

Mechanisms of enhanced prevalence of asthma and atopy in developed countries

JM Hopkin

Atopy – a T helper 2 cell driven hypersensitivity to innocuous antigens (allergens) which causes most cases of asthma – is of complex genetic and environmental origins. There is compelling epidemiological evidence for a rise in atopic disease in 'westernised' communities. The changing pattern of microbial exposure in early childhood is suggested to be the principal candidate mechanism for this rise.

Addresses

Lung Research Laboratory, Osler Chest Unit, Churchill Hospital, Oxford OX3 7LJ, UK; e-mail: jhopkin@immsvr.jr2.ox.ac.uk

Current Opinion in Immunology 1997, 9:788–792

<http://biomednet.com/elecref/0952791500900788>

© Current Biology Ltd ISSN 0952-7915

Abbreviations

FcεRI	the high-affinity IgE receptor
HAV	hepatitis A virus
IFN	interferon
IL	interleukin
Th	T helper

Introduction

Atopy is the immune disorder of hypersensitivity to common, rather innocuous environmental antigens derived from agents such as pollens and house dust mites. It manifests as recurrent or chronic inflammatory disorder of the respiratory mucosa (causing the syndromes of asthma and rhinitis) and the skin (causing eczema), and more rarely as an acute systemic disease. Atopy is the leading cause of asthma, rhinitis and eczema between the ages of 5 and 25 years [1]. Chronic disease or repeated episodes of acute disease in affected individuals impose a burden of morbidity in young people and create a demand for great volumes of relief medication, including topical anti-inflammatory agents such as cromoglycate and beclomethasone, but none of which fundamentally modify the underlying immune disorder. This article explores the mechanisms that may underlie the recent epidemiological trends in the occurrence of atopic disease.

Increased levels of atopy

The clinical atopic disorders (asthma, rhinitis, eczema) have long been recognised, but have become steadily more prominent in recent decades so that 30% of the population in some communities may manifest some atopic disease at some time in their early lives and 10% of children in the same communities manifest atopic asthma [1–4]. Changes in diagnostic fashion, including a strong lead towards early diagnosis and treatment of asthma, have contributed to this rising prominence [5]. A number of

carefully controlled studies, however, point to a real rise in the frequency of asthma, wheeze, and the other atopic syndromes in developed communities [1–4]; early studies have been subject to methodological criticism [5] but the weight of opinion and common clinical experience supports a rising trend [1]. In addition, studies across different societies show highly variable international rates for both atopic disease and atopic sensitisation assayed by allergen skin prick tests [6–9]; they provide strong and objective evidence for an association of atopic disease with westernisation, or economic wealth. Moreover, migrants from underdeveloped to developed countries acquire more atopic disease [10–11].

Cellular and molecular events underlying atopy

Whilst these demographic trends have been emerging, steady progress has been made in understanding the cellular and molecular events that underlie atopic hypersensitivity and the mucosal inflammation it causes, such inflammation being the substrate for clinical disease. Sustained and exuberant production of IgE against environmental antigens is a key process underlying atopy [12]. Another is the binding of IgE to mucosal mast cells via the high affinity IgE receptor FcεRI: following contact with allergen, and the subsequent cross-linking of the FcεRI-bound IgE molecules, mast cell activation occurs through FcεRI and this leads to the release of a complex array of biological mediators which orchestrate local mucosal inflammation [13].

The molecular mechanisms governing the B cell switch to IgE production and the IgE-associated effector mechanisms are also emerging. A crucial control mechanism lies in the character of the helper T lymphocytes and their associated cytokine products (reviewed in [14]). Th1 lymphocyte development is primed by IL-12 and is associated with IFN-γ and IL-2 cytokine production; these Th1 cytokines play a crucial role in the development of cell-mediated immunity and the control of a number of pathogens, in particular intracellular pathogens such as viruses and mycobacteria. Th2 lymphocyte development is primed by IL-4, is associated with IL-5 and IL-13 cytokine production and promotes the secretion of IgE, and the recruitment of eosinophils, as part of the natural immune response to large extracellular parasites, such as helminths, at mucosal surfaces. These Th2 mechanisms are central to the development of hypersensitivity to common, innocuous environmental antigens in atopy [13,14].

Central to the Th1/Th2 paradigm are the observations that particular challenges to the immune system demand

particular T helper lymphocyte responses; furthermore, there is an important degree of mutual antagonism between the Th1 and Th2 systems, with IFN- γ and IL-4 being able to repress the growth and cytokine secretion of Th2 and Th1 cells respectively [14,15]. In atopy there is a chronic and persistent Th2 predominance—detectable either in circulating mononuclear cells upon allergen challenge *in vitro* or in direct assays of bronchial mucosa [16,17]; non-atopic patients do not show such Th2 skewing. It is notable that hyposensitisation or antigen immunotherapy for specific allergies deviates mononuclear cell responses to allergens away from a Th2 and towards a Th1 cytokine profile [18**]; furthermore transfection of IFN- γ in the respiratory mucosa represses Th2 immune mechanisms in mice [19].

Factors influencing atopy

It is instructive to consider what forces might promote atopy by considering the epidemiology of the disorder in the context of the known cellular biology. It is generally acknowledged that these forces are mixed and include an important interaction between genetic and environmental variables [20].

Genetic factors

The genetics of atopy has received considerable attention recently on the basis of the long-standing observation of familial aggregation. Formal twin studies fully support a significant genetic contribution. In twins reared apart or together, monozygotes show significantly greater correlations than dizygotes for total serum IgE levels for which heritability is estimated as 50% (proportion of variance attributable to genetic factors). Monozygous twins show a concordance rate of some 70% for IgE response to any common allergen [21]. The analysis of concordance rates in twins, taking account of whether reared together or apart, emphasise two factors: genetic and non-familial environmental variables.

Studies now published on molecular genetic approaches to atopy affirm the significant genetic influences. Genome-wide searches for genetic linkage through microsatellite markers, and genetic association studies on candidate genes, both emphasise the complex and heterogeneous genetic origins of atopy; statistically significant genetic linkages have been identified for asthma, bronchial reactivity, eczema and IgE levels on a range of different human chromosomes [22,23]. Thus there is a very important degree of genetic heterogeneity which implies multiple genetic actions at different phenotypic levels; this has contributed to the contrasting results in different populations. Candidate genes relevant to the immunopathology of atopy are being identified at different chromosomal locations and genetic association of certain variants of these genes with the atopy phenotype has been noted, for example variants of the high affinity IgE receptor on chromosome 11 [22]. The functional significance or action of any mutation has yet to be

demonstrated, however. This link will come but a great deal of work remains to be done.

Environmental factors

The recent rise in atopy in the incidence of westernised communities, along with evidence from studies on migrant populations, emphasises the importance of environmental factors for the development of atopy. As these changes have occurred rapidly, over only decades, in very large, outbred populations, a genetic mechanism with steep changes in gene frequencies is highly unlikely in the absence of either extraordinary mutation rates or very powerful Darwinian selection.

But which environmental factors may have driven this rise in atopy prevalence? The clear message from the epidemiology studies is that the rise relates to westernisation, and that the rates for atopy associate with the higher social classes within communities [24–26]. This finding allows for a wealth of possibilities and the association of Th2-skewing in cord blood with atopy [27,28] indicates that the search for the major factors needs to encompass both pre-natal and early childhood effects.

Allergen loads

The increase in the levels of indoor allergens has been considered as one potential mechanism [29]—in particular, the case for likely increases in house dust mites in more ‘luxurious’ modern homes with more furnishings and higher relative humidities which suit the mite. Though the level of mites can be related to the risk of sensitisation and wheezy illness, it is not believed that rising house dust mite levels account for the general rise in atopy. Asthma has risen in American regions, such as the extreme South West and North East, where relative humidity is low and where sensitisation to the cockroach is more prominent; mite levels cannot account for the different rates of grass sensitisation noted between western and socialist Europe for 1990 [6].

Air pollution

Chemical air pollution has also come under scrutiny—where the pro-inflammatory and perhaps adjuvant properties of particulate matter, sulphur dioxide, nitrogen dioxide and ozone have been investigated [30]. It is generally concluded that such air pollution can act as an irritant and precipitate respiratory symptoms in established asthma. The data of the late 1980s, on West and East Germany, and on the Scandinavian and Baltic countries, provide telling arguments against the promotion of atopy by chemical air pollution [6–8,31]: the rates of atopy were significantly lower in the old socialist states with their more, industry-driven, polluted air. It is notable that nitrogen dioxide levels, a valuable index of traffic-related pollution which is relevant to West Germany, were the same in both Germanies.

Dietary change

Dietary and feeding patterns are certainly different in westernised communities. It has been proposed that

different intakes of vitamin C (an anti-inflammatory, free radical scavenger), omega 3 fatty acids typically found in fish (and potential shifters of eicosanoid production away from the arachidonic pathway to the prostenoic pathway which produces less pro-inflammatory leucotrienes) and salts such as sodium, potassium and magnesium (with potential effects on smooth muscle function in the airways) might predict the risk of asthma [32,33]. There are, as yet, insufficient data to support such ideas. Moreover no conclusive evidence has emerged from a good deal of research on whether breast feeding protects against atopy [34].

Microbial exposure

One environmental factor, infectious disease and the pattern of microbial exposure in childhood, has changed considerably with westernisation as a result of cleaner water and food, and less crowded accommodation; the natural history of exposure has been modified by better nutrition, immunisation and antimicrobial treatments. Exposure to pathogens and colonising microbes is a key process in the programming of both immune function and memory; therefore the changing patterns of microbial exposure in recent decades in westernised communities represents one important candidate mechanism for the rise of atopy.

A relationship between atopy and fewer siblings [35,36] has been documented in the last decade and may be evidence that less exposure to infection promotes atopy; thus a decline in infections in recent times in 'westernised' countries might have altered immune programming and released an epidemic of atopy. More specific data on infections and in support of the infection-atopy hypothesis are now beginning to emerge.

An historical cohort study in Guinea-Bissau, West Africa, examined the relationship between a history of measles in childhood and the results of allergen skin prick testing to a range of aero-allergen preparations, including those from the mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and mixed grass pollens, in young adulthood [37••]. A history of measles infection associated with less atopy (any skin prick test positive - with an odds ratio of 0.36), and with less frequent skin test positivity to *D. pteronyssinus* specifically - with an odds ratio of 0.24.

A cross-sectional retrospective study of military students in Italy [38••] examined the relationship between positive serology to hepatitis A virus (HAV) and the presence of IgE to common aero-allergens by skin prick testing and serology. Atopy, defined as any positive skin prick test, was significantly less common in those students positive, using serology, for HAV as compared with those who were HAV negative (21.9% versus 30.2%, respectively); also those with positive HAV serology showed lower specific IgE concentrations and a lower lifetime prevalence of either

allergic rhinitis, asthma or both conditions (8.4% versus 16.7% for HAV positive versus negative respectively).

In a population of Japanese school children [39••], association between delayed hypersensitivity to *Mycobacterium tuberculosis*, as measured by tuberculin skin testing, and the presence of clinical atopic disease, total and allergen-specific serum IgE levels and serum levels of different Th1 and Th2 cytokines has been assessed. Strongly positive tuberculin skin tests, indicative of exposure and an immune response to *M. tuberculosis*, were associated, as compared with negative tuberculin skin tests, with fewer subsequent asthma attacks (3.7% versus 13.4% respectively), lower total serum IgE levels (98 interaxional units (IU)/ml versus 208 IU/ml respectively), lower serum levels of Th2 cytokines (e.g. 0.92 pg/ml versus 1.88 pg/ml respectively for IL-4) and higher Th1 serum cytokine levels (e.g. 13.2 pg/ml versus 7.8 pg/ml respectively for IFN- γ).

In each of these three studies [37••–39••], exposure to an intracellular infection early in life predicted less atopy subsequently; as intracellular infections typically recruit Th1 immunity which might downregulate Th2 mechanisms that are implicated in atopy, then these associations are understandable and credible. Nevertheless, there is more complexity to the immunology of this issue. Measles virus infection leads to a profound suppression of cell-mediated immunity, probably through downregulation of IL-12 production via cross-linking of the cellular receptor, CD46, by the measles virus [40]; as part of this disturbance there is a Th2 cytokine preponderance both during and after measles infection. The immune response to HAV infection, acquired by the faecal-oral route, involves both effective cell-mediated immunity and antibody response. Also certain respiratory viruses, such as the rhinovirus and the respiratory syncytial virus, can act as effective promoters of symptoms, or indeed as Th2 cytokine promoters, in asthma [41,42•].

In tuberculosis, the necessary Th1 predominant immune response and the possibility for the suppression of Th2 mechanisms for atopy is clearer. It can be envisaged that exposure to *M. tuberculosis* in early childhood (causing a protracted infection even in the absence of disease) at the time of the first exposure to allergens might, through Th cytokine balance mechanisms, encourage the formation of allergen-specific clones, including memory cells, of a preponderantly Th1 type [43]. Indeed, in young people with strongly positive tuberculin reactions, we have recently found that their circulating mononuclear cells secrete more IFN- γ in response to an *in vitro* challenge with common allergens than tuberculin negative individuals (L Pierson, B Ferrie, JM Hopkin, unpublished data) [44]. Thus it can be envisaged that exposure to other microbes with strong Th1 promoting properties early in childhood might have a similar effect on the character of allergen specific clones [44]. It should be

recalled that these microbes may not necessarily be pathogens, since colonising microbes also are important for programming the developing immune system, particularly those microbes that constitute the microflora of the gut and which impact on systemic immunity through the gut-associated lymphoid tissue [45]; the density and character of these microflora may be significantly affected by life-style or oral antibiotics with the potential to disturb immune programming [46].

The retrospective data cited above [37–39] on the link between certain infections and atopy point to the need for prospective studies to critically test the notion that patterns of microbial exposure in childhood impact on the immune response to allergens and thereby atopic disease. If true, then there are exciting prospects for manipulating the earliest responses to allergen in childhood and disrupting the march of the atopic diseases.

Conclusions

Epidemiological data, based on national trends and international comparisons, point to an important rise over recent decades in atopic sensitisation and atopic clinical disease which associates with 'westernisation'. The data point to some major environmental determinant(s). The evidence, to date, provides little support for the aetiological hypotheses of changing indoor allergen exposure, chemical air-pollution, infant feeding or dietary patterns as explanations for the rise. Instead, the changing patterns of microbial exposure in childhood emerge as the principal candidate mechanism. Retrospective studies provide evidence for an inverse association between certain viral and mycobacterial infections and atopy levels, and link this to Th immune cytokine profiles. Prospective and experimental studies are now needed to test the hypothesis that patterns of microbial exposure at the start of life can crucially determine the character of the immune response to allergens, and the likelihood of subsequent atopic disease.

Acknowledgements

This work has been supported by the Oxford Asthma Research Fund, based on generous donations from patients and their relatives at the Osler Chest Unit. I thank S Poulter for her help in preparing the manuscript.

References and recommended reading

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

- of special interest
- of outstanding interest

1. Woolcock AJ, Peat JK: **Evidence for the increase in asthma worldwide.** In *The Rising Trends in Asthma*. Edited by the Ciba Foundation. Chichester: Wiley; 1997, 206:122-134.
2. Aberg N, Hesselman B, Aberg B, Eriksson B: **Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991.** *Clin Exp Allergy* 1995, 25:815-819.
3. Whinchup PH, Cook DG, Strachan DP, Papacosta O: **Time trends in respiratory symptoms in childhood over a 24 year period.** *Arch Dis Child* 1993, 68:729-734.
4. Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ: **Changing prevalence of asthma in Australian children.** *BMJ* 1994, 308:1591-1596.
5. Magnus P, Jaakkola JJ: **Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys.** *BMJ* 1997, 314:1795-1799.
6. Von Mutius E, Fritzsch C, Welland SK, Roll G, Magnussen H: **Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison.** *BMJ* 1992, 305:1395-1399.
7. Braback L, Breborowicz A, Dreborg S, Knutsson A, Picklik H, Bjorksten B: **Atopic sensitization and respiratory symptoms among Polish and Swedish school children.** *Clin Exp Allergy* 1994, 24:826-835.
8. Behrendt H, Kramer U, Dolgner R, Himrichs J, Willer H, Hagenbeck H, Schlipkoter HW: **Elevated levels of total serum IgE in East German children: atopy, parasites or pollutants? A comparative study among 2054 preschool children in East and West Germany.** *Allergol J* 1993, 2:31-40.
9. Braback L, Breborowicz A, Julge K, Knutsson A, Riikjarv MA, Vasar M, Bjorksten B: **Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area.** *Arch Dis Child* 1995, 72:487-493.
10. Crane J, O'Donnell TV, Prior IA, Waite DA: **Symptoms of asthma, methacholine airway responsiveness and atopy in migrant Tokelauan children.** *N Z Med J* 1989, 102:36-38.
11. Morrison-Smith J, Cooper S: **Asthma and atopic disease in immigrants from Asia and the West Indies.** *Postgrad Med J* 1981, 57:774-776.
12. Droste IHJ, Kerkhof M, Demonchy JGR, Schouten JP, Rijcken B: **Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study.** *J Allergy Clin Immunol* 1996, 97:922-932.
13. Nagai H, Yamaguchi S, Maeda Y, Tanaka H: **Role of mast cells, eosinophils and IL-5 in the development of airway hyperresponsiveness in sensitized mice.** *Clin Exp Allergy* 1996, 26:642-647.
14. Romagnani S: **Induction of Th1 and Th2 responses: a key role for the 'natural' immune response?** *Immunol Today* 1992, 13:379-381.
15. Sur S, Lam J, Bouchard P, Sigounas A, Holbert D, Metzger WJ: **Immunomodulatory effects of IL-12 on allergic lung inflammation depend on timing of doses.** *J Immunol* 1996, 157:4173-4180.
16. Ochi H, Tanaki T, Katada Y, Naka T, Aitani M, Hashimoto S, Maeda K, Toyoshima K, Igarashi T, Suemura M, Kishimoto T: **Peripheral blood T lymphocytes and basophils, freshly isolated from house-dust-mite-sensitive patients, produce interleukin-4 in response to allergen-specific stimulation.** *Int Arch Allergy Immunol* 1996, 111:253-261.
17. Kasaian MT, Clay MJ, Happ MP, Garman RD, Hirani S, Luqman M: **IL-4 production by allergen-stimulated primary cultures: identification of basophils as the major IL-4 producing cell type.** *Int Immunol* 1996, 8:1287-1297.
18. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RW, Mackay IS, Kay AB, Hamid OA: **Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4(+) T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma.** *J Allergy Clin Immunol* 1996, 97:1356-1365.
- A controlled study on grass pollen immunotherapy showing that inhibition of allergen-induced T lymphocyte and eosinophil recruitment to the nasal mucosa is associated with an increase in the number of local cells expressing IFN- γ mRNA. This study links clinical and molecular immune findings, thereby providing support for the role of Th1/Th2 phenotypes in allergen-induced clinical disease.
19. Lack G, Bradley KL, Hamelmann E, Renz H, Loader J, Leung DYM, Larsen G, Gelfand EW: **Nebulized IFN-gamma inhibits the development of secondary allergy responses in mice.** *J Immunol* 1996, 157:1432-1439.
20. Hopkin JM: **Genetics of atopy.** *Pediatr Allergy Immunol* 1995, 6:139-144.
21. Hanson B, McGue M, Roitman-Johnson B, Segal NL, Bouchard TJ Jr, Blumenthal MN: **Atopic disease and immunoglobulin E in twins reared apart and together.** *Am J Hum Genet* 1991, 48:873-879.

22. Daniels SE, Bhattacharya S, James A, Leaves NI, Young A, Hill MR, Faux JA, Ryan GF, le-Souef PN, Lathrop GM *et al.*: **A genome-wide search for quantitative trait loci underlying asthma.** *Nature* 1996, **383**:247-250.
23. The Collaborative Study on the Genetics of Asthma (CGSA): **A genome-wide search for asthma susceptibility loci in ethnically diverse populations.** *Nat Genet* 1997, **15**:389-392.
24. Luczynska CM, Walker LA, Burney PGJ: **Skin test sensitivity in school children in two different areas of London.** *Eur Respir J* 1995, **8**:350S.
25. Barbee RA, Lebowitz MD, Thompson HC, Burrows B: **Immediate skin test reactivity in a general population sample.** *Ann Intern Med* 1976, **84**:129-133.
26. Williams HC, Strachan DP, Hay RJ: **Childhood eczema: disease of the advantaged?** *BMJ* 1994, **308**:1132-1135.
27. Warner JA, Miles EA, Jones AC, Quint DJ, Colwell BM, Warner JO: **Is deficiency of interferon gamma production by allergen-triggered cord blood cells a predictor of atopic eczema?** *Clin Exp Allergy* 1994, **24**:423-430.
28. Miles EA, Warner JA, Lane AC, Jones AC, Colwell BM, Warner JO: **Altered T lymphocyte phenotype at birth in babies born to atopic parents.** *Pediatr Allergy Immunol* 1994, **5**:202-208.
29. Platts-Mills TAE, Sporik RB, Wheatley LM, Heymann PW: **Is there a dose-response relationship between exposure to indoor allergens and symptoms of asthma?** *J Allergy Clin Immunol* 1995, **96**:435-440.
30. Anderson HR: **Air pollution and trends in asthma.** In *The Rising Trends in Asthma*. Edited by the Ciba Foundation, Chichester: Wiley; 1997, **206**:190-203.
31. Riikjarv M, Julge K, Vasar M, Braback L, Knutsson A, Bjorksten B: **The prevalence of atopic sensitisation and respiratory symptoms among Estonian school children.** *Clin Exp Allergy* 1995, **25**:1198-1204.
32. Britton J, Pavord I, Richards K: **Dietary sodium intake and the risk of airway hyperreactivity in a random adult population.** *Thorax* 1994, **49**:875-880.
33. Schwartz J, Weiss ST: **Dietary factors and their relationship to respiratory symptoms: the second National Health and Nutrition Examination Survey.** *Am J Epidemiol* 1990, **132**:67-76.
34. Kramer MS: **Does breast feeding help protect against atopic disease? Biology, methodology and a golden jubilee of controversy.** *J Pediatr* 1988, **112**:181-190.
35. Strachan DP: **Allergy and family size: a riddle worth solving.** *Clin Exp Allergy* 1997, **27**:235-236.
36. Von Mutius E, Martinez FD, Fritsch C, Nicolai T, Reitmar P, Thiemann HH: **Skin test reactivity and numbr of siblings.** *BMJ* 1994, **308**:692-695.
37. Shaheen SO, Aaby P, Hall AJ, Barker DJP, Heyes CB, Shiell AW, Goudiaby A: **Measles and atopy in Guinea-Bissau.** *Lancet* 1996, **347**:1792-1796.

A clinical study of young adults in Guinea-Bissau, West Africa, which shows the relationship between a history of measles infection, as part of a local epidemic, and subsequent atopic status. Measles infection predicted fewer positive skin prick tests, especially to *Dermatophagoides* (dust mite) species.
38. Matricardi PM, Rosmini F, Ferigno L, Nisini R, Raoucetta M, Chionne P, Stroffolini T, Pasquini P, D'Amelio R: **Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus.** *BMJ* 1997, **314**:999-1003.

A large-scale study in Italian military recruits relating positive serology for hepatitis A virus (HAV) with atopic status. Positive serology to HAV was associated with fewer positive allergen skin prick tests (i.e. lower levels of atopy) and with a lower prevalence of allergic rhinitis or asthma during life-time.
39. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM: **The inverse association between tuberculin responses and atopic disorder.** *Science* 1997, **275**:77-79.

A large-scale study relating tuberculin skin responses to atopic status in school children in Japan where the prevalence of tuberculosis is moderate and where Bacillus Calmette-Guérin vaccine coverage is uniform. Strongly positive tuberculin responses, indicative of exposure to *M. tuberculosis*, predicted a less frequent incidence of asthma, rhinitis and eczema, lower IgE levels, and predominantly Th1 cytokine profiles in the circulating blood.
40. Karp CL, Wysocka M, Wahl LM, Ahearn JM, Cuomo PJ, Sherry B, Trinchieri G, Griffin DE: **Mechanism of suppression of cell-mediated immunity by measles virus.** *Science* 1996, **273**:228-231.
41. Noma T, Mori A, Yoshizawa I: **Induction of allergen-specific IL-12 responsiveness of lymphocytes after respiratory syncytial virus infection and prediction of onset of recurrent wheezing and bronchial asthma.** *J Allergy Clin Immunol* 1996, **98**:816-826.
42. Busse W, Gern JE, Dick FC: **The role of respiratory virus in asthma.** In *The Rising Trends in Asthma*. Edited by the Ciba Foundation, Chichester: Wiley; 1997, **206**:208-213.

A comprehensive report of this international symposium, which includes discussions of scientific presentations, on the subject of the rise of asthma and atopy, and the current status of research into the causes of the rise.
43. Parronchi P, De Carli M, Manetti R, Simonelli C, Sampognaro S, Piccinni MP, Macchia D, Maggi E, Del Prete G, Romagnani S: **IL-4 and IFN (alpha and gamma) exert opposite regulatory effects on the development of cytolytic potential by Th1 or Th2 human T cell clones.** *J Immunol* 1992, **149**:2977-2983.
44. Holt PG: **Infections and the development of allergy.** *Toxicology Letters* 1996, **86**:205-210.
45. Berg RD: **The indigenous gastrointestinal microflora.** *Trends Microbiol* 1996, **4**:430-435.
46. Hopkin Jm, Farooqui IS: **Microbial exposure in childhood and atopy: pertussis immunisation and oral antibiotics.** *Thorax* 1997, **52**(Suppl 6):A8(S29).