

# Role of exposure to inhalant irritants and infections for the development of allergic diseases

Björkstén B. Role of exposure to inhalant irritants and infections for the development of allergic diseases.  
*Pediatr Allergy Immunol* 1996; 7 (suppl 9): 111–116. © Munksgaard 1996.

## **B. Björkstén**

University Hospital, Linköping, Sweden

B. Björkstén, Department of Paediatrics, University Hospital, S-581 85 Linköping, Sweden

Key words: sensitization; allergy; IgE; genetic predisposition; allergen exposure; infections; air pollution; tobacco smoke

Sensitivity to allergens and manifest disease are the end results of an interaction between genetically determined susceptibility to atopy, exposure to allergen and exposure to adjuvant factors. Recent epidemiological studies show that there are large regional differences in the prevalence of asthma and allergies both in children and in adults (1, 2). With the exception of a few isolated groups of people, the reported differences between populations are not genetically determined. A temporary formation of IgE antibodies directed against environmental allergens appears to be part of the normal immune response (3). In most instances, at least in children, these antibodies are only temporary, as the continuing IgE antibody formation is rapidly suppressed (4). But when genetically predisposed individuals are exposed to an allergen at a time when the regulation of the immune system is immature, then higher levels of IgE antibodies lasting for a long time may appear (5).

The influence of environmental factors is modified by the genetic susceptibility and individual factors that may vary over time. The potential role of a certain environmental influence should therefore be studied in populations who are defined with regard to these individual factors.

Environmental factors that influence the development of allergic disease are either specific or non-specific. In order to develop an allergy the individual has obviously to be exposed to the allergen. Allergens are present in almost every part of the world, but the relative importance of the individual allergens varies, depending on climatic conditions. In subarctic regions, like the Nordic countries, house dust mites used to be absent, but there is now evidence for an increasing prevalence (6, 7). This may, at least partly, be due to modern technol-

ogy used for building houses and energy conservation measures (8).

It has traditionally been assumed that air pollution primarily occurs outdoors. A number of studies have, however, shown that indoor concentrations of some pollutants may be far in excess of the outdoor concentrations (9). There is probably no air outdoors that is so polluted as that in a room where people are smoking. In many countries, outdoor air pollution has decreased over the past decades. Furthermore, there is no clear relation between air pollution and the prevalence of allergy. On the contrary, Swedish studies have reported a higher prevalence of allergy in the northern, less polluted part of the country than in the southern, more industrialised parts, which are also more affected by pollution from central Europe (10). The indoor environment therefore probably plays an equally large or even larger role for the development of allergic sensitization and the appearance of allergic disease in the sensitized individual.

There is increasing experimental and clinical evidence that the conditions under which an allergen is encountered in infancy may have consequences for many years, perhaps even for life (5).

The likelihood of developing allergic disease in an individual is not constant over time, even if the general propensity is genetically determined. For example, the risk of sensitization is affected by the time for, and the conditions under which, exposure to allergens takes place. A higher incidence of allergy to birch and grass pollen has thus been reported in children born in the spring (11, 12). This relationship between season of birth and development of allergy seems to be limited to children with a congenital propensity to develop allergic disease (13). Similarly, early feeding with foreign proteins is associ-

Table 1. Adjuvant factors thought to be involved either in sensitization or manifestations of allergic disease

|                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------|
| Air pollution and sources:                                                                                           |
| Tobacco smoke                                                                                                        |
| Industry and traffic; solid particles, SO <sub>2</sub> , NO <sub>x</sub>                                             |
| Combustion by-products; CO <sub>2</sub> , CO, SO <sub>2</sub> , NO <sub>2</sub> , NO, formaldehyde, volatile vapours |
| Photochemical reactions; ozone, NO <sub>2</sub>                                                                      |
| Building materials; formaldehyde, decoration and paints; solvents, furnishings                                       |
| Tight, poorly ventilated homes                                                                                       |
| Pesticides and consumer products; organic substances, aerosols                                                       |
| Respiratory tract infections; viral, pertussis                                                                       |
| Ongoing allergic reaction (facilitates sensitization to new allergens)                                               |

ated with an increased risk for allergic disease, but mostly so in genetically susceptible individuals (14). It is reasonable to conclude that a search for environmental triggers of allergy should be directed towards infancy, rather than towards factors prevailing at the time of onset of clinical symptoms.

### Inhalant irritants

It is well established that various environmental factors may enhance sensitization and also trigger an allergic reaction in a sensitized individual (Table 1). While allergy to most of the compounds listed in the table is rare, they do play a role, both in enhancing sensitization to allergens and in eliciting and aggravating clinical symptoms.

### Air pollution

Air pollution such as ozone, SO<sub>2</sub> and NO<sub>2</sub> may all enhance sensitization, at least in experimental animals (3, 5). Data are less clear-cut in humans, but in an epidemiological survey of 5300 children in Sweden, bronchial hyperreactivity and pollen allergy were both more common in children living near a

moderately air-polluting paper factory than among children living in a forested poorly industrialised area about 40 km away from the factory (15). If the parents smoked at home, then the prevalence of bronchial hyperreactivity and allergy were further increased, indicating a synergistic effect between the two pollutants.

The prevalence of allergic manifestations is lower in rural, than in nearby urban areas in western Europe (16, 17). The most likely explanation for this is different levels of air pollution. A similar difference was also noted in the formerly Soviet-occupied Estonia (18, 19) (Table 2). Thus, the prevalence of at least one positive skin prick test was significantly higher in Tallinn, an industrialised coastal city with considerable pollution, than in Tartu, which is an inland university town.

### Exposure to tobacco smoke

Tobacco smoke is the major indoor air pollutant. Tobacco smoke is strongly associated with allergic sensitization, asthma and other respiratory diseases. Increased serum IgE levels and an increased prevalence of positive skin tests towards occupational allergens have been shown in multiple studies (1). Thus, smokers are sensitized more easily to occupational allergens than non-smokers who are exposed to the allergens to a similar degree (20).

The effect of tobacco smoke is, however, not limited to active smoking. Infants and young children are particularly susceptible to the adjuvant effects of tobacco smoke as trigger of sensitization and wheezing. Children of parents who smoke at home have a significantly earlier onset of allergy and wheezy bronchitis than children of non-smoking parents (21).

The effect of tobacco smoke on sensitization to allergens may be explained by a local effect on the

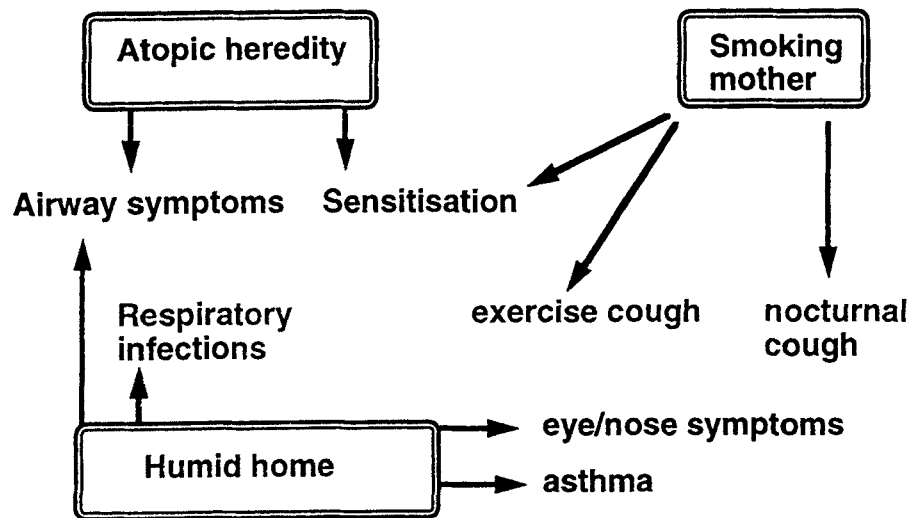
Table 2. Prevalence of positive skin tests and airway symptoms among 11- to 12-year-old schoolchildren in five regions around the Baltic and the levels of certain common air pollutants

|                                          | Sweden   |          | Poland   | Estonia |       |
|------------------------------------------|----------|----------|----------|---------|-------|
|                                          | Urban    | Rural    | Konin    | Tallinn | Tartu |
| ≥1 pos SPT, %                            | 24.2     | 35.3     | 13.7     | 14.3    | 8.1   |
| OR                                       | 1        | 1.71     | 0.49     | 0.46*   | 0.28* |
| Cough >2 weeks, %                        | 5.7      | 12.0     | 15.1     | 18.8    | 13.8  |
| Resp. inf. >6/year, %                    | 6.3      | 8.0      | 14.0     | 10.4    | 10.5  |
| Wheeze, %                                | 3        | 11.6     | 10.4     | 9.4     | 5.8   |
| Asthma diagnosed, %                      | 6.7      | 9.5      | 2.9      | 3.2     | 2.5   |
| SO <sub>2</sub> µg/m <sup>3</sup> , mean | 1.9      | 2.3      | 17.1     | ?       | ?     |
| Range                                    | 0.8–3.9  | 1.0–14.7 | 4.3–70.9 |         |       |
| NO, µg/m <sup>3</sup> , mean             | 8.4      | 19.0     | 17.5     | ?       | ?     |
| Range                                    | 1.0–34.8 | 1.3–66.9 | 3.9–25.9 |         |       |
| Particles, µg/m <sup>3</sup> , mean      | 4.9      | 4.4      | 32.3     | ?       | ?     |
| Range                                    | 0–11.2   | 0–21.2   | 4.9–99.0 |         |       |

\*Odds ratio for a positive skin prick test among children in Tallinn (industrialised city) was 1.81 as compared to Tartu (university town).

?= not determined.

Fig. 1. The identified risk factors for sensitization and respiratory symptoms (within squares) were similar among 11-year-old children living in Estonia (Tallinn and Tartu), Poland (Konin) and Sweden (urban and rural Sundsvall).



airways or by a direct effect on the immune system. The former notion is supported by the finding that smoking rats exposed to antigen in aerosol develop higher IgE responses than subcutaneously immunised animals and non-smoking aerosol-immunised controls (22).

In conclusion, passive smoking is by far the best identified risk factor for the development of allergic disease, particularly in early childhood, and this is independent of how "allergy" is defined. There is little doubt that exposure to tobacco smoke is the most important environmental risk factor for childhood allergy and respiratory disease that has been identified so far. The long time effects of childhood exposure to tobacco smoke are unknown.

### Housing

Most children in Europe and North America spend at least 90% of their time indoors. It is, therefore, likely that the indoor environment is even more important than geographical and other macroenvironmental factors. Modern, well-insulated buildings with poor ventilation represent a definite risk factor for allergic sensitization (8). Many new compounds are used in modern buildings, e.g. plastic material, synthetic paints and chemical substances, with unknown effects on human health. Combined with efficient insulation and a reduced ventilation, this has created a new indoor climate. In temperate climates, the energy crises and increased interest in energy-conserving measures have resulted in changed building standards, particularly better insulation and reduced ventilation. This in turn has resulted in more "sick buildings", characterized by damage due to dampness, indoor mould growth and presence of various symptoms among people dwelling in the houses. At least one well-documented consequence

of this is a much increased prevalence of sensitivity to house dust mite allergens in regions with a temperate climate (7, 23, 24). Sensitivity to these allergens used to be rare in a climate with cold and dry winters, but the creation of a warm and humid "sub-tropical" indoor climate has changed this.

In an epidemiological survey, it was found that homes with damage due to dampness were associated with both a higher incidence of atopic disease and/or bronchial hyperreactivity in the children. In children living in houses with damage by dampness and whose parents in addition smoked at home, there was a marked increase in allergic asthma and bronchial hyperreactivity, compared with children exposed to only one of these factors. The effects of the living conditions were most marked for children with a family history of asthma. This supports the notion that the environmental influences mainly play a particular role in individuals with a genetic susceptibility to allergic disease.

Much more has to be learnt about the role of the indoor climate for sensitization and triggering of allergic manifestations, e.g. the role of moulds and other micro-organisms. It is, however, reasonable to conclude that a search for environmental factors influencing the development of asthma and allergy should be directed towards factors affecting the indoor climate.

### Comparisons between eastern and western Europe

An understanding of the role of environmental factors has become complicated by some recent observations. Air pollution is a major problem in many formerly socialistic countries in central and eastern Europe, yet the prevalence of atopy among children is much lower than in western Europe. As an example, the prevalence of positive skin prick tests in

Leipzig in eastern Germany is less than half of that among children of the same age living in Munich in western Germany (25). Similarly, atopic sensitization is much lower in Konin in central Poland and in Estonia than in northern Sweden (17, 19, 25). Mirroring the observed differences in skin prick test positivity in an urban and rural area of Sweden, the prevalence of at least one positive skin prick test was significantly higher in Tallinn, an industrialised coastal city, than in Tartu, which is an inland university town. The same risk factors were identified however in the formerly socialist countries and in Sweden, including maternal tobacco smoking, a family history of allergy, humid homes and urban living (Table 2, Fig. 1). Thus, although air pollution does seem to play a role in the development of atopy, other factors connected with western lifestyle are much more important. The nature of these factors is unknown.

In addition to the introduction of many new chemicals in the environment, there have been many changes in lifestyle in industrialised countries over the past decades. The type of foods eaten has changed dramatically with the introduction of new industrial products with numerous additives. Even fresh food items differ in many respects from those available only a few decades ago. As an example, by genetic manipulation and use of various chemical compounds the storage time of food has been much prolonged, often allowing a shelf life of e.g. apples for months. Virtually nothing is known regarding the possible influence on childhood allergy of such changes in the diet.

### Infections

The role of infections, notably in the respiratory tract, as risk factors for the development of childhood allergic disease is complex. An infection induces an inflammatory reaction in the respiratory mucosa, which in turn modifies the local immune response. They may also possibly alter the immune defence and act as adjuvants or as allergens. Furthermore, it is common knowledge that infections may trigger clinical symptoms in already sensitized individuals and that infections increase bronchial hyperreactivity. Earlier animal experiments support the clinical observations, showing enhanced IgE production after allergen exposure and concomitant viral infection (7, 26).

Epidemiological studies of the relation between infections and manifestation of allergic disease are, however, complicated by the fact that symptoms like a runny nose, wheezing and cough may all be caused by either an infection or an allergic reaction and that the aetiology of the symptoms is, therefore,

not always easily identified by patients and researchers.

Certain infectious agents, e.g. respiratory syncytial virus, Epstein Barr virus and *Bordetella pertussis* seem to be of particular interest, as they appear to enhance sensitization. The mechanisms are probably different, however. Bronchiolitis caused by RS virus in early infancy has been associated with the development of atopy and asthma. The mechanism may be that the G-protein of RS virus may directly stimulate Th2-like cells, thus enhancing IgE antibody formation and other components of the allergic inflammation.

The relationship between bronchiolitis caused by respiratory syncytial virus (RSV) during the first 6 months of life and the development of asthma was recently studied prospectively in 47 infants (27). For each child two matched controls were selected, making a study population of 140 participating in the follow-up at three years. Asthma, defined as three episodes of bronchial obstruction verified by a physician, was found in 11 of the 47 children with RSV bronchiolitis (23%) and in only one of 93 controls. A positive test for IgE antibodies against a mixture of allergens was recorded in 32% of the RSV children and 9% of the controls ( $p=0.02$ ). Of particular interest was the observation that among the former children, 6 of 11 children with a family history of allergy developed asthma, as compared to only 5 of 36 without this family history. Thus, the risk for asthma after RSV bronchiolitis was much higher in infants with a genetic propensity to allergy.

Among the infectious agents *Bordetella pertussis* is of particular interest, as it is a well established adjuvant for the induction of IgE antibody formation in experimental animals (28). Furthermore, whooping cough is associated with bronchial hyperreactivity for several months (29). It has also been shown that IgE antibodies to pertussis toxin appear after an infection (30) and after immunisation against pertussis (31). The latter observation raises the question about a possible role of vaccinations as a risk factor for allergic disease. This notion is further strengthened by the fact that aluminium, which is used as an adjuvant in many vaccines, is also one of the most potent adjuvants for IgE antibody synthesis in animals. Properly designed epidemiological studies are needed to clarify a possible relationship between routine immunizations of infants and the development of atopic disease.

Infections with Epstein-Barr virus are associated with atopic disease (32). This is possibly explained by the general stimulatory effects on B-cells that is exerted by the virus.

The understanding of the interaction between infections and sensitization has become more complicated recently, however, in the light of experimental

studies and epidemiological observations. Thus, rat pups who are protected against infections are more easily sensitized to inhaled allergens than pups exposed to various microbial agents (5). The data from the recent animal experiments are supported by the results of epidemiological studies. In a British study an inverse relationship between many respiratory tract infections and atopy was observed (33). An inverse relationship between the number of siblings (34), particularly younger siblings (33, 35), and atopy has also been reported. In the latter study, there was no significant relationship between atopy and presence of, indicating that many infections during the first year of life could protect against sensitization. Very recently it was observed that the prevalence of positive skin prick tests may be lower in tuberculin-positive than in tuberculin-negative children, indicating that bacterial infections and vaccinations early in life may possibly enhance the down-regulation of the IgE antibody formation to allergens encountered at the time of the infection. The low prevalence of atopy among schoolchildren in the formerly socialist countries of eastern Europe (17, 18, 25, 36) could lend some support to the relevance of these findings.

Based on the experimental and clinical findings, Holt (5, 37) suggested that improvements in public health and general living standards in the developed countries over the last 2–3 generations has progressively reduced the level of exposure of infants and young children to the natural microbial environment. According to this hypothesis, the lowered microbial stimulation has resulted in a delayed postnatal development of immune competence, resulting in a prolonged period during which the immune system is at risk of generating a Th-2 type immune response with IgE antibody formation and stimulation of mast cell and eosinophil proliferation.

## Conclusion

It is possible that the apparent increase in the prevalence of atopic disease in many countries over the past decades are caused by unknown changes in lifestyle operating in early life. Even if all the known factors that may influence the incidence of allergic disease are added, however, this can only explain a fraction of the regional differences and changes over time in the prevalence of allergy. The role of infections for the development of allergic diseases may depend on the type of infection and when the infections occur. Thus, they may possibly help to down-regulate IgE responses to ubiquitous environmental inhalant allergens at the time of primary exposure to the allergens, while facilitating allergic manifestations in the sensitized individual.

## References

1. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9: 687–695.
2. PEARCE N, WEILAND S, KEIL U, et al. Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. *Eur Respir J* 1993; 6: 1455–61.
3. BJÖRKSTÉN B. Risk factors in early childhood for the development of atopic diseases. *Allergy* 1994; 49: 400–7.
4. HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Appearance of IgE antibodies to ingested and inhaled allergens during first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993; 4: 182–9.
5. HOLT P. Environmental factors and primary T-cell sensitization to inhalant allergens in infancy: reappraisal of the role of infections and air pollution. *Pediatr Allergy Immunol* 1995; 6: 1–10.
6. WICKMAN M, NORDVALL S, PERSHAGEN G, SUNDELL J, SCHWARTZ B. House dust mite sensitization in children and residential characteristics in a temperate region. *J Allergy Clin Immunol* 1991; 88: 89–95.
7. MUNIR AKM, BJÖRKSTÉN B, EINARSSON R, et al. Mite allergens in relation to home conditions of asthmatic children from three climatic regions. *Allergy* 1995; 50: 55–64.
8. MUNIR A, BJÖRKSTÉN B. Indoor air pollution and allergic sensitization. In: KNÖPPEL H, WOLKOFF P, eds. Chemical microbiological health and comfort. Brussels: ECSC, EEC, 1992: 181–99.
9. ABRAMSON M. Air pollution health effects and air quality objectives. *Med J Aust* 1991; 154: 716–7.
10. ÅBERG N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy* 1989; 19: 59–63.
11. BJÖRKSTÉN F, SUONIEMI I. Time and intensity of first pollen contacts and risk of subsequent pollen allergies. *Acta Med Scand* 1981; 209: 299–303.
12. BJÖRKSTÉN F, SUONIEMI I, KOSKI V. Neonatal birch-pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980; 10: 585–91.
13. CRONER S, KJELLMAN N-I. Predictors of atopic disease: cord blood IgE and month of birth. *Allergy* 1986; 41: 68–70.
14. BJÖRKSTÉN B. Does breast feeding prevent the development of allergy? *Immunol Today* 1983; 4: 215–7.
15. ANDRAE S, AXELSON O, BJÖRKSTÉN B, FREDRIKSSON M, KJELLMAN N-IM. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. *Arch Dis Child* 1988; 63: 473–8.
16. BRÅBÄCK L, KÄLVESTEN L. Urban living as a risk factor for atopic sensitization in Swedish schoolchildren. *Pediatr Allergy Immunol* 1991; 2: 14–9.
17. BRÅBÄCK L, BREBOROWICZ A, DREBORG S, KNUTSSON A, PIEKLIK H, BJÖRKSTÉN B. Atopic sensitization and respiratory symptoms among Polish and Swedish schoolchildren. *Clin Exp Allergy* 1994; 24: 826–35.
18. RIIKJÄRV M, JULGE K, VASAR M, BRÅBÄCK L, KNUTSSON A, BJÖRKSTÉN B. The prevalence of atopic sensitization and respiratory symptoms among Estonian school children. *Clin Exp Allergy* 1995; 25: 1198–204.
19. BRÅBÄCK L, BREBOROWICZ A, JULGE K, et al. Risk factors for respiratory symptoms and atopic sensitization in the Baltic area. *Arch Dis Child* 1995; 72: 487–93.
20. ZETTERSTRÖM O, OSTERMAN K, MACHADO L, JOHANSSON S. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *BMJ* 1981; 283: 1215–7.

21. HALKEN S, HØST A, NILSSON L, TAUDORF E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 1995; 50: 97–105.
22. ZETTERSTRÖM O, NORDVALL SL, BJÖRKSTÉN B, AHLSTEDT S, STELANDER M. Increased IgE antibody responses in rats exposed to tobacco smoke. *J Allergy Clin Immunol* 1985; 75: 594–8.
23. WICKMAN M, NORDVALL SL, PERSHAGEN G. Risk factors in early childhood for sensitization to airborne allergens. *Pediatr Allergy Immunol* 1992; 3: 128–33.
24. WICKMAN M. Residential characteristics and allergic sensitization in children especially to mites [dissertation]: Stockholm: Karolinska Institutet, 1993.
25. MUTIUS VON E, FRITZSCH C, WEILAND S, RÖLL G, MAGNUSSEN H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *BMJ* 1992; 305: 1395–9.
26. FRICK OL, BROOKS DL. Immunoglobulin E antibodies to pollens augmented in dogs by virus vaccines. *Am J Vet Res* 1983; 44: 440–5.
27. SIGURS N, BJARNASON R, SIGURBERGSSON F, KJELLMAN B, BJÖRKSTÉN B. Asthma and IgE antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995; 95: 500–5.
28. PAUWELS R, VAN DER STRAETEN M, PLATTEU B, BAZIN H. The non-specific enhancement of allergy. *In vitro* effects of *Bordetella pertussis* vaccine on IgE synthesis. *Allergy* 1983; 38: 239–46.
29. SEN D, ARORA S, GUPTA S, SANYAL R. Studies of adrenergic mechanisms in relation to histamine sensitivity in children immunized with *Bordetella pertussis* vaccine. *J Allergy Clin Immunol* 1974; 54: 25–31.
30. HEDENSKOG S, BJÖRKSTÉN B, BLENNOW M, GRANSTRÖM G, GRANSTRÖM M. Immunoglobulin E response to pertussis toxin in whooping cough and after immunization with a whole-cell and an acellular pertussis vaccine. *Int Arch Allergy Appl Immunol* 1989; 89: 156–61.
31. BLENNOW M, GRANSTRÖM M, BJÖRKSTÉN B. Immunoglobulin E response to pertussis toxin after vaccination with acellular pertussis vaccine. In: MANCLARK CR, ed. *Proceedings of the Sixth International Symposium on Pertussis*. Bethesda, Maryland: Department of Health and Human Services, United States Public Health Service, 1990: 184–8.
32. STRANNEGÅRD I-L, STRANNEGÅRD Ö. Epstein-Barr virus antibody in children with atopic disease. *Int Arch Allergy Appl Immunol* 1981; 64: 314–9.
33. STRACHAN D. Hay fever, hygiene and household size. *BMJ* 1989; 289: 1259–60.
34. VON MUTIUS E, MARTINEZ FD, FRITZSCH C, NICOLAI T, REITMEIR P, THIEMANN HH. Skin test reactivity and number of siblings. *BMJ* 1994; 308: 692–5.
35. STRACHAN D. Epidemiology of hay fever: towards a community diagnosis. *Clin Exp Allergy* 1995; 25: 296–303.
36. WICHMANN H. Environment, life-style and allergy: the German answer. *Allergol J* 1995; 4: 315–6.
37. HOLT P. Postnatal maturation of immune competence during infancy and childhood. *Pediatr Allergy Immunol* 1995; 6: 59–70.