

# Why is allergy increasing? – environmental factors

R. J. DAVIES, C. RUSZNAK and J. L. DEVALIA

*Department of Respiratory Medicine, The London Chest Hospital, London, UK*

## Summary

Data from epidemiological studies have shown that allergic conditions have increased over the last 30–40 years, particularly in developed countries, despite a decrease in the severity of grass pollen seasons. Other epidemiological studies suggest an interaction between allergic diseases and traffic pollution, and laboratory findings indicate that diesel exhaust particles enhance sensitivity to allergens. In an *in vitro* study, we found evidence to suggest that cigarette smoke may render the airway epithelium more susceptible to adverse effects of allergens. Evidence from other studies indicates that O<sub>3</sub> and NO<sub>2</sub>, with or without SO<sub>2</sub>, can enhance the airway allergic response in susceptible individuals such as those with asthma and rhinitis. Studies investigating cellular and subcellular mechanisms suggest that pollutants are likely to influence the actions and interactions of a variety of cells, and lead to the synthesis of proinflammatory mediators that modulate the activity and functions of inflammatory cells.

**Keywords:** allergy, epidemiology, prevalence, environment, pollution, house-dust mites, pro-inflammatory mediators, hyperresponsiveness.

## Introduction

The symptoms of seasonal allergic rhinitis (SAR) coincide closely with the pollen season, and it has long been recognized that SAR is due in large part to the presence of plant pollens in the atmosphere. However, there are several anomalies that suggest it is not a direct and simple relationship and that other factors must be taken into account. Thus, while the prevalence of allergic rhinitis is increasing, the severity of grass pollen seasons, as measured by the pollen count, has been decreasing progressively since the 1960s. This decrease in pollen count is thought to be due to the substantial decreases in the area of grassland around cities (40% over the 40-year period) [1]. This article seeks to explore the environmental factors that are contributing to the increased sensitivity of the population to allergens.

## Increasing prevalence of allergic diseases

Several studies have shown that allergic diseases such as asthma, rhinitis and eczema have increased four-fold over the last 30 years. Surveys conducted by Russell and colleagues [2,3] in school children in Aberdeen, UK, over a 30-year period between 1964 and 1994, indicated

that the prevalence of respiratory symptoms and atopy had increased. They demonstrated an increased diagnosis of asthma (from 4.1% in 1964 to 19.5% in 1994); hayfever (from 3.2% in 1964 to 12.9% in 1994); and eczema (from 5.3% in 1964 to 17.7% in 1994). Recent data indicate that this increase has continued since 1994; analysis of the prevalence of allergic airways disease (AAD) in 1996 demonstrated that whilst the prevalence of asthma rose to 21% amongst 12–13-year-old school children, the prevalence of allergic rhinitis increased even further to 30% [4–6]. Studies from eastern Switzerland reported similar findings and showed that the increase in the prevalence of allergic disease was paralleled by an increase in sensitization to grass pollen [7].

Clearly there is an additional factor besides the absolute level of the pollen count that is influencing the prevalence of allergic rhinitis. It can be hypothesized that there is an interaction between air pollutants or irritants and allergens that exacerbates the development of atopy and the symptoms of allergic disease.

## Association between environmental factors and allergic airways disease

Studies from Japan have demonstrated that the incidence of rhinoconjunctivitis in residents living along-

Correspondence: Professor R. J. Davies, London Chest Hospital, Bonner Road, London E2 9JX, UK.

side main roads lined with old cedar trees, with heavy traffic all day long, was much higher (13.2%) than that in residents living in the cedar forest (5.1%) where there was less traffic – despite the cedar pollen counts being similar in both areas [8]. These studies suggested that the disparity in the incidence of rhinoconjunctivitis in the different areas was the result of vehicle exhaust pollution, which was the predominating factor in the areas with high incidence of rhinoconjunctivitis.

The indoor environment is also an important factor in the increased incidence of allergic disease, since as much as 90% of an individual's time is spent indoors [9]. Luczynska and colleagues investigated skin sensitivity to a panel of indoor and outdoor allergens in 222 10–11-year-old school children living in Tower Hamlets and Eltham, two areas of London chosen on the basis of their disparate socio-economic status and level of traffic pollution. They demonstrated that the prevalence of skin sensitivity to house-dust mite (HDM), grass pollen and cockroach allergens was significantly higher in Tower Hamlets, the more deprived and polluted of the two areas [10].

These data provide supportive evidence that interactions between environment and allergens are important.

#### **Mechanisms underlying the pollution-induced increase in airway reactivity**

Although it has been increasingly recognized that exposure to pollutants enhances the airway response to inhaled allergens, the mechanisms underlying these effects are not fully understood. A possible culprit of this enhanced sensitivity is diesel exhaust particles (DEP). Diaz-Sanchez and colleagues investigated the effect of topical application of DEP on the local immune response in the nasal airways of normal healthy volunteers and demonstrated that it led to a significant increase in IgE, but not IgG, IgA or IgM, when compared with saline challenge [11]. More recently, the same authors investigated the ability of DEP to act as an adjuvant to antigen by performing nasal provocation challenges with DEP, the ragweed allergen Amb aI, or both simultaneously, in a group of ragweed-sensitive individuals [12]. Nasal washes were performed at 18 h, as well as 4 and 8 days after challenge. When subjects were challenged with ragweed alone there was an increase in both IgE and IgG3 in nasal lavage fluid, which was slightly greater than that seen with DEP. In addition, ragweed-specific IgE was detectable in the lavage fluid after challenge. By contrast, the concentration of ragweed-specific IgE was 16 times higher following ragweed plus DEP challenge compared with ragweed alone.

#### **The importance of house-dust-mite allergens**

Although sensitization to an allergen can occur at any age, the importance of early exposure to HDM allergens in primary sensitization has been demonstrated by Sporik *et al.* [13], who followed 67 children prospectively from birth until the age of 11 years. These authors found that exposure in infancy to *Dermatophagoides pteronyssinus* 1 (Der p 1) (a major allergen of HDM) at levels greater than 10 µg/g of household dust was associated with a 4.8-fold relative risk of developing asthma by the age of 11 years. They found that exposure to high Der p 1 levels at the age of 1 year was inversely related to the age of onset of asthma in HDM-sensitive children. Price and colleagues have also found a strong association between sensitivity (positive skin-prick tests and IgE antibodies) to HDM and the presence of Der p 1 in home air [14]. The Dust Mite Task Force of the International Association of Allergy and Clinical Immunology [15] proposed that 2–10 µg Der p 1 or *Dermatophagoides farinae* 1 (Der f 1) per gram of household dust poses a risk for sensitization and development of asthma, whilst levels of greater than 10 µg/g of either allergen pose a major risk for the development of acute asthma in HDM-allergic patients.

Such a potent sensitizing capability of HDM allergens is not surprising, since Der p 1 and other HDM allergens exhibit proteolytic activity [16]. Whilst Der p 1 has cysteine and serine protease activity, Der p 2 exhibits lysozyme, Der p 3 trypsin, Der p 4 amylase, Der p 6 chymotrypsin and Der p 8 serine protease activity [17]. Using primary cultures of human bronchial epithelial cells (HBEC), we have demonstrated that incubation in the presence of 300 ng/mL Der p 1 increases the electrical resistance – a surrogate for permeability – of the cell cultures [18].

Additionally, Der p 1 is capable of disregulating the immune system by proteolytically cleaving the low-affinity IgE Fc receptor (CD23) from the surface of B cells.

Several studies have suggested that exposure to cigarette smoke (CS) is associated with the development of atopy. Therefore, we have proposed that CS impairs the barrier function of the airway epithelium, leading to ready access of allergens such as Der p with subsequent sensitization of the airways. To test this hypothesis, we exposed HBECs for 20 min to CS or air and incubated them further in the absence or presence of 300 ng/mL Der p over a period of 24 h. We found that exposure of HBEC to CS for 20 min did not significantly alter the permeability of the HBEC layer, when compared with exposure to air. In contrast, incubation of HBEC with Der p 1 led to a significant increase in the permeability of these cells, an effect further enhanced by exposure of the cells to CS. Moreover, movement of Der p 1 itself was also increased by exposure

to CS, suggesting that although short-term exposure to CS may not increase epithelial permeability, it may render the epithelium more susceptible to adverse effects of allergens such as Der p 1 [18].

A possible mechanism to explain these interactions is that protease activity of the allergen disrupts the tight junctions between cells and thereby increases the ability of allergen to breach the epithelial barrier and reach antigen-presenting cells (Fig. 1) [19].

Ehnert and colleagues investigated the effects of reducing domestic exposure to HDM allergen on bronchial hyper-responsiveness (BHR) of asthmatics in a double-blind, placebo-controlled trial [20]. Children with mild or moderate asthma and hypersensitivity to Der p and Der f were assigned randomly to one of three groups with respect to treatment of their mattress with one of the following:

- 1) acaricide (benzyl benzoate);
- 2) placebo;
- 3) fitting of a mattress cover.

Mite allergen levels in the mattress, together with determination of bronchial responsiveness, were measured before and after the 12-month treatment. The authors found that a significant reduction in allergen concentrations occurred in homes using mattress covers. This was accompanied by a significant reduction of BHR in children with asthma after 8 months of mattress treatment. Placebo and benzyl benzoate were without effect, demonstrating that dust exposure is an important factor in bronchial hyperresponsiveness.

### The impact of environment on the prevalence of allergic diseases

Early studies from Germany, particularly by von Mutius and colleagues, demonstrated that allergic conditions

such as hayfever were more common in West German cities than East German cities [21]. Recent studies from Germany have demonstrated that whilst the prevalence of atopic diseases has not altered significantly in West Germany, there has been a significant increase in the prevalence of these diseases in East Germany, suggesting that there is already a converging tendency of self-reported asthma and asthma symptoms [22]. Overall, the difference in the respiratory conditions have largely disappeared following unification of East and West Germany and it has been suggested that this is likely to be a result of two factors: (1) the change in air pollution patterns resulting from changes in industrialization and traffic; and (2) (probably more importantly) living habits in the former East Germany [23]. The Western lifestyle, in all its aspects, is recognized as the major risk factor for the development of atopy, increased prevalence of sensitization and ultimately allergic diseases.

While these studies have demonstrated the involvement of atmospheric pollutants in the development of atopy, it is also important to assess the influence of different levels of exposure and the nature of the pollutant.

Romieu and colleagues studied the relationship between the number of daily emergency visits for asthma at a major paediatric hospital in Mexico City and air pollutant levels in the city. They found that the level of atmospheric ozone ( $O_3$ ) exposure was associated significantly with the number of emergency visits for asthma. After adjustment for potential confounding factors, the multivariate regression model predicted that an increase of 50 parts per billion (ppb) in the 1-h maximum  $O_3$  level would lead to a 43% increase in the number of emergency visits for asthma on the following day. Exposure to high  $O_3$  levels ( $> 110$  ppb) for 2 consecutive days increased the number of asthma-related emergency visits by 68% [24]. Studies of

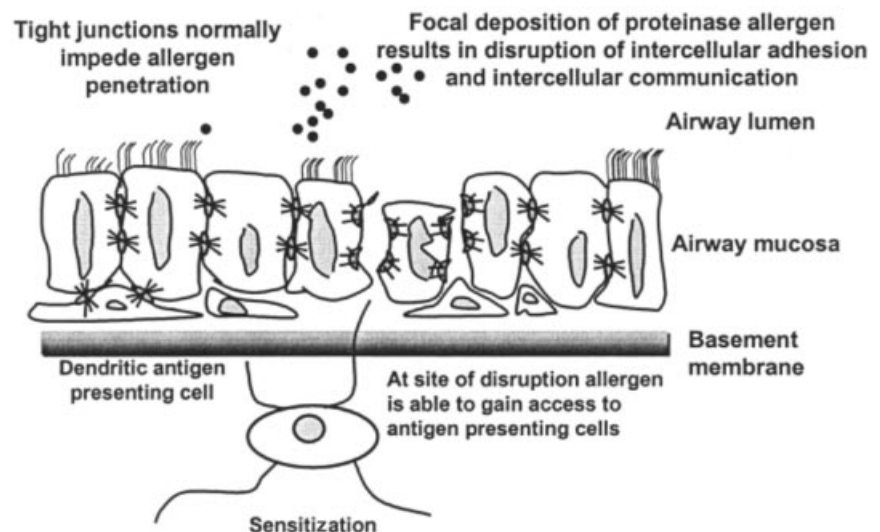


**Fig 1** Proposed mechanisms of house-dust mite induction of allergy [19].

respirable particulate matter under 10 µm diameter (PM<sub>10</sub>) in Seattle, USA, demonstrated that PM<sub>10</sub> levels were significantly associated with emergency room visits for asthma the following day [25]. The mean PM<sub>10</sub> level for the previous 4 days was an even better predictor ( $P < 0.005$ ).

Jarvis and colleagues studied 1200 young adults living in East Anglia using a questionnaire, blood sampling (for analysis of total and specific IgE) and lung function tests, to see whether or not there were any associations between the use of domestic gas appliances and increased risk of respiratory symptoms and sensitization to common environmental allergens [26]. The authors demonstrated that women were at a greater risk than men of developing asthma-like symptoms (presumably because they did more cooking). In women who used mainly gas for cooking, the odds ratios for wheeze, waking with shortness of breath, and asthma attacks were significantly more than for those who used mainly electricity. Additionally, airway obstruction was increased and lung function was reduced in these individuals.

#### The enhancement of allergic responses by environmental pollutants

Exposure chamber studies of asthmatic individuals exposed to O<sub>3</sub>, NO<sub>2</sub> and a combination of NO<sub>2</sub> and SO<sub>2</sub> have indicated that these agents increase the airway responsiveness of asthmatics to inhaled allergen. We investigated the effect of exposure for 6 h to either air, 400 ppb NO<sub>2</sub>, 200 ppb SO<sub>2</sub>, or a combination of the two pollutants on the airway response of non-exercising mild asthmatic patient volunteers to inhaled Der p allergen. We found that exposure to the combination of the two pollutants caused a significant reduction in the dose that provoked a mean 20% fall in forced expiratory volume in one second (PD<sub>20</sub> FEV<sub>1</sub>) when compared with exposure to air, without any significant effect on lung function. Exposure to the pollutants individually did not cause a significant reduction [27]. We also showed that the enhanced airway response to inhaled allergen in asthmatic individuals, resulting from exposure to the combination of 400 ppb NO<sub>2</sub> + 200 ppb SO<sub>2</sub>, not only occurred immediately after exposure but also persisted over a period of 24–48 h and was maximal by 24 h after exposure [28].

Using nasal lavage, it has been found that prior exposure to NO<sub>2</sub> primes eosinophils for subsequent activation by allergen [29], as shown by a significant increase in eosinophil cationic protein (ECP) in response to allergen, only in individuals pre-exposed to NO<sub>2</sub>.

To investigate whether treatment with steroids can alter the inflammatory response in the nasal airways

under these conditions, we investigated patients with seasonal allergic rhinitis randomized to receive either topical fluticasone propionate aqueous nasal spray (FP) 200 µg once daily or matched placebo for 4 weeks in a double-blind, crossover design [30,31]. Analysis of lavage samples showed a significant increase in ECP following exposure to NO<sub>2</sub> + allergen when the individuals were treated with placebo. In contrast, there was a much smaller effect of exposure to NO<sub>2</sub> + allergen challenge on ECP levels when these individuals were treated with FP. The difference in changes of ECP levels between placebo and FP treatments was significant, suggesting that FP may downregulate NO<sub>2</sub> allergen-induced eosinophil activation in allergic rhinitis (Fig. 2).

#### The effect of pollutants on airway epithelial cells

Airway epithelial cells play a pivotal role in the pathogenesis of AAD, as they can express and synthesize a variety of inflammatory cytokines and adhesion molecules (including IL-1β; IL-6; IL-8; IL-16; granulocyte-macrophage colony stimulating factor [GM-CSF]; tumour necrosis factor [TNF]α; regulated on activation normal T-cell expressed and secreted [RANTES]; and intercellular adhesion molecule-1 [ICAM-1]) that influence the activity of eosinophils and lymphocytes, which in turn play important roles in the allergic reaction [32–36]. RANTES, IL-8 and GM-CSF in combination are chemoattractant for eosinophils, and GM-CSF plays an important part in delaying apoptosis of eosinophils.

Using an *in vitro* cell culture of HBEC, it has been demonstrated that DEP can reduce rapidly and dramatically the ciliary beat frequency in a dose-related manner [37]. This will promote allergen retention within the airways.

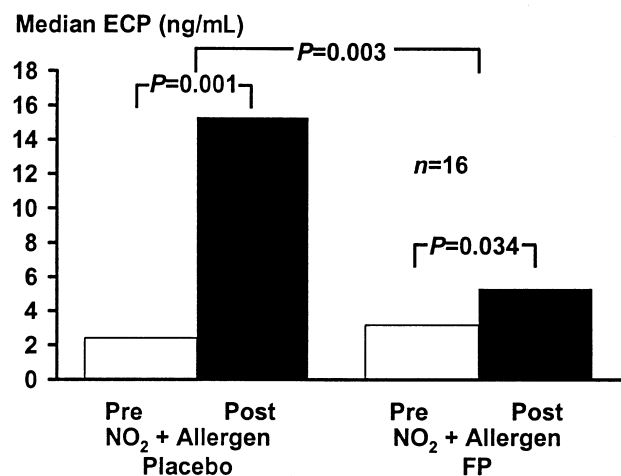


Fig 2 Topical steroid effects on release of ECP (FP = fluticasone propionate) [31].

Studies from our laboratory showed that exposure of HBECs to 400–800 ppb  $\text{NO}_2$  *in vitro*, leads to increased permeability of HBEC; decreased ciliary activity; and release of pro-inflammatory mediators, including  $\text{LTC}_4$ , GM-CSF,  $\text{TNF}\alpha$  and IL-8 [38,39]. Similarly, studies have demonstrated that exposure of these cells to ambient concentrations of  $\text{O}_3$  (10–50 ppb), well below the World Health Organization safety guidelines, induced significant release of IL-8, GM-CSF,  $\text{TNF}\alpha$  and soluble ICAM-1. Treatment of the cells with  $10^{-4}$ – $10^{-7}$  M concentrations of nedocromil sodium inhibited IL-8 release; this effect was significant at a concentration of  $10^{-5}$  M and was maximal at  $10^{-4}$  M nedocromil sodium [40]. These findings suggest that nedocromil sodium may mediate its anti-inflammatory effects, at least in part, by affecting the synthesis and/or release of inflammatory cytokines that directly or indirectly influence differentiation, growth and migration of inflammatory cells.

Studies in our laboratory demonstrated that there are differences between the abilities of epithelial cells of atopic and non-atopic individuals to synthesize different amounts and/or profiles of proinflammatory cytokines. This suggests that genetic predisposition and manifestation of the symptoms of AAD in the atopic individuals may, at least in part, be a consequence of these differences.

Studies of bronchial epithelial cells have demonstrated that the cells of asthmatic patients synthesize greater quantities of IL-1 $\beta$ , IL-16, monocyte chemoattractant protein-1 (MCP-1) and GM-CSF than the cells of non-asthmatic subjects *in vivo* [36,41–43], and that the expression of GM-CSF and IL-16 correlates well with the numbers of activated eosinophils [44] and  $\text{CD4}^+$  cells [36], respectively. Studies of epithelial cells cultured from bronchial biopsies from well-characterized groups of asthmatic and non-asthmatic subjects in our laboratory also demonstrated that bronchial epithelial cells of atopic asthmatics release significantly greater amounts of constitutive IL-8, GM-CSF, RANTES and soluble ICAM-1 (sICAM-1) than do the cells of non-atopic non-asthmatics [45]. Similar to our findings for nasal epithelial cells of atopic rhinitic and non-atopic non-rhinitic individuals, the cells of atopic asthmatics also release significantly more RANTES, and are also more susceptible after exposure to  $\text{O}_3$  and  $\text{NO}_2$ , compared with the cells of non-atopic non-asthmatics [46].

Collectively, these studies suggest that genetic predisposition and manifestation of the symptoms of AAD in atopic individuals may, at least in part, be a consequence of increased expression, synthesis and release of specific pro-inflammatory mediators from their airway epithelial cells – both constitutively and following exposure to external factors such as allergens and pollutants (Fig. 3).

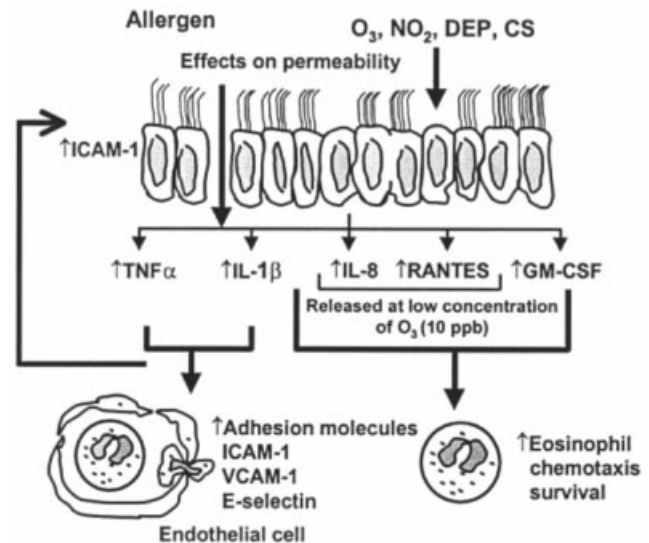


**Fig 3** Proposed mechanisms of pollutant action in enhancing allergic disease.

## Conclusion

Epidemiological studies have clearly demonstrated that allergic diseases in general are on the increase, particularly in developed countries. It is now recognized that the Western lifestyle, with its characteristic allergen/irritant load in both the indoor and outdoor environment, is a risk factor for increased sensitization and ultimately allergic diseases. Effective allergen avoidance measures are needed to prevent – or at least decrease – sensitization, and also to reduce symptoms resulting from exposure of the sensitized individual to the offending allergen.

The findings of both epidemiological and laboratory-based studies provide evidence that exposure to air pollutants is likely to precipitate attacks of asthma and rhinitis, and possibly contributes to the increase in prevalence of these diseases. Recent laboratory-based studies have demonstrated that exposure to pollutants such as  $\text{O}_3$ , and  $\text{NO}_2$  with or without  $\text{SO}_2$ , can enhance the airway response of particularly susceptible individuals, such as those with asthma and rhinitis, to inhaled allergen. Studies investigating the effects of pollutants at the cellular and subcellular levels have suggested that a variety of cells are likely to be involved and will interact with one another to determine the overall inflammation and airway hyperresponsiveness observed in AAD. At the cellular and molecular level, the cell–cell and irritant/allergen–cell interactions lead to the synthesis of pro-inflammatory mediators, including cytokines and cell adhesion molecules, which modulate the activity and function of inflammatory cells.

## References

- 1 Emberlin JC. Grass, tree and weed pollens. In: Kay AB. (ed.) *Allergy and Allergic Diseases*. London: Blackwell Science 1997; 835–57.
- 2 Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *Br Med J* 1992; 304:873–5.
- 3 Omran M, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. *Br Med J* 1996; 312:34.
- 4 Warner JO. Childhood factors in the development of rhinitis and asthma. In: Is the nose a surrogate for the lungs? Proceedings of the World Allergy Forum Symposium, Cancun, Mexico 1997; 56.
- 5 Burr ML, Miskelly FG, Butland BK *et al.* Environmental factors and symptoms in infants at high risk of allergy. *J Epidemiol Comm Health* 1989; 43:125–32.
- 6 Kaur B, Butland B. Trends in asthma mortality. Asthma mortality is falling in most age groups in Scotland [letter]. *Br Med J* 1997; 315:1014.
- 7 Wuthrich B, Schindler C, Leuenberger P *et al.* Prevalence of atopy and pollinosis in the adult populations of Switzerland (SAPALDIA Study). *Int Arch Allergy Immunol* 1995; 106:149–56.
- 8 Ishizaki T, Koizumi K, Ikemori R *et al.* Studies of prevalence of Japanese cedar pollinosis among residents in a densely cultivated area. *Ann Allergy* 1987; 58:265–70.
- 9 Pope AM, Patterson R, Burge H. *Indoor Allergens*. Washington DC: National Academy Press 1993; 35.
- 10 Luczynska CM, Walker LA, Burney PGJ. Skin sensitivity in school children in two different areas of London. *Eur Respir J* 1995; 8 (19):250s [Abstract].
- 11 Diaz-Sanchez D, Dotson AR, Takenaka H *et al.* Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest* 1994; 94:1417–25.
- 12 Diaz-Sanchez D. The role of diesel exhaust particles and their associated hydrocarbons in the induction of allergic airway disease. *Allergy* 1997; 52 (38):52–6.
- 13 Sporik R, Holgate ST, Platts-Mills TAE *et al.* Exposure to house dust mite allergen (Der p1) and the development of asthma in childhood. *N Engl J Med* 1990; 323:502–7.
- 14 Price JA, Pollock I, Little SA *et al.* Measurement of airborne mite antigen in the homes of asthmatic children. *Lancet* 1990; 336:895–7.
- 15 Dust Mite Task Force of International Association of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 1989; 83:416–27.
- 16 Stewart GA, Thompson PJ, Simpson RJ. Protease antigens from house dust mite. *Lancet* 1989; ii:154–5.
- 17 Roche N, Chinnet TC, Huchon GJ. Allergic and nonallergic interactions between house dust mite allergens and airway mucosa. *Eur Respir J* 1997; 10:719–26.
- 18 Rusznak C, Devalia JL, Sapsford RJ *et al.* Effect of cigarette smoke on house dust mite allergen (Der p1)-induced increase in human bronchial epithelial cell permeability *in vitro*. *J Allergy Clin Immunol* 1997; 99 (1):S364.
- 19 Robinson C, Kalsheker NA, Srinivasan N *et al.* On the potential significance of the enzymatic activity of mite allergens to immunogenicity. Clues to structure and function revealed by molecular characterisation. *Clin Exp Allergy* 1997; 27:10–21.
- 20 Ehnert B, Lau-Schadendorf S, Weber A *et al.* Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992; 90:135–8.
- 21 von Mutius E, Fritzsche C, Weiland SK *et al.* Prevalence of asthma and allergic disorders among children in united Germany. *Br Med J* 1992; 305:1395–9.
- 22 Heinrich J, Richter K, Magnussen H *et al.* Do asthma and asthma symptoms in adults already converge between East and West Germany? *Am J Respir Crit Care Med* 1996; 153 (4):A856 [Abstract].
- 23 Wichmann HE. Possible explanation for the different trend of asthma and allergy in East and West Germany. *Clin Exp Allergy* 1996; 26:621–3.
- 24 Romieu I, Meneses F, Sienra-Monge JJ *et al.* Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. *Am J Epidemiol* 1995; 141:546–53.
- 25 Schwartz J, Slater D, Larson TV *et al.* Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis* 1993; 147:826–31.
- 26 Jarvis D, Chinn S, Luczynska C *et al.* Association of respiratory symptoms and lung function in young adults with use of domestic appliances. *Lancet* 1996; 347:426–31.
- 27 Devalia JL, Rusznak C, Herdman MJ *et al.* Effect of nitrogen dioxide and sulphur dioxide on the airway response of mild asthmatic patients to allergen inhalation. *Lancet* 1994; 344:1668–71.
- 28 Rusznak C, Devalia JL, Davies RJ. The airway response of asthmatics to inhaled allergen after exposure to pollutants. *Thorax* 1996; 51:1105–8.
- 29 Wang J, Devalia JL, Duddle JM *et al.* The effect of exposure for six hours to nitrogen dioxide (NO<sub>2</sub>) on early phase nasal response to allergen challenge in patients with a history of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1995; 96:669–76.
- 30 Devalia JL, Wang JH, Rusznak C *et al.* The effect of fluticasone propionate aqueous nasal spray on allergen-induced inflammatory changes in the nasal airways of allergic rhinitis following exposure for six hours to 400ppb nitrogen dioxide (NO<sub>2</sub>). *Eur Respir J* 1996; 9 (Suppl. 23):86s [Abstract].
- 31 Wang J, Devalia JL, Rusznak C *et al.* Effect of fluticasone propionate aqueous nasal spray (FP) on allergen-induced inflammatory changes in the nasal airways of allergic rhinitis following exposure for six hours to 400ppb nitrogen dioxide. *Clin Exp Allergy* 1999; in press.
- 32 Devalia JL, Davies RJ. Airway epithelial cells and mediators of inflammation. *Respir Med* 1993; 87:405–8.
- 33 Arai K, Yokota T, Watanabe S *et al.* The regulation of allergic response by cytokine receptor networks. *Chem News* 1992; 4:110–2.
- 34 Kips JC, Joos GF, Peleman RA *et al.* Cytokines in asthma – The latest results. *ACI News* 1992; 4:113–20.

- 35 Wang JH, Devalia JL, Xia C *et al.* Expression of RANTES by human bronchial epithelial cells *in vitro* and *in vivo* and the effect of corticosteroids. *Am J Respir Cell Mol Biol* 1996; 14:27–35.
- 36 Laberge S, Ernst P, Ghaffar O *et al.* Increase in interleukin-16 (IL-16) expression in baseline asthma. *J Allergy Clin Immunol* 1996; 97:313 [Abstract].
- 37 Bayram H, Devalia JL, Sapsford RJ *et al.* The effect of diesel exhaust particles on cell function and release of inflammatory mediators from human bronchial epithelial cells *in vitro*. *Am J Respir Cell Mol Biol* 1998; 18:441–8.
- 38 Devalia JL, Sapsford RJ, Cundell DR *et al.* Human bronchial epithelial cell dysfunction following exposure to nitrogen dioxide, *in vitro*. *Eur Respir J* 1993; 6:1308–16.
- 39 Devalia JL, Campbell AM, Sapsford RJ *et al.* Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells *in vitro*. *Am J Respir Cell Mol Biol* 1993; 9:271–9.
- 40 Rusznak C, Devalia RJ, Sapsford RJ *et al.* Ozone-induced mediator release from human bronchial epithelial cells *in vitro* and the influence of nedocromil sodium. *Eur Respir J* 1996; 9:2298–305.
- 41 Sousa AR, Poston RN, Lane SJ *et al.* Detection of GM-CSF in asthmatic bronchial epithelium and decrease by inhaled corticosteroids. *Am Rev Respir Dis* 1993; 147:1557–61.
- 42 Sousa AR, Lane SJ, Nakhosteen JA *et al.* Increased expression of the monocyte chemoattractant protein-1 in bronchial tissue from asthmatic subjects. *Am J Respir Cell Mol Biol* 1994; 10:142–7.
- 43 Marini M, Vittori E, Hollomberg T *et al.* Expression of the potent inflammatory cytokines granulocyte macrophage-colony stimulating factor and interleukin-6 and interleukin-8 in bronchial epithelial cells of patients with asthma. *J Allergy Clin Immunol* 1992; 89:1001–9.
- 44 Wang JH, Trigg CJ, Devalia JL *et al.* Effect of inhaled beclomethasone dipropionate on expression of pro-inflammatory cytokines and activated eosinophils in the bronchial epithelium of mild asthmatics. *J Allergy Clin Immunol* 1994; 94:1025–34.
- 45 Bayram H, Devalia JL, Khair OA *et al.* Effect of diesel exhaust particles (DEP) on release of inflammatory mediators from bronchial epithelial cell cultures of non-atopic non-asthmatic and atopic asthmatic subjects *in vitro*. *Eur Respir J* 1997; 10 (Suppl. 25):414s [Abstract].
- 46 Devalia JL, Rusznak C, Davies RJ. Allergen/irritant interaction – its role in sensitisation and allergic disease. *Allergy* 1998; 53:335–45.