

Environmental Risk Factors for Atopy

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Introduction

There is now an almost universal consensus that the prevalence of allergic diseases has increased considerably in Western industrialized countries, particularly since the Second World War (1,2). The reasons for this increase obviously have to be looked for in the environment. Several potential risk factors in the environment have been identified. Even if all factors that are known to affect the incidence of allergic manifestations are combined, however, this would only partly explain the increase.

The downfall of the Soviet empire in Europe has opened the formerly socialist countries of Central and Eastern Europe to epidemiological studies. The prevalence of allergic diseases among children and young adults is low in these countries (3–6). The lifestyle is similar in many respects to that prevailing in Western Europe 30–40 yr ago. It is not known whether “Western lifestyle” is associated with an introduction of new unknown adjuvants enhancing sensitization, or whether there is a lack of factors that are necessary for the induction of tolerance.

The etiology of allergy is multifactorial, and depends on the interaction, in genetically susceptible individuals, between the time and amount of allergen exposure and the presence of nonspecific “adjuvant” factors, including air pollution. Environmental factors that influence the development of allergic disease are either specific or nonspecific. It is also common knowledge that psychological factors may trigger, or at least aggravate, clinical manifestations of allergic disease. Whether they could also enhance sensitization to allergens is not known.

Experimental, epidemiological, and clinical observations strongly support the concept that the conditions under which the primary encounter with an allergen takes place influence the immune response, i.e., whether tolerance or sensitization is triggered (7–9). Thus, the conditions under which an allergen is encountered in infancy may have conse-

quences for many years, perhaps even for life. If this is indeed true, then the prevalence in adults would continue to increase for many years, even after institution of effective allergy-preventive measures in childhood.

This article discusses some environmental factors that may affect the incidence of sensitization to allergens with an emphasis on factors encountered in early childhood.

Variations in Susceptibility

The relative risk for allergic disease and the tendency to develop allergic disease are both strongly influenced by genetic factors, age, and the conditions under which exposure takes place. The genetics of atopy is not fully understood. Several research teams are presently involved in a search for candidate genes for atopy. Since atopy is associated with several biochemical and immunological aberrations that could explain parts of the phenotypic expression of allergy, it is reasonable to expect the involvement of several genes, each coding for a certain abnormality. There are now reports indicating that atopy and excessive IgE antibody formation are associated with a gene on the short arm of chromosome 11 (10), although this could not be confirmed in several subsequent studies (11,12). Other studies have reported an association of atopy to a gene on chromosome 5 that controls the regulation of interleukin-4 (IL-4) (13) and to a locus for the β -adrenergic receptor on the same chromosome (14,15).

The likelihood of developing allergic disease in an individual is not constant over time, even if the general propensity is genetically determined. Thus, the risk of sensitization is affected by the time and the conditions under which exposure to allergens takes place. There seems to be a period in early life during which an infant is particularly susceptible to sensitization (8,9). A higher incidence of allergy to birch and grass pollen has thus been reported in children born in the spring (16,17). A similar increase in grass allergy has been reported in British children born in the spring (18) and for the prevalence of ragweed allergy in Americans born in the late summer.

This relationship between season of birth and development of allergy seems to be limited to children with a congenital propensity to develop allergic disease (19). Similarly, early feeding with foreign proteins is associated with an increased risk for allergic disease, but mostly so in genetically susceptible individuals (20).

Animal studies and clinical observations have indicated that stress alters the immune response, as measured by various laboratory tests of the inflammatory responses, immunoglobulin production, and cell-mediated immunity (21,22). Clinical studies also indicate that stress may cause reduced resistance to infections (23,24). Although it is well-

established that psychological factors influence the severity of asthmatic symptoms and allergic reactions in affected patients, little is known regarding a possible adjuvant effect on sensitization.

Variations in individual susceptibility to sensitization over time may also partly be explained by the presence and absence of respiratory tract infection. The role of infections in the respiratory tract as risk factors for the development of childhood allergic disease and asthma is complex, however. It is well-established that infections may trigger and aggravate asthma in already sensitized individuals, and that infections increase bronchial hyperreactivity. The presence and absence of infections may explain variations in susceptibility to disease manifestations in the individual over time. The role of infections in relation to sensitization is discussed in more detail below.

Allergens

In order to develop an allergy, the individual obviously has to be exposed to the allergen. Allergens are present in almost every part of the world, but the relative importance of the individual allergens varies depending on climatic conditions. In subarctic regions, like the Nordic countries, house dust mites used to be absent, but there is now evidence for an increasing prevalence (25–27). This may, at least partly, be owing to modern technology used for building houses and energy conservation measures. Such differences and geographical differences may explain why certain allergies are common in a region, but they may not explain the large geographic differences in the prevalence of allergy in general.

As already indicated, there is a period in early childhood during which exposure to inhalant allergens may result in the development of allergy several years later. In a large epidemiological study comprising 40,000 individuals, a Finnish team observed a significantly higher prevalence of allergy to birch and grass pollen in 10-yr-old children who were born in the spring compared to children who were born at other times of the year (17). Subsequently, the authors reported that the risk of pollen allergy, as diagnosed at 10 yr of age, was affected not only by the month of birth, but also by the intensity of the pollen season the year they were born (16). The intensity of the first pollen season even had a stronger impact than the intensity of the pollen season when their symptoms first appeared. Similarly, early contact with pets and animal epithelia (28), house dust mites (29–31), and early feeding with foreign proteins (32) all appear to be associated with an increased risk for allergic disease. A high concentration of allergens in the house of a newborn baby, particularly if there is a family history of allergy, may thus increase the prevalence of allergy to that allergen several years later.

The fact that exposure to high levels of allergens early in life appears to be a risk factor for sensitization and allergic manifestations later in life has prompted studies of the possible effects of allergy prevention. The results of these studies indicate a modest protective effect against sensitization to the particular allergens that were avoided. From current knowledge of the kinetics of the primary immune responses, it is not reasonable to expect a general allergy-preventive effect by the avoidance of certain allergens, but merely a possible delayed sensitization to that particular allergen. This is further discussed below.

Pre- and Perinatal Risk Factors

During fetal life and infancy, there is a close immunological interaction between the mother and her offspring, through the placenta and the breast milk. Relatively little is known about the exchange of immunological information. There are indications, however, that allergen-specific immune responses may be present already at birth (33,34). It is not known whether they represent normal responses or whether they are associated with allergic manifestations developing later in life, or whether they are responses to intrauterine exposure to allergen or to anti-idiotypic antibodies. Such antibodies have been suggested as stimulators of an immune response to polio virus in unvaccinated infants (35). Also, transplacentally transferred autoantibodies could possibly affect the immune responses in early infancy. Thus, we recently observed that elevated levels of IgG anti-IgE antibodies in the cord blood were associated with less allergy during the first 18 mo of life (36). This was particularly obvious in babies with a strong family history of allergy.

Human milk is another source of immunological information that may be transferred from the mother to her offspring. In addition to numerous components that help in the protection against infection, human milk contains components that enhance the maturation of the immune system of the newborn infant (37). Observations include an early stimulation of IgA antibody synthesis in breast-fed infants (38,39) and transfer of cell-mediated immunity (40,41) and cytokines (42). Thus, human milk would not only provide passive protection against infections, but also actively stimulate infant immunity. There are considerable individual variations in the composition of human milk, however, suggesting that maternal immunity may represent an environmental factor influencing the risk for allergic manifestations in her child, possibly even several years later.

It has also been suggested that perinatal stress factors could increase the risk for later-appearing allergic disease. These studies (summarized in ref. 43) were retrospective, however, and did not con-

Table 1
Adjuvant Factors Thought to Be Involved Either
in Sensitization or Manifestations of Allergic Disease

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

trol for various other possibilities. In unpublished studies, we have not seen any indication that prematurity by itself is a risk factor for atopic sensitization.

Although there is convincing evidence for an association between exposure to tobacco smoke and childhood allergy (cf below), the role of tobacco smoking during pregnancy is less clear. Although there are reports of an association between the two, the studies are inconclusive owing to their design (44). Infants of smoking mothers are, however, exposed to significant amounts of nicotine via the breast milk (45).

Medication with the β -receptor blocking agent propranolol during the first trimester of pregnancy may be associated with an increased risk for allergy in the children (46). This observation is interesting, since β -receptor blockade may enhance IgE antibody formation in animals (47).

Progesterone given to pregnant women for various reasons has also been reported to be associated with increased levels of IgE in cord blood (48). This study was never published in full, however, nor has the observation been confirmed in other studies.

Nonspecific, Environmental Factors, "Adjuvants"

Various environmental factors may enhance sensitization and also trigger an allergic reaction in a sensitized individual (Table 1). Although allergy is rare to most of the compounds listed in the table, they do play a role, both in the sensitization process and for the appearance of clinical symptoms. The results of animal experiments lend strong support to the epidemiological observations that pollution may enhance sensitization, as well as triggering symptoms from the respiratory tract. Compounds shown to enhance sensitization in animal models include tobacco smoke, NO₂, SO₂, and ozone (8), as well as diesel particles (49). It is not entirely clear exactly how the adjuvants act. Possibly, an

inflammatory reaction is induced in the airways, facilitating the penetration of allergens and enhancing antigen presentation.

Tobacco Smoke

Passive smoking is by far the best-identified risk factor for the development of allergic disease. This is particularly true in early childhood and is independent of how "allergy" is defined. There is now convincing evidence that daily exposure to tobacco smoke results in an increased risk of developing wheezy bronchitis, asthma, and bronchial hyperreactivity in children (summarized in ref. 50). An association between passive smoking and an increased risk for sensitization to environmental allergens has also been demonstrated in many clinical studies (51), as well as in animal experiments (52). Moreover, passive smoking results in increased morbidity, increased need for medical treatment, and increased use of asthma medication in asthmatic children (50). Exposure to maternal smoking seems to have the largest effects, possibly because the mother is the parent more often at home with the child. There is little doubt that exposure to tobacco smoke is the most important identified environmental risk factor for childhood allergy and respiratory disease that has been identified so far. The long-term effects of childhood exposure to tobacco smoke are unknown. As the number of cigaret smoking young women has steadily increased in the Western industrialized countries over the last 40 yr, passive smoking early in life may be one of the factors behind the increasing prevalence of allergy.

Indoor Environment

It has traditionally been assumed that air pollution primarily occurs outdoors. A number of studies have shown, however, that indoor concentrations of some pollutants may be far in excess of the outdoor concentrations (53). There is probably no air outdoors that is so polluted as that in a room where people are smoking. In many countries, outdoor air pollution has decreased over the past decades. Furthermore, there is no clear relationship between air pollution and the prevalence of allergy. On the contrary, Swedish studies have reported a higher prevalence of allergy in the northern, less polluted part of the country than in the southern, more industrialized parts, which are also more affected by pollution from central Europe (54,55). Similar results have been reported from Finland and Norway. The indoor environment, therefore, probably plays an equally large, or even larger role in the development of allergic sensitization and the appearance of allergic disease in the sensitized individual.

Modern, well-insulated houses have been associated with an increased risk for the development of allergic manifestations, as well as with sensitization. In temperate climates, where house dust mites used to be scarce, the increased humidity in modern energy-saving homes

has resulted in an increase prevalence of mite allergy (25–27). In a large epidemiological study, comprising 5300 children living in a defined geographical area, it was found that living near an air-polluting paper pulp plant, living in homes with a dampness problem, and having smoking parents were all strong risk factors for allergic disease (56). This relationship was particularly pronounced in children with a family history of allergy. Children living in a house with dampness problems and having smoking parents had an increased prevalence of asthma compared to children not exposed to these risk factors. This was particularly obvious in children with a family history of allergy, in whom 22% had manifest asthma if exposed to the two risk factors.

Psychological Factors

The family-interaction is often disturbed in the families of asthmatic children, and family therapy improves the asthma. A recent prospective study addressed the question concerning whether the disturbed family interaction is a primary finding or a consequence of disease (57). The study included the families of 100 infants with a strong family history of allergy. The entire family participated in a standardized family test when the children were 3 and 18 mo old, assessing the ability to adapt to changing circumstances (“adaptability”) and the balance between emotional closeness and distance (“cohesion”). An unbalanced family interplay was common at 3 mo (37%), but it was not predictive for respiratory illness. At 18 mo, a dysfunctional interaction was significantly more common in families of children with eczema and obstructive symptoms compared to families of healthy children. The study indicates that a dysfunctional family interaction is the result, rather than a cause of recurrent wheezing in infancy.

Infections

The role of infections, notably in the respiratory tract, as risk factors for the development of childhood allergic disease is complex. An infection induces an inflammatory reaction in the respiratory mucosa, which in turn modifies the local immune response. To what extent this enhances sensitization to inhaled allergens is not fully understood, although there are studies indicating that this is the case for at least some viruses, notably respiratory syncytial virus (58) and Epstein-Barr virus (59). Animal experiments support the clinical observations, showing an enhanced IgE production after allergen exposure and concomitant viral infection (8,60). Also, it is common knowledge that infections may trigger clinical symptoms in already sensitized individuals and that infections increase bronchial hyperreactivity. It is possible that some infections may under certain circumstances protect against the development of sensitization. As discussed more in detail below, it is

possible that infections may not only facilitate sensitization, but actually downregulate immune responses involving IgE antibodies.

The relationship between bronchiolitis caused by respiratory syncytial virus (RSV) during the first 6 mo of life and the development of asthma was recently studied prospectively in 47 infants (61). For each child, two matched controls were selected, making a study population of 140 participating in the follow-up at 3 yr. Asthma, defined as three episodes of bronchial obstruction verified by a physician, was found in 11 of the 47 children with RSV bronchiolitis (23%) and in only 1 of 93 controls. A positive test for IgE antibodies against a mixture of allergens was recorded in 32% of the RSV children and 9% of the controls ($p = 0.02$). Of particular interest was the observation that among the former children, 6 of 11 children with a family history of allergy developed asthma compared to only 5 of 36 without this family history. Thus, the risk for asthma after RSV bronchiolitis was much higher in infants with a genetic propensity to allergy.

As summarized in ref. 9, *Bordetella pertussis* is of particular interest among the infectious agents, since it is a well-established adjuvant for the induction of IgE antibody formation in experimental animals (62). Furthermore, whooping cough is associated with bronchial hyperreactivity for several months (63). It has also been shown that IgE antibodies to pertussis toxin appear after an infection and after immunization against pertussis (64,65). The latter observation raises the question about a possible role of vaccinations as a risk factor for allergic disease. This notion is further strengthened by the fact that aluminum, which is used as an adjuvant in many vaccines, is also one of the most potent adjuvants for IgE antibody synthesis in animals (66). Properly designed epidemiological studies are needed to clarify a possible relationship between routine immunizations of infants and the development of atopic disease.

Recent Changes in the Environment

The environment has undergone major changes. The discussion on the possible impact of the various environmental changes on the incidence of asthma and other allergies has mostly been limited to the possible effects of a deteriorating air quality, poorly ventilated houses, and an increased exposure to certain allergens, notably house dust mites. "Environment" is much more than emissions from traffic and exposure to mites, however. The concept of "lifestyle" should therefore be expanded considerably (Table 2), since an altered lifestyle also includes dietary changes, the microbial environment, extensive traveling to new environments, stress, and much more.

Any hypothesis trying to explain a decisive connection between a certain environmental factor on one hand and manifestations of atopy

Table 2
Some Examples of Changes in "Lifestyle" and Environment After
the Second World War in Industrialized Countries with a Market Economy

Urbanization	Major changes in habits, exposure to air pollution
Diet	Foods that are new to the area, a wider range of foods, food additives, foods processed by industry, altered intestinal microbial flora
Buildings	New building materials, more efficient insulation, altered methods for construction, construction around the year even in temperate climates
Homes	Larger dwellings, many new compounds at home (chemicals), increased indoor humidity in temperate and cold climates
Lifestyle	Most time spent indoors, extensive traveling, and exposure to new environments

Table 3
Epidemiologic Observations Related to Allergic Diseases of Confirmed
or Likely Significance for the Understanding of Risk Factors in the Environment

General	Sensitization often triggered early in life
Industrialized countries with a market economy	Prevalence higher in urban than in rural areas Prevalence higher in Northern than in Southern Scandinavia Increasing prevalence over the last century, particularly last 30 yr Increase first observed in privileged socioeconomic groups Increase most obvious in children and young adults Regional differences can only in small part be explained by air pollution, respiratory infections, and breast-feeding practice
Developing countries	Highest prevalence among privileged socioeconomic groups Increasing prevalence with increasing industrialization

on the other should accommodate a number of certain or probable facts from previous research (Table 3). It is also necessary to define precisely the relationship, e.g., when and on whom the factor is exerting its effect. It is also necessary to define which outcome variables are studied, e.g., obstruction or asthma according to certain defined criteria, clinical symptoms, or appearance of IgE antibodies. Is there an interaction among several environmental factors?

Geographic Differences

Several studies of individuals belonging to the same ethnic group, but living under different conditions, clearly demonstrate that the incidence of allergic disease is higher in industrialized countries than in

rural areas of developing countries. There are considerable differences in the prevalence of allergy within industrialized countries, i.e., between urban and rural areas. As an example, the relative risk for a positive skin prick test is 70% higher among 11-yr-old children living in a moderately polluted town in northern Sweden than among children living in the neighboring countryside (3,67).

Studies trying to compare the prevalence of atopy in different environments are complicated by the lack of uniform diagnostic criteria and of standardized procedures. Very recently, however, international questionnaire surveys have been implemented that will shortly provide comparative prevalence figures in adults (1) and in children (68).

The reported differences between populations are not genetically determined. Rather, they seem to be explained by differences in living conditions. The results of migrant studies demonstrate a higher prevalence of allergic disease in developing countries in people living under privileged conditions than among the poor. Thus, a low prevalence of asthma was observed in children migrating to Britain from the West Indies with their parents, whereas the prevalence of asthma in the younger children in these families, who were born in Britain, was similar to that of the native British children (18,69). A South African study yielded similar results, in that children of the Xhosa tribe who were born in a rural area had much less asthma and other allergies than Xhosa children raised in Cape Town (70).

The influence of living conditions on childhood asthma has also been noted by a migrant study in the Pacific. Part of the population on the island Tokelau was evacuated to New Zealand. After some years, an increasing incidence of childhood asthma was noted among the people living in New Zealand, whereas the prevalence remained low among those remaining on the island (71).

An understanding of the role of environmental factors has become complicated by some recent observations. Air pollution is a major problem in many formerly socialistic countries in Central and Eastern Europe, yet the prevalence of atopy among children is much lower than in Western Europe. As an example, the prevalence of positive skin prick tests in Leipzig in eastern Germany is less than half of that among children of the same age living in Munich in western Germany (4,72). Similarly, atopic sensitization is much lower in Konin in central Poland (3) and in Estonia (6,73,74) than it is in northern Sweden. Mirroring the observed differences in skin prick test positivity in an urban and rural area of Sweden, the prevalence of at least one positive skin prick test was significantly higher in Tallinn, an industrialized coastal city, than in Tartu, which is an inland university town (Table 4). Thus, although air pollution does seem to play a role in the development of atopy, other factors connected with Western lifestyle are much more important. The nature of these factors is unknown.

Table 4
Prevalence of Positive Skin Tests and Airway Symptoms Among
11- to 12-yr-old School Children in Five Regions Around the Baltic Sea
and the Levels of Certain Common Air Pollutants

	Sweden		Poland	Estonia	
	Urban	Rural	Konin	Tallinn	Tartu
≥1 Pos SPT, %	24.2	35.3	13.7	14.3	8.1
OR	1	1.71	0.49	0.46 ^a	0.28 ^a
Cough > 2 wk, %	5.7	12.0	15.1	18.8	13.8
Resp. inf. >6/yr, %	6.3	8.0	14.0	10.4	10.5
Wheeze, %	0.3	11.6	10.4	9.4	5.8
Asthma diagnosed, %	6.7	9.5	2.9	3.2	2.5
SO ₂ , µg/m ³ , mean	1.9	2.3	17.1	?	?
Range	0.8–3.9	1.0–14.7	4.3–70.9		
NO, µg/m ³ , mean	8.4	19.0	17.5	?	?
Range	1.0–34.8	1.3–66.9	3.9–25.9		
Particles, µg/m ³ , mean	4.9	4.4	32.3	?	?
Range	0–11.2	0–21.2	4.9–99.0		

^aOdds ratio for a positive skin prick test among children in Tallinn (industrialized city) was 1.81 compared to Tartu (university town). ? = Not determined.

The hypothesis that early childhood is a period of particular susceptibility to environmental influences and the onset of the “atopic march” is supported by the studies of Wichmann showing that the large differences between eastern and western Germany in the prevalence of sensitization to inhalant allergens are limited to the age groups born after 1961 (5). Very recently, similar data were obtained in a comparative study between two university towns in Estonia and Sweden (74).

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

The Immunology of Primary Sensitization

In rodents, there are two major types of T-helper cells, i.e., TH-1 and TH-2. It is likely that similar subpopulations exist in humans (75). The TH-1 cells are associated with a lymphokine profile that stimulates, e.g., IgM and IgG antibody formation, while suppressing IgE antibody

synthesis. In contrast, the TH-2-type cells are associated with IgE antibody formation and the appearance of mast cells and eosinophils. Recent development of basic and clinical immunology and the results of several epidemiological studies have given rise to a model for IgE immunoregulation, viz. that the magnitude of the IgE component of antigen-specific immune responses to persistent allergens is ultimately determined by the relative balance between antigen-specific TH-1 and TH-2 cells that become established in relevant T-memory populations.

Animal experiments show that repeated inhalation of an allergen by immunologically naive rat pups usually results in a transient low-level IgE antibody response (Fig. 1). Susceptibility to this form of tolerance induction is genetically determined, but it can be markedly influenced by a range of environmental factors, including chemical air pollutants and also infection. The T-cell responses in rat pups of a strain with the normal low propensity to IgE antibody formation, "low responders," were mostly of the TH-1 type, whereas the TH-2 phenotype dominated in pups of an IgE high responder strain, indicating that the propensity for a certain type of immune response was genetically determined. The ultimate expression of TH profiles was, however, influenced by environmental factors. Thus, the TH-2 responses in the high responder rat pups could be suppressed by exposure to infections and microbial adjuvants concomitantly with the allergen, and by high antigen doses. A switch toward a TH-2 responses could be induced in pups of the low responder strain by simultaneously exposing them to allergen and air pollutants, e.g., tobacco smoke.

It is important to note that it was only possible to induce tolerance in animals via inhalation or ingestion against antigens to which the animals were immunologically naive; i.e., once stable immunological memory is established in the TH-2 population and persistent IgE responses develop, further exposure to the relevant antigens only further boosts the ongoing responses. Additionally, this form of tolerance is preferentially directed against IgE, since the animals typically manifest IgG responses against the same allergens (76).

The data accumulating on cytokine regulation of IgE synthesis in humans are broadly consistent with the major predictions from the animal models. The human immune system appears to begin responding to ubiquitous inhalant allergens in early infancy. There are also indications that blood mononuclear cells from infants with a family history of allergy have less capacity to produce IFN γ , which would support a less efficient induction of TH-1-type responses in them (2,19,77). Furthermore, infants who develop allergic disease during their first 18 mo of life have elevated serum levels of IL-4, which is the major cytokine from TH-2-type cells (28).

The clinical relevance of the data generated in animal studies is further supported by some data from epidemiological studies. These

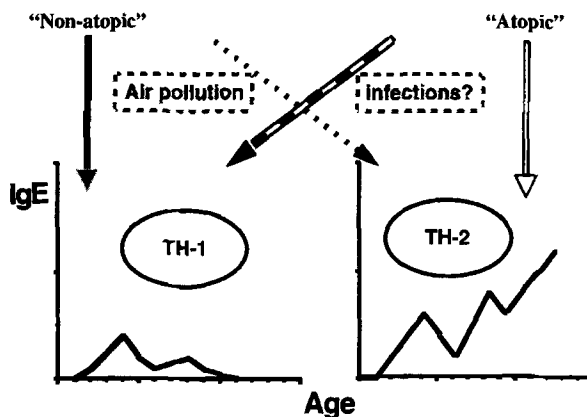


Fig. 1. Suggested difference between the primary immune response to inhaled allergens in nonatopic and atopic individuals. The hypothesis is based on studies in rat pups of two strains of rodents with either a high or a low propensity to IgE antibody formation. In both strains, the pups express a temporary low-level IgE antibody formation on exposure to an allergen. In the pups of the low, but not the high, responder strain, the antibody formation is suppressed by subsequent exposures to the allergen. This suppression can be inhibited by the simultaneous exposure to certain air pollutants. Similarly, a suppression of the IgE antibody formation can be achieved in the pups of the high responder strain by an infection or by exposure to very high levels of antigen.

studies lend some support to the notion that recurrent infections in infancy could protect against sensitization to inhalant allergens.

The kinetics of humoral antibody responses to food antigens and inhalant allergens in infants and young children lend further support to the relevance of the animal model. Thus, IgG antibodies to ubiquitous environmental antigens appear very early in life, and remain detectable in serum from the majority of both atopic and normals throughout life (7). The picture for IgE antibodies is markedly different, however. Prospective analysis of serum IgE levels to environmental allergens in individual children indicates that antibodies to foods are commonly detected both in atopic and nonatopic infants during the first year of life, although the magnitude of the responses is higher and of longer duration in the former (72,78). In virtually all children, however, these initial IgE responses to foods are terminated spontaneously by age 2–4 yr, leaving intact IgG responses to the same antigens that persist into adulthood. In support of these findings, transient skin test reactivity to food allergens is also common during this period (79).

The pattern for IgE responses to ingested and inhaled allergens differs in at least two significant aspects. First, the latter responses rarely appear until after 1 yr of age, i.e., at a higher age than the IgE responses to foods. Second, whereas IgE responses against foods do not

usually persist beyond early childhood, a much larger proportion of children continue to produce IgE antibodies against one or more inhalant allergens into adulthood. The induction of antibody responses to both groups of allergens appears to be induced very early in life, however.

The Role of Infections Reassessed

The clinical observations, data from epidemiologic studies, and animal experiments summarized in the previous section all suggest that the conditions under which exposure against ubiquitous environmental allergens take place in early childhood may have consequences for many years, perhaps even for life (7,9,80). In light of these studies, the role of respiratory tract infections in early childhood has been partly reassessed. Thus, an infection at the time of primary sensitization of rat pups may result in the suppression of IgE antibody responses owing to a preferential TH-1-type immune response (7). Epidemiological studies lend some support to a reassessment of the role of infections. For example, the number of siblings (81), particularly older siblings (82,83), and crowded living conditions (73) have all been reported to be associated with less atopic disease. Furthermore, data from a Japanese study indicate that there may exist an inverse relationship between allergic disease and S-IgE levels and positive skin reactions to tuberculin in school children (83a).

Prevention

A great interest has been taken over the past 10 yr in the possibility of preventing allergic disease, notably asthma, by primary prevention, i.e., by avoiding sensitization in early life. Since some newborn babies who will develop allergic disease can be identified already at birth by an elevated level of IgE in cord blood, the possibility has been discussed that sensitization may take place already during fetal life. The IgE antibodies in cord serum seem more to be the consequence of nonspecific spontaneous IgE synthesis, however, than of antigen stimulation. This notion would be supported by the negative outcome of randomized studies of manipulation of the maternal diet during pregnancy (79,84–88). On the other hand, antigen-specific T-cell responses have been recorded in cord blood (33,34). These studies did not, however, control for several alternative possibilities, and they are therefore not conclusive. The possible role of intrauterine sensitization therefore remains an open question.

The efforts for postnatal prevention have been focused on various allergen-avoidance procedures, including administration of infant formulas with reduced allergen content. The original hypothesis for the

allergy preventive efforts was that allergic disease could be avoided by preventing the onset of the "allergic march" in early infancy. Thus, by preventing the development of food allergy and eczema in early life, the later onset of asthma and then allergic rhino conjunctivitis would be avoided. Recent, prospective studies of infants with a genetic propensity to allergic disease have not confirmed this hypothesis. In these studies, exposure to allergenic foods during the first months of life, notably cow's milk and egg, was avoided (31,78,84,89). The mothers of breast-fed babies adhered to a diet free from cow's milk, eggs, and certain other allergenic foods, and any supplementary feeding to the babies was in the form of extensively hydrolyzed products with low allergenicity. The dietary manipulation of breast-feeding mothers and infants was associated with a lower incidence of allergic manifestations and demonstrable IgE antibodies to foods. The effect was, however, limited to the first year or possibly first two years of life and to eczema, whereas the incidence of respiratory symptoms and later-appearing allergic manifestations was not affected. The results are not surprising in light of the more recent knowledge concerning the primary sensitization discussed above. The experimental studies discussed in the previous section clearly indicate that the effects of avoidance of exposure to allergens during the period of particular susceptibility in early life are antigen-specific. Thus, dietary restrictions would not be expected to have an effect on sensitization to inhaled allergens, or to reduce the incidence of sensitization to food antigens not avoided. The conclusion from a practical point of view would be that the various "hypoallergenic" infant formulas, some of which should not even be regarded as "hypoallergenic," do not represent a major improvement in the search for effective allergy prevention. At best, they would only be expected to reduce the incidence of cow's milk allergy in infants, provided truly hypoallergenic preparations are used. To avoid sensitization to other allergens, each of them has to be avoided. Thus, to prevent allergic asthma, either all important inhalant allergens should be avoided or adjuvants for sensitization should be avoided. Neither of these is easily achieved.

Concluding Remarks

The prevalence of allergies is increasing in many countries, and the increase appears mostly to be a consequence of the lifestyle that is characteristic of Western industrialized countries. The major lifestyle and environmental factors are probably exerting much of their influence during the first few years of life. Figure 2 depicts schematically the "allergic march" and where primary, secondary, and tertiary preventions are instituted. Numerous risk factors have been identified, all of

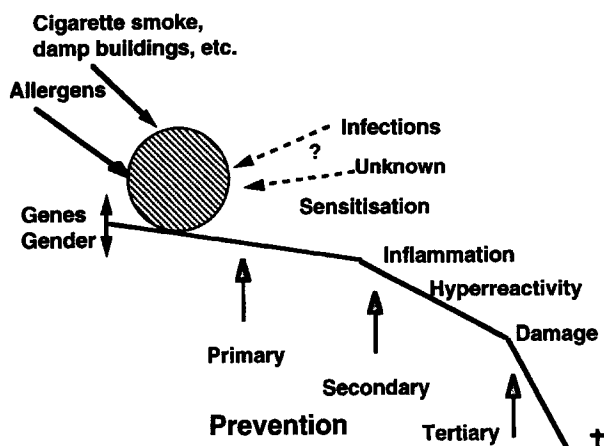


Fig. 2. Allergic sensitization and manifestations of disease are the end result of an interaction between various environmental influences and a genetically determined propensity for allergy. The likelihood for the process to begin is determined by the genetic propensity to allergy and to some extent by sex (boys are more susceptible).

which can influence the likelihood for sensitization and to trigger symptoms in already sensitized individuals. Even if they are all taken together, however, they cannot explain the large geographic differences in the prevalence of allergy. The conclusion from a broad compilation of what is known regarding triggers of allergy is that we cannot identify which environmental factors are the major reasons for the large increase in the prevalence in recent years. We can, however, make a list of various conditions that are not of major significance. The future search for significant environmental factors should be directed toward other areas that have not yet been explored. Future research should be truly interdisciplinary and "lifestyle" should be given a broad interpretation.

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