Furthermore, as infants can be sensitized to food allergen in breast milk, variations in maternal diet while lactating may also contribute to the conflicting relationships in the literature.

It is not clear what role infant feeding practices have had (if any) in the significant increase in allergic disease during the last 20–30 years. Future studies in this area are also likely to be confined by the inability to conduct randomized controlled trials, confounding factors and potential recruitment biases [34]. Although the relationships between breastfeeding and the development of allergic immune responses remain unclear, breastfeeding has many advantages for both mother and child and is recommended for many other reasons.

The role of early food allergen exposure and hydrolysed formulae

Mucosal events which lead to oral tolerance or allergic disease are poorly understood. Most current guidelines for allergy prevention are based on limited evidence derived from population studies with inherent problems. Cumulatively, the literature suggests that delaying the introduction of solid foods may to some extent reduce or delay the onset of infantile allergic diseases, including atopic dermatitis and food allergies. However, these effects are not particularly strong, and the long-term benefits are less convincing. Most recently, preliminary results of multicentre interventions to reduce allergy – including delayed introduction of solids, breastfeeding or hydrolysed formulae and house dust mite (HDM) reduction strategies – showed disappointing results [35•].

A 2002 Cochrane meta-analysis [36•] reviewed the results of six randomized control trials which examined the effects of hydrolysed formulae and dietary restriction in infants at high risk of allergy. Although the authors concluded that these interventions were associated with reduced risk (RR 0.4; 95% CI 0.19–0.85) of wheezing at 1 year of age, there are no data to confirm that this has any long-term benefits in reducing asthma, particularly in view of the heterogeneous aetiology of early infant wheeze. At present, most centres continue to recommend delaying introduction of solids (until 4–6 months) and the use of hydrolysed formula if breastfeeding is not possible. It is clear that these guidelines should be regularly reviewed and modified as more data becomes available.

The role of early house dust mite exposure

While a number of recent studies confirm that sensitization to aeroallergens (such as HDM) is a strong risk factor for the development of asthma [37,38] the relationships between early exposure and later disease are less clear. One large, long-term prospective study confirmed previous reports that aeroallergen sensitization is a strong risk factor for asthma, wheeze and bronchial hyperactivity [39]. However, the investigators failed to show any relationship between early allergen exposure and these clinical symptoms, and proposed that the development of immunoglobulin-E responses occurs by processes which are independent of those which lead to asthma.

Most of the multicentre studies assessing the effects of HDM avoidance interventions are still incomplete, or only have data on the relationship between HDM reduction and early clinical outcomes.

Although early results from one study observed that interventions were associated with less respiratory symptoms at 1 year of age [40], more recent reports from other multicentre studies suggest no differences in lung function or atopic symptoms at 18 months [35•] or 2 years [41••]. All of these studies require further follow-up analysis before any further conclusions or recommendations can be made. At this stage there is not a strong case for HDM allergen avoidance in the prevention of allergic disease.

The role of early pet exposure

A growing number of studies showing a protective relationship between pet exposure and allergen sensitization have challenged traditional concepts and approaches. In a recent North American cohort, Ownby *et al.* [42••] reported that having pets (two or more cats or dogs) in the household during the first year of life was not only associated with less sensitization to these allergens at 6 years of age, but less sensitization to other

allergens, including moulds and pollens. This is also consistent with findings of a recent Dutch study [43•]. Many pet-exposed children who do not develop immunoglobulin-E responses have immunoglobulin-G4 antibody responses to pets [44••,45••], which are believed to be the result of type 2 cytokine driven immunoglobulin isotype switching. It has been proposed that these children have 'modified type 2' responses without immunoglobulin-E production and its adverse effects. The potential mechanisms are not yet understood. Thus, there is accumulating evidence that recommendations for pet allergen avoidance to prevent allergic disease are not justified. Before alternative recommendations can be made further studies are required to determine the mechanisms of this emerging protective relationship that may be related to higher levels of bacterial endotoxin [46] in the presence of cats, dogs and cockroaches in the home [47•].

The role of bacterial exposure in early immune development

A similar protective effect of early animal exposure on allergic sensitization was also observed in European farming communities [48•], leading to further speculation that this may be related to the type 1-immunostimulant effects of bacterial endotoxin [46]. This has provided ongoing support for the 'hygiene hypothesis' that rising rates of allergic disease are due to increasingly 'clean' environments, which fail to provide adequate type 1 stimulation for suppression of type 2 allergic responses [49••]. A number of recent observations suggest that this relationship may begin in the antenatal period. Neonates with in-utero infections have stronger type 1 interferon- γ immune responses [50], and higher maternal endotoxin exposure in pregnancy has been associated with lower cord blood immunoglobulin E levels [51•]. Conversely, lower levels of bacterial recognition proteins (soluble CD14) in amniotic fluid were associated with the development of atopy and eczema [52••]. One recent study also linked the use of antibiotics and infection in pregnancy and a higher risk of subsequent allergic disease [53•], but the interpretation of this is difficult. Thus, while there is accumulating epidemiologic and experimental evidence to support the hygiene hypothesis, there is no definitive proof and it remains an area of heavy debate [49••,54••].

The therapeutic use of bacterial products in allergy prevention

Despite reservations about the hygiene hypothesis, there has been growing interest in the administration of bacterial products for allergy prevention. Probiotics have recently emerged as one of the leading microbial candidates for early immune modification (recently reviewed by Cross *et al.* [55]). In a recent animal (mouse) model of food anaphylaxis, the intraperitoneal

administration of a lactobacillus strain [56•] induced interleukin-12 responses and suppressed the development of immunoglobulin-E responses and anaphylaxis. In humans, there was one study [57] which claimed a potential benefit of probiotics in allergic disease prevention. There are currently a number of ongoing studies to determine the significance of this before recommendations can be made.

As potent type 1 immunostimulants, mycobacteria antigens have also been considered as vaccine candidates for both prevention and treatment of allergic disease (reviewed by Beasley *et al.* [58•]). In sensitized animals, mycobacteria have also been associated with improved pulmonary function [59•], reduced airways inflammation [60•], eosinophilia [61•] and expression of adhesion molecules [62•]. Although the mechanisms are unclear, there is some evidence (again in mice) that mycobacteria give rise to allergen specific CD4+CD45B-low regulatory cells which mediate a reduction in airways inflammation through the production of TGF β and interleukin-10 [63•]. In humans, bacillus Calmette–Guerin (BCG) vaccination was also recently associated with reduced total and specific immunoglobulin-E in allergic individuals [64•,65•,66], and improved lung function in asthmatic patients [67•]. Intradermal administration of mycobacteria has been used therapeutically in children with existing atopic dermatitis with some success [68]. In newborns, BCG can influence immune responses to other antigens (vaccine antigens) promoting both type 1 and type 2 responses [65•]. However, in humans, mycobacterial antigens have not yet shown any benefits in disease prevention. Although Shirakawa [69] reported an inverse association between tuberculin responses (in BCG vaccinated individuals) and atopic diseases, this relationship was not confirmed in a recent Norwegian cohort [70•].

The role of irritants and pollutants

Although the adverse effects of maternal smoking in infant lung development are well recognized, the effects on early immune development are less clear. The role of other indoor pollutants is also poorly understood. One study reported that house renovation during pregnancy was associated with reduced cord blood γ producing T-cells, but the significance of this is not known [6].

The role of other exposures (including dietary polyunsaturated fatty acids)

There is accumulating evidence that maternal dietary polyunsaturated fatty acids (PUFAs) have effects on immune function and inflammation [71•]. It has been proposed that increasingly 'proinflammatory' n-6-PUFA-rich maternal western diets may favour immunological reactivity and type 2 differentiation during critical periods of early development, and that this may be

contributing to the recent increase in allergic sensitization [72]. This has generated interest in early supplementation with antiinflammatory omega-3 (n-3) PUFAs for disease prevention. Effects of maternal dietary PUFAs on neonatal T-cell function (reviewed by Field [73]) have provided the basis for investigating the effects of fish oil supplementation in pregnancy. One preliminary study [74] recently documented that maternal n-3 PUFA-rich fish oil supplementation from 20 weeks gestation until birth was associated with significantly higher n-3 PUFA levels and lower levels of interleukin-13 cytokine in neonatal plasma, suggesting effects on T-cell function. Further studies are needed to examine the role in allergy prevention.

Other strategies

Vaccines have been proposed for both the prevention and the treatment of allergic disease [75,76]. Strategies to induce allergen-specific T-cell tolerance include the induction of systemic or local allergen-dependent or independent type 1 immune responses, through the use of killed bacteria (or bacterial components), CpG oligodeoxynucleotides or plasmid DNA. Although there has been some success with these approaches in animals [77], there are still concerns about negative side effects particularly when vaccinating young children. This is likely to be a major factor delaying human trials.

Conclusion

There is a growing need to reduce the mounting personal, social and economic cost of allergic disease. While there has been some success in managing established disease, strategies to prevent the development of these processes will be of greater value in the long term. Currently, our capacity to prevent allergic disease is constrained by limited understanding of disease pathogenesis and aetiological factors, particularly of the early exposures responsible for the recent increase in allergic disease. There is also an inability to accurately identify atopic individuals before sensitization occurs. All of these areas need to be investigated more fully in order to determine how tolerance mechanisms can be promoted without adverse effects.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Ng TW, Holt PG, Prescott SL. Cellular immune responses to ovalbumin and house dust mite in egg-allergic children. *Allergy* 2002; 57:207–214.

This study demonstrated that clinical food allergy correlated with ovalbumin-specific type 2 cytokine responses but was not associated with inability to produce ovalbumin-specific Th1 responses. The other notable finding was that development of clinical food tolerance was associated with persistent cytokine responses to food, suggesting persistent 'regulatory' populations rather than clonal deletion of all food responsive T-cells.

- 2 Smart JM, Kemp AS. Increased Th1 and Th2 allergen-induced cytokine responses in children with atopic disease. *Clin Exp Allergy* 2002; 32:796–802.

Consistent with other studies, atopic children in this study showed increased type 2 responses to both allergens and polyclonal stimulation compared with non-atopic children. Of note, this study demonstrated that while atopic children had reduced type 1 interferon- γ to polyclonal stimulation, they actually had significantly higher interferon- γ responses to the allergens. This is consistent with the findings of Ng *et al.* [1*] and suggests that while allergic infants have increased (type 1 and type 2) responsiveness to allergens, this coexists with a decreased capacity for polyclonal type 1 responses. The reason for this is unclear.

- 3 Kimura M, Yamaide A, Tsuruta S, *et al.* Development of the capacity of peripheral blood mononuclear cells to produce IL-4, IL-5 and IFN- γ upon stimulation with house dust mite in children with atopic dermatitis. *Int Arch Allergy Immunol* 2002; 127:191–197.

- 4 Schade RP, Van Ieperen-Van Dijk AG, Versluis C, *et al.* Cell-surface expression of CD25, CD26, and CD30 by allergen-specific T cells is intrinsically different in cow's milk allergy. *J Allergy Clin Immunol* 2002; 109:357–362.

This study demonstrated that food antigen-specific T cells from patients with food allergy display an increased expression of cell-surface activation markers (such as CD25 and CD30) compared with cells of patients without food allergy, and suggests an intrinsically stronger food-specific T-cell response in food-allergic patients.

- 5 Ribeiro-do-Couto LM, Boeijs LC, Kroon JS, *et al.* High IL-13 production by human neonatal T cells: neonate immune system regulator? *Eur J Immunol* 2001; 31:3394–3402.

Neonatal T cells were demonstrated to produce less interferon- γ and higher levels of interleukin-13 than adult T cells. Naïve fetal T cells produced more interleukin-13 than naïve adult T cells. This is consistent with both the relative type 2 skewed milieu of pregnancy and immaturity of neonatal responses.

- 6 Lehmann I, Thoeke A, Weiss M, *et al.* T cell reactivity in neonates from an East and a West German city: results of the LISA study. *Allergy* 2002; 57:129–136.

- 7 Devereux G, Seaton A, Barker RN. In utero priming of allergen-specific helper T cells. *Clin Exp Allergy* 2001; 31:1686–1695.

These authors found that 50% of cord blood responses to grass pollen were mediated by T cells of the CD45RO+ 'memory' phenotype. Although this suggests that these cells may have been previously primed by allergen, it is of note that the remaining 50% of responses were mediated by CD45RA+ cells which are assumed to be 'naïve'. Thus, the origin and significance of allergen-responsive T cells in cord blood remains unclear.

- 8 Prescott SL, Jones CA. Cord blood memory responses: are we being naïve? *Clin Exp Allergy* 2001; 31:1653–1656.

- 9 Szepefalusi Z, Loibichler C, Pichler J, *et al.* Direct evidence for transplacental allergen transfer. *Pediatr Res* 2000; 48:404–407.

- 10 Smillie FI, Elderfield AJ, Patel F, *et al.* Lymphoproliferative responses in cord blood and at one year: no evidence for the effect of in utero exposure to dust mite allergens. *Clin Exp Allergy* 2001; 31:1194–1204.

- 11 Marks GB, Zhou J, Yang HS, *et al.* Cord blood mononuclear cell cytokine responses in relation to maternal house dust mite allergen exposure. *Clin Exp Allergy* 2002; 32:355–360.

This study demonstrated that there was no relationship between HDM-specific (lymphoproliferation and cytokine) responses in cord blood and levels of mite allergens measured in maternal beds at 36 weeks gestation. The long-term relationship between immune development and allergic disease outcomes remains to be determined.

- 12 Chan-Yeung M, Ferguson A, Chan H, *et al.* Umbilical cord blood mononuclear cell proliferative response to house dust mite does not predict the development of allergic rhinitis and asthma. *J Allergy Clin Immunol* 1999; 104 (2 Pt 1):317–321.

- 13 Sverremark Ekstrom E, Nilsson C, Holmlund U, *et al.* IgE is expressed on, but not produced by, fetal cells in the human placenta irrespective of maternal atopy. *Clin Exp Immunol* 2002; 127:274–282.

Because humoral immune function is less mature in the neonate, the type 2 responses in pregnancy do not appear to have the same pro-immunoglobulin E effects as these cytokines have in the postnatal period. This recent study by Sverremark Ekstrom *et al.* revealed that immunoglobulin E is expressed in high levels in the foetal compartments of the placenta, regardless of maternal allergic status. The origin of the immunoglobulin E is unclear, but it was found largely expressed on foetal macrophages in the placenta (possibly by Fc γ R1). Further studies are needed to determine the functional significance of this observation.

- 14 Spinozzi F, Agea E, Russano A, *et al.* CD4+IL13+ T lymphocytes at birth and the development of wheezing and/or asthma during the 1st year of life. *Int Arch Allergy Immunol* 2001; 124:497–501.

- 15 Kopp MV, Zehle C, Pichler J, *et al.* Allergen-specific T cell reactivity in cord blood: the influence of maternal cytokine production. *Clin Exp Allergy* 2001; 31:1536–1543.

This study demonstrated that maternal allergy was associated with lower type 1 responses to milk allergen (β -lactoglobulin) *in vitro*. Although allergic mothers did not show higher type 2 responses to β -lactoglobulin (compared with non-allergic mothers), their neonates had significantly higher type 2 interleukin-13 responses to this milk allergen. This suggests a relationship between maternal and foetal immune responses to a specific allergen, but does not indicate what the mechanisms of this proposed interaction could be.

- 16 Ohshima Y, Yasutomi M, Omata N, *et al.* Dysregulation of IL-13 production by cord blood CD4+ T cells is associated with the subsequent development of atopic disease in infants. *Pediatr Res* 2002; 51:195–200.

- 17 Langrish CL, Buddle JC, Thrasher AJ, Goldblatt D. Neonatal dendritic cells are intrinsically biased against Th-1 immune responses. *Clin Exp Immunol* 2002; 128:118–123.

Langrish *et al.* derived dendritic cell from cord blood (cultured with interleukin-4 and granulocyte macrophage-colony stimulating factor) and demonstrated that these had significantly attenuated expression of interleukin-12, class II antigens (HLA-DR), co-stimulator molecules (CD86) and maturation markers (CD83 and CD25) compared with dendritic cells derived from adults. The capacity for interleukin-10 and TNF α was comparable to adults. This provides further strong evidence that neonatal dendritic cells are intrinsically programmed against type 1 responses.

- 18 Upham JW, Lee PL, Holt BJ, *et al.* Development of interleukin-12 producing capacity throughout childhood. *J Infect Immunol* 2002; 70:6583–6588.

This cross-sectional study demonstrated the age related changes in IL-12 responses (to LPS) from birth to adulthood. They demonstrated significantly attenuated IL-12 responses in the perinatal period, which did not approach adult levels until adolescence. They also demonstrated that the main source of IL-12 in the culture system were dendritic cells.

- 19 Gabrielson S, Soderlund A, Nilsson C, *et al.* Influence of atopic heredity on IL-4-, IL-12- and IFN- γ -producing cells in in vitro activated cord blood mononuclear cells. *Clin Exp Immunol* 2001; 126:390–396.

This study demonstrated that interleukin-12 responses to allergens were lower in neonates with a family history of allergic disease compared to those at low risk of allergy. The authors also observed that the high risk infants had higher interleukin-4/interferon- γ ratios in response to phytohaemagglutinin, and lower numbers of interleukin-12-producing cells after allergen stimulation. The significance of interleukin-12 responses to allergens is unclear, but leads to speculation that the capacity for type 1 signaling is sub-optimal in high risk children. It is not known how these observations relate to later allergy development.

- 20 Janefjord CK, Jenmalm MC. PHA-induced IL-12R β 2 mRNA expression in atopic and non-atopic children. *Clin Exp Allergy* 2001; 31:1493–1500.

These authors found that atopic children show reduced interleukin-12 receptor (β 2) messenger RNA expression after phytohaemagglutinin stimulation compared with nonatopic children. This also correlated with lower ratio of interferon- γ /interleukin-4 production. They suggested that this may indicate a reduced capacity of atopic children to respond to type 1-trophic stimuli.

- 21 White GP, Watt PM, Holt BJ, Holt PG. Differential patterns of methylation of the IFN- γ promoter at CpG and non-CpG sites underlie differences in IFN- γ gene expression between human neonatal and adult CD45RO+ T cells. *J Immunol* 2002; 168:2820–2827.

This group recently demonstrated reduced neonatal expression of interferon- γ by naïve CD4+ T cells associated with hyper-methylation of interferon- γ promoter CpG sites, relative to adult CD4+ T cells which produce higher interferon- γ responses. This was not seen for neonatal CD8+ T cells which showed similar methylation patterns as adults. It is not yet clear how variation in perinatal type 1 gene methylation status relates to the risk of subsequent allergic disease.

- 22 Macaubas C, Lee PT, Smallacombe TB, *et al.* Reciprocal patterns of allergen-induced GATA-3 expression in peripheral blood mononuclear cells from atopics versus non-atopics. *Clin Exp Allergy* 2002; 32:97–106.

These authors observed that the atopic (interleukins 4, 5 and 13) response is associated with increased expression of transcription factor GATA-3, whereas this gene is downregulated in allergen-stimulated peripheral blood mononuclear cells from non-allergic adults. The processes controlling this are not understood.

- 23 Liu AH. Allergy and asthma prevention: the cup half full. *Allergy Asthma Proc* 2001; 22:333–336.

- 24 Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002; 32:43–50.

This study examined the relationship between the magnitude of neonatal lymphoproliferation responses to allergens and multiple early life factors. The authors observed that stronger lymphoproliferation responses were associated with a family history of atopic disease, maternal smoking, decreasing birth order and low maternal dietary intake of vitamin E. Although this does not provide evidence of causal associations, it highlights the need to explore the influence of antenatal factors in early immune development.

- 25 Sears MR, Greene JM, Willan AR, *et al.* Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360:901–907.
- These authors report that New Zealand children born in the 1970s were more likely to develop subsequent allergic disease and sensitization at 13 years if they were breast fed ($n=504$) than if they were formula fed ($n=533$). The study principally examined the effects of 'receiving any breast milk' for at least 4 weeks and the 'duration of breastfeeding' on later atopic outcomes, with some convincing positive associations. However, very few of these infants were 'exclusively' breast fed, and the authors indicated that it was commonplace for breastfed infants to have complementary formula feeds during the neonatal period.
- 26 Bergmann RL, Diepgen TL, Kuss O, *et al.* Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002; 32:205–209.
- In this cohort ($n=1314$) a longer duration of breastfeeding was associated with parental allergy, older maternal age, and higher socio-economic status. After adjusting for confounders, atopic dermatitis was associated with longer duration of breastfeeding.
- 27 Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001; 56:192–197.
- This study assessed whether the association between maternal allergy and allergic status of the child was altered by breastfeeding. They observed that specific sensitization in the mother was associated with specific sensitization in the child only if the child was breast fed. This has led to speculation that milk content may differ with maternal allergic status.
- 28 Oberle D, Von Kries R, Von Mutius E. Asthma and breast feeding [letter]. *Thorax* 2001; 56:896.
- 29 Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001; 139:261–266.
- This meta-analysis of the relationship between breastfeeding and asthma examined 12 prospective studies (including 8183 infants), and found that exclusive breastfeeding in the first months of life was associated with reduced rates of subsequent asthma (OR 0.70; 95% CI 0.60–0.81).
- 30 Dell S, To T. Breastfeeding and asthma in young children: findings from a population-based study. *Arch Pediatr Adolesc Med* 2001; 155:1261–1265.
- 31 Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol* 2002; 110:65–67.
- In this prospective study of 2602 infants, the risk of childhood asthma increased if exclusive breastfeeding was stopped (other milk was introduced) before 4 months (odds ratio, 1.28; 95% CI, 1.01–1.62; $P=0.038$). This risk was not altered by atopy or maternal asthma status. After adjusting for covariates, exclusive breastfeeding for less than 4 months was a significant risk factor for current asthma (OR 1.35; 95% CI, 1.00–1.82; $P=0.049$).
- 32 Rusconi F, Galassi C, Corbo GM, *et al.* Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999; 160 (5 Pt 1):1617–1622.
- 33 Sly PD, Holt PG. Breast is best for preventing asthma and allergies: or is it? *Lancet* 2002; 360:887–888.
- 34 Zeiger RS. Dietary aspects of food allergy prevention in infants and children. *J Pediatr Gastroenterol Nutr* 2000; 30 (Suppl):S77–S86.
- 35 Tauber E, Gartner C, Halmerbauer G, *et al.* Predictors of lung function in infants at high risk of atopy: effect of allergen avoidance. *Respir Med* 2002; 96:230–235.
- This study included a subgroup of 60 babies from atopic families who had lung function as part of the Prevention of Allergy in Children in Europe (SPACE) programme. They found that allergen avoidance strategies had no differences in lung function or atopic symptoms at 18 months. Longer term studies and information about sensitization are still required.
- 36 Ram FS, Ducharme FM, Scarlett J. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy. *Cochrane Database Syst Rev* 2002; 3:CD003795.
- This *Cochrane Database* review compared outcomes in infants who had cows milk formulae in the first 4 months of life with those who avoided these formulae. They found that infants who had received hydrolysed formula instead of cows milk protein had a reduced risk of experiencing asthma or wheeze during the first year of life (RR 0.40; 95% CI 0.19, 0.85). However many of the studies included in this meta-analysis involved other interventions (additional dietary restrictions and in some cases dust-mite reduction measures). The significance of 'asthma and wheeze' in the first 12 months of life is also debatable.
- 37 Platts-Mills T, Vaughan J, Squillace S, *et al.* Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; 357:752–756.
- 38 Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001; 108:E33.
- 39 Lau S, Nickel R, Niggemann B, *et al.* The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). *Paediatr Respir Rev* 2002; 3:265–272.
- 40 Custovic A, Simpson BM, Simpson A, *et al.* Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001; 358:188–193.
- 41 Koopman LP, van Strien RT, Kerkhof M, *et al.* Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002; 166:307–313.
- This is a preliminary report on early clinical outcomes (at 2 years of age) from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study group. They randomized 1282 allergic pregnant women to have allergen-impermeable bedding covers ($n=416$) for parents' and children's beds, placebo covers ($n=394$) or no intervention ($n=472$). Although bedding covers reduced HDM exposure, there was no difference in allergic sensitization, atopic eczema dermatitis syndrome, or respiratory symptoms (apart from night cough) in the first 2 years of life.
- 42 Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002; 288:963–972.
- In this prospective birth cohort study, Ownby *et al.* reviewed 474 children (out of 835 recruited at birth) at 6–7 years of age. They reported that having pets (two or more cats or dogs) in the household during the first year of life was not only associated with less sensitization to these allergens at 6 years of age, but less sensitization to other allergens, including moulds and pollens (adjusted OR, 0.23; 95% CI, 0.09–0.60).
- 43 Anyo G, Brunekreef B, de Meer G, *et al.* Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy* 2002; 32:361–366.
- In this population of 2729 Dutch children, Anyo *et al.* observed that an inverse relationship between current pet ownership and both sensitization and allergy symptoms was mainly due to removal of pets by families with sensitised children, indicating a potential source of bias in similar studies. After allowing for this, however, pet ownership in the first 2 years of life was associated with reduced sensitization to pollens.
- 44 Platts-Mills TA. Paradoxical effect of domestic animals on asthma and allergic sensitization. *JAMA* 2002; 288:1012–1014.
- 45 Platts-Mills TA, Perzanowski M, Woodfolk JA, Lundback B. Relevance of early or current pet ownership to the prevalence of allergic diseases. *Clin Exp Allergy* 2002; 32:1259.
- The above two editorials review the emerging relationship between early exposure to animals and domestic pets and subsequent atopic sensitization and disease, debating the role of endotoxin and aspects of the immune processes which appear unique to pet allergen responsiveness. Specifically, the discussions review the concept of 'modified Th2 responses' which appear to lead to immunoglobulin G4 but not immunoglobulin E antibodies to the allergen.
- 46 von Mutius E, Braun-Fahrlander C, Schierl R, *et al.* Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; 30:1230–1234.
- 47 Heinrich J, Gehring U, Douwes J, *et al.* Pets and vermin are associated with high endotoxin levels in house dust. *Clin Exp Allergy* 2001; 31:1839–1845.
- In this study, endotoxin levels in the home were significantly increased by the presence of dog (1.64, 95% CI 1.09–2.46), cats (1.50, 95% CI 1.03–2.18) and cockroaches (3.01, 95% CI 1.37–6.60), after adjusting for confounding factors.
- 48 Horak F, Studnicka M, Gartner C, *et al.* Parental farming protects children against atopy: longitudinal evidence involving skin prick tests. *Clin Exp Allergy* 2002; 32:1155–1159.
- In this recent Austrian study parental farming was inversely associated with sensitization to allergens in 1150 children aged 8–11 years (OR 0.34; 95% CI 0.12–0.98).
- 49 von Mutius E. Pro: the increase in asthma can be ascribed to cleanliness. *Am J Respir Crit Care Med* 2001; 164:1106–1107; discussion 1108–1109.
- This article is part of an interesting editorial debate of the 'hygiene hypothesis'. It presents the case in support of this theory. See Ref. [54••] below for the opposing argument.
- 50 Matsuoka T, Matsubara T, Katayama K, *et al.* Increase of cord blood cytokine-producing T cells in intrauterine infection. *Pediatr Int* 2001; 43:453–457.
- 51 Heinrich J, Bolte G, Holscher B, *et al.* Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. *Eur Respir J* 2002; 20:617–623.
- In this large cohort study ($n=1332$) cord blood immunoglobulin E levels (in the one-third of cases in which these were detectable) were positively associated with high cat-allergen exposure and medium exposure to mite allergen, but were inversely associated with exposure to endotoxin. This association between prenatal allergen and endotoxin exposures and immunoglobulin E production, suggests antenatal influences on foetal immune development.

- 52 Jones CA, Holloway JA, Popplewell EJ, *et al.* Reduced soluble CD14 levels in amniotic fluid and breast milk are associated with the subsequent development of atopy, eczema, or both. *J Allergy Clin Immunol* 2002; 109:858–866.

The levels of receptor (soluble CD14) for bacterial endotoxin in early life were compared in relation to atopic outcomes. Children who developed subsequent atopy had significantly lower soluble CD14 levels in amniotic fluid collected midgestation. Soluble CD14 levels in breast milk collected 3 months postpartum were also significantly lower in children with eczema at 6 months of age, irrespective of whether they were atopic. Because the (toll-like) receptors which enable transmembrane signaling for lipopolysaccharide/sCD14 complexes were expressed within foetal gut and skin, the authors proposed that soluble CD14 could influence immune development during this early period.

- 53 McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med* 2002; 166:827–832.

In the last few months, the authors of a large cohort study (of 24 690 British children) reported a dose-dependent relationship between exposure to antibiotics during pregnancy and the subsequent development of asthma, atopic dermatitis and allergic rhinitis. The increasing use of antibiotics (and reduced microbial burden) has been used to support the 'hygiene hypothesis', but the findings of this study could equally argue against this as infections during pregnancy were associated with increased risk of subsequent disease.

- 54 Platts-Mills TA, Woodfolk JA, Sporik RB. Con: the increase in asthma cannot be ascribed to cleanliness. *Am J Respir Crit Care Med* 2001; 164:1107–1108; discussion 1108–1109.

See Ref. [49••] above.

- 55 Cross ML, Gill HS. Can immunoregulatory lactic acid bacteria be used as dietary supplements to limit allergies? *Int Arch Allergy Immunol* 2001; 125:112–119.

- 56 Shida K, Takahashi R, Iwadata E, *et al.* *Lactobacillus casei* strain Shirota suppresses serum immunoglobulin E and immunoglobulin G1 responses and systemic anaphylaxis in a food allergy model. *Clin Exp Allergy* 2002; 32:563–570.

In this murine food allergy model, *Lactobacillus casei* administration resulted in suppressed immunoglobulin E and immunoglobulin G1 secretion by splenocytes, type 1 dominant cytokine responses, and reduced reactivity to food allergen.

- 57 Kalliomaki M, Salminen S, Arvilommi H, *et al.* Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. *Lancet* 2001; 357:1076–1079.

- 58 Beasley R, Shirtcliffe P, Harper JL, *et al.* Mycobacterium-based vaccines for the prevention of allergic disease: a progress report. *Clin Exp Allergy* 2002; 32:1128–1130.

This article provides a useful review of the use of mycobacterial antigens for the modification of immune responses to allergens.

- 59 Hopfenspirger MT, Agrawal DK. Airway hyperresponsiveness, late allergic response, and eosinophilia are reversed with mycobacterial antigens in ovalbumin-prensensitized mice. *J Immunol* 2002; 168:2516–2522.

Using a murine model of (ovalbumin induced) allergic airway hyperresponsiveness, Hopfenspirger *et al.* demonstrated that sensitized animals pretreated with BCG had attenuation of the late allergic response, airway hyperreactivity, peribronchial eosinophilia, and bronchoalveolar lavage fluid interleukin-5 levels compared with placebo treated sensitized controls. The effect was stronger for intranasal (rather than intraperitoneal) BCG, and BCG was more effective than *Mycobacterium vaccae* under the same conditions.

- 60 Tsai JJ, Liu YH, Shen HD, *et al.* Prevention of Der p2-induced allergic airway inflammation by Mycobacterium-bacillus Calmette Guerin. *J Microbiol Immunol Infect* 2002; 35:152–158.

In this Der p2-induced allergy murine model, intraperitoneal BCG inoculation with Der p2 resulted in increased type 1 responses by splenocytes, reduced specific immunoglobulin G1 production, and reduced airways inflammation compared with animals inoculated with Der p2 alone.

- 61 Major T, Wohlleben G, Reibetanz B, Erb KJ. Application of heat killed Mycobacterium bovis-BCG into the lung inhibits the development of allergen-induced Th2 responses. *Vaccine* 2002; 20:1532–1540.

In this murine model, pretreatment with intranasal mycobacterial antigens inhibited the development of airway eosinophilia, and reduced type 2 T cells in the airway and regional lymph nodes after sensitization with ovalbumin. This effect was seen with both live and heat killed BCG but not mycobacterial purified protein derivative.

- 62 Yang X, Fan Y, Wang S, *et al.* Mycobacterial infection inhibits established allergic inflammatory responses via alteration of cytokine production and vascular cell adhesion molecule-1 expression. *Immunology* 2002; 105:336–343.

In another animal model, inhibition of asthma-like reactions by BCG infection was associated with a dramatic decrease of vascular cell adhesion molecule-1 (VCAM-1) expression in the lung (as well as the previously observed with a shift of allergen-driven cytokine production).

- 63 Zuany-Amorim C, Sawicka E, Manlius C, *et al.* Suppression of airway eosinophilia by killed Mycobacterium vaccae-induced allergen-specific regulatory T-cells. *Nat Med* 2002; 8:625–629.

This is the first paper to demonstrate that allergen-specific CD4+CD45RB(Lo) regulatory T cells induced by mycobacterial antigens play a central role in reducing airways inflammation. These regulatory T cells produced interleukin-10 and TGF β , which were directly associated with the inhibition of airway inflammation, as antibodies against these cytokines completely reversed the anti-inflammatory effect.

- 64 Cavallo GP, Elia M, Giordano D, *et al.* Decrease of specific and total immunoglobulin E levels in allergic patients after BCG vaccination: preliminary report. *Arch Otolaryngol Head Neck Surg* 2002; 128:1058–1060.

This study provided preliminary evidence that BCG vaccination in 20 volunteers with allergic rhinitis had significantly lower total and allergen-specific immunoglobulin E levels 4 months after BCG vaccination (compared with baseline). However, this was not a randomized control trial.

- 65 Ota MO, Vekemans J, Schlegel-Haueter SE, *et al.* Influence of Mycobacterium bovis bacillus Calmette-Guerin on antibody and cytokine responses to human neonatal vaccination. *J Immunol* 2002; 168:919–925.

This study demonstrated that although BCG vaccination induced a potent type 1 response to mycobacterial antigens in newborns, it also promoted both type 1 and type 2 cytokine responses to unrelated vaccines, and altered antibody responses (to oral polio vaccine). This confirms that BCG can influence the responses to unrelated antigens in early life.

- 66 Barlan IB, Tukenmez F, Bahceciler NN, Basaran MM. The impact of in vivo Calmette-Guerin Bacillus administration on in vitro IgE secretion in atopic children. *J Asthma* 2002; 39:239–246.

- 67 Choi IS, Koh YI. Therapeutic effects of BCG vaccination in adult asthmatic patients: a randomized, controlled trial. *Ann Allergy Asthma Immunol* 2002; 88:584–591.

This randomized double-blinded study found that BCG vaccination significantly increased lung function (forced expiratory volume in 1 s and forced expiratory flow rate) at weeks 4, 8, and 12 after vaccination. Asthma symptom scores were not significantly changed, but weekly medication scores were significantly decreased. In contrast, medication scores and sputum eosinophils were significantly increased in the placebo group.

- 68 Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; 107:531–534.

- 69 Shirakawa T, Enomoto T, Shimazu S, Hopkin J. Inverse association between tuberculin responses and atopic disorder. *Science* 1997; 272:77–79.

- 70 Jentoft HF, Omenaas E, Eide GE, Gulsvik A. Absence of relationship between tuberculin reactivity and asthmatic symptoms, level of FEV1 and bronchial hyperresponsiveness in BCG vaccinated young adults. *Allergy* 2002; 57:336–340.

In this randomly selected adult population (20–44 years), who were BCG vaccinated at the age of 14 (n=558), there was no significant relationship between tuberculin reactivity and asthmatic symptoms, level of forced expiratory volume in 1 s or bronchial hyperresponsiveness.

- 71 Calder PC, Yaqoob P, Thies F, *et al.* Fatty acids and lymphocyte functions. *Br J Nutr* 2002; 87 (Suppl 1):S31–48.

This is a comprehensive review of the effects of altered dietary fatty acid intakes and the effects on the fatty acid composition and immune function of lymphocytes and other immune cells. It also examines the evidence for beneficial effects of fish oil in inflammatory diseases including allergic disease.

- 72 Duchon K, Bjorksten B. Polyunsaturated n-3 fatty acids and the development of atopic disease. *Lipids* 2001; 36:1033–1042.

- 73 Field CJ, Clandinin MT, Van Aerde JE. Polyunsaturated fatty acids and T-cell function: implications for the neonate. *Lipids* 2001; 36:1025–1032.

- 74 Dunstan J, Mori T, Barden A, *et al.* Maternal fish oil supplementation in pregnancy reduces IL-13 levels in cord blood of infants at high risk of atopy. *Clin Exp Allergy* (in press).

- 75 Erb K, Wohlleben G. Novel vaccines protecting against the development of allergic disorders: a double-edged sword? *Curr Opin Immunol* 2002; 14:633–643.

- 76 Horner AA, Takabaysahi K, Zubeldia JM, Raz E. Immunostimulatory DNA-based therapeutics for experimental and clinical allergy. *Allergy* 2002; 57 (Suppl 72):24–29.

- 77 Nguyen MD, Cinman N, Yen J, Horner AA. DNA-based vaccination for the treatment of food allergy. *Allergy* 2001; 56 (Suppl 67):127–130.