

Childhood risk factors for atopy and the importance of early intervention

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The increasing prevalence of atopic diseases, particularly atopy-associated asthma, has become a major challenge for allergists and public health authorities in many countries. The understanding of the natural history of the atopic march, including the determinants that are modifiable and might become candidates for preventive intervention, is still very limited. Information provided by cross-sectional studies can only generate hypotheses, which need to be supported by prospective, longitudinal, cohort studies. Ultimately, it will depend on the results of well-controlled intervention studies to identify which nutritional, environmental, or lifestyle-related factors should be considered for early intervention and might be useful to reverse the epidemiologic trend. (*J Allergy Clin Immunol* 2001;107:567-74.)

Key words: Atopy, prediction, prevention, epidemiology, atopic march, asthma

Atopic diseases, such as hay fever, asthma, and eczema, are allergic conditions that tend to cluster in families and are associated with the production of specific IgE antibodies to common environmental allergens. The process of sensitization may or may not be associated with the induction of clinical symptoms that by themselves are characterized by inflammation, corresponding to hyperresponsiveness of skin or mucous membranes.

The term *atopic march* refers to the natural history of atopic manifestations, which is characterized by a typical sequence of IgE antibody responses and clinical symptoms (Fig 1)¹ that appear during a certain age period, persist over years and decades, and often show a tendency for spontaneous remission with age.²

Epidemiologic studies of the development of atopic diseases and their determinants have received much attention over the past decade:

- Cross-sectional studies, like the International Study of Asthma and Allergies in Children, have provided evidence for remarkable differences in the prevalence

of certain atopic phenotypes, including asthma, in children aged between 6 and 13 years between continents and countries and even within countries.^{3,4}

- Repeated cross-sectional studies using a standard questionnaire and, in some studies, objective measures of bronchial hyperresponsiveness and atopy suggest that the prevalence of some of these phenotypes in defined age groups is increasing, which is only in part attributable to changes in public awareness and diagnostic habits.^{5,6}

- Longitudinal follow-up studies, including birth cohorts, such as the Children's Respiratory Study in Tucson or the Multicenter Allergy Study (MAS) in Germany, 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.^{1,7,8}

- Few intervention studies to assess the role of various environmental factors have been conducted.⁹

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 and, in case of consistent findings across numerous studies, to suggest causal relations, particularly if dose-response patterns can be observed.
2. Prospective longitudinal cohort studies without intervention are more suggestive in describing a time sequence between potential risk factors and health effects.
3. Controlled longitudinal intervention studies, whenever applicable and acceptable, provide the most useful information.

One of the important messages from the epidemiologic data thus far available is that it is obviously meaningful to disentangle various atopic phenotypes (Table I) and focus on single manifestations in certain age windows because different specific phenotypes may be induced or modulated by different genetic, environmental, or lifestyle factors in various ways.

It is obvious that a prerequisite for any intervention aiming at the prevention of atopic manifestations is the identification of nongenetic determinants, such as exposure to environmental factors, food, or lifestyle-related factors, which are modifiable on an individual basis or as a result of public health measures.

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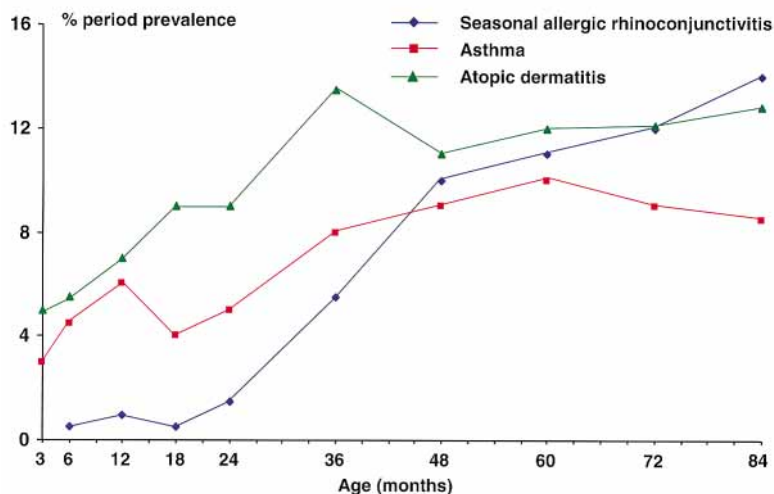


FIG 1. Development of atopic dermatitis, asthma, and allergic rhinoconjunctivitis with age. Data obtained from the German multicenter atopy study.¹

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 thereby to the maturation of the immune system. In general, no clinical symptoms are detectable at birth, and although the production of IgE starts in the eleventh week of gestation, no specific sensitization to food or inhalant allergens, as measured by elevated serum IgE antibodies, can be detected in cord blood with standard methods.

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

Sensitization to environmental allergens from indoor and outdoor sources requires more time and is generally observed between the first and tenth year of life. 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.⁸

It has recently been demonstrated that strong infantile IgE antibody responses to food proteins have to be considered as markers for atopic reactivity in general and are predictors of subsequent sensitization to aeroallergens.¹⁰

As far as clinical symptoms are concerned, atopic dermatitis in general is the first manifestation, with the highest incidence during the first 3 months of life and the highest period of prevalence during the first 3 years of life (Fig 1).

Seasonal allergic rhinoconjunctivitis is generally not observed during the first 2 years of life, although a minority of children will have specific IgE antibodies during this early period. Obviously, at least 2 seasons of pollen allergen exposure are required before classical

seasonal allergic rhinoconjunctivitis with typical symptoms in association with specific serum IgE antibodies becomes manifest.

Asthmatic wheezing may already be observed during early infancy. The majority of early wheezers turn out to be transiently symptomatic, whereas a minority may persist throughout school age and adolescence.⁷ Still, our understanding of the natural history of childhood asthma is limited, and numerous data sets support the existence of various asthma subtypes in childhood. During the first 3 years of life, the manifestation of wheeze is not related to elevated serum IgE levels or specific sensitization, and a positive parental history of atopy and asthma seems to be of minor importance during the first 2 years of life. Those who have persistent wheezing show an increasing association with sensitization to aeroallergens with age.¹¹ In addition, the association with a positive family history for atopy and asthma in first-degree relatives becomes more and more obvious.

HEREDITARY FACTORS

It has been known for many years that atopic diseases run in families.¹² The risk of neonates having atopic symptoms during the first 2 decades of life strongly depends on the manifestation of the disease in their parents and siblings. At the phenotype level, it is already obvious that there is a closer association between specific symptoms, such as asthma or atopic dermatitis, in the child and the same manifestation in parents or siblings than with other atopic manifestations in the family. These clinical observations already suggest the presence of phenotype-specific genes.

Several studies indicate that the influence of the maternal phenotype on the development of the disease in children is stronger than that of the paternal phenotype.

During the last 2 decades, molecular genetic studies have been performed for various allergic diseases, including asthma. Two approaches are being applied to

identify genes related to disease. The first is *positional cloning*, in which the entire genome is screened with a panel of polymorphic DNA markers. This approach attempts to demonstrate linkage of a certain phenotype to genetic markers of known chromosomal localization.^{13,14} The second approach is examination of candidate genes already known to be involved in the pathophysiology 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.¹⁵⁻¹⁹

If genetic studies turn out to be fruitful, they might contribute to the identification of candidates for primary prevention measures and individuals who may respond to certain therapeutic interventions in the future.

EARLY IMMUNOLOGIC MARKERS

A necessary prerequisite for effective primary prevention measures is the ability to predict in whom atopic disease will develop. As long as no genetic markers are available, it would be highly desirable 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 genetically controlled. Therefore the measurement of IgE concentrations in cord blood was thought to be a useful screening test.²⁰ Unfortunately, more recent studies have shown that neither the sensitivity, specificity, nor the predictive value of cord blood IgE measurements are acceptable for use as a screening test. Taking data from the German MAS study, Edenharter et al²¹ were recently able to demonstrate that elevated cord blood IgE concentrations are capable of predicting early sensitization but not airway or skin symptoms.

As far as the prediction of asthma is concerned, eosinophils and their mediators have been studied in infancy to identify individuals in whom chronic disease will develop. In a Norwegian cohort study, wheezing infants had significantly higher levels of serum eosinophil cationic protein compared with control infants.²² Whether concentrations of mediators from eosinophils also predict the chronic disease process remains to be shown. Pohunek et al²³ studied eosinophils in bronchial biopsy specimens and suggested that increased numbers of eosinophils are risk factors for persistent asthma.

Recently, several groups have studied the *in vitro* response of fetal or cord blood PBMCs to allergens or mitogens with respect to later development of atopic disease. It could be demonstrated that fetal T cells have the capacity to respond on incubation with allergen and that there are differences in immune responses between those infants in whom atopic disease develops later on and those who stay healthy. The risk of atopic disease is obviously associated with a reduced capacity to secrete IFN- γ after PHA stimulation at birth.²⁴⁻²⁷ Martinez et al²⁸ were able to demonstrate that low T_H1 cytokine production at 12 months was associated with atopic sensitization to inhalant allergens at 6 years of age.

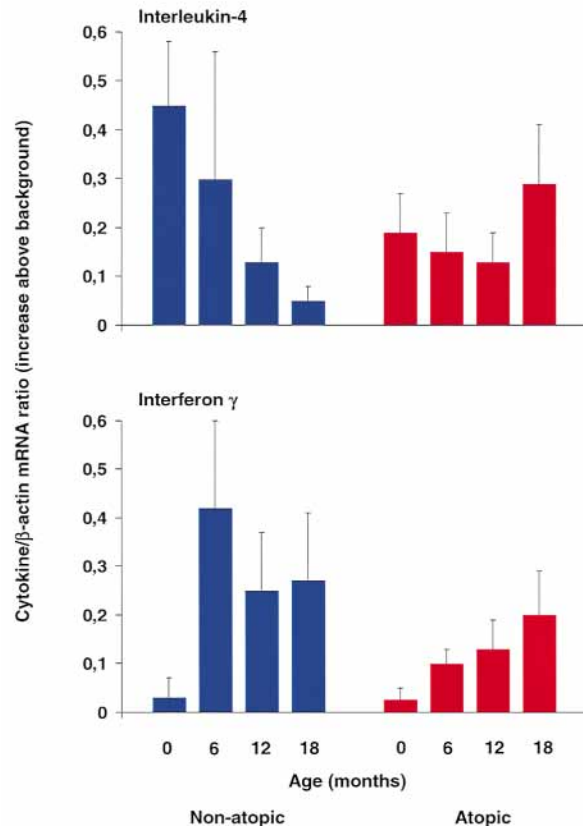


FIG 2. Allergen-specific IL-4 and IFN- γ mRNA production by cord blood mononuclear cells from children who were atopic or nonatopic at age 2 years.²⁹

In a small birth cohort study, Prescott et al²⁹ 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 T_H2 response during infancy and a decreased capacity for the production of the T_H1 cytokine IFN- γ in those children who subsequently had atopic disease (Fig 2).

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 type of immunodeviations that 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 for subsequent sensitization to aeroallergens and to the development of allergic airway symptoms inducing asthma.¹⁰ These findings might become important with regard to strategies for secondary prevention because infantile IgE responses to hen's egg are observed very early, generally during infancy.

ENVIRONMENT AND LIFESTYLE

During the last 2 decades, 2 general hypotheses have been proposed in the literature in connection with the observed increase of atopy and asthma in childhood.

1. New risk factors that were unknown several decades ago have become relevant in connection with nutrition, environmental exposure, or lifestyle.
2. Protective factors that were related to a more traditional lifestyle in the past have been lost, which has led to a greater susceptibility for atopic diseases.

DOMESTIC ENVIRONMENT

No other environmental factor has been studied as extensively as exposure to environmental allergens as a potential risk for sensitization and manifestation of atopy and asthma. From a number of cross-sectional studies performed with children and adults, it has become obvious that there is a close association between allergen exposure, particularly in the domestic environment, and sensitization to that specific allergen. Longitudinal studies like the MAS study in Germany 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 to cats and mites, respectively.⁸

However, as far as the manifestation of atopic dermatitis and asthma is concerned, the situation is much less clear. Earlier studies performed by Sporik et al³¹ in sensitized children suggested that exposure to dust mite allergens not only determines the risk of asthma but also the time of onset of the disease. More recent investigations by the same group, however, suggest that other factors beside allergen exposure are important in determining which children will have asthma.³²

In a comprehensive meta-analysis, Peat and Li³³ 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 that on the basis of the literature, indoor allergen exposure is the environmental factor with by far the strongest effect on the manifestation of asthma.

In recent years, however, the paradigm that exposure induces asthma with airway inflammation through sensitization has been challenged. In several countries the prevalence of asthma in children has been increasing independent of allergen exposure. In genetically manipulated mice allergic sensitization (ie, the production of specific IgE antibodies) is regulated differently from the manifestation of disease and airway inflammation: although IL-4 has been shown to be a crucial cytokine for the process of sensitization, other cytokines, particularly IL-5, obviously play a central role in the pathogenesis of murine eosinophilic inflammation.³⁴

Data sets obtained from the birth cohort study MAS 90 (Fig 3)³⁵ suggest that although domestic allergen exposure is a strong determinant for early sensitization in childhood, it cannot be considered to be a cause of airway hyperresponsiveness or asthma.

A number of intervention studies are currently being performed in cohorts followed prospectively from birth, examining the effect of indoor allergen elimination on the incidence of asthma.³⁶ The results will have a strong effect on public health policies because they will clarify whether it is meaningful to consider indoor allergen elimination an important element of primary prevention of various atopic manifestations. However, even if it turns out that other factors play a major part in determining whether an atopic child will have asthma, so that allergen elimination as a measure of primary prevention is proved inefficient, a reduction of allergen exposure will still remain a very important element in secondary prevention.

POLLUTANTS AND TOBACCO SMOKE AS ADJUVANT FACTORS

After guinea pig and mouse experiments suggested an increase of allergic sensitization to ovalbumin after experimental exposure with traffic- or industry-related pollutants,^{37,38} a strong association between allergic rhinitis caused by cedar pollen allergy and exposure to heavy traffic was reported from Japan.³⁹ Other investigators were unable to describe any relationship between traffic exposure and the prevalence of hay fever or asthma.⁴⁰

The role of tobacco smoke, a complex mixture of various particles and organic compounds, has been extensively studied. The studies that have recently been reviewed consistently demonstrate that the risks of lower airway disease (eg, bronchitis), recurrent wheezing in infants, and pneumonia are increased. Whether passive tobacco smoke exposure is causally related to the development of asthma is still disputed.⁴¹⁻⁴⁴

Until recently, there has been a lack of data about the risk of sensitization. From the prospective birth cohort study MAS in Germany, it was reported that an increased risk for 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 regarding IgE antibodies to food proteins, particularly those to hen's egg and cow's milk, was only observed during infancy, whereas sensitization rates later on were not different from those of children who had never been exposed to tobacco smoke. 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.⁴⁵

LIFESTYLE AND THE DEVELOPMENT OF ATOPIC DISEASE

Taking into account that the risk of atopic sensitization and disease manifestation early in life is particularly high in industrialized Western countries and that within these countries concomitant variations⁴⁶ in the socioeconomic status and the prevalence of atopy are evident, the question was brought up as to what factor related to Western lifestyle might be responsible for increasing the suscep-

tibility for atopic sensitization. Studies of Swiss,⁴⁷ as well as Bavarian and Austrian, children have shown that the prevalence of symptoms of allergic rhinitis and of allergen-specific IgE antibodies is much lower among offspring of farmers than among other children in these rural areas. In a recent Swedish study,⁴⁸ the prevalence of atopy in children from anthroposophic families was found to be lower than that in children from other families, 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 East, which was particularly striking in areas with little genetic difference, such as East and West Germany, where it was found that the critical period during which lifestyle mainly influences the development of atopy is probably the first years of life.⁴⁹

Recent observations from the MAS cohort study in Germany suggest that within the population of an industrialized country with a Western lifestyle, high socioeconomic status has to be considered as a risk factor for early sensitization and the manifestation of atopic dermatitis and allergic airway disease.⁵⁰

CAN EARLY EXPOSURE TO INFECTIONS BE PROTECTIVE?

One of the hypotheses that had been attracting the most interest is that a decline in certain childhood infections or a lack of exposure to infectious agents during the first years of life, which is associated with smaller families in the middle-class environment of industrialized countries, could be causal for the recent epidemic in atopic disease and asthma. Although this area is obviously very complex, several pieces of information appear to support this hypothesis.

Studies from several countries provide indirect evidence for the hypothesis that early exposure to viral infections, although triggering lower airway symptoms during early life, may have long-lasting protective effects. Children who were born into families with several, particularly older, siblings have been found to have a reduced risk of allergic sensitization and asthma at school age.^{51,52} Studies in children who had attended day care centers during infancy support this concept.^{53,54}

Recovery from natural measles infection reduces the incidence of atopy and allergic responses to house dust mites to half that seen in vaccinated children.⁵⁵ Obviously, the fact that certain infections are inducing a systemic and nonspecific switch to T_H1 activities could be responsible for an inhibition of the development of atopy during childhood.⁵⁶⁻⁵⁸

Prenatal or perinatal bacterial infections should also be taken into account as potential modulators of the atopic march. Preterm birth in many cases is nowadays understood as the result of bacterial infections during pregnancy. The observation that infants with very low birth weight have a lower prevalence of atopic eczema and atopic sensitization could therefore fit with this hypothesis.⁵⁹

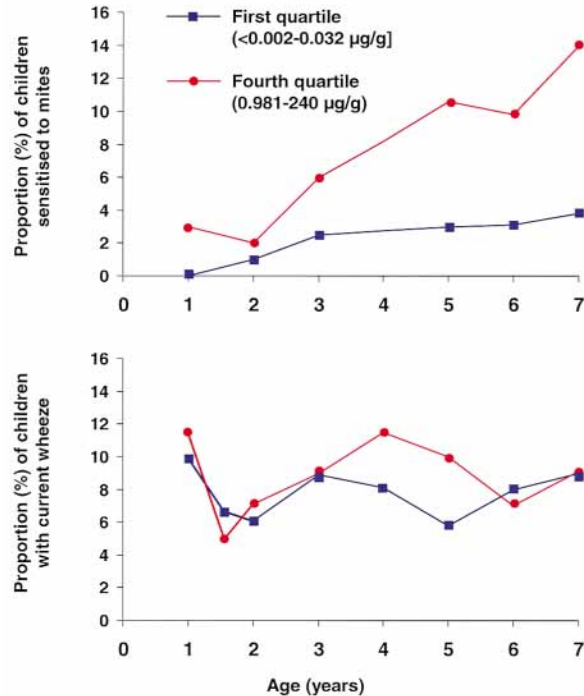


FIG 3. House dust mite allergen exposure in relation to specific sensitization and prevalence of wheezing at age 1 to 7 years.³⁵

TABLE I. Atopic phenotypes in childhood

1. Atopic dermatitis
2. Seasonal allergic rhinoconjunctivitis
3. Bronchial hyperresponsiveness
4. Recurrent wheeze
5. Elevated concentrations of allergen-specific IgE in serum
6. Blood eosinophilia
7. Skin test reactivity to specific allergens
8. Food allergy
9. Elevated serum IgE levels

The role of endotoxin exposure as a possible element of atopy prevention in early life has recently been discussed.⁶⁰ Endotoxins consist of a family of molecules called LPS and are an intrinsic part of the outer membrane of gram-negative bacteria. LPS and other bacterial wall components, which can also be found abundantly in stables where pigs, cattle, and poultry are kept, engage with antigen-presenting cells through CD14 ligation and elicit strong IL-12 responses. IL-12, in turn, is regarded as an obligatory signal for the maturation of naive T cells into T_H1-type cells. Endotoxin concentrations were recently found to be highest in the stables of farming families and also in dust samples from kitchen floors and mattresses in rural areas. These findings support the hypothesis that environmental exposure to endotoxin and other bacterial walls is an important protective determinant regarding the development of atopic diseases.

Another aspect is that the intestinal microflora might well be the major source of microbial stimulation of the immune system in early childhood.⁶¹ Also, the intestinal

microflora could enhance T_H1 -type responses.⁶²⁻⁶⁴ 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, which are associated with a lower prevalence of atopic disease.⁶⁵

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,⁶⁴ which unfortunately was not blinded, infants with milk allergy and atopic dermatitis had milder symptoms and fewer markers of intestinal inflammation if their milk formula was fortified with lactobacilli.

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 T_H1 type⁶⁶ were supported by animal experiments that demonstrated that the IgE response to ovalbumin in mice could be downregulated by a previous infection with BCG.^{67,68}

Although these observations on the relationship between immune responses to infectious agents and atopic sensitization and disease expression are most stimulating and challenging, conclusions regarding the relevance for the atopic march should be drawn with care. In different parts of the world, completely different infectious agents have been addressed in different study settings. It appears to be quite fashionable to join Rook and Stanford,⁵⁸ who in a recent review article in *Immunology Today* pleaded, "give us this day our daily germs." But which germ at what time under which circumstances, and what is the price we have to pay? Definitely, pediatricians should resist questioning most successful immunization programs, such as the one for measles.⁶⁹

OTHER LIFESTYLE-RELATED FACTORS

Obviously, a long list of lifestyle-related factors exists that might be associated with the apparent epidemic of the 21st century and might have relevance for the atopic march in children. Obesity has been proposed^{70,71} because it has been found in some US studies to be associated with certain types of childhood asthma. The question still remains whether asthma causes obesity or vice versa or whether are they both explained by a common cause, such as immobility.

Finally, the hypothesis has been raised that the use of Omega 3 versus Omega 6 dietary fatty acids in certain populations might be responsible for an increased risk of allergic inflammation. Both hypotheses deserve attention, but at this stage, preventive advice should not be based on them.

ATOPY AND ASTHMA PREVENTION: A CHALLENGE FOR THE FUTURE

It is obvious that in many industrialized countries, the observed increase in prevalence of atopy and asthma has become a serious public health issue.⁷² If preventive

intervention could be effective at all,⁷³ it would have to be applied early in life, most probably in early infancy. Unfortunately, our understanding of the natural history of the process of atopic sensitization, atopic dermatitis, and allergic airway disease is still very limited. On the other hand, the evaluation of risk factors and determinants is a necessary prerequisite for any effective intervention.

PRIMARY PREVENTION

Measures for primary prevention are aimed at a population that is still healthy but at risk of the disease. Unfortunately, all predictors investigated thus far are insufficient in sensitivity and specificity. Therefore it seems mandatory to recommend possible preventive measures only if the following conditions are met:

- applicability for the whole population,
- absence of risk, and
- low cost.

Although the extent of a preventive effect of breast-feeding remains controversial, several other beneficial aspects of breast-feeding justify the recommendation for exclusive breast-feeding for at least 4 months. If breast milk is not sufficiently available during the first 3 to 4 days, water is recommended.⁷⁴ An avoidance of exposure to tobacco smoke should be guaranteed, particularly during pregnancy and infancy.

Because maternal smoking during pregnancy is significantly associated with a reduced respiratory function and recurrent wheezing in infancy and early childhood and the risk of development of IgE responses to food proteins early in life, smoking should be avoided in any case.

"HIGH-RISK" CHILDREN

Because children with a positive family history for atopy in first-degree relatives have been shown to be more susceptible to allergic sensitization and the manifestation of atopy and asthma, additional measures for primary prevention have been studied during the last decade for this high-risk group.

If maternal breast milk is not sufficient, the use of hydrolyzed formulas for atopy prevention has been extensively studied over the years. Some studies indicate that a preventive effect of extensively hydrolyzed formulas in combination with avoidance of cow's milk proteins and solid foods for at least 4 months in children with a positive family history of atopy have some preventive effect, but this is related to the food proteins that were avoided and cannot be considered as a long-lasting prevention of atopic manifestations of the skin or the airways in general. Partially hydrolyzed formulas with moderately reduced allergenicity have been investigated in randomized prospective studies. However, their application remains controversial.^{75,76}

As long as no conclusive prospective study comparing partially and extensively hydrolyzed formulas has been published, the use of extensively hydrolyzed products should be preferred.

The introduction of complementary food during the first 4 months of life has been associated with a higher risk of atopic dermatitis. It is still not clear how much the risk for atopic sensitization and disease manifestation may be decreased by dietary intervention in early infancy. The majority of studies seem to indicate that the effects are transient and that the development of asthma later in childhood will not be prevented.

The majority of the studies aiming at prevention during pregnancy indicate that there is no real evidence for a protective effect of any maternal exclusion diet during that time. The effect of maternal avoidance of potential food allergens (milk, egg, and fish) during the breast-feeding period seems at best to be marginal.

SECONDARY PREVENTION

Measures for secondary prevention are aimed at children who have not yet had a definite phenotype (eg, allergic airway manifestation) but have markers indicating a high risk of subsequent disease manifestation. With regard to atopy, this means that children with a positive family history for asthma who have sensitization to food protein in infancy or atopic dermatitis have to be considered a candidate group for secondary prevention. A reduction of indoor allergen exposure by introducing mattress encasings, eliminating wall-to-wall carpets, avoiding damp housing conditions by increasing ventilation, and avoiding furred pets at home has been demonstrated to be a meaningful intervention for secondary prevention.⁷⁷

In young children with atopic dermatitis and a positive family history for atopy, pharmacologic intervention with ceterizine led to a significant reduction in the incidence of asthma in a subgroup that had early sensitization to grass pollen or house dust mites by the second year of life. Before this type of intervention can generally be recommended, confirmatory studies are necessary.⁷⁸

Allergen-specific immunotherapy, which has been demonstrated to be effective for the treatment of seasonal allergic rhinitis, has recently been investigated in young children. In the cohort, which was followed prospectively over a period of 3 years, this early intervention was shown not only to reduce seasonal symptoms of the upper airways but also to reduce the incidence of seasonal asthma.⁷⁹

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