The Development of Atopic Phenotypes: Genetic and Environmental Determinants

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Abstract

Atopic manifestations may be present from infancy to adolescence. Atopic dermatitis represents the first clinical manifestation followed by allergic symptoms of the upper or lower airways. IgE responses to alimentary or environmental allergens are hallmarks of atopy in childhood. Characteristically infantile IgE responses to cow’s milk and hen’s egg are the first immunological markers of atopy. In many cases they are followed by IgE responses to indoor or outdoor allergens, which suggests a high risk for the development of persistent asthma in childhood. During recent years a variety of genes for both asthma and atopic dermatitis have been described. Infantile diet, early exposure to environmental allergens and a variety of environmental and lifestyle factors may act as strong modulators of atopy during the first decade of life.

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Introduction

Atopic phenotypes such as hay fever, asthma and eczema are allergic conditions (table 1) 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, which by themselves are characterized by inflammation, corresponding to hyperresponsiveness of skin or mucous membranes.

A prerequisite for allergic inflammation is a specific sensitization which requires antigen-presenting cells and their interaction with T lymphocytes. This interaction is provided by HLA class molecules and the T cell receptor together with co-stimulatory signals. T cells will then develop into either Th1 or Th2 cells. It is the Th2 cell which provides help for B lymphocytes to
Table 1. 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

develop into IgE-secreting plasma cells. After secretion of IgE the molecule will bind with high affinity to the Fcε receptor on mast cells or basophils, expecting a new allergen contact. Subsequent allergen exposure with bivalent allergens may lead to cross-linking of cell-bound IgE and to an activation of the effector cells resulting in the release of preformed or newly generated mediators. These mast cell mediators either directly induce symptoms of anaphylaxis or contribute together with other cytokines to the adhesion or diapedesis of eosinophilic granulocytes, which themselves subsequently have the capacity to release proinflammatory mediators.

The Natural History of Atopic Diseases

Although wide individual variations may be observed, atopic phenotypes 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 11th 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 to hen’s egg and cow’s milk [1]. Even in completely breastfed 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 via 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 (Multicenter Allergy Study, 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.
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.

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 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 develop specific IgE antibodies during this early period. Obviously, at least two 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 in a minority symptoms may persist throughout school age and adolescence. 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 [2, 3]. During the first 3 years of life, the manifestation of wheezing 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. In addition, the association with a positive family history for atopy and asthma in first degree relatives becomes more and more obvious.

**Fig. 1.** Development of atopic dermatitis (AD), asthma and allergic rhinoconjunctivitis with age (MAS cohort, 1–13 years). Data from the German MAS study.
The 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 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 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 cat and mites, respectively [4, 6].

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 al. [7] suggested that in sensitized children 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 besides allergen exposure are important in determining which children develop asthma.

In recent years, however, the paradigm that exposure induces asthma with airway inflammation via 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, i.e. the production of specific IgE antibodies, is regulated differently from the manifestation of disease and airway inflammation: while 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.

Data sets obtained from the birth cohort study MAS 90 suggest that while domestic allergen exposure is a strong determinant for early sensitization in childhood it cannot be considered to be a cause of airway hyperresponsiveness or asthmatic symptoms during preschool age (fig. 2).

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. The results will have a strong impact on public health policies, since they will clarify 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 part in determining whether an atopic child will develop asthma, so that allergen elimination as a measure of primary prevention is 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 to traffic- or industry-related pollutants, a strong association between allergic rhinitis caused by cedar pollen allergy and exposure to heavy traffic was reported from Japan. Other investigators were unable to describe any relationship between traffic exposure and the prevalence of hay fever or asthma.

The role of tobacco smoke, a complex mixture of various particles and organic compounds, has been extensively studied. The studies which have recently been reviewed consistently demonstrate that the risk of lower airway disease such as bronchitis, recurrent wheezing in infants as well as pneumonia is increased. Whether passive tobacco smoke exposure is causally related to the development of asthma is still disputed [8, 9].

Until recently there has been a lack of data about the risk of sensitization. In the prospective birth cohort study MAS in Germany it was reported that an increased risk of sensitization was found only in children whose mothers

Fig. 2. Exposure to house dust mite allergen in relation to specific sensitization and prevalence of wheezing at age 1–7 years.
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 to hen’s egg and cow’s milk, was only observed during infancy, whereas sensitization rates later on were not different from 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 his or her mother.

**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 variations in the socioeconomic status and the prevalence of atopy are evident, the question was brought up of what factor related to western lifestyle might be responsible for increasing the susceptibility to atopic sensitization [10]. Studies of Swiss 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 the offspring of farmers than among other children in these rural areas. In a recent Swedish study, the prevalence of atopy in children from anthroposophic families was found to be lower than in children from other families, which led the authors to conclude that lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood. Several studies focussing 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 like 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.

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

**Can Early Exposure to Infections Be Protective?**

One of the hypotheses which has attracted 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 a 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 [11].
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. Studies in children, who had attended day care centers during infancy, support this concept [12].

Recovery from natural measles infection reduces the incidence of atopy and allergic responses to house dust mite to half that seen in vaccinated children. 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 [13].

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 this hypothesis.

The role of endotoxin exposure as a possible element of atopy prevention in early life has recently been discussed. Endotoxins consist of a family of molecules called lipopolysaccharides and are an intrinsic part of the outer membrane of Gram-negative bacteria. Lipopolysaccharides and other bacterial walls, which can also be found abundantly in stables, where pigs, cattle and poultry are kept, interact with antigen-presenting cells via 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 Th2-type cells. Endotoxin concentrations were recently found to be highest in 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 [14].

Another aspect is that the intestinal microflora might well be the major source of microbial stimulation of the immune system in early childhood. Also, the intestinal microflora could enhance Th1-type responses. 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 is associated with a lower prevalence of atopic disease [16].

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, 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 profiles bias toward Th1-type were supported by animal experiments which demonstrated that the IgE response to ovalbumin in mice could be downregulated by a previous infection with BCG. [17]

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 their 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 [15], who in a recent review article in *Immunology Today* pleaded ‘give us this day our daily germs’, but which germs at what time under which circumstances and what is the price we have to pay? Pediatricians should definitely resist questioning most successful immunization programs like the one for measles.

**Genetic Factors**

Multiple twin and family analyses strongly imply a genetic basis for asthma and atopy [5, 17]. A recent study of 11,688 Danish twin pairs suggested that 73% of asthma susceptibility is due to genetic factors [18]. However, atopy-associated phenotypes do not appear to follow any Mendelian inheritance pattern, which is characteristic of complex genetic (multifactorial) traits. The dissection of these traits is hampered by phenocopy, incomplete penetrance, and genetic heterogeneity. The complexity of the genetics of asthma and atopy is reflected by an increasingly large number of chromosomal regions showing (mostly weak to moderate) evidence for linkage, as well as various genetic variations in multiple candidate genes that are associated with asthma or associated phenotypes.

Multiple chromosomal regions showed evidence for linkage to asthma and atopy. Few regions show evidence for linkage in more than one population, which may be due to racial differences, a different definition of phenotypes or (most likely) insufficient numbers of affected sib pairs. Theoretically, at least 1,000 affected sib pairs seem to be required to avoid type 1 and type 2 errors in genetic analyses of complex traits.

A genome-wide linkage study in nuclear families of European origin with affected siblings with early age of onset atopic dermatitis revealed highly significant evidence for linkage on chromosome 3q21 \( (Z_{\text{all}} = 4.31, p = 8.42 \times 10^{-6}) \). Moreover, this locus provided significant evidence for linkage of allergic sensitization under the assumption of paternal imprinting \( (\text{hlod} = 3.71; \alpha = 44\%) \), further supporting the presence of an atopy gene in this region [20].

Despite the high degree of inconsistent findings, it is intriguing that chromosomal regions linked to asthma have also shown evidence for linkage to
other inflammatory and autoimmune diseases. Regions linked to atopic dermatitis have also been linked to psoriasis [21].

**Candidate Gene Studies**

This approach is chosen to test whether chromosomal regions containing distinct genes (of known biological function and location) are linked to disease, followed by mutational analysis of respective candidate genes. Commonly, genotyping of selected STRPs that map closely to candidate genes (e.g. IL-4) is performed in affected sib pairs (allele-sharing analysis) or trios [affected offspring and parents; transmission disequilibrium test (TDT) analysis] to establish linkage.

The most solid chromosomal regions showing evidence for linkage or associations with atopy-related traits are on chromosome 6p, 5q, 11q, 12q and 13q. These chromosomal regions contain many genes that are critically involved in the allergic inflammation. Screening for mutations/polymorphisms in the majority of the candidate genes has been performed. Multiple (mostly weak to moderate) associations with atopy-related traits have been reported [22–24].

**Gene-Environment Interactions**

The analysis of gene-environment interactions to date is hypothesis driven and stands at the very beginning [25]. The difficulties in quantifying and characterizing environmental risk factors for atopy (including onset and length of period of exposure) make these studies a challenge. Very high numbers of affected and unaffected subjects carefully characterized (longitudinally) for both the environmental setting and disease expression may be required to test for interactions between genetic variants and nongenetic influences.

However, recent genetic studies support the 'hygiene hypothesis', which postulates that atopy may be the result of a misdirected immune response in the absence of infection:

- Resistance to *Schistosoma mansoni* as well as *Plasmodium falciparum* blood levels was linked to chromosome 5q31–33, a region (containing the IL-4 cytokine gene cluster) that has shown strong evidence for linkage to atopy-associated traits. Furthermore, a major locus closely linked to the interferon-γ receptor gene appears to control the switch from a Th2 to a Th1 cytokine profile during *S. mansoni* infection.
- SNPs within the FcεRI-β gene have been related to IgE levels in heavily parasitized Australian aborigines indicating a protective role in parasitic infection. These SNPs have also been related to asthma, bronchial hyperresponsiveness, atopic dermatitis and atopy. FcεRI-β maps to 11q13, a region that showed evidence for linkage to asthma and associated traits in multiple studies.
A polymorphism in the β2AR encoding gene (Arg16) that has been related to asthma was also associated with higher levels of parasitic infection.

**Conclusion**

Asthma and atopy are complex multifactorial disorders. Major strides have been made in identifying chromosomal regions and candidate genes linked to asthma. However, the significant increase in the prevalence of atopy-related disorders over the last decades cannot be explained by changes in the genetic pool. It is rather likely that various preexisting genetic factors in a dramatically changing environment (decline of infectious diseases, change in diet, immunizations, and others) have rendered a large percentage of the population susceptible to asthma and atopy. Genetic variations that evolved to improve resistance to infections may very likely be misdirected to promote allergic inflammation in the absence of infection in western societies. Redundancies in host defense mechanisms may explain the large number of chromosomal regions as well as a steadily growing number of genetic variants related to atopy. Inconsistent findings summarized in this article may be explained by ethnic differences in host defense genes, but also by limitations to take gene-gene as well as gene-environment interactions into account. Large prospective multicenter studies in addition to retrospective collaborations may help to better understand genetic and environmental risk factors for atopy.

**References**

Discussion

Dr. B. Koletzko: Thank you for a very stimulating and fascinating talk. I was particularly impressed by your observation that early specific sensitization to food allergens is a strong predictor of later respiratory disease. Is this related to your choice of putting IgE on top of your list of atopic phenotypes? From the clinical point of view, IgE is a rather frustrating molecule because we see a lot of patients with allergy who don’t have elevated IgE, particularly if they have food allergy or GI manifestations. Moreover, we see a lot of patients with elevated IgE that don’t have disease. In your MAS data you found that the frequency of IgE sensitization to food allergens was pretty stable between age 1 and 13 years, even though point prevalence of food allergy varies markedly during this age range. Thus I wonder whether you might be able to offer any better perspective for the future? Would there be an opportunity to develop a better algorithm where IgE may act as one factor, and the combination with other markers, such as genetic polymorphisms or environmental markers, might increase sensitivity and specificity of prediction?

Dr. Wahn: The reason why the prevalence of food allergies seems to decrease with age and not to increase was due to the fact that we always used the same panel of 4 food proteins, food allergens. This was the classical infant-type panel and Dr. Lack would immediately say why didn’t you add peanut? We did not add peanut because 15 years ago nobody in this country was concerned about peanut. Now we would have...
added it. We actually took hen’s egg, cow’s milk, soy and wheat, which are the top 4 of
the German list. Now I would say peanut has entered the top 4 even in this country
where there is hazelnut exposure but not peanut exposure in babies. But one thing is
quite clear, I don’t think total IgE is a good predictor but the specific IgE responses
indeed are. Whether this is a causal link between the early response and the sub-
sequent sensitization to anything; whether phase A is a prerequisite for phase B or
whether it is the other way round, and is just a co-expression of different atopic phe-
notypes that are not causally linked but just associated, I don’t know. But for the group
of cohort children we know that the concentration for food-specific IgE antibodies in
the serum is important in two regards. If you have very high concentrations you are
more likely to develop food allergy and not just sensitization, and if you have very high
concentrations you are more likely to develop other IgE responses and even clinical
phenotypes. Whether this has any preventative aspect, I don’t know, I would even
doubt it.

**Dr. Szajewska:** You only briefly mentioned parasites in the prevention and treat-
ment. Could you please comment on whether or not you see any place for the use of
parasite antigens in the treatment and/or prevention of all allergic disease?

**Dr. Wahn:** As I said many people are developing wild ideas. One candidate is
*Trichuris suis* which is known to gastroenterologists and is involved in Crohn’s dis-
ease and chronic inflammatory disease. We are about to start a placebo-controlled trial
on both the prevention and intervention of atopic phenotypes in hay fever.

**Dr. Szajewska:** Also in children?

**Dr. Wahn:** We would never recommend this for treatment but we strongly recom-
 mend it for study.

**Dr. Kaulfersch:** You mentioned that there is no risk that allergic symptoms are
enhanced in children due to vaccinations; but you listed vaccinations as a risk factor.
So, I am still confused.

**Dr. Wahn:** Gruber [1] has studied this extensively and the answer is that the atopic
child should have the same rights as any other child to get the whole panel of immu-
nizations. There is no additional risk of developing any allergic phenotype even with
injections such as those for measles and rubella, which in public opinion are always
the bad guys. Some parent organizations still claim this without any evidence.

**Dr. Saavedra:** We typically establish respiratory phenotypes such as upper respi-
ratory (rhinitis), lower respiratory (asthma) and skin (atopic dermatitis) as pheno-
types. As gastroenterologists we feel a little left out because we think allergy of the GI
system also has a phenotype. We don’t quite understand these eosinophilia pheno-
mena yet. But they clearly do respond to the protein management children get. So it
seems to be one of those phenotypes, and from the nomenclatural point of view we
also tend to confuse ‘food allergy’ as a phenotype, but we don’t use ‘aero-allergy’ as a
phenotype. Would you agree with that? It does look like there is a difference or an
association between the first and latter manifestations, like atopic dermatitis which is
associated with a higher incidence of other phenotypes later in life. With GI allergy
some of it seems to be food related. Does the GI tract-associated lymphoid system
handle things better than the respiratory tract lymphoid system, and therefore are
there different associations? How can we ever decide if we begin with a food versus an
air-borne allergen, or is it a GI manifestation versus lung manifestation? Those two
organs are not only origins but also targets of the allergic march.

**Dr. Wahn:** I apologize for not pointing it out clearly enough, food allergy is a phe-
notype. I left it out because I know it will be covered elsewhere. If you compare it to
the skin or the airway manifestation, we would also say it is an important phenotype.
If you look at the first age window of let’s say 0–5 years, food allergy is more important
than hay fever for example. When it comes to all kinds of food-related allergic reac-
tions according to our experience it is the second most important manifestation after the skin. Then all kinds of GI symptoms come before we see anything in the airways, but this might actually be due to the kind of patient who you see as a physician. What I am not so clear about and I would like to share my doubts with you, is what we see in the clinics. There apparently is a typical or characteristic sequential manifestation of certain phenotypes and a sequential manifestation of sensitization patterns. Food comes first, then comes inhalant; skin frequently comes before the GI tract, and then come the others. Is it just associated but independent? I would favor this now because many intervention studies aiming at secondary prevention have taken this window of opportunity between phenotype 1 and 2 and tried to intervene for example with the cetirizine, the H1 blocker, and they have failed to show anything. In my opinion it is not unlikely that we are facing independent, associated but not causally linked phenotypes and it will be very difficult to interfere at a later stage in order to block the atopic march.

Dr. S. Koletzko: I assume that language is only a marker for how many generations they have been in this country. But did you look for other environmental and also genetic markers?

Dr. Wahn: There are a couple of factors which account for this difference. We are in the process of starting a new Turkish cohort called the allergy prevention cohort. We want to understand more but this has to be done separately. A purely cross-sectional study with the school doctors generated hypotheses but did not prove anything, so now we want to understand whether it is related to nutrition or the domestic environment.

Dr. Fusch: One thing that considerably changed during the last 20 years in children is the oral exposure to antibiotics, especially aminopenicillin and erythromycin. What is the influence on allergy?

Dr. Wahn: There has also been a study by Niggemann et al. [2] in a variety of pediatric populations. My current conclusion is we don't have the answer to the question but there is something. Even if the exposure to a lot of antibiotics during the first year of life could be a slight modulatory factor, it still does not explain the whole epidemiologic trend. It could at least modulate this in terms of favoring manifestations. This has clearly been a candidate for anthroposophic research because this hypothesis was generated in a Swedish study. We don't have the final answer.

Dr. Sorensen: When you talk about atopic dermatitis being a risk factor for the atopic march, atopic dermatitis in the first year of life can be very different from one child to another. Very often it just persists for 1 or 2 months, in others it persists for an entire year. Did you see a relationship between the intensity and the persistence of atopic dermatitis and the risk for developing asthma?

Dr. Wahn: We have followed the natural history of all these children in the cohort with regard to their eczema persistence. Actually by the age of 7, 64% lost their eczema completely, 20% had persistent eczema from infancy to the 7th year of life, and 16% were intermediate, they had eczema which came and went away again. The prediction for persistence was actually the same as for the subsequent manifestation of asthma, which was severe in infancy, and food allergy. Once you had this you had a much lower chance of growing out of it. This was published last year in the Journal of Clinical Investigation.

Dr. Kamenwa: I would like to go back to the issue of infection being protective against developing allergy. I work in a developing country where we have a lot of infections, parasitic, bacterial and viral. In my work as a gastroenterologist, I see more and more gut allergy evolving, which we never saw before. It is possible that these infections are actually a risk factor for developing allergy. Now I hear that they could be protective. So I wonder if some specific infections could be protective while others put
the children at risk. In my observation, children who have had previous GI infections, especially viral in etiology, appear to have a higher risk of developing allergy.

**Dr. Wahn:** This is what the data say so far. I also heard from other developing countries that allergies are really on the rise, particularly hay fever for example. I wouldn’t tell anyone that infection might be good because it would be confusing. It is important for us to understand the right message. Certain infections might have long-term consequences on the infantile immune system. If this is true, we must understand the effect in order to mimic it and develop something which might be protective in the end; but so far this is not the final message.

**Dr. Rivera:** My question is related to the issue that we should learn something from infection and allergy. You mentioned the issue of hepatitis A and later on pertussis vaccine; as far as I know good work has been done with pertussis vaccine. I raise this question because we know the relationship of the worsening of wheezing and infection in children, and about hepatitis A and the so-called pertussis relationship. Do we have any scientific data about the difference in hepatitis A and pertussis in relation to infection?

**Dr. Wahn:** No, again we are just collecting data. It was Matricardi et al. [3] who did a study on Italian conscripts. All the data on these Italian conscripts are available, including their hepatitis A sero status. Two things are clear: the more older siblings they had in the family (if they were born in Italy when families still had many children), the more they were exposed to infections fairly early in their lives and the less likely they were to have developed airway allergies by the age of 18, and the same was true for hepatitis A. They concluded it was just oro-fecal infections which were protective. But then the tuberculosis investigators found that in countries where tuberculosis was still prevalent that allergies were relatively rare, not totally unknown, but relatively rare. Then animal experiments were made; we have several thousand allergic mice here at the Charité and we test for LPS or BCG for example. The mouse does not respond with IgE anymore; the mouse does not develop asthma anymore when exposed, and even if the mother is exposed before birth to LPS this helps her offspring. It is very difficult to come up with a final conclusion. It is an interesting field, research is ongoing, so let’s keep an open mind and in the end we will understand.

**Dr. Lack:** I just want to push you a bit on your comments about the association between early egg allergy and the subsequent development of atopic disease, particularly asthma. You said you thought it was more likely to be an association between food allergies and development of asthma than causality. You also documented very nicely in your MAS study that there is very little inhalant allergen sensitization. If foods are relevant in the genesis of asthma and there is no inhalant sensitization around and the pathways for asthma being laid down very early in the first few years of life, then one could argue that allergy has nothing to do with it because aero allergens aren’t there yet, food allergy is but it is irrelevant. I wonder whether there may be a causal link? It is very interesting that Heymann et al. [4] 20 years ago were already able to measure quantities of egg allergen and milk allergen in the dust of children’s bed sheets. The same levels can actually be measured for house dust mites, and in fact in adults, in occupational asthma, egg and milk proteins can actually play a very significant role. Do you think there might be a link after all?

**Dr. Wahn:** I discussed it several times with those authors and they have some support for their idea that sensitization occurs via the skin and not via the route which we usually expect. We are having another meeting in which we will share our confusion on the atopic march. Spergel [5] has suggested that it starts in the skin and it ends up in the airways; this is true for the mouse but whether it is true for babies, we don’t know. I would at the present time feel more comfortable with a rather conservative view. I also have to say that we were very enthusiastic about the ETAC and EPAAC trial
which unfortunately turned out to be negative. So this confuses us even more. I am not so sure what we will end up with but we should at least leave the option open that the skin is more important than we think with regard to sensitization.

References
