

Review article

Can we prevent allergy?

Allergic conditions continue to increase steeply. The last two decades have seen many prevention trials, studying the effect of dietary and environmental interventions. These trials have yielded invaluable information about the atopic march and also highlighted the need for a clear and commonly used nomenclature as well as a need for better outcome measures. This review discusses primary and secondary prevention studies and their results.

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In 1903 the Austrian paediatrician Baron Clemens von Pirquet coined the terms allergy and allergen (from greek *άλλος* = other/alterd and *έργον* = energy/response) after observing 'altered responses' of his patients to certain substances (1, 2). He could not have foreseen the extent of the human and economic costs allergies would cause a century later. Since those early days we have come a long way toward understanding many of the immunological pathways involved in these 'altered responses', but despite numerous hypotheses the root-cause and thus the key to prevention remains elusive.

The hygiene hypothesis introduced by Strahan in 1989 remains the strongest one to date (3). It is based on his observation that with decreasing family size and improved living conditions allergic conditions increase. With this, microbial pressure is thought to have decreased and thus the stimulus for the switching from the in utero/neonatal immunological Th2 driven responses to the balanced Th1–Th2 responses has been taken away, allowing an immunological response pattern which favours allergic responses to persist (4). This straightforward concept of Th2 response *vs.* Th1 response has since been complicated by the discovery of the recently proposed 'modified Th2 response' and a better understanding of the role of regulatory T cells (5).

There is mounting evidence from observational and cross-sectional studies supporting the theory that a less hygienic, more exposed environment with more siblings, childcare and/or domestic animals, may protect children from developing allergic conditions. Martinez et al. and others have shown that increased viral infections in infancy and day care attendance may have a protective effect on the development of asthma (6, 7). In addition,

presence of a dog in the home in infancy was associated with less wheezing at age 13 but not with decreased allergic sensitization (8). Frequent 'runny nose' episodes in infants have been linked to a decreased risk of asthma at age 7 years, in contrast to more than two wheezy lower respiratory tract infections, which led to an increased asthma incidence at age 7 years (9). Taking exposure further, Riedler et al. demonstrated in a cross-sectional study of schoolchildren that living on a farm with frequent visits to the stables in early childhood appeared to be protect against asthma, eczema and allergic rhinitis (10). This protective effect is currently in part attributed to higher endotoxin exposure in infancy, although paradoxically, it is also known to cause increased wheezing in infancy and exacerbations of established asthma (11). The mechanism of the protective action is unclear but it appears that endotoxin may reduce the development of allergic disease rather than preventing sensitization (12). Endotoxin is being studied as part of the Boston birth cohort and the German Lifestyle-related factors on the Immune System and the Development of Allergies in childhood (LISA) birth cohort study and long-term observations from these studies should help to clarify its mechanisms and importance in the development of allergy (11, 13). Finally there is the theory that it may be the ultimately unhygienic place – the gut that could hold more clues. Bjoerksten et al. have shown that the native human gut flora changes with a more westernized lifestyle (14). Westernized societies show a decrease of 'friendly bacteria' such as Lactobacilli and Bifidobacteria and an increase of other bacteria (unfriendly?) such as coliforms and *Staphylococcus aureus* in their gastrointestinal tracts, which coincides with rising incidence of atopic conditions

in these societies (14). Children suffering from allergic conditions appear to have fewer Lactobacilli and Bifidobacteria and more Clostridia compared with their nonallergic contemporaries (15, 16). At present, however, decreasing hygiene to levels found a century ago in order to prevent allergy is not going to be acceptable as a general measure and currently available research evidence has not provided a single prevention tool.

Microbial products such as those derived from mycobacteria, bacterial extracts, oligodeoxynucleotides as well as probiotics are subject of ongoing experimental and clinical studies (17). Apart from probiotics they are mainly being investigated as treatment modalities and the evidence for their efficacy is still scant (17). Probiotics as a preventive measure will be discussed below.

What is 'allergy' and what exactly are we trying to prevent?

Since Baron von Pirquet's 1903 definition of the term 'allergy' it has become more and more complicated to succinctly describe the many things this term could mean today. The variability of its meaning makes direct comparisons between studies difficult and impairs communication between doctors, patients and researchers alike.

Broadly speaking allergy is often divided into:

- (1) Allergic sensitization (Atopy?): not necessarily accompanied by symptoms.
- (2) Allergic symptoms (atopic diseases?): wheeze, asthma, atopic dermatitis/eczema, food allergies, allergic rhinitis etc. – not necessarily accompanied by sensitization.

Because one can exist without the other but be an important predictor for future development of disease it is important to clearly distinguish between the different groups. In the 2001 European Academy of Allergology and Clinical Immunology (EAACI) position paper on a revised nomenclature for allergy the task force attempted to disentangle the different groups and proposes some new definitions for old terms such as atopy (18). Figure 1 gives a simplified overview of this proposed revised nomenclature. It is clearly important to have a worldwide agreement on the terminology and definitions used, to allow better comparison and interpretation of results. However, this agreement has not been reached yet and a number of studies illustrate why it is prudent to define enrolment criteria and the outcomes more precisely (Table 1A,B and Table 2; 19).

What are we trying to prevent? Sensitization or symptoms or both?

For the purposes of this review the terms sensitization [specific IgE or positive skin prick test (SPT)] and allergic symptoms (asthma, atopic dermatitis, food allergy, aller-

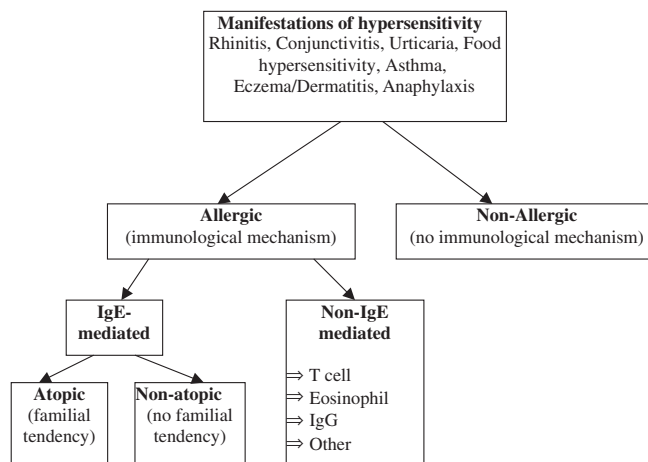


Figure 1. Simplified model of the proposed revised nomenclature for allergy (for further details see EAACI nomenclature task force position statement 2001) (18).

gic rhinitis) are used as they are in the majority of publications referred to, with the understanding that they can exist independent of each other or in combination.

A major problem is, that we cannot at present predict, what comes first, and how prevention of disease and/or sensitization in infancy may influence future development of allergic disease or even produce undesirable side-effects. The atopic march appears to have different starting points as well as different routes for progression, possibly dependent on genetic susceptibility or the types and combinations of environmental exposure. This makes targeted intervention difficult.

Ideally we want to prevent the atopic march altogether, i.e. the development and progression of sensitization and/or disease with primary prevention measures. There is however also a role for secondary prevention, i.e. prevention of progression of the atopic march, once it has begun.

Who are the candidates for prevention and can we use screening?

The only predictor definitely accessible before the onset of the atopic march is a family history of atopy (6, 20, 21). The problem of selecting only those with a genetic risk (i.e. a positive family history) is that all children in the low risk category, who will develop allergy, will be missed. Currently this means missing the larger proportion of those who will become allergic/atopic in the future (21, 22). Cord blood IgE levels have been disappointing as predictors, although their predictive value increases if used in conjunction with a family history (23–25). Early sensitization to hen's egg and/or the presence of eczema is highly predictive of future

Table 1A. Primary prevention trials – dietary interventions

Study	Enrolment criteria and FU	Preventive measures	Outcome measures	Results
Dietary avoidance				
Prenatal food avoidance, Sweden (34) RCT, <i>n</i> = 209	≥1 FHx atopy FU prenatal – 5 years	Last trimester maternal dairy and egg avoidance only	Incidence of allergic disease SPT, IgE	Age 1.5 and 5 years: no difference between groups. NS finding: active group <i>n</i> = 6 egg allergic, none in control group
Dietary avoidance San Diego, USA (28, 43, 44) RCT, <i>n</i> = 288	≥1 parent atopic with raised IgE FU prenatal – 7 years	Last trimester and lactation: allergenic food avoidance. No dairy in first year. Allergenic food avoided up to 3 years	Incidence of allergic disease SPT, IgE, nasal eosinophils	Age 1 year: active group less of any atopic disorder Age 2 years: active group cumulative food allergy significantly reduced Age 3, 4 and 7 years: no differences food avoidance did not prevent A or AR
Infant feeding Wales (UK) (48) RCT, <i>n</i> = 497	≥1 FHx atopy FU birth – 7 years	Restricted (not total) dairy in pregnancy and lactation. Soya or breast milk, no dairy until 4/12-old	Incidence of allergic disease SPT, IgE, IgG4, PEFR, House dust Der p 1	Age 7 years: no difference in allergic disease. Breast-feeding protected from wheeze, this effect only for nonatopics beyond 2 years
Mother and infant diet intervention (Canada) (45) RCT, <i>n</i> = 221	≥1 FHx atopy FU birth – 1.5 years	Allergenic food avoided during lactation. Bottle-fed: soya, casein eHF or standard formula	Incidence/severity of AD Cord blood IgE	Age 1.5 years: breast-fed active significantly less and milder AD vs controls. Casein hydrolysate group significantly less and milder AD than in soya and standard formula groups
Infant feeding Canada (47) RCT, <i>n</i> = 228	≥1 FHx atopy FU birth – 5 years	Exclusive breast-feeding to 4/12 or randomized to soya, standard or partially hydrolysed whey formula	Incidence of allergic disease SPT, IgE (soya, milk) DBPCFC age 5	Age 1 and 1.5 years: BF and pHF groups significantly less AD, other allergic symptoms and less sensitization Age 5 years: BF and pHF significantly lower cumulative incidence of atopic disease (AD, A, FA). No difference between standard and soya groups
Hydrolysed vs standard formulas, Sweden (46) RCT, <i>n</i> = 155	2 FHx atopy or 1 FHx + ↑cord IgE FU birth – 1.5 years	Allergenic food avoidance during lactation and for infant up to 1 year. Bottle: eHF, pHF or standard formula	Incidence atopic symptoms, Cord IgE, SPT	Age 1.5 years: In eHF group significantly lower cumulative incidence of atopic symptoms from 6 to 18 months. No differences for SPT, IgE, final cumulative diagnosis of atopy at 1.5 years
German Infant Nutrition Intervention Study (GINI) (49–51) RCT, <i>n</i> = 2252	≥1 FHx atopy FU birth – 1 year ongoing	Breast-feeding recommended until 4/12. If bottle: whey pHF, whey eHF, casein eHF or standard formula until at least 6/12-old No allergenic food in first year	Incidence of ‘allergic manifestations’ IgE	Age 1 year: <i>BF vs Std</i> : BF significantly less AD <i>All formula groups</i> : only casein eHF significantly fewer allergic manifestations. Trend for whey pHF. No significant effect of whey eHF vs Std
Dietary supplementation				
Probiotics – primary prevention trial Finland (40) RCT, <i>n</i> = 159 (60)	≥1 FHx atopy FU birth – 4 years	<i>Lactobacillus</i> GG vs placebo capsules antenatal and lactation mother; postnatal infant	Incidence/severity of atopic eczema Cord IgE, serum IgE, SPT	Age 2 years: probiotic group significantly less eczema (child or mother tx) No differences in sensitization (total or specific IgE and SPT) Age 4 years: probiotic group still significantly less eczema. No differences in sensitization (SPT). Exhaled nitric oxide less in probiotic group although trend to more diagnosed hayfever and asthma (small numbers)
Childhood Asthma Prevention Study (CAPS), Australia (56, 57). Diet intervention arm, RCT, <i>n</i> = 308 See also Table 1B	≥1 FHx atopy, no cats FU birth – 1.5 years ongoing (at least age 5)	One group received exclusive omega 3 fatty acid supplementation (vs placebo)	Level of IgE, SPT. Symptoms of allergic disease	Age 1.5 years: Omega 3 vs placebo, no difference in sensitization but significant reduction in wheeze

A, asthma; AD, atopic dermatitis; AR, allergic rhinitis; BHR, bronchial hyper-reactivity; FA, food allergy; FHx, family history; tx, treatment; HDM, house dust mite; RCT, randomized controlled trial; SPT, skin prick test; eHF, extensively hydrolysed formula; pHF, partially hydrolysed formula; FU, follow-up; BF, breast-feeding.

Table 1B. Primary prevention trials – dietary and environmental interventions

Study	Enrolment criteria and FU	Preventive measures	Outcome measures	Results
Combined dietary and environmental intervention				
Childhood Asthma Prevention Study (CAPS) Australia (56, 57) RCT (whole), <i>n</i> = 616	≥1 FHx atopy, no cats FU birth – 1.5 years Ongoing (at least age 5)	Omega 3 supplementary from 6/12 or start of bottle Mite avoidance and Omega 3 supplements Mite avoidance and placebo supplement Placebo supplement, no mite avoidance	Level of IgE, SPT Symptoms of allergic disease Plasma fatty acid analysis Exposure (Der p 1)	Age 1.5 years: no significant reduction in sensitization, no difference in mean IgE Omega 3 supplements only: reduction of wheeze Mite avoidance only: increased eczema, Der p 1 ↓ but levels still >2 mcg/g No significant interaction between dietary supplementation and avoidance
Isle of Wight Infant Allergen Avoidance Study UK (61, 63, 64, 86) RCT, <i>n</i> = 120	2 FHx atopy or 1 FHx + ↑ cord IgE FU birth – 8 years Ongoing	Allergenic food avoidance during lactation and in first year of life (breast-fed, or eHF or soya) Mite avoidance (mattress covers, Arcarosan)	Incidence of allergic disease Cord IgE, SPT, Exposure (Der p 1, Fel d 1)	Age 1 year: active group significantly less asthma (wheeze), AD, FA, sensitization Age 2 years: active group significantly fewer children with allergic conditions Age 4 years: active group significantly less total allergy, AD, positive SPTs, symptoms with sensitization (SPT positive) Age 8 years: active group significantly less atopy (any positive SPT) and nocturnal cough. Significantly ↓ risk for current wheeze, nocturnal cough and asthma (wheeze and BHR)
Combined Allergen Avoidance Study Canada (65) RCT, <i>n</i> = 545	≥2 FHx atopy or ≥1 asthma FU prenatal to 1 year	Ante- and postnatal allergenic food avoidance HDM avoidance (mattress covers, Arcarosan) Advice on pet and ETS avoidance	Incidence of possible or probable asthma at age 1 SPT Exposure (Der p 1, Fel d 1)	Age 1 year: active group successful reduction of Der p 1 and Fel d 1 but no difference in sensitization to inhalant or food allergens. Risk for 'asthma' and 'rhinitis' significantly reduced in active group
Study on Prevention of Allergy in Children of Europe (SPACE) (66) (birth cohort arm) multicentre RCT, <i>n</i> = 696	FHx atopy and positive SPT or ↑ one specific IgE FU birth – 1 year Ongoing	In first 4 weeks of life: breast-feeding for ≥3/12, eHF preferred, solids and soya after 6/12, avoid allergenic foods until 12/12 Mite avoidance (mattress cover, hot wash) Control: general advice only	Incidence of sensitization and symptoms; SPT, serum IgE <i>Subgroup:</i> nasal ECP, lung function (rapid thoracic-abdominal compression) Vmax FRC	Age 1 year: active group significantly less sensitization to HDM and food allergens NB: doctor diagnosed food allergy higher in active group Age 1.5 years: <i>subgroup</i> <i>n</i> = 28 active, <i>n</i> = 32 control; no difference in lung function High nasal ECP weakly associated with decreased lung function
Environmental intervention				
Manchester Asthma and Allergy Study (MAAS) UK (38, 39, 69) RCT, <i>n</i> = 620	<i>High risk:</i> two parents atopic (both positive SPT) <i>Medium risk:</i> one parent atopic (positive SPT) <i>Low risk:</i> neither parent atopic (both negative SPT) FU prenatal – 5 years Ongoing	High risk active (HRA): Rigorous HDM avoidance from second trimester. No intervention for: High risk control, no pets (HRC) High risk with pets (HRP) Low risk, no pets (LR)	Incidence of allergic disease Cord IgE, SPT, serum IgE Specific airway resistance (sRaw) Exposure: Der p 1, Fel d 1, Can f 1	Age 1 year: HRA group reduced respiratory symptoms vs HRC; significant for severe wheeze with SOB, treated wheezy attacks, wheeze on exertion Sustained significant reduction in Der p 1 Age 3 years: lung function (sRaw) findings Wheeze ever (vs never wheezed): sign increased sRaw Asymptomatic high risk (vs low risk, medium risk): significantly higher sRaw Asymptomatic, nonatopic high risk (vs medium and low): significantly higher sRaw Atopic (vs nonatopic) significantly increase sRaw Parent's and child's atopic status = significantly independent risk factor for high sRaw
Prevention and Incidence of Asthma ma + Mite Allergy (PIAMA) Study Holland (70) RCT, <i>n</i> = 810	Mother Hx of atopy FU prenatal – 4 years Ongoing	Active: mite covers for infant/parent bed, advice to hot wash bedding Control: placebo covers, advice on washing	Incidence of allergic disease Serum IgE Exposure: Der p 1, Der f 1	Age 2 years: significant reduction of mite-allergen levels Active group: only finding slight significant reduction in night-time cough without cold No effect on wheeze, runny nose, sensitization (specific IGE to HDM), respiratory symptom severity or atopic dermatitis

A, asthma; AD, atopic dermatitis; AR, allergic rhinitis; BHR, bronchial hyper-reactivity; FA, food allergy; FHx, family history; tx, treatment; HDM, house dust mite; RCT, randomized controlled trial; SPT, skin prick test; eHF, extensively hydrolysed formula; pHF, partially hydrolysed formula; FU, follow-up.

asthma but any intervention at this point would only be secondary (26–28). Too little is known about the role of gut flora to advocate screening families according to their bacterial colonization.

Unselected population-wide prevention is not feasible because of cost and predicable compliance issues making a reliable screening tool essential for the future (29).

Table 2. Secondary prevention trials and their results

Study	Enrolment criteria	Preventive measures	Primary outcome	Results
Environmental measures				
Tsitoura et al. (74) (SPACE) 2002, RCT <i>n</i> = 636	Parent positive SPT Child 1.5–5 years not sensitization to HDM A or AR or AD	Mattress cover and specific advice vs general advice	Sensitization to dust mite	Active: significantly less sensitization to HDM (<i>P</i> = 0.04; 3% vs 6%) HDM sensitization children more symptomatic
Arshad et al. (75) (SPACE) 2002, RCT <i>n</i> = 242	Parent hx atopy Child 5–7 years, sensitization to ≥ aeroallergen, but not to HDM	Mattress cover and specific advice vs general advice	Sensitization to dust mite	Active: significantly less sensitization to HDM (<i>P</i> = 0.03, 2.6% vs 9.4%) 15 needed to treat to prevent 1
Pharmacological intervention				
Ikura et al. (76) 1992 RCT <i>n</i> = 121	Atopic dermatitis age 2–34/12 No asthma	Ketotifen vs placebo for 1 year	Asthma Y/N (2× treated wheezy episode)	Significantly less 'asthma' in active group if also IgE > 50 IU/ml (13.1% vs 41.6% control)
Bustos et al. (77) 1995 RCT <i>n</i> = 100	Family positive SPT Child <2 years, raised IgE, no asthma	Ketotifen vs placebo for 3 years	Asthma Y/N (≥3× distress with bronchial obstruction)	Significantly less 'asthma' in active group (9% vs 35% control) Sensitization rates same (SPT)
Diepgen et al. (85) (ETAC Group) 1998 RCT <i>n</i> = 817	FHx atopy Child 12–24/12, atopic dermatitis	Cetirizine vs placebo for 18 months	Asthma Y/N (three separate episodes of wakening night-cough or wheeze)	Overall no difference Active group significantly less asthma only if raised IgE or specific IgE to HDM or grass. Less urticaria in active group
Specific immunotherapy				
Des Roches et al. (79) 1997, case-control <i>n</i> = 44	Age 2–6 years with asthma +/- AR HDM monosensitized	SIT vs open pharmaco-tx for 3 years	Incidence of new sensitization	SIT group 10/22 vs non-SIT group 0/22 monosensitized after 3 years.
Mastruzzo et al. (81) 2002 RCT <i>n</i> = 30	Adults with AR, monosensitized to parietora judaica	SIT vs placebo injections for 3 years	Effect on airways (BHR)	SIT significantly improved airway function. Borderline significantly less asthma in SIT group (<i>P</i> = 0.056)
Sarva et al. (80) 2002, retrospective survey <i>n</i> = 371	Age 18–40 years with AR, no asthma	SIT (3 years) vs pharmaco-tx. retrospective 3 year survey	Asthma Y/N at 10 year follow-up	SIT group 41.6% develop asthma vs 53.1% in non-SIT group
Moeller et al. (82) (PAT Study) 2002 RCT <i>n</i> = 208	Age 6–14 years with birch/grass-pollen rhinoconjunctivitis No asthma	SIT vs open pharmaco-tx. for 3 years	Asthma and/or effect on BHR	SIT group significantly less rhinitis symptoms and BHR better 'OR 2.52 (1.3–5.1) for SIT preventing asthma in children with pollinosis'.

A, asthma; AD, atopic dermatitis; AR, allergic rhinitis; BHR, bronchial hyper-reactivity; FA, food allergy; FHx, family history; tx, treatment; SIT, specific immunotherapy; HDM, house dust mite; RCT, randomized controlled trial; SPT, skin prick test.

How early should prevention of allergy start and how long does it need to continue?

There is some evidence that sensitization to food allergens may occur in utero and result in raised specific IgE in cord blood, but the significance of this is unclear (30). Evidence for in utero sensitization to inhalant allergens is currently weak and controversial (31–33). Studies on food allergen avoidance during pregnancy have until recently failed to show a benefit and been associated with adverse effects such as impaired maternal and foetal weight gain (34–36). These studies advised the avoidance of multiple food allergens thus severely restricting what mothers could eat, causing potential problems with compliance and the interpretation of results (34, 35). Grimshaw et al. recently reported first findings from their ongoing randomized controlled trial of strict maternal egg avoidance

during pregnancy and lactation (37). When the infants were seen at age of 18 months a significantly reduced sensitization rate to egg and inhalant allergens was observed in the active group without any significant differences in atopic dermatitis and wheeze (37). The reduced sensitization rate to egg in particular is encouraging as it represents a major risk factor for the development of asthma. It is not clear from the published data at present how many mothers also chose to avoid egg for their infants and how this has affected the outcome. The long-term results from this well designed antenatal food avoidance trial should reveal if the successful reduction of one risk factor for asthma can prevent its development.

In several of the birth cohort studies avoidance of inhalant and/or food allergens commenced antenatally and was continued postnatally (28, 38–40). Therefore, no

conclusions can be drawn on the effectiveness of sole antenatal inhalant allergen avoidance.

How long birth cohorts need to be followed up is not known and many studies ceased follow-up in early childhood (some as early as age 1 or 2 years).

Recent results from cohort studies which have been ongoing for several decades have revealed how absolutely crucial a very long-term follow-up is for the interpretation of preventive effects. One example is the report from Sears et al. on the long-term effects of breast-feeding on the development of asthma, which is in contrast to some results from other studies (41, 42). Studies of that magnitude and length will have to be very carefully designed to cater for the loss of participants and for all the potential lifetime confounders. At present it is neither known how long preventive measures need to be maintained, nor when follow-up can cease.

Primary prevention birth cohort studies

Dietary intervention – avoidance

Foods such as egg, cow's milk, soya, shellfish and nuts are the most common ones to cause adverse reactions. Because of their link to sensitization, symptomatic food allergy and atopic dermatitis multiple trials have investigated how avoidance of these foods affects the onset and progression of the atopic march (Table 1A). These trials have had various designs and often limited follow-up and are thus difficult to compare. Multiple food avoidance during lactation and for the infant until age 1 appears to confer some benefit in infancy, with some groups reporting less of any atopic disorder in the first 2 years of life (28, 43–46). Mostly, however, the follow-up stops at age 2 years, but in children followed up longer conflicting results emerge. Chandra et al. saw a sustained difference for the cumulative incidence of atopic disease at age 5 in those children who had been breast-fed or received partially hydrolysed whey formula as opposed to receiving standard or soya formula (47). Zeiger et al. however reported no difference between groups (complex food avoidance vs standard advice) for allergic sensitization or symptoms of disease at age 7 (28). Falth Magnusson et al. and investigators for the Wales infant feeding study saw no difference at any age (34, 48). Recently the German Infant Nutrition Intervention (GINI) Study reported first findings (49–51). This birth cohort study benefits from large numbers (total $n = 2252$) and improved design to investigate differences between available 'hypoallergenic feeds'. Unfortunately, their reported outcome measure at 1 year has been restricted to 'allergic manifestations' only and does not include sensitization. Schoetzau et al. reported a protective effect from breast-feeding compared with standard formula up to the age of 1 year (significantly less atopic dermatitis). The comparison between formula groups (see

Table 1A for details) showed a significant protective effect of the extensively hydrolysed casein based formula only, some effect of the partially hydrolysed whey formula but no beneficial effect of the extensively hydrolysed whey formula (51). Future findings from this cohort should help to identify if any of the tested types of formula result in sustained prevention of allergic disease especially when objective measures of sensitization and airway function are included at an older age.

Overall, it appears that there is a benefit of allergenic food avoidance in infancy, but no convincing evidence at present that this is sustained long-term. These diets are not easy to adhere to, the parents need to be supported well and especially the extensively hydrolysed formulas are not always accepted by the babies therefore reducing compliance. Thus, multiple allergenic food avoidance diets are not useful as a population-wide prevention measure although they may be beneficial in high-risk infants in early life.

Dietary intervention – supplementation

In recent years several dietary supplements have been identified as being of possible benefit in the prevention and treatment of allergic disease (52–54). Antioxidants are thought help in established asthma but no large-scale primary prevention trials have been performed (53, 55). Omega 3 fatty acids (as found in 'oily fish') are currently being investigated for their preventive effects in the Australian Childhood Asthma Prevention (CAPS) Study (Table 1A,B) (56, 57). Findings from the 18 months follow-up showed that omega 3 fatty acid supplementation protected infants from wheezing but did not reduce sensitization. There was no synergistic effect with house dust mite avoidance and the latter alone did not reduce sensitization or symptoms of wheezing either. The mite avoidance group did show a slightly increased incidence of eczema, which the investigators suspected to be a side-effect of the mattress/pillow covers (57). Clearly future data is needed for any firm conclusions about preventative or adverse effects.

The other primary prevention trial involving dietary supplementation studied the effect of adding probiotics (*Lactobacillus* GG) to the mother's diet in the last 4 weeks of pregnancy and during lactation as well as to the infant's diet for the first 6 months of life (40, 58). At 2 year follow-up a significant lower prevalence of atopic eczema was seen in the active group although there was no effect on sensitization (40). Interestingly this effect was significant even if only the breast-feeding mother took the probiotic (59). Follow-up at age 4 years showed a sustained effect on the prevention of eczema but again failed to prevent sensitization (60). Exhaled nitric oxide was significantly lower in the probiotic group, although the trend for diagnosed airways disease (asthma and hayfever) was higher in the probiotic group.

Combined dietary and environmental intervention

Several studies have combined food avoidance with aeroallergen avoidance (Table 1B). Except for the CAPS study all have used a design, which does not permit any conclusions on the individual effects or any synergistic effects compared with single intervention.

The Isle of Wight Study showed a sustained protective effect (less total allergy, sensitization) until age 4, although it appeared to be weakening with time (loss of protective effect on the airways by age 4 years) (61–63). At age 8 years, however, the protective effects from the intervention in infancy appeared to be stronger than at age 4 years (64). Seven years after the intervention measures were stopped, children in the intervention group had significantly reduced risk for being sensitized and also for asthma (defined as wheeze plus bronchial hyper-responsiveness) (64).

Chan-Yeung et al. found less 'probable or possible asthma' at age 1 year after a combined dietary-environmental intervention (65). No further follow-up has been reported on, which makes it difficult to confirm asthma as opposed to infantile wheeze in these children or to assess any lasting protection.

Recently Halmerbauer et al. reported significantly less sensitization to dust mite and food allergens at age 1 in their intervention group (dietary restriction and dust mite avoidance) as part of the Study on the Prevention on Allergy in Children in Europe (SPACE) Study (66). Interestingly, there appeared to be a trend for a higher incidence of doctor diagnosed food allergy in the active group although parentally reported symptoms of food intolerance were reduced. This finding remains unexplained at present and stresses the importance of understanding the immunological events if certain environmental stimuli are manipulated.

Environmental intervention – aeroallergen avoidance

Aeroallergen avoidance has been studied widely. Whilst the house dust mite has remained securely in the 'to be avoided' field, pets are experiencing somewhat of a comeback with recent findings that their presence may possibly confer some benefits (endotoxin, modified Th2 response) (5, 10). Pet allergens are ubiquitous and thus almost impossible to avoid (67, 68).

Primary prevention trials involving aeroallergens have thus been limited to house dust mite avoidance although investigators have tried to take pets out of the equation to avoid confounding effects (Table 1B).

Two large prospective birth cohort studies investigating the effect of sole mite avoidance are currently ongoing. The Manchester Asthma and Allergy Study (MAAS) enrolled families antenatally and used extremely stringent environmental control measures in the intervention arm of the study: the parental bed received

impermeable mattress covers in the second trimester of pregnancy, the babies' mattress (cot and carry-cot) was covered and the babies' bedroom was furnished with hard wood flooring. Soft toys were limited and either hot washed or frozen regularly. Bedding was washed hot once a week, HEPA filter vacuum cleaners (Nilfisk, Brøndby, Denmark) were supplied. Arcarosan was used regularly on soft furnishings. With these stringent measures Der p 1 levels dropped dramatically in the intervention group (well below the 2 mcg/g threshold) (38). At age 1 year there was no difference in mite sensitization but a significant reduction of wheeze at the severe end of the spectrum was observed (39). No difference was seen for mild wheeze or cough symptoms or the presence of atopic dermatitis. Specific airway resistance (sRaw) was measured at age 3 years and reported for children in the observational arm of the study. This showed that being in the high-risk group and/or atopic at age 3 was significantly associated with increased sRaw (i.e. poorer lung function) (69).

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study investigates the effect of less stringent mite avoidance measures from birth on the development of sensitization and symptoms (70). In the active group mite covers were provided for the infants' and parents' beds and advice on regular hot washing of the bedding was given. Whilst a significant reduction in Der 1 was achieved, the effect on symptoms was disappointing. At age 2 years the only difference seen was a slight but significant reduction in night-time cough in children in the active group (70).

Breast-feeding

'Breast is best' – this statement has not changed because of the undisputed benefits it gives to mother and child. Regarding prevention of allergic disease its effect has been controversial for a long time with many studies showing mild preventative effects and others failing to show these effects (42, 71–73). Recently Sears et al. reported that breast-feeding (for greater than or equal to the first 4 weeks of life) may increase the risk of asthma in later life (41). These findings need to be confirmed and substantiated in other long-term cohorts before we can ever contemplate advice against breast-feeding in high-risk groups. At present breast-feeding should remain the diet of choice, irrespective of its effect on the development of allergy.

Secondary prevention trials

Secondary prevention is designed to halt the progression of disease not to alleviate its symptoms (which would be tertiary intervention). Only a small number of true secondary prevention trials exist (Table 2).

House dust mite avoidance

As part of the multicentre SPACE study the protective effect of house dust mite avoidance in high-risk allergic (asthma, hayfever or eczema but not sensitized to mite) children of different ages was investigated (74, 75). One arm of the study randomized 636 young children aged 1.5–5 years to mite impermeable mattress covers and specific advice *vs* general advice only. The rate of sensitization to mite after 1 year was reduced in the active group. Symptoms of allergic disease were more common in the sensitized group (74). Interestingly allergic sensitization was reduced significantly at all centres except the UK centre (increased, not significant) but the reason for this is unclear. Arshad et al. reported on a similar intervention in schoolchildren age 5–7 years (75). A total of 242 children were randomized into active and control group as described above. After 1 year fewer children were newly sensitized to house dust mite in the active group with a trend to fewer wheezing symptoms. Both studies show that sensitization to dust mite can be prevented in the short-term. Further follow-up of these children should show if this can be sustained, and what the impact on allergic disease will be.

Pharmacological measures

Iikura et al. investigated the effect of Ketotifen given to infants (age 2–34 months) with atopic dermatitis but without respiratory disease on the future development of asthma (76). At the end of the 1 year treatment period they saw significantly less asthma (defined as two wheezy episodes requiring bronchodilators) but only in children who had total serum IgE > 50 IU/ml. Unfortunately there was no long-term follow-up for this study and the diagnosis of 'asthma' was not confirmed by objective measures.

Bustos et al. randomized 100 children with a positive family history of atopy and increased serum IgE (described as 'preasthmatic') to receive Ketotifen or placebo for 3 years (77). Children in the active group developed significantly less asthma (defined as ≥ 3 episodes of bronchial obstruction with distress) but there was no difference in the rate of sensitization (SPT) at the end of the study. Again the diagnosis of asthma was not confirmed by more objective measures and no long-term follow-up has been reported on.

The Early Treatment of the Atopic Child (ETAC[®]) study investigated the preventive effect of the antihistamine cetirizine on the development of asthma in children with manifest atopic dermatitis aged 12–24 months (78).

The children received cetirizine or placebo for 18 months and were assessed at regular intervals. The antihistamine prevented asthma ('three separate episodes of wheeze or waking with nocturnal cough') only if the child had either raised total IgE or specific IgE to dust mite or grasses. The effect on the whole active group was not significant however. An additional finding was the reduction of urticaria in the active group. Atopic dermatitis was not significantly reduced or alleviated although there was less use of additional antihistamines in the active group.

Immunotherapy

Several studies have investigated the effect of specific immunotherapy on development of further sensitization and/or asthma (79–82). It appears that immunotherapy may prevent further sensitization in monosensitized children and possibly prevent the onset of asthma. Unfortunately some of these studies are underpowered and none of the childhood studies are double-blind placebo controlled because of the ethical problem of giving placebo injections to children for several years. Clearly more research is necessary in this area and improved study designs and compliance may be possible with alternative routes of administration, e.g. sublingual immunotherapy (83).

Conclusion

If we believe a thing to be bad, and if we have a right to prevent it, it is our duty to try to prevent it and to damn the consequences (Lord Milner 1854–1925) (84).

Allergic disease is undoubtedly 'bad' because it causes suffering and loss of life. We certainly have a desire to prevent it, but it is the individual's choice as to whether or not to use preventive measures. As to the consequences, too little is known at present to allow us to ignore them.

We still do not understand enough about all the involved immunological mechanisms to allow implementation of general population-wide preventive measures. Ongoing observational, primary and secondary prevention cohorts have provided us with a wealth of information and much more is required before we can be sure that our interventions do not cause any harm. We need more information from the ongoing studies and more well designed trials that allow the assessment of each individual part of the intervention before we can give any advice to our patients.

References

- VON PIRQUET C. Allergie. *Munchen Med Wchnschr* 1906;**53**:1457.
- COHEN SG. Pioneers and milestones. Clemens von Pirquet, MD (1874–1929). *J Allergy Clin Immunol* 2002;**109**: 722–724.
- STRACHAN DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**: 1259–1260.
- MARTINEZ FD, HOLT PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999;**354** (Suppl 2):SII12–SII15.
- PLATTS-MILLS T, VAUGHAN J, SQUILLACE S, WOODFOLK J, SPORIK R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;**357**:752–756.
- MARTINEZ FD, WRIGHT AL, TAUSSIG LM, HOLBERG CJ, HALONEN M, MORGAN WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–138.
- MALLIA P, JOHNSTON SL. Respiratory viruses: do they protect from or induce asthma? *Allergy* 2002;**57**:1118–1129.
- REMES ST, CASTRO-RODRIGUEZ JA, HOLBERG CJ, MARTINEZ FD, WRIGHT AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;**108**:509–515.
- ILLI S, von MUTIUS E, LAU S, BERGMANN R, NIGGEMANN B, SOMMERFELD C et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;**322**:390–395.
- RIEDLER J, BRAUN-FAHRLANDER C, EDER W, SCHREUER M, WASER M, MAISCH S et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;**358**:1129–1133.
- LITONJUA AA, MILTON DK, CELEDON JC, RYAN L, WEISS ST, GOLD DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. *J Allergy Clin Immunol* 2002;**110**:736–742.
- BRAUN-FAHRLANDER C. Do only European cattle protect from allergies? *Allergy* 2002;**57**:1094–1096.
- GEHRING U, BOLTE G, BORTE M, BISCHOF W, FAHLBUSCH B, WICHMANN HE et al. Exposure to endotoxin decreases the risk of atopic eczema in infancy: a cohort study. *J Allergy Clin Immunol* 2001;**108**:847–854.
- BJORKSTEN B, NAABER P, SEPP E, MIKELSAAR M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999;**29**:342–346.
- BJORKSTEN B, SEPP E, JULGE K, VOOR T, MIKELSAAR M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001;**108**:516–520.
- KALLIOMAKI M, KIRJAVAINEN P, EEROLA E, KERO P, SALMINEN S, ISOLAURI E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 2001;**107**: 129–134.
- MATRICARDI PM, BJORKSTEN B, BONINI S, BOUSQUET J, DJUKANOVIC R, DREBORG S et al. Microbial products in allergy prevention and therapy. *Allergy* 2003;**58**:461–471.
- JOHANSSON SG, HOURIHANE JO, BOUSQUET J, BRUINZEEL-KOOMEN C, DREBORG S, HAAHTELA T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
- HOST A, HALKEN S. Can we apply clinical studies to real life? Evidence-based recommendations from studies on development of allergic diseases and allergy prevention. *Allergy* 2002;**57**: 389–397.
- TARIQ SM, MATTHEWS SM, HAKIM EA, STEVENS M, ARSHAD SH, HIDE DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;**101**:587–593.
- WAHN U. What drives the allergic march? *Allergy* 2000;**55**:591–599.
- BERGMANN R, WOODCOCK A. Whole population or high-risk group? Childhood asthma. *Eur Respir J* 1998;**27**(Suppl):9s–12s.
- HALONEN M, STERN D, TAUSSIG LM, WRIGHT A, RAY CG, MARTINEZ FD. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. *Am Rev Respir Dis* 1992;**146**:866–870.
- TARIQ SM, ARSHAD SH, MATTHEWS SM, HAKIM EA. Elevated cord serum IgE increases the risk of aeroallergen sensitization without increasing respiratory allergic symptoms in early childhood. *Clin Exp Allergy* 1999;**29**:1042–1048.
- EDENHARTER G, BERGMANN RL, BERGMANN KE, WAHN V, FORSTER J, ZEPP F et al. Cord blood-IgE as risk factor and predictor for atopic diseases. *Clin Exp Allergy* 1998;**28**:671–678.
- NICKEL R, KULIG M, FORSTER J, BERGMANN R, BAUER CP, LAU S et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;**99**:613–617.
- RHODES HL, SPORIK R, THOMAS P, HOLGATE ST, COGSWELL JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J Allergy Clin Immunol* 2001;**108**: 720–725.
- ZEIGER RS, HELLER S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;**95**:1179–1190.
- ASHER I, BONER A, CHUCHALIN A, CUSTOVIC A, DAGLI E, HAUS M et al. Prevention of allergy and asthma: interim report. *Allergy* 2000;**55**:1069–1088.
- SZEPFALUSI Z, LOIBICHLER C, PICHLER J, REISENBERGER K, EBNER C, URBANEK R. Direct evidence for transplacental allergen transfer. *Pediatr Res* 2000;**48**: 404–407.
- SZEPFALUSI Z, PICHLER J, ELSASSER S, van DUREN K, EBNER C, BERNASCHEK G et al. Transplacental priming of the human immune system with environmental allergens can occur early in gestation. *J Allergy Clin Immunol* 2000;**106**: 530–536.
- HOLLOWAY JA, WARNER JO, VANCE GH, DIAPER ND, WARNER JA, JONES CA. Detection of house-dust-mite allergen in amniotic fluid and umbilical-cord blood. *Lancet* 2000;**356**:1900–1902.
- PLATTS-MILLS TA, WOODFOLK JA. Cord blood proliferative responses to inhaled allergens: is there a phenomenon? *J Allergy Clin Immunol* 2000;**106**: 441–443.
- FALTH-MAGNUSSON K, KJELLMAN NI. Allergy prevention by maternal elimination diet during late pregnancy – a 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992;**89**:709–713.

35. FALTH-MAGNUSSON K, OMAN H, KJELLMAN NI. Maternal abstinence from cow milk and egg in allergy risk pregnancies. Effect on antibody production in the mother and the newborn. *Allergy* 1987;**42**:64–73.
36. KRAMER MS. Maternal antigen avoidance during pregnancy for preventing atopic disease in infants of women at high risk. *Cochrane Database Syst Rev* 2000;CD000133.
37. GRIMSHAW KEC, VANCE GHS, BRIGGS RA, WARNER JO. The effect of maternal egg avoidance on atopy at 18 months. *J Allergy Clin Immunol* 2003;**111**:S396. (Abstract)
38. CUSTOVIC A, SIMPSON BM, SIMPSON A, HALLAM C, CRAVEN M, BRUTSCHE M et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000;**105**(2 Pt 1):252–258.
39. CUSTOVIC A, SIMPSON BM, SIMPSON A, KISSEN P, WOODCOCK A. 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.
40. KALLIOMAKI M, SALMINEN S, ARVILOMMI H, KERO P, KOSKINEN P, ISOLAURI E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;**357**:1076–1079.
41. SEARS MR, GREENE JM, WILLAN AR, TAYLOR DR, FLANNERY EM, COWAN JO 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.
42. SAARINEN UM, KAJOSAARI M. Breast-feeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;**346**: 1065–1069.
43. ZEIGER RS, HELLER S, MELLON MH, FORSYTHE AB, O'CONNOR RD, HAMBURGER RN et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989;**84**: 72–89.
44. ZEIGER RS, HELLER S, MELLON M, O'CONNOR R, HAMBURGER RN. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J Allergy Clin Immunol* 1986; **78**(1 Pt 2):224–238.
45. CHANDRA RK, PURI S, HAMED A. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ* 1989;**299**:228–230.
46. OLDAEUS G, ANJOU K, BJORKSTEN B, MORAN JR, KJELLMAN NI. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child* 1997;**77**:4–10.
47. CHANDRA RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. *J Pediatr Gastroenterol Nutr* 1997;**24**:380–388.
48. BURR ML, LIMB ES, MAGUIRE MJ, AMARAH L, ELDRIDGE BA, LAYZELL JC et al. Infant feeding, wheezing, and allergy: a prospective study. *Arch Dis Child* 1993;**68**:724–728.
49. SCHOETZAU A, FILIPIAK-PITTOFF B, FRANKE K, KOLETZKO S, VON BERG A, GRUEBL A et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002;**13**:234–242.
50. SCHOETZAU A, GEHRING U, FRANKE K, GRUBL A, KOLETZKO S, VON BERG A et al. Maternal compliance with nutritional recommendations in an allergy preventive programme. *Arch Dis Child* 2002;**86**:180–184.
51. VON BERG A, KOLETZKO S, GRUBL A, FILIPIAK-PITTOFF B, WICHMANN HE, BAUER CP et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003;**111**:533–540.
52. BAKER JC, AYRES JG. Diet and asthma. *Respir Med* 2000;**94**:925–934.
53. ROMIEU I, SIENRA-MONGE JJ, RAMIREZ-AGUILAR M, TELLEZ-ROJO MM, MORENO-MACIAS H, REYES-RUIZ NI et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *Am J Respir Crit Care Med* 2002;**166**:703–709.
54. MELLIS CM. Is asthma prevention possible with dietary manipulation? *Med J Aust* 2002;**177**(Suppl):S78–S80.
55. BAKER JC, TUNNICLIFFE WS, DUNCANSON RC, AYRES JG. Dietary antioxidants and magnesium in type 1 brittle asthma: a case control study. *Thorax* 1999;**54**:115–118.
56. MIHRSHAHI S, PEAT JK, WEBB K, TOVEY ER, MARKS GB, MELLIS CM et al. The childhood asthma prevention study (CAPS): design and research protocol of a randomized trial for the primary prevention of asthma. *Control Clin Trials* 2001;**22**:333–354.
57. MIHRSHAHI S, PEAT JK, MARKS GB, MELLIS CM, TOVEY ER, WEBB K et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003;**111**:162–168.
58. ISOLAURI E, ARVOLA T, SUTAS Y, MOILANEN E, SALMINEN S. Probiotics in the management of atopic eczema. *Clin Exp Allergy* 2000;**30**:1604–1610.
59. RAUTAVA S, KALLIOMAKI M, ISOLAURI E. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol* 2002;**109**:119–121.
60. KALLIOMAKI M, SALMINEN S, POUSSA T, ARVILOMMI H, ISOLAURI E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;**361**:1869–1871.
61. ARSHAD SH, MATTHEWS S, GANT C, HIDE DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;**339**:1493–1497.
62. ARSHAD SH, STEVENS M, HIDE DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;**23**:504–511.
63. HIDE DW, MATTHEWS S, TARIQ S, ARSHAD SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;**51**:89–93.
64. ARSHAD SH, BATEMAN B, MATTHEWS SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;**58**: 489–493.
65. CHAN-YEUNG M, MANFREDA J, DIMICHWARD H, FERGUSON A, WATSON W, BECKER A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med* 2000;**154**:657–663.
66. HALMERBAUER G, GARTNER C, SCHIERL M, ARSHAD H, DEAN T, KOLLER DY et al. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2003;**14**:10–17.

67. ALMQVIST C, WICKMAN M, PERFETTI L, BERGLIND N, RENSTROM A, HEDREN M et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001;**163**(3 Pt 1):694–698.
68. ALMQVIST C, LARSSON PH, EGMAR AC, HEDREN M, MALMBERG P, WICKMAN M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *J Allergy Clin Immunol* 1999;**103**:1012–1017.
69. LOWE L, MURRAY CS, CUSTOVIC A, SIMPSON BM, KISSEN PM, WOODCOCK A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet* 2002;**359**:1904–1908.
70. KOOPMAN LP, van STRIEN RT, KERKHOF M, WIJGA A, SMIT HA, de JONGSTE JC 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.
71. von MUTIUS E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000;**105**(1 Pt 1):9–19.
72. WRIGHT AL, HOLBERG CJ, MARTINEZ FD, MORGAN WJ, TAUSSIG LM. Breast feeding and lower respiratory tract illness in the first year of life. Group Health Medical Associates. *BMJ* 1989;**299**:946–949.
73. ODDY WH, HOLT PG, SLY PD, READ AW, LANDAU LI, STANLEY FJ et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;**319**:815–819.
74. TSITOURA S, NESTORIDOU K, BOTIS P, KARMAUS W, BOTEZAN C, BOJARSKAS J et al. Randomized trial to prevent sensitization to mite allergens in toddlers and preschoolers by allergen reduction and education: one-year results. *Arch Pediatr Adolesc Med* 2002;**156**:1021–1027.
75. ARSHAD SH, BOJARSKAS J, TSITOURA S, MATTHEWS S, MEALY B, DEAN T et al. Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized controlled study. *Clin Exp Allergy* 2002;**32**:843–849.
76. IKURA Y, NASPITZ CK, MIKAWA H, TALARICOFICHO S, BABA M, SOLE D et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992;**68**:233–236.
77. BUSTOS GJ, BUSTOS D, BUSTOS GJ, ROMERO O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995;**25**:568–573.
78. WARNER JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001;**108**:929–937.
79. DES ROCHES RA, PARADIS L, MENARDO JL, BOUGES S, DAURES JP, BOUSQUET J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;**99**:450–453.
80. SARVA M, PLOSA R, PALERMO F, LISITANO N, CRIMI N. Allergic rhinitis as an independent risk factor for asthma: effect of specific immunotherapy. *J Allergy Clin Immunol* 2002;**109**:S91. (Abstract)
81. MASTRUZZO C, CRIMI N, LI GOTTI F, SARVA M, MANGANO G, PAOLINO G et al. Effect of specific immunotherapy on clinical and inflammatory markers in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2003;**109**:S201. (Abstract)
82. MOLLER C, DREBORG S, FERDOUSI HA, HALKEN S, HOST A, JACOBSEN L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;**109**:251–256.
83. MASTRANDREA F, SERIO G, MINELLI M, MINARDI A, SCARCIA G, CORADDUZZA G et al. Specific sublingual immunotherapy in atopic dermatitis. Results of a 6-year follow-up of 35 consecutive patients. *Allergol Immunopathol (Madr.)* 2000;**28**:54–62.
84. Oxford Concise Dictionary of Quotations. 3rd edn. Oxford, UK: Oxford University Press, 1996.
85. DIEPGEN TL. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002;**13**:278–286.
86. HIDE DW, MATTHEWS S, MATTHEWS L, STEVENS M, RIDOUT S, TWISELTON R et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994;**93**:842–846.