

Review article

What drives the allergic march?

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The “allergic march”, which refers to the natural history of *atopic* diseases, is characterized by a typical sequence of sensitization and manifestation of symptoms which appear during a certain age period, persist over years or decades, and often show a tendency for spontaneous remission with age.

“Atopy” refers to those allergic conditions which tend to cluster in families, including hay fever, asthma, and eczema, and which are associated with the production of specific IgE antibodies to common environmental allergens. Sensitization may or may not be relevant to the induction of clinical symptoms, which by themselves are characterized by inflammation, corresponding to hyperresponsiveness of the skin or mucous membranes.

Epidemiologic studies of atopic diseases have received much attention over the past decade.

Cross-sectional studies such as the International Study of Asthma and Allergies in Children (ISAAC) have provided evidence of remarkable differences in the prevalence of certain atopic phenotypes in children aged 6 and 13 years between continents and countries and even within countries (1, 2).

Sequential cross-sectional studies using a standard questionnaire suggest that the prevalence of some of these phenotypes in defined age groups is truly increasing, and is not simply explicable by an increase in awareness or a change in diagnostic methods (3, 4).

Longitudinal follow-up studies including cohorts from birth such as the Tucson Study on Asthma (USA) (5) or the Multicenter Allergy Study in Germany (6, 7) have been designed to clarify the natural history of the disease; to describe associations between phenotypes and genetic, environmental, or lifestyle factors; and to generate hypotheses for causal relationships.

Intervention studies have been conducted to assess the role of different environmental factors in the UK (8), Germany, The Netherlands, Canada, and Australia.

It is to be hoped that these studies will not only contribute to a better understanding of the genetic and environmental factors that regulate early immune responses to allergens and the development of symptoms, but will also lead to more rational strategies for primary and secondary prevention.

One of the important implications of the epidemiologic data so far available is that it is obviously useful to disentangle various phenotypes and focus on single manifestations at a certain age window, since different specific phenotypes (clinical symptoms, sensitization, total serum IgE, etc., at a certain age) may be induced or modulated by different genetic, environmental, or lifestyle factors. Although most investigators seem to agree that a complex interaction between genetic and environmental factors regulates the manifestation and development of different atopic features, much of the natural history of atopy and asthma and its determinants is still not well understood.

Criteria for causal inferences

The following general criteria were accepted in order to assess the effect of specific exposures or other lifestyle-related factors that cannot be randomly assigned (randomized) by investigators, as published in a report by the US Department of Health and Education in 1964 (9).

- 1) *Strength of an association.* The stronger the observed association, the less likely it is that the association is entirely due to various sources of error.

- 2) *Dose-response effect.* The observation that the frequency of a disease increases with the dose or level of exposure usually lends support to a causal interpretation.
- 3) *Lack of temporal ambiguity.* It is important to demonstrate that the hypothetical causes preceded the occurrence of the disease.
- 4) *Consistency of the findings.* All studies dealing with a given relationship produce similar results, so that a causal interpretation is enhanced.
- 5) *Biologic plausibility of the hypothesis.* If the hypothetical effect makes sense in the context of current biologic knowledge, we are more likely to accept a causal interpretation.
- 6) *Coherence of the evidence.* A causal interpretation is strengthened if the findings do not seriously conflict with our understanding of the natural history of the disease or with other accepted facts about disease occurrence.
- 7) *Specificity of the association.* A causal interpretation is suggested if the study factor is found to be associated with only one disease or if the disease is found to be associated with only one factor.

There is a *hierarchy of evidence* that can be extracted from differently designed studies. As far as causal inferences are concerned,

- 1) cross-sectional surveys and case-control studies are able to *generate hypotheses*
- 2) prospective longitudinal cohort studies without intervention are *more suggestive* in describing a time sequence between potential causes and the health effect
- 3) controlled longitudinal intervention studies, whenever applicable and acceptable, provide information with *the greatest relative weight*.

The natural history of atopic diseases

Although wide individual variations may be observed, atopic diseases tend to be related to the first decades of life, and obviously require a juvenile immune system. In general, no clinical symptoms are detectable at birth (Fig. 1), and although the production of IgE antibodies is possible from the 11th week of gestation, no specific sensitization to food or inhalant allergens as measured by elevated serum IgE antibodies can be detected with standard methods.

During the first months of life, the first IgE responses to food proteins develop (Fig. 2a), particularly those to hen's egg and cow's milk (10). Even in completely breast-fed infants, high amounts of specific serum IgE antibodies to hen's egg may be detected. It has been proposed that exposure to hen's egg proteins occurs via the mother's milk, but this needs further clarification.

Sensitization to environmental allergens from indoor and outdoor sources (Fig. 2b and c) requires more time

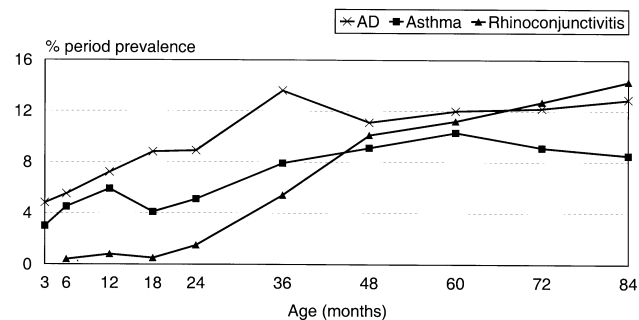


Figure 1. Development of atopic dermatitis (AD), asthma, and allergic rhinoconjunctivitis with age. Data from German Multicenter Atopy Study (7).

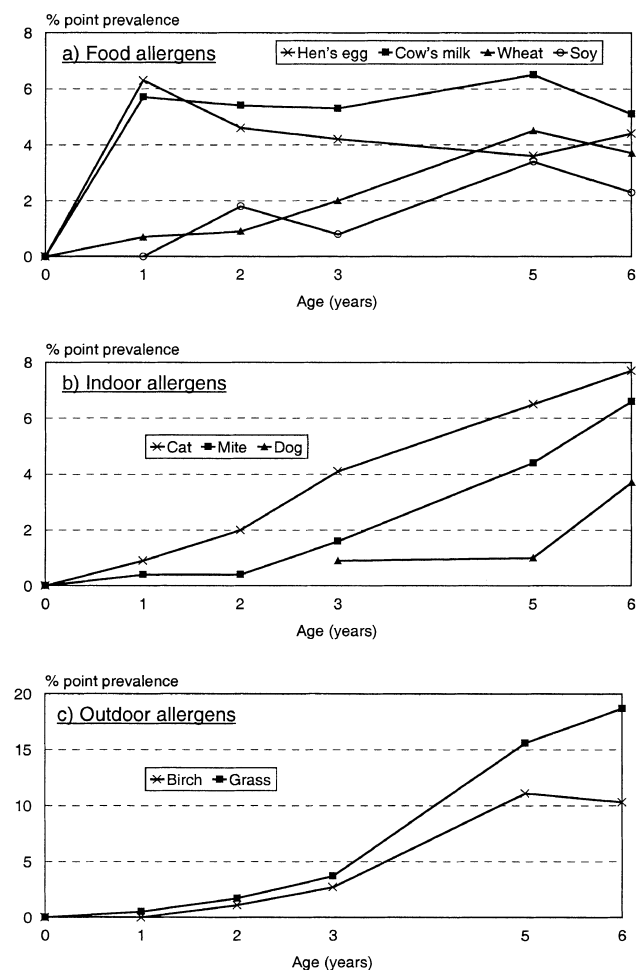


Figure 2. Point prevalence of sensitization to food (a), indoor (b), and outdoor (c) allergens in German children. Data from MAS cohort study with estimates for original population-based sample of 4882 children (cutoff level for serum specific IgE 0.7 kU/l) (10).

and is generally observed between the first and tenth birthdays. The annual incidence of early sensitization depends on the amount of exposure. In a longitudinal birth cohort study in Germany (MAS), a dose-response relationship could be shown between early exposure to cat and mite allergens and the risk of sensitization during the first years of life (Fig. 3).

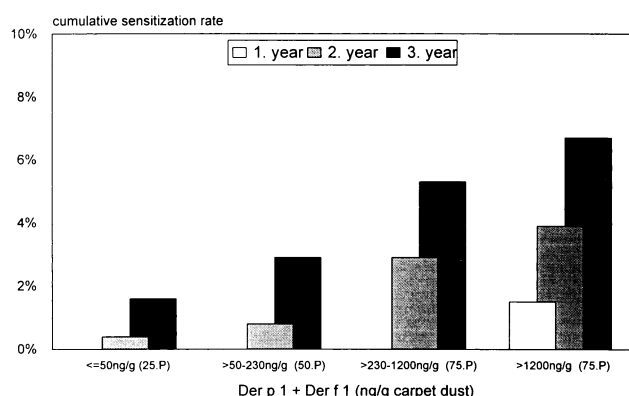


Figure 3. Early exposure to major allergens of *Dermatophagoides pteronyssinus* (Der p 1) and *D. farinae* (Der f 1) and specific sensitization at ages of 1, 2, and 3 years (6).

Hereditary factors

It has been known for many years that atopic diseases run in families. The risk of neonates developing atopic symptoms during the first two decades of life strongly depends on the manifestation of the disease in their parents and siblings. Already at the phenotype level, it is obvious that there is a closer association between specific disorders such as asthma or atopic dermatitis in the child and the same manifestations in parents or siblings than with other atopic manifestations in the family (11). These clinical observations already suggest the presence of phenotype-specific genes.

Although the role of the family history, which was studied in the 1970s by Kjellmann & Croner (21), is undoubtedly strong, the majority of children developing atopic dermatitis or asthma during the first years of life in a country such as Germany had been born into families without any manifestation of atopic disease (Fig. 4). Therefore, the majority of prospectively affected children will not be identified at birth by family history.

During the last two decades, molecular genetic studies have been performed for various allergic diseases including asthma. They were stimulated by the assumption that atopic phenotypes might become preventable once the precise recognition of genetically predisposed children was possible.

Various genes predisposing to atopy have since been identified, influencing specific IgE responses to particular allergens, as well as the bronchial tone or bronchial hyperresponsiveness and non-IgE-mediated inflammation.

Two approaches are being applied in order to identify genes related to disease:

- 1) Positional cloning in which the entire genome is screened with a panel of polymorphic DNA markers. This method tries to demonstrate the genetic linkage of a certain phenotype and genetic markers of known chromosomal localization.

- 2) Examination of candidate genes which are already known to be involved in the pathophysiologic mechanism contributing to a certain phenotype. The role of candidate genes may be assessed by defining polymorphisms within the respective genes and testing for associations with the disease.

A linkage of atopy to the chromosomal region 11q13 was first reported by the Oxford group of Cookson et al. in 1989 (12, 13).

Marsh et al. (14) found in Amish families a linkage between total IgE levels and several markers in the 5q23–31 region, which contains genes coding for IL-3, IL-4, IL-5, IL-9, IL-12B, and IL-13 as well as the glucocorticoid receptor and the β_2 -adrenergic receptor.

Barnes et al. (15) have recently reported the linkage of asthma and total serum IgE concentrations on chromosome 12q in Afro-Caribbean families. In this region, the genes for interferon-gamma and stem-cell factor are present. In the German MAS cohorts, a linkage was found to high total serum IgE concentrations during the first 3 years of life at D12S 379 (16).

The human major histocompatibility complex (MHC) includes genes coding for HLA class II molecules, which are involved in the recognition and presentation of exogenous peptides. An HLA influence on specific IgE responses to a minor ragweed antigen (Amb AV) was described already in 1982 by Marsh et al. (17). Like the human MHC, the T-cell receptor has become a candidate for studies investigating the linkage between IgE responses and microsatellites from certain regions of one of the chains.

From the genetic studies published so far, it can be concluded (18, 19) that

- 1) both asthma and other allergic diseases are genetically heterogeneous disorders
- 2) each of the atopic phenotypes is probably the result of a polygenic inheritance and a complex interaction between genes and environmental factors.

In contrast to single-gene disorders in asthma and atopic phenotypes, there may be a dissociation of genotype and phenotype, whereby genes may increase the susceptibility but not necessarily lead to full disease expression (20). Currently, whole genome screen studies are under way, focusing on different atopic phenotypes, including asthma; if fruitful, these studies will contribute to the identification of individuals at risk, who might become candidates for primary prevention measures, as well as of individuals who may respond to certain therapeutic interventions in the future.

Early immunologic markers

An obvious prerequisite for effective primary prevention measures is the ability to predict which individuals will develop atopic disease. Therefore, it would be highly

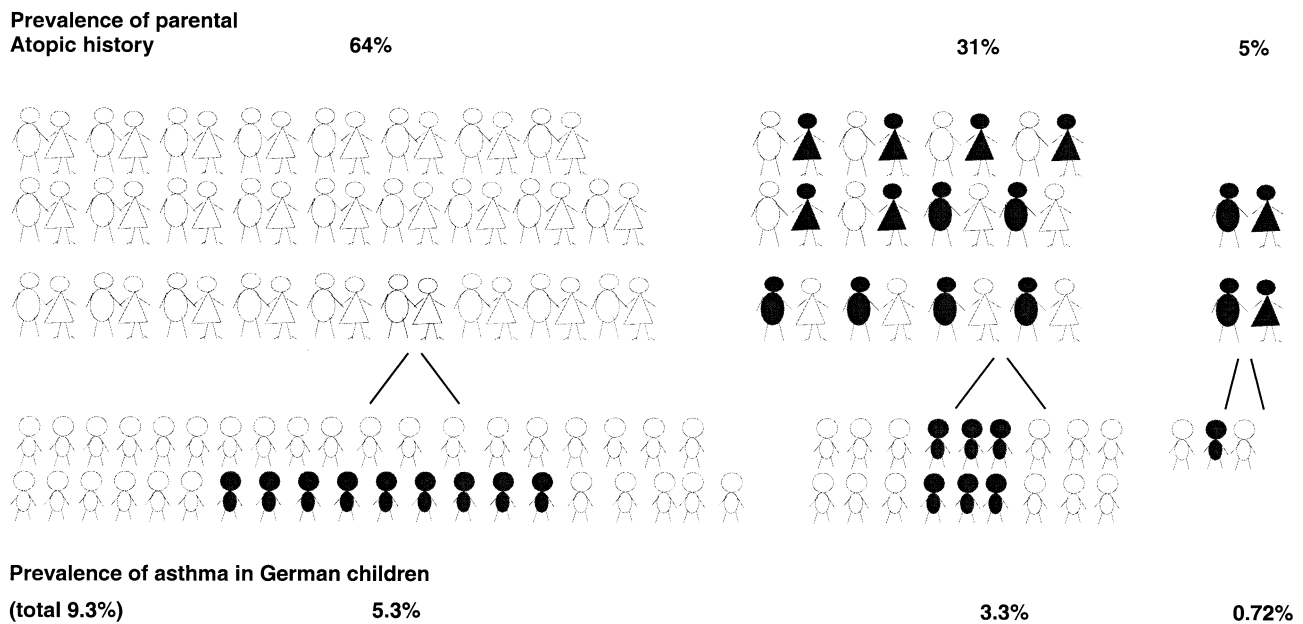


Figure 4. Population-based lifetime prevalence of asthma in German children at 5 years of age in relation to parental history of atopy (5).

desirable, if no genetic markers are available, to have access to immunologic markers capable of identifying individuals at risk before the process of sensitization has been induced or the disease has become manifest. The production of IgE is known to be largely genetically controlled. Therefore, the measurement of IgE concentrations in cord blood, which was first investigated by Kjellmann & Croner (21), was at first thought to be a useful screening test (22). Unfortunately, more recent studies have shown that neither the sensitivity, the specificity, nor the predictive value of cord-blood IgE measurements is acceptable for use of this factor as a screening test. Using data from the German MAS study, Edenharter et al. (23) were recently able to demonstrate that elevated cord-blood IgE concentrations can predict early sensitization, but not airway or skin symptoms.

As far as the prediction of asthma is concerned, eosinophils and their mediators (eosinophil cationic protein [ECP], eosinophil peroxidase, and eosinophil protein X) have been studied in infancy in order to identify individuals who are developing chronic disease. In a Norwegian cohort study, wheezing infants had significantly higher levels of serum ECP than controls (24). Whether concentrations of mediators from eosinophils also predict the chronic disease process remains to be shown. Pohunek et al. (25) studied eosinophils in bronchial biopsies and suggested that increased numbers of eosinophils are a risk factor for chronic asthma.

Recently, several groups have studied the *in vitro* response of fetal or cord-blood peripheral blood mononuclear cells to allergens or mitogens with respect to later development of atopic disease (26–29). It was

shown that fetal T cells have the capacity to respond on incubation with allergen, and that there are differences in immune responses between those infants who develop atopic disease later, and those who stay healthy. The risk of developing atopic disease is obviously associated with a reduced capacity to secrete interferon-gamma after PHA stimulation at birth. Martinez et al. were able to demonstrate that low TH1 cytokine production at 12 months was associated with atopic sensitization to inhalant allergens at 6 years of age (30).

In a small birth cohort study, Prescott et al. measured mononuclear cell-proliferative and cytokine responses to specific allergens every 6 months from birth to 2 years of age. They demonstrated a continuation of fetal allergen-specific TH2 response during infancy, and a decreased capacity for production of the TH1 cytokine interferon-gamma in those children who subsequently developed atopic disease (31, 32).

From the data published so far, it appears unlikely that immunologic markers obtained during the neonatal period might serve as predictors for atopic disease in the near future. Nevertheless, these observations are leading to a better understanding of the mode of immunodeviations which facilitate the manifestation of atopic disease.

As long as we lack genetic and immunologic markers as potential predictors for atopic diseases, primary prevention of atopy will be difficult to achieve.

Several groups, including our own, have reported elevated serum IgE antibodies to hen's egg proteins as predictors of subsequent sensitization to aeroallergens and to the development of allergic airway symptoms (33, 34). These findings might become important in strategies for secondary prevention, since infantile IgE responses

to hen's egg are observed very early, generally during infancy.

Environment and lifestyle

During the last decade, a number of environmental and lifestyle factors have been found to be significantly associated with certain atopic phenotypes. Whether these associations are of biologic relevance needs to be demonstrated by longitudinal intervention studies. The evaluation of certain factors has turned out to be particularly complex, since several factors such as smoking, breast-feeding, or pet ownership have to be considered surrogate markers of socioeconomic status.

Allergen exposure

No other environmental factor has been studied as extensively as exposure to environmental allergens as a potential risk factor for sensitization and manifestation of atopy and asthma (35, 36). From a number of cross-sectional studies (37, 38) performed in children and in adults, it has become obvious that there is a close association between allergen exposure, particularly in the domestic environment, and sensitization. Longitudinal studies such as the MAS study in Germany (6) have clearly demonstrated that during the first years of life, there is a dose-response relationship between indoor allergen exposure to dust-mite and cat allergens and the risk of sensitization.

However, as far as the manifestation of atopic dermatitis (39) and asthma is concerned, the situation is much less clear. Earlier studies performed by Sporik et al. (40) suggest that in sensitized children exposure to dust-mite allergens determines not only the risk of asthma, but also the time of onset of the disease. More recent investigations by the same group, however, suggest that factors other than allergen exposure are important in determining which children develop asthma (41).

In a comprehensive meta-analysis, Peat & Li (42) have evaluated several environmental factors said to be responsible for the incidence and severity of atopic diseases, particularly asthma. Comparing the strength of the various effects, they concluded, on the basis of the literature, that indoor allergen exposure is the environmental factor with by far the strongest impact on the manifestation of asthma.

In recent years, however, the hypothesis that exposure *induces* asthma with airway inflammation via sensitization has been challenged; in several countries, the prevalence of asthma in children has been increasing independently of allergen exposure (43, 44). Clearly, at least in genetically manipulated mice, allergic sensitization, i.e., the production of specific IgE antibodies, is regulated differently from the manifestation of disease

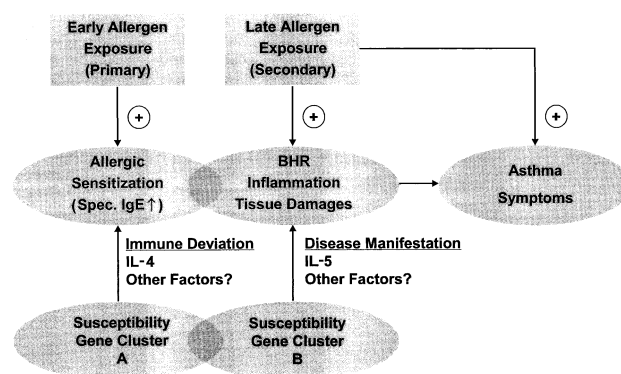


Figure 5. Diagram of hypothetical role of genetic factors and environmental allergen exposure in specific sensitization and development of asthma.

and airway inflammation: while IL-4 has been shown to be a cytokine crucial for the process of sensitization, other cytokines, particularly IL-5, obviously play a central role in the pathogenesis of asthmatic inflammation (45). Fig. 5 summarizes a hypothesis of the role of genetic factors, and early as well as late allergen exposure, in sensitization and the development of asthma.

A number of intervention studies are currently being performed (8), in cohorts followed prospectively from birth, on the effect of indoor allergen elimination on the incidence of asthma. Their results will have a strong impact on public health policies, since they will determine whether it is meaningful to consider indoor allergen elimination an important element of primary prevention of various atopic manifestations. But even if it turns out that other factors play a major role in determining whether the atopic child will develop asthma, so that allergen elimination as a measure of primary prevention is ineffective, the reduction of allergen exposure will still remain a very important element in secondary prevention for allergists and chest physicians.

Adjuvant factors

The interest of epidemiologists and experimental researchers has been attracted by several environmental factors which, though not acting as allergens, are capable of upregulating existing IgE responses or leading to either disease manifestation or an aggravation of symptoms. After guinea-pig and mouse experiments suggested an increase of allergic sensitization to ovalbumin after experimental exposure to traffic- or industry- related pollutants (46, 47), a strong association between allergic rhinitis caused by cedar-pollen allergy and exposure to heavy traffic was reported from Japan (48). Important sociodemographic confounders turned out to be a problem in this study. Other investigators were unable to describe any relationship between traffic exposure and the prevalence of hay fever or asthma (49). The role of tobacco smoke, a complex mixture of

various particles and organic compounds, has been extensively studied (50, 51). The studies which have recently been reviewed (52, 53) consistently demonstrate that the risk of lower airway diseases, such as bronchitis, recurrent wheezing in infants, and pneumonia, is increased. Whether passive tobacco smoke exposure is causally related to the development of asthma is still disputed.

As far as the risk of sensitization is concerned, until recently there was a lack of data. The prospective birth cohort study MAS in Germany reported that an increased risk of sensitization was found only in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth. In this subgroup of the cohort, a significantly increased sensitization rate with IgE antibodies to food proteins, particularly hen's egg and cow's milk, was observed only during infancy, whereas sensitization rates later were not different from those of children who had never been exposed passively to tobacco smoke (54). These observations might be related to the fact that in children the highest urinary cotinine concentrations are detected during the first years of life, when the child spends most of the time close to the mother.

Lifestyle and the development of atopic disease

Recently, new hypotheses have been generated by epidemiologic surveys, some of them backed up by animal experimental studies, which consider more general, lifestyle-related environmental factors.

In view of the fact that the risk of atopic sensitization and disease manifestation early in life is particularly high in Western, industrialized countries with relatively high standards of living, and that within these countries socioeconomic variations (55, 56) and the prevalence of atopy are evident, one may ask what factor related to Western lifestyle might be responsible for increasing the susceptibility to atopic sensitization. In addition, recent studies of Swiss, Bavarian, and Austrian children have shown that the prevalence of symptoms of allergic rhinitis and of allergen-specific IgE antibodies is much lower among the offspring of farmers than among other children in these areas (57). In a recent Swedish study (58), the prevalence of atopy in children from anthroposophic families was found to be lower than in children from other families, a finding which led the authors to the conclusion that lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Several studies focusing on differences between the former socialist countries and Western European societies reported lower prevalence rates for atopy in the former socialist countries, a finding which was particularly striking in areas with little genetic difference such as East and West Germany. These studies found that the critical period during which lifestyle mainly influences

the development of atopy is probably the first years of life (59).

The lifestyle factors which have been proposed so far

The hypothesis which has attracted the most interest is the proposal that a decline in certain childhood infections or a lack of exposure to infectious agents during the first years of life, a factor which is associated with smaller families in the middle-class environment of industrialized countries, could have caused the recent epidemic of atopic disease and asthma (60, 61). Although this area is obviously very complex, several pieces of information appear to support this concept.

Infections are known to have long-lasting, nonspecific systemic effects on the nature of the immune response to antigens and allergens (62). For example, recovery from natural measles infection reduces the incidence of atopy and allergic responses to house-dust mites to half that seen in vaccinated children (62). Obviously, the fact that certain infections induce a systemic and nonspecific switch to Th1 activities could be responsible for an inhibition of the development of atopy during childhood (64–66).

Prenatal or perinatal bacterial infections should also be taken into account as potential modulators of the atopic march. In many cases, preterm birth is now understood as the result of bacterial infections during pregnancy. Therefore, the observation that very low-birth-weight infants have a lower prevalence of atopic eczema is consistent with this concept (67).

Another aspect was recently discussed in an editorial by Björkstén, who pointed out that the intestinal microflora might well be the major source of microbial stimulation of the immune system in early childhood (68). The intestinal microflora could also enhance Th1-type responses (69–72). The results of a comparative study of Estonian and Swedish children demonstrated that there are indeed differences in the intestinal microflora. In Estonia, the typical microflora includes more lactobacilli and fewer clostridia, a condition which is associated with a lower presence of atopic disease (73).

Intervention studies are needed to demonstrate the relevance of these findings and to examine the effect of adding probiotics to infant formulas. In one recently published study from Finland, infants with milk allergy and atopic dermatitis had milder symptoms and fewer markers of intestinal inflammation if their milk formula was fortified with lactobacilli (74).

Observations from Japan suggesting that positive tuberculin responses in children predict a lower incidence of asthma, lower serum IgE levels, and cytokine profile bias toward the Th1 type (75) were supported by animal experiments which demonstrated that the IgE response to ovalbumin in mice could be downregulated by a previous infection with BCG (76, 77).

Although these observations on the relationship between immune responses to infectious agents and atopic sensitization and disease expression are quite stimulating and challenging, conclusions regarding their relevance to the atopic march should be drawn with caution. In different parts of the world, completely different infectious agents have been investigated in different study settings. It appears to be quite fashionable to support Rook & Stanford (66), who entitled a recent review article in *Immunology Today*, "Give us this day our daily germs", but, the question is, which germ at what time under which circumstances, and what is the price we have to pay? Pediatricians should certainly not question most successful immunization programs such as that for measles.

Other lifestyle-related factors

Obviously, the list of lifestyle-related factors which might be associated with the imminent epidemic of the 21st century and might have relevance to the atopic march in children is long. Obesity has recently been proposed to be such a factor (78, 79), since some studies have found it to be associated in the USA with certain types of childhood asthma. If obesity and asthma really are associated, we still have the question of whether asthma can cause obesity, or vice versa. Or are they both explained by a common cause such as immobility and the fact that children tend to watch television longer nowadays, as suggested by Platts-Mills? (personal communication).

Recent reports describe an association of the use of antibiotics during the first 2 years of life with an increased risk of asthma. Finally, the hypothesis has been proposed that the use of omega3 instead of 6

dietary fatty acids in certain populations might cause an increased risk of allergic inflammation. Both hypotheses deserve attention, but, at this stage, preventive advice should not be based on them.

Principles for prevention today

From the data collected on the recent trends in the prevalence of atopic disease and the potential determinants which are involved, only the following principles regarding primary and secondary prevention remain and should be put into action for public health:

- 1) Since no good predictor beside positive family history is available to identify children at risk, we should propose only primary prevention measures which are suitable for everybody: breast-feeding in infancy and introduction of solid food after the fourth month of life, and the avoidance of smoking and passive smoke exposure of children should be recommended to everybody for good reasons.
- 2) For children from high-risk families, low indoor allergen levels are still to be recommended in spite of doubts of the efficacy of this measure in order to decrease the risk of atopic sensitization. Whether or not this will decrease the incidence of asthma remains to be shown.
- 3) For secondary prevention, allergen avoidance in the domestic environment is an intervention of first choice. In addition, a smoke-free environment should be established.
- 4) Moreover, under certain circumstances, early pharmacotherapy, as well as early immunotherapy, may be useful to prevent the progression of the disease.

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