

Why are allergies increasing?

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The incidence of atopic allergy is increasing in certain 'Western' countries but this remains unexplained. Various hypotheses with differing amounts of evidence and/or relevance have been assessed, including increased awareness of the diseases, improved diagnostics, genetic susceptibility, psycho-social influences, allergen exposure, decreased immune-system stimulation, underlying disease, anti-allergic therapy and pollution.

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Introduction

The incidence of atopic allergic diseases is increasing

Allergy is a major health problem in most modern societies [1,2]. Although the allergic diseases per se are not new — they were described in ancient Chinese and Greek literature (reviewed in [3,4]) — there is broad consensus that the prevalence of certain allergic diseases has increased in most industrialized countries of the world during the past few decades [5–9]. This phenomenon holds true for the so-called type I (atopic) diseases, namely extrinsic bronchial asthma, allergic rhinoconjunctivitis ('hay fever') and atopic-eczema/dermatitis. A similar trend has not been found for other types of allergic diseases, namely type II (cytotoxic), type III (immune-complex) or type IV (delayed-type) hypersensitivity reactions such as allergic contact dermatitis.

The increase in prevalence of atopic diseases is real

Studies from different authors reporting an increase in prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema have to be interpreted carefully with regard to potential differences in methodology [10].

Several studies by a few groups that used a similar methodology have also shown a significant increase in atopic diseases between 1960 and 1990 (Table 1; for references, see [2]).

Until recently there were no standardized methods to compare prevalence rates of the different atopic diseases. Therefore the International Study of Asthma and Allergies in Childhood (ISAAC) [11•] was started, whereby symptoms were investigated with standardized questionnaires and by implementation of a video showing an asthmatic patient. The results of the first phase of the ISAAC

programme have revealed dramatic differences in symptom prevalence of the different diseases in various countries of the world (156 study centres in 56 countries [11]). The highest asthma prevalence rates were found in Australia, New Zealand, the United Kingdom, the USA and some cities in Latin America. Lower prevalence rates were found in non-industrialized countries and more-rural areas. There was no concordant pattern between prevalence rates of atopic eczema and respiratory atopic diseases [12,13•,14].

According to many authors, the most rapid increase in prevalence of atopic diseases occurred in Western countries in the years between 1960 and 1990 [15]. The reasons for this increase in prevalence of atopy are not known. There exist, however, a number of hypotheses which are controversially and often emotionally discussed (Table 2) [16]. In this review, the pros and cons of the various hypotheses will be considered.

Hypothetical concepts to explain the increase in prevalence of atopic diseases

Increased awareness and improved diagnostics

Undoubtedly, allergic diseases are recognized more easily today than 50 years ago. This may be due to increasing public interest in these diseases as well as to the development of modern and more reliable diagnostic techniques. However, this improved diagnostic methodology and increased awareness may only contribute to the explanation rather than totally explain the increased prevalence, which has been documented in cross-sectional population-based studies.

Genetic susceptibility

Since the first description of 'atopy' [17], a genetic predisposition determining the susceptibility to develop atopic diseases has become established.

It is also known that the three atopic diseases are inherently connected within families, showing a considerable overlap (asthma plus atopic eczema, rhinoconjunctivitis plus asthma, etc.). This has been shown by classical genetics in family or twin studies [18]. Using modern molecular biology techniques, segregation and genetic linkage studies, several loci for specific atopy-associated genes have been determined on various chromosomes [19–21] (Table 3). Some authors have found genetic polymorphisms in allergy-relevant gene products — for example CD14, which is a receptor for endotoxin [22].

Of special interest is the obvious dominance of the maternal genetic influence over the paternal in many studies, giving rise to speculations about the role of environmental influences *in utero*. In the explanation of these findings, a possible role of genomic imprinting or of mitochondrial DNA has been discussed [13•,20,21].

Table 1**Changes in prevalence of atopic diseases over the past few decades (reviewed in [2]).**

Age group	Study year*	Number of subjects	Age range	% Actual asthma	% Diagnosed asthma
Country					
Children					
Australia	1982	769	8–11	6.5	12.9
	1992	795	8–11	9.9	19.3
New Zealand	1975	?	12–18	–	26.2†
	1989	435	12–18	–	34.0
Finland	1977	4335	12–18	0.1†	–
	1991	3059	12–18	2.8†	–
England	1989	3403	9–11	10.2	–
	1994	4034	9–11	19.6	–
Israel	1980	834	7–12	9.0‡	–
	1989	802	7–12	13.0‡	–
Adult					
Australia	1981	553	18–55	5.4	9.0
	1990	1028	18–55	6.3	16.3
Finland	1975	14468	33–59	2.0	–
	1981	15317	33–59	–	2.1
	1990	12219	33–59	3.0	–

*The year in which prevalence was assessed. †Self-reported. ‡Patients who had ever had asthma.

The more we know about the multiple genes involved in the development of atopy, the clearer it becomes that the genetic background alone cannot explain the increase in prevalence. This became particularly clear in studies comparing East and West German populations after the fall of the Berlin Wall in 1989; these were populations of a similar genetic and geographic background living under similar climatic conditions yet under quite different lifestyles (see below) [23*,24,25] (Figure 1).

Psycho-social influences

One of the most characteristic features of a 'Western society' is the individual freedom within a more or less democratic community trying to provide equal rights for all its members. This has led to increased mobility of individual people but also to increased social mobility within the society. One factor may be the increase during the past few decades in the mean age at which women give birth to their first child (K Thesdrup-Pedersen, personal communication), which

often is connected with higher parental educational level and professional life. Several studies have found significant inverse correlations between the parental educational level and the prevalence of atopy in the offspring: children from 'academic' parents have a significantly higher risk of developing atopic sensitization — measured in skin-prick test or radio-allergo-sorbent test (RAST) — and disease [26,27].

At the same time, family size has decreased; there seems to be an inverse correlation between the number of children or the number of people living within one apartment and the frequency of atopy [28].

Table 3**Gene-loci relevant for allergic diseases.**

Chromosome	Gene product	Phenotype
3	?	Infantile atopic eczema
5 q 31–35	'Cytokine cluster' IL-4 IL-13 IL-5 IL-3 IL-9 CD14 (endotoxin receptor) ADRB2 (β-adrenergic receptor) GLR (glucocorticoid receptor on lymphocytes)	↑ IgE, asthma, BHR
6 p 21	MHC II TNF-α	↑ Specific IgE Asthma
7	TCR α	↑ IgE
11 q 13	β-chain Fcε RI	↑ IgE
12 q 15	?	↑ Total IgE

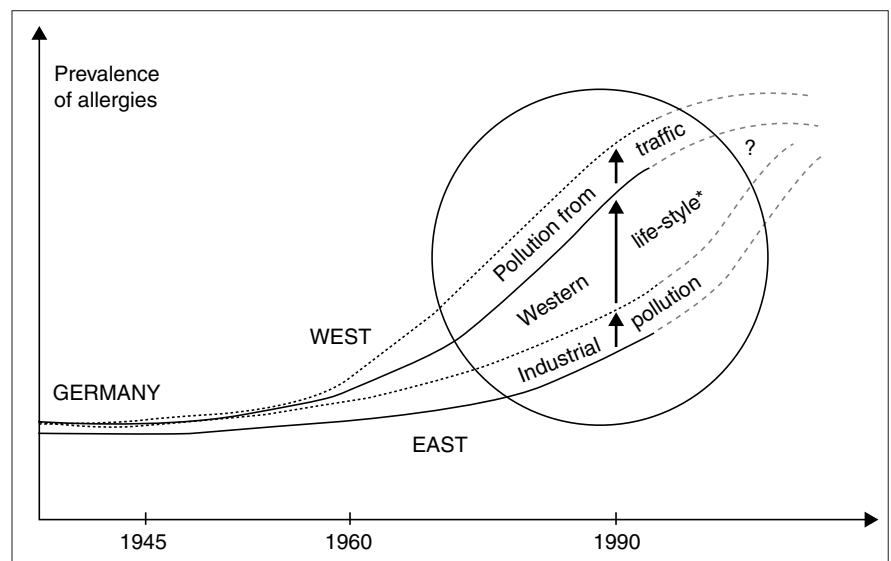
BHR, bronchial hyper-reactivity.

Table 2**Hypothetical concepts to explain the increase in prevalence of atopic diseases.**

Increased awareness and improved diagnostics
Genetic susceptibility
Psycho-social influences
Allergen exposure
Decreased stimulation of the immune system ('jungle' or 'hygiene' hypothesis)
Underlying disease
Anti-allergic therapy
Environmental pollution

Figure 1

Prevalence of allergies in East and West Germany plotted against year of birth. Solid lines indicate no additional pollutant exposure; dotted lines indicate additional pollutant exposure. The circle indicates the years with the most dramatic increase. Adapted, with permission, from [15].



The changes in living habits include also the increased trend of young women to smoke, increased psychologic stress, and altered living and entertainment habits of children, who sit for many hours in front of the TV, thereby decreasing their physical activity and increasing the exposure to indoor allergens (T Platts-Mills, personal communication).

Allergen exposure

There is no allergy without exposure to allergen. This exposure to allergens, both indoors and outdoors, has considerably changed both quantitatively and qualitatively during the past few decades. Eating habits show a tendency towards more and more exotic foods and spices already in early life followed by a trend towards more and more 'fast food'.

Indoor exposure to house-dust-mite allergens [29*,30–34] probably has increased during the past few years due to the striving for insulation and energy saving. The number of

homes with wall-to-wall carpeting has also increased. At the same time, there is an increasing tendency to keep pets, as shown in Germany (Table 4; [34]).

The exposure to pollen allergens may also have changed due to atmospheric pollution over the big cities leading to longer-lasting elevated pollen counts even during the night as well as to altered allergen release from pollen by interaction with pollutants (see below) [35*].

Decreased stimulation of the immune system because of improved hygiene ('jungle' or 'hygiene' hypothesis)

There is no doubt that the immune system of people living in Western societies is no longer 'trained' or challenged as it used to be in the past by severe infectious diseases of viral, bacterial, fungal or parasitic origin. A major defense mechanism for parasitic infestation — namely IgE antibodies — is still present and may now be directed against

Table 4

Increasing prevalence of pet-keeping in East and West German homes (n = 19 090) [34].

Area	Year	% Dog-owners	% Cat-owners	% Hamster-, guinea-pig-owners	% Rabbit-owners
East					
City	1991	12.4	12.9	12.6	3.9
	1994	15.3	15.0	16.0	5.4
	1997	25.9	20.2	23.4	11.9
Rural	1991	26.0	28.3	5.0	9.3
	1994	32.8	30.1	6.6	12.4
	1997	43.6	39.3	10.0	18.3
West					
City	1991	27.4	21.7	7.3	8.3
	1994	14.8	20.7	0.3	11.6
	1997	29.7	25.9	9.2	13.2
Rural	1991	35.9	15.3	4.9	14.7
	1994	29.2	11.7	10.4	13.6
	1997	40.0	16.3	7.1	15.4

Table 5

Arguments pro/contra the 'hygiene' hypothesis.

Pro

Early infections are inversely associated with atopy
 Populations with high prevalence of parasitic infestation have low prevalence of hay fever and asthma
 Anthroposophic children have less allergies
 Gastrointestinal flora with high lactobacillus counts in children with low prevalence of atopy
 Children raised in a farmhouse have less allergies than non-farmers' children in the same living area
 Children from academic parents have increased atopy risk
 CD14 gene polymorphism may explain the variable prevalence of atopy

Contra

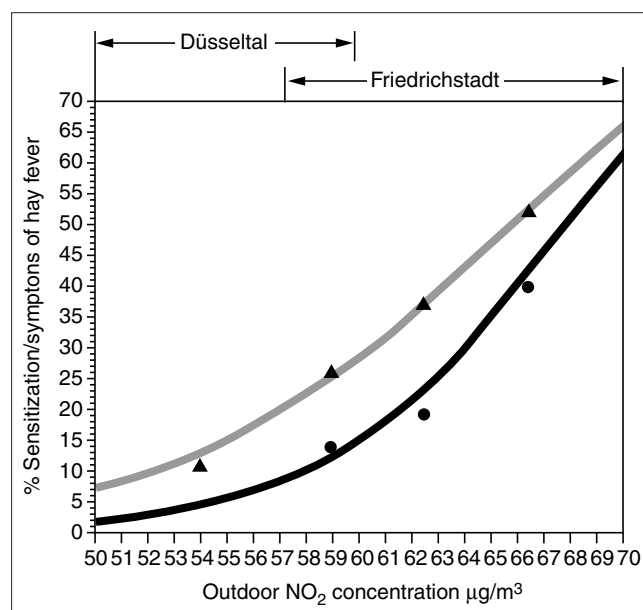
Parasitic infestation associated with higher risk of urticaria and atopic eczema
 Several microorganisms (*B. pertussis*, RSV) increase IgE production
 Active tuberculosis does not decrease Th2 reactivity
 Pertussis vaccination can protect children from atopy by preventing pertussis infection
 High prevalence of allergy in poor areas of developing countries or inner city 'slums'
 Modern ('type II') air pollution is associated with higher prevalence of respiratory atopy
 Mouse models of atopic eczema are normal under SPF conditions and develop eczema only when kept in normal cages

RSV, respiratory syncytial virus; SPF, specific-pathogen-free.

innocent environmental substances such as pollen or other particles (i.e. the 'jungle' or 'hygiene' hypothesis) [36^{*}]. Populations with a high degree of parasitic infestation usually show increased values of total serum IgE but lower prevalence rates of asthma and hay fever [16,36^{*}]. In the comparison of East and West German school children, serum concentrations of total IgE were strikingly higher in the East [37], which was not reflected by specific IgE antibodies against common environmental allergens in RAST assays, but was dependent upon the number of people living in one apartment. There was a significantly higher proportion of East German children with parasitic infestation compared with the West [37]. Children who grew up in early life in a day-care facility develop less allergies later in life during school years [38].

In almost all epidemiological studies comparing urban and rural areas, it was found that allergies are more prevalent in the city. Children who were raised in a farmhouse with heavy exposure to farm animals and endotoxin had less allergies than children living in the same area but not in a farmhouse. These results have been shown for Swiss, Austrian, Finnish and German children as well as Aborigines in Australia [39^{*},40–42]. The exposure to various infectious agents and endotoxin may lead to stimulation of blood mononuclear cells, leading to production of IFN- γ and a Th1 cytokine secretion pattern [43,44]. Notably, a genetic polymorphism in the transcription of

Figure 2



Outdoor NO₂ concentration and prevalence of pollen sensitization and hay fever in schoolchildren in suburbs of Düsseldorf (Düsseltal and Friedrichstadt). It shows the association between exposure to traffic-related outdoor NO₂ levels, atopic sensitization against aeroallergens and symptoms of hay fever in 306 nine-year-old German children. Percentages were adjusted and regression lines plotted for equidistant exposure groups in urban areas. In Düsseldorf, there were <40 351 vehicles per 24 hours; in Friedrichstadt, there were <50 914 vehicles per 24 hours. Adapted, with permission, from [61].

the CD14 gene has been shown to be associated with increased IgE formation [22].

It may be that the microbial stimulation in the gastrointestinal tract plays a more important role than respiratory infections. Studies investigating Italian military men showed a much lower rate of gastrointestinal infection in allergic recruits [45]. Studies from Northern Europe found characteristic differences in the intestinal microflora regarding *Lactobacillus* species and anaerobic organisms in children with and without allergy [46].

Upper-respiratory-tract infections in the first year of life as well as herpesvirus-type infections seem to have an allergy-protective effect leading to decreased prevalence rates of asthma, wheezing or hay fever at 7 years of age; however, repeated lower-respiratory-tract infections, especially with respiratory syncytial virus (RSV), showed a positive association with asthma and wheezing [47,48].

The supporters of the 'hygiene' hypothesis also quote studies from anthroposophic children with less atopic diseases [49] or people who, after measles infection, seemed to be protected against allergies [50]. This has led to practical recommendations against vaccination programs in order to prevent allergy. Our own studies have shown that pertussis vaccination is able to protect children from

atopic diseases by preventing pertussis infection (U Krämer, J Ring, H Behrendt, unpublished data). Furthermore, recent animal models of atopic eczema have been described in which mutant mice kept under specific-pathogen-free (SPF) conditions were symptom-free; however, as soon as they were kept in normal cages, they developed signs and symptoms of atopic eczema [51•].

The interactions between infections and the development of allergy are complex and partly conflicting (Table 5): one has to distinguish the different kinds of microbial organisms (parasites, fungi, bacteria and viruses), the atopic disease manifestation (respiratory atopy versus atopic skin disease), the period of life, the nature of the stimulus (vaccination or infection) and maybe other underlying diseases (see below). Obviously, among different kinds of bacterial infections, quite contrary effects can be observed: *Bordetella pertussis* is a strong enhancer of IgE formation, whereas *Mycobacterium* species may push the immune system towards the Th1 pattern [52]. Active tuberculosis does not protect from Th2 reactivity [53].

It is definitely too early to give practical recommendations such as “don’t vaccinate” or “don’t wash your children” on the basis of the existing knowledge!

Underlying diseases

Apart from the genetic background, there may be certain underlying diseases exerting a strong stimulus against a Th2-secretion pattern: recently an inverse association between the prevalence of type I diabetes mellitus and atopic sensitization and disease has been reported [54].

Anti-allergic therapy

Recent evidence suggests that, possibly through symptomatic anti-allergic medication (e.g. H1 antagonists), lymphocytes may be shifted towards a Th2 pattern — histamine playing a role as immuno-regulator [55•]. These data are in conflict with the results of the multicentre study ‘Early treatment of the atopic child’ (ETAC), where prophylactic use of an H1 antagonist (namely cetirizine) was able to reduce the risk of asthma in children with atopic eczema sensitized to house-dust-mite and pollen [56]. Little is known about the long-term effects of other pharmacotherapeutic regimens at the immunoregulatory level.

Environmental pollution

Environmental pollutants have been recognized to be harmful to human health, especially with respect to cytotoxicity, mutagenicity and carcinogenicity. The role of pollutants in allergy is still controversial. In studies evaluating the role of pollutant exposure, it is crucial to distinguish between different qualities of air pollutants, at least between two types, as detailed below.

Type I air pollution is characterized by primary pollutants such as SO₂, large particles and dust fall, emitted predominantly from outdoor sources. This type of air pollution was

characteristic for Eastern Germany and is still present in some Eastern European countries. It is associated with adverse health effects, namely upper respiratory tract inflammation and infection [57].

Type II air pollution is characterized by the presence of primary and secondary pollutants being emitted from outdoor as well as indoor sources. It is found in highly populated industrialized urban areas in the Western world. This type of air pollution has been found to be associated with allergic sensitization and disease in several studies [57].

A large number of animal experimental studies in various species have shown that air pollutants can enhance IgE antibody formation [58•]. *In vitro* studies using different cell populations showed that several pollutants (especially diesel exhaust particles) are able to shift the T-cell response towards the Th2 secretion pattern [59]. Other pollutants may have a dual effect: cadmium can induce leukotriene synthesis from rat mast cells while at the same time inhibiting histamine release (reviewed in [57]).

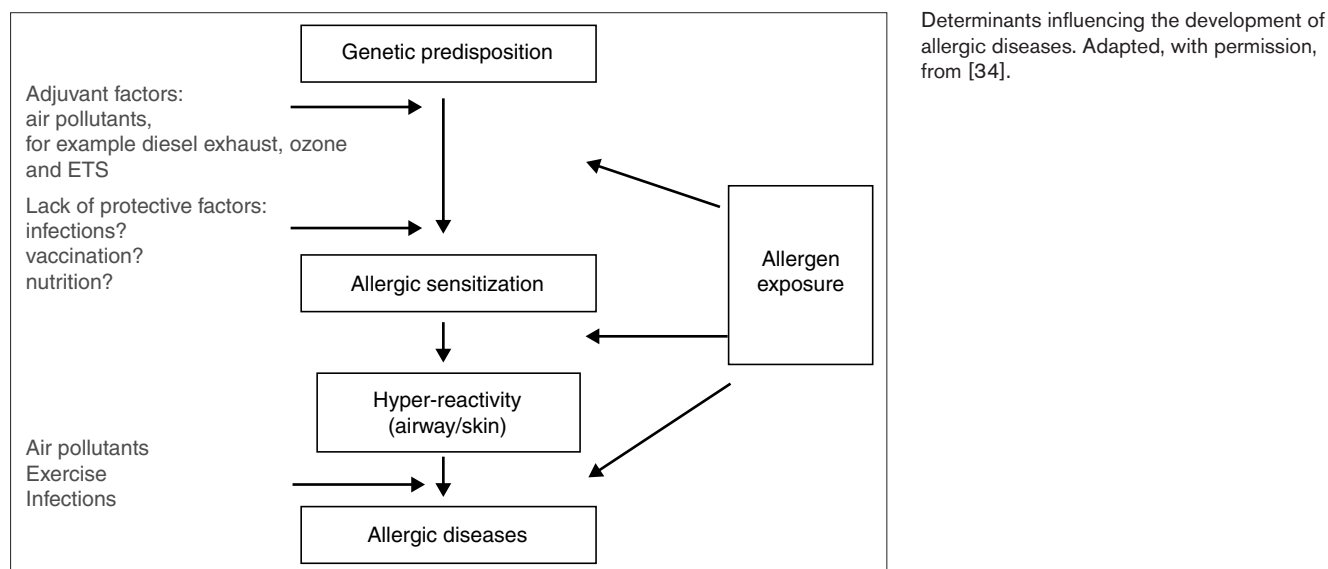
Extracts from atmospheric pollutant particles collected over large cities in Western Germany were able to induce histamine release from human basophils and prime anti-IgE-induced histamine and leukotriene release as well as IL-8 secretion from neutrophil leukocytes [57]. These experimental findings have been supported by epidemiological studies [60], especially the well-known comparison studies of East and West German schoolchildren with higher prevalences of respiratory atopic disease in type-I-polluted East Germany. Similarly, associations between exposure to vehicle exhaust and allergy prevalence have been reported in West German children. In a recent study in the city of Düsseldorf it was shown that NO₂ (a marker of outdoor pollution) was significantly associated with increasing rates of pollen sensitization and hay fever [61] (Figure 2).

In the indoor environment, exposure to environmental tobacco smoke has been shown in many studies to increase the risk of the development of atopic diseases, especially when mothers were smoking during pregnancy and/or lactation [62,63].

Pollen grains as the major source of outdoor aeroallergen have been shown to interact with pollutant particles, leading to agglomeration and changes in surface structure. In a specially designed fluidized-bed reactor chamber, exposure to different gaseous air pollutants was shown to alter the allergen release from pollen into an aqueous milieu. Thus SO₂ induced a decrease in allergen release, whereas type-II pollutants such as volatile organic compounds promoted pollen-grain activation [64].

Recently we found that, under humid conditions, pollen grains themselves secrete significant amounts of pro-inflammatory eicosanoid-like substances able to attract neutrophil granulocytes and activate eosinophils. This process of ‘initiation of allergy’ precedes the allergen-APC

Figure 3



(antigen-presenting cell) interaction and may be the first step in the process of atopic sensitization (see the review by Behrendt and Becker, this issue, pp 709–715).

Conclusions

Although there is no doubt that the prevalence of certain allergic, especially atopic, diseases has increased during the past few decades in many countries of the world, the causes of this increase cannot be explained satisfactorily at the moment. There exist only hypothetical explanations with higher or lower degrees of plausibility. It may well be that not only one, but several, factors act together in this respect. It becomes more and more obvious that factors characteristic of a 'modern society' ('Western society') that may originate from the physical, chemical, biological or psycho-social environment play a role in the development of allergy. It is crucial to distinguish between causal factors (e.g. allergens) and adjuvant/enhancing factors (biologic or chemical) as well protective inhibitory factors that may be lost. At the same time it is important to distinguish between the different levels at which these factors may interfere in the process of a developing allergy — from genetic susceptibility, via allergic sensitization, to airway and skin hyper-responsiveness and finally a manifest allergic disease (Figure 3). Only when there is reliable knowledge about which factor or substance is responsible for what, and to what degree, may rational consequences be drawn for primary prevention of allergic diseases.

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. Anonymous: *European Allergy White Paper: Allergic Diseases as a Public Health Problem*. Brussels: The UCB Institute of Allergy, Brussels; 1997.
2. Woolcock AJ: **The burden of asthma**. *ACI Int Suppl* 2000, 1:53-56.
3. Simons E (Ed): *Ancestors of Allergy*. New York: New York Global Medical Communications Ltd.; 1994.
4. Ring J: **Erstbeschreibung einer atopischen Familienanamnese im julisch-claudischen Kaiserhaus: Augustus, Claudius, Britannicus**. *Hautarzt* 1983, 36:470-474. [Title translation: First report of a family anamnesis of atopy in the House of the julian-claudian emperors: Augustus, Claudius, Britannicus.]
5. Burr ML (Ed): *Epidemiology of Allergic Diseases*. Basel: Karger; 1993.
6. Wahn U, Wichmann H: *Special Report on Allergies (in German)*. Federal Statistical Office FS. Stuttgart: Metzler-Poeschel; 2000.
7. Taylor B, Wadsworth M, Wadsworth J, Peckham C: **Changes in the reported prevalence of childhood eczema since the 1939–45 war**. *Lancet* 1984, 2:1255-1258.
8. Varjonen E, Kalimo K, Lammintausta K, Terho P: **Prevalence of atopic disorders among adolescents in Turku, Finland**. *Allergy* 1992, 47:234-248.
9. Wüthrich B: **Epidemiology of the allergic diseases: are they really on the increase?** *Int Arch Allergy Appl Immunol* 1989, 90:3-10.
10. Diepgen Th L: **Is the prevalence of atopic dermatitis increasing?** In *Atopic Dermatitis*. Edited by Williams W. Cambridge, UK: Cambridge University Press; 2000: 96-109.
11. Anonymous: **Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee**. *Lancet* 1998, 351:1225-1232.

This report of the ISAAC program shows a tremendous variation in allergy prevalence around the world.

12. Williams H (Ed): *Atopic Dermatitis: the Epidemiology, Causes and Prevention of Atopic Eczema*. Cambridge, UK: Cambridge University Press; 2000.
13. Schäfer T, Vieluf D, Behrendt H, Krämer U, Ring J: **Atopic eczema and other manifestations of atopy: results of a study in East and West Germany**. *Allergy* 1996, 51:532-539.
- For the first time it was shown that atopic eczema — other than hay fever — was more prevalent in East German children compared with the West, a finding showing the discrepancy in atopic respiratory and skin disease.
14. Schulz-Larsen F: **The epidemiology of atopic dermatitis**. *Monogr Allergy* 1993, 31:9-28.
15. Wichmann H: **Environment, life-style and allergy: the German answer**. *Allergol J* 1995, 4:315-316.

16. Ring J: **Allergy: a disease of modern society.** *Int Arch Allergy Immunol* 1997, **113**:7-10.
 17. Coca AF, Cooke RA: **On the classification of the phenomena of hypersensitiveness.** *J Immunol* 1923, **8**:163-182.
 18. Schnyder UW: **Neurodermitis – Asthma – Rhinitis. Eine genetisch-allergologische Studie.** *Acta Genet Stat Med* 1960, **10(suppl 18)**:1-106. [Title translation: Neurodermitis – asthma – rhinitis. A genetic and allergologic study.]
 19. Holgate ST: **The epidemic of allergy and asthma.** *Nature Suppl* 1999, **402**:B2-B4.
 20. Cookson WO, Sharp PA, Faux JA, Hopkin JM: **Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q.** *Lancet* 1989, **1**:1292-1295.
 21. Blumenthal M, Björkstén B (Eds): *Genetics of Allergy and Asthma.* New York: Marcel Dekker; 1997.
 22. Baldini M, Lohman IC, Halonen M, Erickson RP, Holt P, Martinez FD: **A polymorphism in the 5'-flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum IgE.** *Am J Resp Cell Mol Biol* 1999, **20**:976-983.
 23. Von Mutius E, Fritzsche C, Weiland SK, Röhl G, Magnussen H: **Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison.** *Br Med J* 1992, **305**:1395-1399.
- Here, in a comparison between Munich and Leipzig, a higher hay fever prevalence was found for West German children compared with the East.
24. Krämer U, Behrendt H, Dolgner R, Ranft U, Ring J, Willer J, Schlipkötter HW: **Airway diseases and allergies in East and West German children during the first 5 years after reunification: time trends and the impact of sulphur dioxide and total suspended particles.** *Int J Epidemiol* 1999, **28**:865-873.
 25. Heinrich J, Hoelscher B, Jacob B, Wjst M, Wichmann H-E: **Trends in allergies among children in a region of former East Germany between 1992-1993 and 1995-1996.** *Eur J Med Res* 1999, **4**:107-113.
 26. Krämer U, Altmann L, Behrendt H, Dolgner R, Islam MS, Kaysers HG, Ring J, Stiller-Winkler R, Turfeld K, Weisshoff-Houben et al.: **Comparison of the influence of socioeconomic factors on air pollution health effects in West and East Germany.** In *Air Pollution Epidemiology Health Series Report Nr 8 Commission of the European Union* 1997. Brussels: Commission of the European Union; 1997.
 27. Heinrich J, Popescu M, Wjst M, Goldstein I, Wichmann H: **Atopy in children and parental social class.** *Am J Public Health* 1998, **88**:1319-1324.
 28. Von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmeir P, Thiemann H-H: **Skin test reactivity and number of siblings.** *Br Med J* 1994, **308**:692-695.
 29. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ: **Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood.** *N Engl J Med* 1990, **323**:502-507.
- In this paper, threshold concentrations of house-dust-mite allergen are given, determining an increased risk for sensitization or manifest allergy.
30. Kuehr J, Frischer T, Karmaus W, Meiner R, Barth R, Herrmann-Kunz E, Forster J, Urbanek R: **Early childhood risk factors for sensitization at school age.** *J Allergy Clin Immunol* 1992, **90**:358-363.
 31. Custovic A, Taggart SCO, Woodcock A: **House dust mite and cat allergen in different indoor environments.** *Clin Exp Allergy* 1994, **24**:1164-1168.
 32. Wickmann M, Emenius G, Egmar AC, Axelsson G, Pershagen G: **Reduced mite allergen levels in dwellings with mechanical exhaust and supply ventilation.** *Clin Exp Allergy* 1994, **24**:109-114.
 33. Platts-Mills TAE, Vaughan JW, Blumenthal K, Pollart-Squillace S, Sporik RB: **Serum IgG and IgG4 antibodies to Fel d 1 among children exposed to 20 µg Fel d 1 at home: relevance of a nonallergic modified Th2 response.** *Int Arch Allergy Immunol* 2001, **124**:126-129.
 34. H Behrendt, Ewers HJ, Hüttl R, Jänicke M, Plassmann E, Reh binder E, Sukopp H: *National Council for Environmental Issues: Environment and Health. The Problem of Risk Assessment.* Stuttgart: Metzler-Poeschel; 2000.
 35. Behrendt H, Becker WM, Friedrichs KH: **Interaction between aeroallergens and airborne particulate matter.** *Int Arch Allergy Immunol* 1992, **99**:425-428.
- For the first time a direct interaction of air pollutants and allergen carriers (pollen) was shown to be of possible allergological relevance.
36. Larrick JW, Buckley CE III, Machamer CE, Schlagel GD, Yost JA, Blessing-Moore J, Levy D: **Does hyperimmunoglobulinemia-E protect tropical populations from allergic disease?** *J Allergy Clin Immunol* 1983, **71**:184-188.
- The observation of highly elevated IgE levels and low – almost non-existent – prevalence of atopy in Latin-American Indians living in the jungle gave rise to what later was called 'jungle' or 'hygiene' hypothesis.
37. Behrendt H, Krämer U, Dolgner R, Hinrichs J, Willer J, Hagenbeck H, Schlipkötter HW: **Elevated levels of total IgE in East German children: atopy, parasites or pollutants?** *Allergo J* 1993, **2**:31-40.
 38. Krämer U, Heinrich J, Wjst M, Wichmann HE: **Age of entry to day nursery and allergy in later childhood.** *Lancet* 1999, **353**:450-454.
 39. Gassner-Bachmann M, Wüthrich B: **Bauernkinder leiden selten an Heuschnupfen und Asthma.** *Dtsch Med Wochenschr* 2000, **125**:923-931. [Title translation: Farmers' children suffer rarely from hay fever and asthma.]
- These authors were the first who noted that farmers' children had a decreased allergy risk in a small village in Switzerland already in the 1980s.
40. Riedler J, Eder W, Oberfeld G, Schreuer M: **Austrian children living on a farm have less hay fever, asthma and allergic sensitization.** *Clin Exp Allergy* 2000, **30**:194-200.
 41. Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, Vuille JC, Wüthrich B: **Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community.** *Clin Exp Allergy* 1999, **29**:28-34.
 42. Le Souef P: **Allergy in the Australian Aboriginal population.** *ACI Int Suppl* 2000, **1**:43-45.
 43. Strachan DP: **Hay fever, hygiene and household size.** *Br Med J* 1989, **299**:1259-1260.
 44. Holt P: **Parasites, atopy and the hygiene hypothesis: resolutions of a paradox?** *Lancet* 2000, **356**:1699-1701.
 45. Matricardi PM, Franzinelli F, Franco A, Caprio G, Murru F, Cioffi D, Ferrigno L, Palermo A, Ciccarelli N, Rosmini F: **Sibship size, birth order, and atopy in 11,371 Italian young men.** *J Allergy Clin Immunol* 1998, **101**:439-444.
 46. Björkstén 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.
 47. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B: **Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls.** *Pediatrics* 1995, **95**:500-505.
 48. Illi S, von Mutius E, Kau S, Bergmann R, Niggemann B, Sommerfeld C, Wahn U, MAS study group: **The role of early childhood infectious diseases in the development of asthma up to school age.** *Allergy Clin Immunol Int* 2001, **13**:99-106.
 49. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G: **Atopy in children of families with an anthroposophic lifestyle.** *Lancet* 1999, **353**:1485-1488.
 50. Shaheen SO, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW, Goudiaby A: **Measles and atopy in Guinea-Bissau.** *Lancet* 1996, **347**:1792-1796.
 51. Matsuda H, Watanabe N, Geba GP, Sperl J, Tsudzuki M, Hiroi J, Matsumoto M, Ushio H, Saito S, Askenase PW, Ra C: **Development of atopic dermatitis-like skin lesions with IgE hyperproduction in NC/Nga mice.** *Int Immunol* 1997, **9**:461-468.
- The murine model of spontaneously occurring atopic eczema in NC/Nga mice strongly contradicts the 'hygiene hypothesis' in that the animals are symptom-free under SPF (specific-pathogen-free) conditions and only develop eczema in a normal environment.
52. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM: **The inverse association between tuberculin response and atopic disorder.** *Science* 1997, **275**:77-79.
 53. Suzuki, Kudo K, Sano Y, Ito K: **Can Mycobacterium tuberculosis infection prevent asthma and other allergic disorders?** *Int Arch Allergy Immunol* 2001, **124**:113-116.

54. Olesen A, June S, Thesdrup-Pedersen K: **Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study.** *Lancet* 2001, **357**:1749-1752.
55. Jutel M, Watanaba T, Klunker S, Blaser K: **Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors.** *Nature* 2001, in press.
 The demonstration of an immunoregulatory effect of histamine upon T cells can lead to the speculation of antiallergic symptomatic therapy as contributing to the maintenance of allergy.
56. Anonymous: **Allergic factors associated with the development of asthma and the influence of Cetirizine in a double-blind, randomized, placebo-controlled trial: first results of ETAC (Early Treatment of the Atopic Child).** *Pediatr Allergy Immunol* 1998, **9**:116-124.
57. Behrendt H, Friedrichs K, Krämer U: **The role of indoor and outdoor air pollution in allergic diseases.** In *Progress in Allergy and Clinical Immunology*. Edited by Johansson S. Berne: Hogrefe & Huber; 1995:83-89.
58. Muranaka M, Suzuki S, Koizumi K, Takafuji S, Miyamoto T, Ikemori R, Tokiwa H: **Adjuvant activity of diesel-exhaust particulates for the production of IgE antibody in mice.** *J Allergy Clin Immunol* 1986, **77**:616-623.
 This Japanese group was the first to recognise an adjuvant influence of environmental pollutants, namely diesel-exhaust particles, on IgE-mediated allergy.
59. Diaz-Sanchez D: **The role of diesel exhaust particles and their associated polyaromatic hydrocarbons in the induction of allergic airway disease.** *Allergy* 1997, **52**:52-56.
60. Hirsch T, Weiland SK, von Mutius E, Safeca AF, Grafe H, Csaplovics E, Duhme H, Keil U, Leupold W: **Inner city air pollution and respiratory health and atopy in children.** *Eur Respir J* 1999, **14**:669-677.
61. Krämer U, Koch T, Ranft U, Ring J, Behrendt H: **Traffic-related air pollution is associated with atopy in children living in urban areas.** *Epidemiology* 2000, **11**:64-70.
62. Martinez FD, Antognoni G, Macri F, Bonci E, Midulla F, De Castro G, Ronchetti R: **Parental smoking enhances bronchial responsiveness in nine year old children.** *Am Rev Resp Dis* 1998, **138**:518-523.
63. Schäfer T, Dirschedl B, Kunz B, Ring J, Uberla K: **Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring.** *J Am Acad Derm* 1997, **36**:550-556.
64. Behrendt H, Krämer U, Schäfer T, Kasche A, Eberlein-König B, Dasson U, Ring J: **Allergotoxicology – a research concept to study the role of environmental pollutants in allergy.** *Allergy Clin Immunol Int* 2001, **13**:127.