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The environmental predictors of allergic disease

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The prevalence of allergic diseases has been on the rise for the last 200 years, when hay fever, an easy and obvious-to-recognize illness, was virtually unknown in Europe and North America. Genetic factors are unlikely to explain these rapid increases. Among the potential environmental factors, exposure to ambient air pollution has been intensely debated. Besides passive smoking, which has convincingly been shown to increase the risk for asthma and bronchial hyperresponsiveness among exposed children, the evidence to suggest that outdoor pollution to sulfur dioxide, particulate matter, diesel exhaust, and ozone is causally related with the inception of allergic diseases is poor. Rather, factors associated with the lifestyle of populations or families, such as socioeconomic status, allergen exposure, sibship size, early childhood infections, dietary habits, and growing up in anthroposophic families or a farming environment, may prove to be of greater relevance. The future challenge is to tackle the complex interplay between environmental factors and genetic determinants that will eventually contribute to a better understanding and to better prevention strategies for such multifactorial conditions as asthma and allergies. (*J Allergy Clin Immunol* 2000;105:9-19.)

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At the turn of the millenium hay fever and other allergic diseases are common conditions in affluent Western societies. The prevalence of hay fever in adolescents, for example, is estimated to be 38.6% in the United Kingdom and 33.6% in the United States.¹ Yet 200 years ago hay fever, an easy and obvious-to-recognize illness, was virtually unknown in Europe and North America.² It was only in the early 19th century that hay fever was carefully described, but at that time it was regarded as an unusual illness.

In this century allergic conditions have been on the rise.³ But disparities similar to the impressive change over time can still be found as significant differences over space when the prevalence of allergic diseases in Western regions is contrasted to rates in countries with lower living standards, such as eastern Europe or the

Abbreviations used

BHR:	Bronchial hyperresponsiveness
CI:	Confidence interval
ETS:	Environmental tobacco smoke
LRI:	Lower respiratory tract illness
NO ₂ :	Nitrogen dioxide
OR:	Odds ratio
RSV:	Respiratory syncytial virus

developing world. In fact, prevalences of hay fever and asthma have been shown to be exceedingly low to nonexistent in some rural areas of Africa, eastern Russia, and the developing world.^{1,4,5} Because genetic factors can neither explain the increase in prevalence over the last decades nor the significant and in part large differences in prevalence between regions of similar ethnic backgrounds, a strong environmental influence on the expression of allergic diseases is very likely. This notion is furthermore supported by the observation that the familial aggregation of atopic diseases is rather low.⁶ The λ for asthma (ie, the risk that a sibling of an asthmatic subject also has asthma) divided by the risk that an unrelated individual from the same population has asthma is only around 2, as compared to cystic fibrosis or schizophrenia, where $\lambda = 500$ and $\lambda = 8.6$, respectively.

The concept that environmental influences are important for the development of illnesses dates back to the observation of epidemics and the subsequent identification of their causes, such as cholera in the case of John Snow in London or *Mycobacterium tuberculosis* by Robert Koch. These concepts have dramatically improved medical care in the last century. As a consequence, mortality rates for infectious diseases, the leading causes of death at the beginning of this century, have dropped markedly and have been replaced by other causes such as death from cardiovascular disease or malignancy.⁷

However, over time other "modern" chronic conditions have evolved where such unidirectional concepts of a germ invading a host or a factor adversely affecting an individual may prove misleading. Adaptation to a hostile environment has for centuries been a prerequisite for survival and may have been selected as the "normal," "healthy" status over the generations. Not only are we exposed to novel influences, but we may also lack "pro-

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protective" environmental stimuli. Chronic disease conditions may thus in part reflect a "normal" but no longer well-adapted response to the modern environment we are exposed to.

Allergic conditions share numerous characteristics such as the production of IgE antibodies in response to allergens,⁸ an impaired balance between cytokines of T_H1- and T_H2-type lymphocytes,⁹ a positive family background for atopic diseases,¹⁰ and sometimes the expression of several atopic conditions in one individual. Because of these similarities, many clinical and epidemiologic investigations have grouped subjects with different phenotypic manifestations of atopy into one class of illness to study the mechanisms involved in the disease process, the risk factors, and the response of affected subjects to therapy.

There is, however, increasing evidence that even subjects with the same symptom (eg, wheeze) may differ markedly with respect to associated features such as the detection of IgE antibodies to environmental allergens, bronchial responsiveness to direct and indirect stimuli, age of onset of the disease, and response to medication.¹¹ Thus distinct subtypes of disease may eventually result in similar clinical conditions, depending on a subject's complex genetic background and on her or his encounter with various environmental influences. In light of the immensely rapid increase in knowledge about genetic determinants of human diseases, which also marks the turn into the next millennium, more dissimilarities than common ground will probably be detected, thereby adding more complexity and challenging our limited capacities to understand the nature of multifactorial chronic conditions such as allergic diseases.

AMBIENT AIR POLLUTION

Air pollution is felt by many to be one of the more pressing problems toward the end of this century, posing a potential threat to the health and well-being of entire populations. When an attempt is made to understand the potential adverse effects of air pollution, the distinction between exacerbation of pre-existing disease in already-affected subjects from the potential adverse effects on the inception of newly developing cases of allergic disease seems essential. Although increasing evidence suggests that asthma exacerbations may be triggered by different air pollutants and that allergen responses are enhanced by exposure to certain pollutants,¹² there is little evidence to suggest that exposure to air pollution increases the incidence of allergic diseases.

A unique opportunity to study the effects of air pollution on the development of asthma and atopy arose with the reunification of Germany. Genetically similar populations in both parts of the country had been exposed for more than 40 years to radically different environmental conditions. Industrial areas of the former German Democratic Republic had excessively high levels of winter sulfur dioxide (0.105 ppm annual average) and particulate pollution (80 µg/m³ annual average), whereas in the West

German cities outdoor nitrogen dioxide (NO₂) concentrations (0.028 ppm annual average) tended to be higher, reflecting the much denser automobile traffic.¹³ Several studies in children and adults have consistently shown that the prevalence of asthma, bronchial hyperresponsiveness (BHR), hay fever, and atopy were all significantly lower in the polluted cities of East Germany compared with West German cities.^{14,15} Likewise, the prevalence of atopic sensitization and asthma was lower in schoolchildren living in the more-polluted eastern part of the Baltic area compared with western Sweden, with lower levels of air pollution.^{16,17}

TRAFFIC EXPOSURE

It has been argued that other types of pollutants that are associated with increasing traffic exposure characteristic of Western cities may be of greater relevance to the inception of allergic diseases than are the traditional type of pollution occurring with burning of coal and other fossil fuels. Diesel exhaust is the single major contributor to particulate matter in most urban areas worldwide, accounting for up to 90% of the total particle mass in some major cities.¹⁸ The mass median diameter of diesel exhaust particles is approximately 0.2 µm with more than 90% being <1 µm,¹⁹ thereby achieving high levels of peripheral airway deposition. Diesel particles have also been shown to absorb allergens from grass pollen onto their surface and may therefore act as potential carriers to increase their deposition in the lung.²⁰ Thereby both the allergen dose and the antigenicity of the pollen allergen may be enhanced.

Indeed, several studies have demonstrated that exposure to diesel particles after allergen challenge results in increased expression of T_H2-type cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) in *in vivo* nasal challenges of volunteers.²¹ Furthermore, diesel exhaust particulates have been shown to enhance eosinophil adhesion to nasal epithelial cells and to cause degranulation²² and to induce nasal IgE production.²³ The results of these studies suggest that exposure to diesel exhaust might exacerbate pre-existing allergic conditions but not necessarily induce the development of new cases of atopy. Findings of epidemiologic studies indicate, in fact, that the level of exposure to car and truck traffic exhaust plays a minor, if any, role for the inception of asthma and atopy.²⁴⁻²⁶

High rates of road traffic impaired pulmonary function and increased the prevalence of respiratory symptoms in children living in Munich, West Germany.²⁴ However, the prevalence of allergic rhinitis, asthma, BHR, and atopic sensitization was not associated with increasing car traffic counts. Several other surveys have investigated effects of exposure to vehicle emissions in Japan, The Netherlands, the United Kingdom, and Germany. In the Japanese and Dutch studies the prevalence of respiratory symptoms such as wheeze and chronic cough or phlegm was related to living close to major roads in female subjects.^{27,28} Neither study included objective measures of disease.

In the United Kingdom and Sweden preschool children admitted to the hospital because of asthma and wheeze were significantly more likely to live in an area with high traffic flow and increased outdoor NO₂ exposure resulting from traffic emissions.^{29,30} In both studies a significant proportion of these children may have had transient early wheezing with viral infections, which is unrelated to the development of progressive childhood asthma. An often-quoted Japanese survey reported an increased prevalence of cedar pollinosis in areas with high traffic exposure and concomitant increased pollen counts.³¹ The results of this study should, however, be interpreted with much caution because potential confounding factors such as socioeconomic status were not explored. A very recent survey of schoolchildren living in Dresden, East Germany, assessed exposure on an individual level relating mean annual air pollution levels (sulfur dioxide, NO₂, carbon monoxide, benzene, and ozone) that had been measured on a 1-km² grid to the home and school addresses of each study subject. These authors' results confirm the adverse effects of ambient city air pollution on the prevalence of cough and bronchitis but also the lack of an association between pollution levels and the prevalence of hay fever, atopy, and BHR.²⁵ Likewise, exposure to truck traffic was related to small decrements in baseline lung function and respiratory symptoms in Dutch schoolchildren but not to atopy and BHR.²⁶

OZONE

Single ozone exposure has been shown to evoke cough, breathlessness, and chest pain on inspiration; to result in a restrictive ventilatory defect with decrements in forced vital capacity and FEV₁; to induce neutrophilic inflammation of the airway submucosa; and to increase airway reactivity.¹² The response to ozone shows large intersubject variability,^{32,33} with approximately 10% to 20% of the population sensitive to the development of reductions in lung function after ozone exposure^{34,35} while others are insensitive. With repeated exposure, animal and human studies have revealed development of tolerance to the adverse effects of ozone.^{36,37} Studies repeating ozone exposure over 4 to 5 days have shown that the greatest decrement in forced vital capacity and FEV₁ occurs on the second day of exposure, with the effect on symptoms and spirometric changes becoming negligible by day 5. It remains, however, unclear whether ozone-induced airway hyperresponsiveness persists after repeated exposure. Several studies have resulted in conflicting evidence³⁸⁻⁴¹ that awaits further careful investigation.

Most studies have found significant inflammatory changes in the airways after exposure to ozone, with increases in numbers of neutrophils, but not eosinophils, several cytokines, and leukotrienes in bronchoalveolar lavage fluid⁴²⁻⁴⁶ and in large airways mucosal biopsy specimens.⁴⁵ The type of airway inflammation seen after ozone exposure differs, however, substantially from

inflammatory changes occurring in the airways of asthmatic subjects.

Because of the marked inflammatory responses in the airways and the potential for induction of BHR in healthy subjects, there is concern that ozone may enhance the development of asthma in populations exposed to significant concentrations. There are, however, only few epidemiologic studies addressing this question. In the American Six Cities Study⁴⁷ the prevalence of diagnosed childhood asthma increased significantly with rising ozone levels, but hay fever symptoms did not show the same trend. No objective measures of atopy, pulmonary function, or airway responsiveness were included in this study. In the Swiss multicenter study SCARPOL,⁴⁸ which used a similar study design to assess exposure over a wide range of concentrations, the prevalence of both childhood asthma and hay fever was unrelated to long-term exposure to ozone. Likewise, in adults no consistent effects of long-term exposure to ambient ozone concentrations on the development of asthma and atopy have been demonstrated.^{49,50}

ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

There is strong, consistent evidence to suggest that environmental tobacco smoke (ETS) exposure increases the risk of lower respiratory tract illnesses in infancy and childhood.^{51,52} A review on adverse health effects of ETS exposure by the US Environmental Protection Agency⁵¹ concluded that passive smoke exposure is causally associated with an increased risk of lower respiratory tract infections such as bronchitis and pneumonia, mainly in infants and young children, a small but significant and dose-dependent reduction in pulmonary function, and with additional episodes and increased severity of symptoms in children with asthma. Furthermore, in this report ETS exposure was considered to be a risk factor for the inception of new cases of asthma in children not previously displaying symptoms.

The strong link between a mother's smoking during pregnancy and decrements in infant pulmonary function with subsequent occurrence of wheezing lower respiratory tract infections in the first years of life may indicate that mainly the risk of benign transient viral-associated wheeze in early infancy and not the risk for development of childhood asthma is increased by passive smoke exposure. However, in the large birth cohort study in Tucson, Ariz, the occurrence of both transient early wheezing and persistent wheezing up to the age of 6 years, which may be seen as the equivalent of a physician's diagnosis of asthma in other studies, was related to ETS exposure.¹¹ Children of mothers with 12 or fewer years of education and who smoked 10 or more cigarettes per day were 2.5 times more likely to have asthma (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.42-4.59, *P* = .002) than were children of mothers with the same educational level who did not smoke or who smoked fewer than 10 cigarettes a day.⁵³ In a British birth cohort study following

9670 children up to the age of 10 years a 14% increase in childhood wheezy bronchitis was noted when mothers smoked more than 4 cigarettes per day.⁵⁴ This rate increased to 49% when the mother's smoking exceeded 14 cigarettes per day. Interestingly, in a recent case-control study performed in South Africa in 7- to 9-year-old children⁵⁵ the mother's smoking during pregnancy was reported to increase the child's risk for development of asthma and wheeze almost 2-fold (OR 1.9, 95% CI 1.2-2.8). Yet each additional smoking household member added significantly to this odds (OR 1.15, 95% CI 1.0-1.3), suggesting that the risks for asthma do not only increase with passive smoke exposure in utero (although the effect is stronger⁵¹) but also postnatally by passive inhalation of cigarette smoke.

A recent comprehensive meta-analysis has confirmed a significantly increased prevalence and incidence of wheeze and asthma in children exposed to maternal smoking.⁵⁶ This report furthermore observed a small but probably real increase in BHR among children of smoking mothers. Thus convincing evidence exists suggesting a causal link between passive smoke exposure and the development of childhood asthma. Conflicting results arise, however, from studies investigating the effects of ETS exposure on the development of atopic sensitization in children.⁵⁶ The balance of evidence did not support a positive association of allergic sensitization with parental smoking, either prenatally or postnatally, after 36 studies on IgE, skin test reactivity, hay fever, and eczema were reviewed.⁵⁶

SOCIOECONOMIC STATUS

High prevalences of childhood asthma and atopic diseases have been found in affluent Western societies. In the developing world a gradient between affluent and poor regions has been seen. In Harare, the capital of Zimbabwe, the prevalence of airway hyperresponsiveness, as assessed by a free-running test, was significantly higher in a wealthier part of the city than in its poorer districts.⁵⁷ In the United Kingdom high social class was associated with a higher prevalence of atopic eczema.⁵⁸ Moreover, in Italian military recruits a striking relationship between high parental socioeconomic status and increased IgE production to a panel of aeroallergens was found.⁵⁹ These findings cannot be reproduced in all regions, particularly not in inner-city areas of the United States, where low social class has repeatedly been associated with increased asthma morbidity.⁶⁰ Thus the socioeconomic status of families may rather be a surrogate measure for lifestyle characteristics than a risk factor per se. These factors may comprise dietary habits, family size, access to health care, environmental ETS, allergen exposure, or other yet unknown determinants.

NUTRITION

Changes in dietary habits have been implicated as a factor characteristic of societies with increasing afflu-

ence, therefore possibly relating to the increase in the prevalence of asthma and atopy seen over the last decades. In some prospective studies breast-feeding has been found to have a transient beneficial effect on the incidence of eczema, food allergy, and early wheezing illnesses in the first 1 to 3 years of life,^{61,62} but these findings could not be reproduced by others.⁶³ Furthermore, no consistent protective effect on the subsequent development of childhood asthma has been seen. The composition of breast milk may have differed among study populations or uncontrolled confounding by factors related to other characteristics of breast-feeding mothers may have contributed to the conflicting results.

Numerous studies have, however, demonstrated a benefit from feeding hydrolyzed formulas to at-risk infants with a family background of atopic disease.⁶⁴⁻⁶⁷ The effect was, however, again transient, with a reduction of symptoms of eczema and the gastrointestinal tract mainly over the first 18 months of life. Furthermore, the development of asthma and hay fever later in life could not be prevented by these dietary interventions.⁶⁸

Other dietary factors may have changed over the years. The balance of unsaturated to saturated fats in the diet may have changed toward a lower consumption of animal fats and in favor of polyunsaturated oils and trans-fatty acids.⁶⁹ A recent Australian study⁷⁰ showed a lower prevalence of asthma and BHR in children with a high intake of fresh oily fish in the diet. The results of a previous study demonstrated an association between high fish consumption and improved baseline FEV₁ in the United States.⁷¹ Thus children who eat fish regularly may consume adequate amounts of omega-3 fatty acids, protecting them from BHR. Low levels of intake of vitamin C, which functions as antioxidant and coenzyme in the biosynthesis of collagen, have furthermore been shown to relate to increased prevalence and incidence of asthma and wheeze and to lower levels of lung function.⁷² Finally, the severity of asthma, not its inception, has been linked to increased salt intake, but only in men.⁷³ Although these associations are of interest, they cannot explain the substantial changes in asthma prevalence that have occurred in the last decades. If confirmed by further epidemiologic studies, randomized trials and a search for the biologic mechanisms explaining the observed effects of diet may be warranted.

ALLERGEN EXPOSURE

There is increasing evidence to suggest that the level of allergen exposure is a risk factor for the development of atopic sensitization in children.⁷⁴⁻⁷⁶ In the German Multicenter Atopy Study⁷⁶ a large birth cohort following newborn children up to the age of 7 years, house dust mite and cat allergen concentrations in domestic carpet dust were strongly related to the development of atopic sensitization toward that specific allergen in the first 3 years of life. A clear dose-response relationship was found as well as a strong effect modification by the familial background for atopic diseases. In the group of

children with a positive family history of atopy, a mite allergen concentration below 750 ng/g dust resulted in a 3% sensitization rate, whereas in the group of children without a positive family history an exposure up to 25,000 ng/mg dust was necessary to achieve a sensitization rate of 3%. These findings indicate that no general exposure threshold can be proposed, as had been suggested previously, and that in fact children with a genetic risk are susceptible to even very low levels of exposure. The relevance of allergen concentration for the inception of atopic sensitization to that specific allergen may extend beyond infancy because similar findings have been reported for school-aged children.⁷⁵

Whether environmental allergen exposure affects the inception of asthma in ways similar to the development of atopic sensitization remains to be seen. In a prospective longitudinal study of infants born to atopic parents, Sporik et al⁷⁷ demonstrated a strong correlation between wheezing and sensitization to mites at the age of 11 years. Exposure to house dust mites in infancy was weakly associated with sensitization at age 11 years ($P = .062$). There was considerable overlap in the degree of exposure in infancy and no difference in mean exposures between asymptomatic and wheezing schoolchildren was found. However, a significantly increased risk of current asthma was apparent if a subject had in infancy been exposed to an arbitrary cutpoint of more than 10 μ g per gram dust of Der p 1, a major mite allergen.

If the level of exposure to mites in early infancy is indeed crucial for the expression of asthma, children brought up in a mite-free environment at high altitude should have a significantly lower prevalence of asthma and wheeze than children from humid, mite-infested areas. The results of 2 studies performed in the Alps and in New Mexico failed, however, to document a significant effect of a mite-free environment on the occurrence of asthma.^{78,79} Furthermore, in desert areas such as Tucson, Ariz, or inland Australia, where mites are rarely detected, the prevalence of asthma has not been found to be reduced.^{80,81} Thus, in contrast to the immunologic processes involved with the production of specific IgE antibodies, the mechanisms inducing an asthmatic condition might not be as susceptible to changes in allergen exposure levels. The characteristic feature of an asthmatic subject may rather lie in that person's capacity to mount particularly strong IgE responses toward perennial but not seasonal allergens, the strength of response being dependent on the level of exposure to that respective allergen.

FAMILY SIZE

There is increasing consistent evidence that sibship size contributes to the expression of atopy in families. Many authors have shown that the number of siblings is inversely related to the prevalence of self-reported inhalant allergy,⁸² hay fever,⁸³⁻⁸⁶ atopic eczema,⁸⁷⁻⁸⁹ skin test reactivity,^{84,90-93} and the presence of specific IgE antibodies in the serum^{86,94,95} in children, adolescents,

and adults. Most reports that were large enough to allow a separate analysis of the influence of older and younger siblings found a stronger relation with the presence of older siblings than with younger brothers and sisters. The consistency and strength of this association over all age groups and different populations is intriguing and suggests a major underlying determinant of those responses.

Interestingly, the relationship between family size and asthma or airway hyperresponsiveness is less clear. Although some investigators found similar negative associations between the number of siblings and several definitions of asthma,^{86,96-98} others failed to confirm these findings by use of either questionnaire-based estimates of asthma prevalence^{85,98,99} or measures of airway hyperresponsiveness.⁹²

Several hypotheses have been put forward to explain the sibling effect. It seems very unlikely that the age of the mother is the underlying causal factor because in this and other reports the sibling effect was still seen after adjustment for the age of the mother at birth of her child. Furthermore, increasing age of the mother has been related to increasing prevalence of hay fever and skin test reactivity,⁸⁴ which contrasts with the inverse relationship found for sibship size. Strachan,⁸³ who first described the phenomenon in 1989, proposed that "infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children" may prevent the development of allergic diseases. The strong inverse relationship between sibship size and the expression of atopy in families may, however, also be attributable to other mechanisms. The number of older siblings might be a surrogate measure for multiple pregnancies in which fetomaternal immune responses may change with each pregnancy. If this notion were correct, then not only the number of older siblings but also the number of pregnancies including miscarriages should be related to the occurrence of atopic diseases in the offspring.

INFECTIONS

There is still a continuing debate about a potential causal role of virus infections, mainly respiratory syncytial virus (RSV), for the subsequent development of childhood wheezing illness, asthma, and atopy. Two major hypotheses have been proposed to explain the association between respiratory tract infections and subsequent respiratory abnormalities.¹⁰⁰ One hypothesis states that viral infections early in life damage the growing lung or alter host immune regulation. The second hypothesis holds that respiratory infections are more severe in infants and children with some underlying predisposition. In this case, the symptomatic viral infection is merely an indicator of an otherwise silent condition, whereas viral infections were causal risk factors if the first hypothesis holds true. These two arguments are not mutually exclusive. It is conceivable that severe viral lower respiratory tract infections occur primarily in infants and children with an inherent predisposition and

that both the infection and the predisposition contribute to the development of wheezing illness or other long-term respiratory abnormality.

RSV infection is very common in the first year of life. According to Long et al,¹⁰¹ 80% or more of all infants are infected with RSV up to their first birthday, but only approximately 1% of all infants are hospitalized for RSV disease and 0.1% require intensive care. Thus a significant proportion of children undergo inapparent RSV infections in the first years of life, suggesting that there is at least one host factor that determines the development of bronchiolitis after RSV infection.

Several investigators have followed up for several years children with proved RSV bronchiolitis. Most authors¹⁰¹⁻¹⁰³ reported reductions in lung function and increased prevalence of airway hyperresponsiveness in cases compared with controls. These results are, however, also consistent with the notion of an underlying premorbid respiratory abnormality rather than a subsequent damage of the airways through the RSV infection. Pullen and Hey¹⁰³ followed up 130 infants with proved RSV bronchiolitis admitted to hospital at a mean age of 14 weeks and compared them with matched controls. Of the RSV group, 6.2% were wheezing at the age of 10 years compared with 4.5% of the control group. A slightly increased prevalence of repeated mild episodes of wheeze was found during the first 4 years of life (38% vs 15%), but no increased rate of atopic sensitization was seen in the cases compared with the controls. Others confirmed these findings.^{101,102} A recent report from the longitudinal Tucson Birth Cohort Study corroborated the previous observations in a general population sample devoid of potential selection bias through follow-up of a selected hospital population. In the Tucson study RSV LRIs were associated with a diminishing risk of recurrent wheezing over the school years starting with a 4-fold increased risk at age 6 years that then was reduced to no risk at age 13 years.¹⁰⁴ The occurrence of RSV LRI was furthermore unrelated to the development of atopic sensitization. Likewise, viral-associated wheezing may be less related to atopy and BHR and have a better prognosis than atopic asthma does.¹⁰⁵

In several studies an inverse relationship between asthma and the overall burden of respiratory infections has been reported. In Papua New Guinea Anderson¹⁰⁶ observed that respiratory infections were more common among young children in the highlands, where the asthma rate was exceedingly low, compared with the coastal regions of the country, where asthma occurred more frequently. In the Fiji Islands Flynn^{107,108} studied 2 groups of children: the indigenous Fijians who showed a high hospital admission rate for pneumonia and the Fiji Indians whose asthma admission rate was three times higher than in the Fijians. Consistent with the hospitalization rates, Indian children had a 3-fold higher prevalence of asthma and airway hyperresponsiveness than Fijians, whereas respiratory infections were more than twice as common in Fijian than Indian children. In the Eastern European countries a higher prevalence of bronchitis and

respiratory infections was found, whereas atopic sensitization, hay fever, asthma, and BHR were all significantly lower than in Sweden and West Germany.¹⁴⁻¹⁶

The results of other recent studies further substantiate the potential protective effect of infections early in life on the development of mainly atopy and to a lesser extent on asthma in later childhood. In Guinea-Bissau, West Africa, Shaheen et al¹⁰⁹ followed children at the age of 0 to 6 years into young adulthood. The subjects with childhood measles had about half the rate of atopic sensitization defined as skin prick test positivity to aeroallergens than those who had been vaccinated and did not acquire measles (12.8% vs 25.6%). A recent report from southern Italy showed that military recruits who were seropositive for hepatitis A as a potential indicator of hygiene had a significantly lower prevalence of atopic sensitization to common aeroallergens and a lower prevalence of atopic diseases compared with their peers who did not have antibodies to hepatitis A.¹¹⁰ In a recent study from East Germany the development of allergy at the age of 5 to 14 years was significantly reduced if a child from small families entered a day nursery between 6 to 11 months old compared with 12 to 23 months of life or after the second birthday (15.7% vs 21.8% vs 27%).¹¹¹ In the prospective Tucson Cohort Study children who had nonwheezing LRIs such as pneumonia and tracheobronchitis in their first 3 years of life had subsequently reduced skin test reactivity and depressed levels of total serum IgE at the age of 6 years.¹¹² A potential protective effect of parasitic infections (eg, in areas of the developing world) has not yet been explored sufficiently. Microbial stimulation, both from normal commensals and pathogens through the gut may be another route of exposure that may have altered the normal intestinal colonization pattern in infancy. Thereby the induction and maintenance of oral tolerance of innocuous antigens, such as food proteins and inhaled allergens, may substantially be hampered.^{113,114} These hypotheses, although intriguing, have not to date been supported by epidemiologic evidence because significant methodologic difficulties arise when an attempt is made to measure the microbial pattern of the intestinal flora.

A "human model" that may prove interesting in this context is the recent observation reported by several authors that growing up on a farm confers significant protection against the development of atopy¹¹⁵⁻¹¹⁷ (Fig 1). In a Swiss population of 6- to 15-year-old schoolchildren the odds of having seasonal symptoms of hay fever (adjusted OR 0.34, 95% CI 0.12-0.89) and for development of atopic sensitization as measured by the radioallergosorbent test (adjusted OR 0.31, 95% CI 0.13-0.73) were strongly decreased in children raised on a farm compared with their peers from the same rural area whose parents were not farmers.¹¹⁵ Similarly, in a large survey of Bavarian children entering school at ages 5 to 7 years the prevalence of hay fever among children raised on a farm was significantly lower than among their peers from the same villages who did not grow up on a farm



FIG 1. Childhood environment and allergic sensitization. Studies from Switzerland,¹¹⁵ Bavaria,¹¹⁶ and Austria¹¹⁷ indicate that children raised on farms are at greater reduced risk for development of atopy than are non-farm children from the same villages.

(1.8% vs 4.9%, $P \leq .001$).¹¹⁶ Adjustment for potential confounding variables confirmed the strong inverse relationship (adjusted OR 0.52, 95% CI 0.28-0.99). A recent Austrian¹¹⁷ survey of 8- to 10-year-old children has confirmed the findings. In all surveys a slight protective effect was also seen for the prevalence of asthma (eg, adjusted OR 0.65, 95% CI 0.39-1.09 in Bavaria), whereas the development of atopic eczema was not affected by farming activities of the parents.

Living conditions of farming families differ in many respects from lifestyles of other families: larger family size, more pets, frequently heating with wood or coal, less maternal smoking, more dampness, and other dietary habits. None of these factors could so far explain the strong inverse association between atopy and growing up on a farm. In contrast, contact with livestock and poultry was found to explain much of the relationship between farming and atopy in the Austrian study (Riedler, personal communication). Likewise, in the Bavarian survey a strong inverse dose-dependent relationship between exposure to livestock and the prevalence of atopic diseases was found (adjusted OR 0.41, 95% CI 0.23-0.74 for frequent contact to livestock).¹¹⁷ Furthermore, Austrian children with regular contact with farm animals but not growing up on a farm had a significantly lower prevalence of atopic sensitization (13.5% vs 34.8%, $P = .01$) than did children with no contact (Riedler, personal communication). These findings suggest that factors prevalent in stables and presumably thereby also in the homes of farming families confer the protection that is associated with a farming lifestyle. A potential candidate among

other factors is the exposure to bacterial products such as endotoxin and LPS in the stables that may, through binding with the CD14 receptor, result in increased production of IL-12 and thereby activation of the T_H1 pathway.^{118,119} Polymorphisms in the CD14 gene have recently been identified,¹²⁰ which may be of importance for a subject's response to the environmental exposure to bacterial products. Increased or altered microbial exposure may, however, also arise through the consumption of unpasteurized milk. Further investigations including measurements of microbial contamination, a child's immune response, and his or her genetic background among farming environments are needed.

These findings have prompted investigators to speculate about a potential harmful effect of vaccinations and antibiotic use. This discussion was further fueled by a recent article by Shirakawa et al,¹²¹ who reported that, among BCG-immunized Japanese schoolchildren, asthmatic symptoms and several index values of atopy were significantly less likely in positive tuberculin responders compared with negative responders and that remission of atopic symptoms between the ages of 7 and 12 years was much more likely in positive tuberculin responders. The interpretation of these findings has been debated intensively. The inverse association between allergic status and tuberculin reactivity may simply reflect the imbalance of T_H1/T_H2 responsiveness characteristic of atopic individuals who have been shown to express smaller delayed-type hypersensitivity skin reactions to recall antigens than nonatopic subjects do.¹²² This imbalance may relate to genetic or other constitutional factors rather

than to exposure to mycobacteria. Such an interpretation is supported by findings of a Swedish group showing that a single immunization for BCG after birth does not affect the prevalence of atopic diseases at school age.¹²³

Likewise, the role of vaccination for measles has been questioned. The generalizability of the findings from Guinea-Bissau, West Africa, to Western populations must, however, be called in question. In fact, several studies were unable to detect an adverse effect of childhood immunizations on the development of allergic diseases.^{124,125} Moreover, there is no evidence to date to suggest that the use of antibiotics may be causally related to the inception of childhood asthma or allergies. A recent retrospective study by Farooqi and Hopkin¹²⁶ showing a positive association between antibiotic use and asthma must be interpreted with great caution because a potential severe bias by reverse causation (ie, children with pre-existing symptoms of asthma may receive more antibiotics because of their disease) cannot be excluded. This study also pointed toward a potential risk associated with pertussis immunization, as seen in another investigation from New Zealand.¹²⁷ In the latter study no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years were seen in the 23 children who received no diphtheria-pertussis-tetanus and polio immunizations. These numbers are, however, quite small and other studies have failed to show significant associations with immunization status.^{124,125}

OUTLOOK

When we speculate about future avenues to reduce our ignorance about the relevant causal factors for the inception of allergic diseases, several issues come to mind. In epidemiology informative study populations must be identified. These may include populations over a broad range of exposure to a suspected risk factor or populations with a significant contrast in the prevalence of allergic diseases. Within the latter group a comparison of environmental influences in ethnically similar groups may prove particularly interesting. Such "human models" may include subjects living in urban and rural areas in developing countries¹²⁸ exposed or not exposed to anthroposophic lifestyles¹²⁹ or to a farming environment.¹¹⁵⁻¹¹⁷ Furthermore, the timing of exposure may be an important determinant because several studies indicate the importance of the first 1 to 3 years of life for the maturation of immune responses related to asthma and allergies.¹¹⁸ Several "windows of opportunity" may be relevant and differ between atopic conditions. Potential gene-environment interactions must become a focus of attention because complex diseases such as asthma and allergic conditions are likely to be determined by interactions between multiple major and minor genes and involve important environmental factors for their expression.⁶ Both the search for genes and for environmental determinants relies on increasing knowledge about the mutual cofactors.

CONCLUSIONS

Environmental factors play an important role for the development and manifestation of allergic conditions in genetically predisposed subjects. There is little evidence to suggest that exposure to air pollutants such as sulfur dioxide, particulate matter, traffic exhaust, or ozone is associated with the inception of new cases of atopy or asthma. Rather, lifestyle factors relating to the socioeconomic status of a population or a family, its size, and the number of siblings of a given individual, her or his history of early childhood infections with viruses and bacteria, and a subject's dietary habits may be of greater relevance. The future challenge is to tackle the complex interplay between environmental factors and genetic determinants that will eventually contribute to a better understanding and hopefully to better prevention strategies for such multifactorial conditions as asthma and allergies.

REFERENCES

1. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;8:161-76.
2. Emanuel MB. Hay fever, a post industrial revolution epidemic: a history of its growth during the 19th century. *Clin Allergy* 1988;18:295-304.
3. von Mutius E, Martinez FD. Epidemiology of childhood asthma. In: Murphy S, Kelly HW, editors. *Lung biology in health and disease: pediatric asthma*. New York: Marcel Dekker; 1999. p 1-39.
4. Woolcock AJ, Peat JK. Evidence for the increase in asthma worldwide. In: Chadwick DJ, Cardew G. *The rising trends in asthma*. Chichester: John Wiley; 1997. p 122-34. Ciba Foundation Symposium No.: 206.
5. International Study of Asthma and Allergies in Childhood Steering Committee. Worldwide variations in the prevalence of atopic diseases: the International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet* 1998;351:1225-32.
6. Barnes KC, Marsh DG. The genetics and complexity of allergy and asthma. *Immunol Today* 1998;19:325-32.
7. Rose G. *The strategy of preventive medicine*. Oxford: Oxford University Press; 1992.
8. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
9. Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol* 1992;98:279-85.
10. von Mutius E, Nicolai T. Familial aggregation of asthma in a South Bavarian population. *Am J Respir Crit Care Med* 1996;153:1266-72.
11. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
12. von Mutius E. Air pollution and asthma. In: Bousquet J, Yssel H, editors. *Lung biology in health and disease: immunotherapy in asthma*. New York: Marcel Dekker; 1999. p 497-534.
13. von Mutius E, Fritzsche C, Weiland SK, Roell G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *BMJ* 1992;305:1395-9.
14. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
15. Nowak D, Heinrich J, Jörres R, Wassmer G, Berger J, Beck E, et al. Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: West and East Germany. *Eur Respir J* 1996;9:2541-52.
16. Braback L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Björkstén B. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. *Clin Exp Allergy* 1994;24:826-35.

17. Braback L, Breborowicz A, Julge K, Knutsson A, Riikjarv MA, Vasar M, et al. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch Dis Child* 1995;72:487-93.
18. Salvi S, Frew AJ, Holgate ST. Is diesel a cause for increasing allergies? *Clin Exp Allergy* 1999;29:4-8.
19. Salvi S, Holgate ST. Mechanisms of particulate matter toxicity. *Clin Exp Allergy* 1999;29:1187-94.
20. Knox RB, Suphioglu C, Taylor P, Desai R, Watson HC, Peng JL, et al. Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. *Clin Exp Allergy* 1997;27:246-51.
21. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a helper cell 2-type pattern. *J Immunol* 1997;158:2406-13.
22. Terada N, Maesako K, Hiruma K, Hamano N, Houki G, Konno A, et al. Diesel exhaust particulates enhance eosinophil adhesion to nasal epithelial cells and cause degranulation. *Int Arch Allergy Immunol* 1997;114:167-74.
23. Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest* 1994;94:1417-25.
24. Wjst M, Reitmeir P, Dold S, Wulff A, Nicolai T, von Loeffelholz-Colberg E, et al. Road traffic and adverse effects on respiratory health in children. *BMJ* 1993;307:596-600.
25. Nitta H, Sato T, Nakai S, Maeda K, Aoki S, Ono M. Respiratory health associated with exposure to automobile exhaust. I: results of cross-sectional studies in 1979, 1982, and 1983. *Arch Environ Health* 1993;48:53-8.
26. Oosterlee A, Drijver M, Lebert E, Brunekreef B. Chronic respiratory symptoms in children and adults living along streets with high traffic density. *Occup Environ Med* 1996;53:241-7.
27. Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Arch Environ Health* 1994;49:223-7.
28. Pershagen G, Rylander E, Norberg S, Eriksson M, Nordvall SL. Air pollution involving nitrogen dioxide exposure and wheezing bronchitis in children. *Int J Epidemiol* 1995;24:1147-53.
29. Ishizaki T, Koizumi K, Ikemori R, Ishyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. *Ann Allergy* 1987;58:265-70.
30. Hirsch TH, Weiland SK, von Mutius E, Safeca AF, Gräfe H, Csaplovics E, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999;14:669-77.
31. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 1997;8:298-303.
32. Linn WS, Avol EL, Shamoo DA, Spier CE, Valencia LM, Venet TG, et al. A dose-response study of healthy, heavily exercising men exposed to ozone at concentrations near the ambient air quality standard. *Toxicol Ind Health* 1986;2:99-112.
33. Weinmann GG, Bowes SM, Gerbase MW, Kimball AW, Frank R. Response to acute ozone exposure in healthy men: results of a screening procedure. *Am J Respir Crit Care Med* 1995;151:33-40.
34. Horstman DH, Folinsbee LJ, Ives PJ, Abdul-Salaam S, McDonnell WF. Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. *Am Rev Respir Dis* 1990;142:1158-63.
35. Hazucha MJ. Relationship between ozone exposure and pulmonary function changes. *J Appl Physiol* 1987;62:1671-80.
36. Linn WS, Medway DA, Anzar UT, Valencia LM, Spier CE, Tsao FSD, et al. Persistence of adaptation to ozone in volunteers exposed repeatedly for six weeks. *Am Rev Respir Dis* 1982;125:491-5.
37. Farrell BP, Kerr HD, Kulle TJ, Sauder LR, Young JL. Adaptation in human subjects to the effects of inhaled ozone after repeated exposure. *Am Rev Respir Dis* 1979;119:725-30.
38. McDonnell WF, Horstman DH, Abdul-Salaam S, Raggio LJ, Green JA. The respiratory responses of subjects with allergic rhinitis to ozone exposure and their relationship to nonspecific airway reactivity. *Toxicol Ind Health* 1987;3:507-17.
39. Dimeo MJ, Glenn MG, Holtzman MJ, Sheller JR, Nadel JA, Boushey HA. Threshold concentration of ozone causing an increase in bronchial reactivity in humans and adaptation with repeated exposures. *Am Rev Respir Dis* 1981;124:245-8.
40. Folinsbee LJ, Horstman DH, Kehrl HR, Harder S, Abdul-Salaam S, Ives PJ. Respiratory responses to repeated prolonged exposure to 0.12 ppm ozone. *Am J Respir Crit Care Med* 1994;149:98-105.
41. Kulle TJ, Sauder LR, Kerr HD, Farrell BP, Bermel MS, Smith DM. Duration of pulmonary function adaptation to ozone in humans. *Am Ind Hyg Assoc J* 1982;43:832-7.
42. Basha MA, Gross KB, Gwizdala CJ, Haidar AH, Popovich J. Bronchoalveolar lavage neutrophilia in asthmatic and healthy volunteers after controlled exposure to ozone and filtered purified air. *Chest* 1994;106:1757-65.
43. Koren HS, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DH, et al. Ozone-induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis* 1989;139:407-15.
44. Devlin RB, McDonnell WF, Mann R, Becker S, House DE, Schreinemachers D, et al. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1981;4:72-81.
45. Aris RM, Christian D, Hearne PQ, Kerr K, Finkbeiner WE, Balmes JR. Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. *Am Rev Respir Dis* 1993;148:1363-72.
46. Scannell C, Chen L, Aris RM, Tager I, Christian D, Ferrando R, et al. Greater ozone-induced inflammatory responses in subjects with asthma. *Am J Respir Crit Care Med* 1996;154:24-9.
47. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG. Effects of inhalable particles on respiratory health of children. *Am Rev Respir Dis* 1989;139:587-94.
48. Braun Fahrlander C, Vuille JC, Sennhauser FH, Neu U, Kunzle T, Grize L, et al. Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren, SCARPOL Team: Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. *Am J Respir Crit Care Med* 1997;155:1042-9.
49. Detels R, Sayre JW, Coulson AH, Rokaw SN, Massey FJ, Tashkin DP, et al. The UCLA population studies of chronic obstructive disease, IV: respiratory effect of long-term exposure to photochemical oxidants, nitrogen dioxide and sulfates on current and never smokers. *Am Rev Respir Dis* 1981;124:873-80.
50. Linn WS, Hackney JD, Pederson EE, Breisacher P, Patterson JV, Mulry A, et al. Respiratory function and symptoms in urban office workers in relation to oxidant air pollution exposure. *Am Rev Respir Dis* 1976;114:477-83.
51. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington (DC): National Academy Press; 1986.
52. Cook DG, Strachan DP. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54:357-66.
53. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992;89:21-26.
54. Neuspiel DR, Rush D, Butler NR, Golding J, Bijur PE, Kurzon M. Parental smoking and post-infancy wheezing in children: a prospective Cohort study. *Am J Public Health* 1989;79:168-71.
55. Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, et al. Risk factors for childhood asthma and wheezing: importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996;154:681-8.
56. Forastiere F, Agabiti N, Corbo GM, Pistelli R, Dell'Orco V, Ciappi G, et al. Passive smoking as a determinant of bronchial responsiveness in children. *Am J Respir Crit Care Med* 1994;149:365-70.
57. Keeley DJ, Neill P, Gallivan S. Comparison of the prevalence of reversible airways obstruction in rural and urban Zimbabwean children. *Thorax* 1991;46:549-53.
58. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994;308:1132-5.
59. Strachan DP, Harkins LS, Johnston ID, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;99:6-12.
60. Matricardi PM, Franzinelli F, Franco A, Caprio G, Murru F, Cioffi D, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 1998;101:439-44.
61. Wade S, Weil C, Holden G, Mitchell H, Evans R III, Kruszon-Moran D, et al. Psychosocial characteristics of inner-city children with asthma, a description of the NCICAS psychosocial protocol: National

- Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997;24:263-76.
62. Chandra RK. Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediatr Scand* 1979;68:691-4.
 63. Fergusson DM, Horwood JL, Shannon FT, Taylor B. Breast feeding, gastrointestinal and lower respiratory illness in the first two years. *Aust Paediatr J* 1981;17:191-5.
 64. Zeiger RS, Heller S, Mellon M, O'Connor R, Hamburger RN. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J Allergy Clin Immunol* 1986;78:224-38.
 65. Chandra RK, Singh G, Shridhara B. Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. *Ann Allergy* 1989;63:102-6.
 66. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989;84:72-89.
 67. Halcken S, Jacobsen HP, Host A, Holmenlund D. The effect of hypo-allergenic formulas in infants at risk of allergic disease. *Eur J Clin Nutr* 1995;49:S77-83.
 68. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-90.
 69. Weiland SK, von Mutius E, Hüsing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. *Lancet* 1999;353:2040-1.
 70. Peat JK, Hodge L, Salome CM, Woolcock AJ. Dietary fish intake and asthma in children [abstract]. *Am J Respir Crit Care Med* 1995;151(Suppl):A469.
 71. Schwartz J, Weiss ST. The relationship of dietary fish intake to level of pulmonary function in the first National Health and Nutrition Survey (NHANES I). *Eur Respir J* 1994;7:1821-4.
 72. Weiss ST. Diet as a risk factor for asthma. In: *The rising trends in asthma*. Chichester: John Wiley; 1997. p 244-53. Ciba Foundation Symposium No.: 206.
 73. Carey OJ, Locke C, Cookson JB. Effect of alterations of dietary sodium on the severity of asthma in men. *Thorax* 1993;48:714-8.
 74. Lau S, Falkenhörst G, Weber A, Werthmann I, Lind P, Buettner-Goetz P, et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989;84:718-25.
 75. Kuehr J, Frischer T, Meinert R, Barth R, Forster J, Schraub S, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994;94:44-52.
 76. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99:763-9.
 77. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house dust mite allergen (Der p I) and the development of asthma in childhood: a prospective study. *N Engl J Med* 1990;323:502-7.
 78. Charpin D, Birnbaum J, Haddi E, Genard G, Lanteaume A, Toumi M, et al. Altitude and allergy to house-dust mites: a paradigm of the influence of environmental exposure on allergic sensitization. *Am Rev Respir Dis* 1991;143:983-6.
 79. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TAE. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. *Am J Respir Crit Care Med* 1995;151:1388-92.
 80. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356-61.
 81. Peat JK, Woolcock AJ. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyperresponsiveness in children from three different climatic areas of Australia. *Clin Exp Allergy* 1991;21:573-81.
 82. Strachan DP, Harkins LS, Golding J, ALSPAC Study Team. Sibship size and self-reported inhalant allergy among adult women. *Clin Exp Allergy* 1997;27:151-5.
 83. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
 84. Strachan DP, Taylor EM, Carpenter G. Family structure, neonatal infection, and hay fever in adolescence. *Arch Dis Child* 1996;74:422-6.
 85. Räsänen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen LA. Hay fever, asthma and number of older siblings—a twin study. *Clin Exp Allergy* 1997;27:515-8.
 86. Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997;27:240-5.
 87. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ* 1997;314:1003-8.
 88. Golding J, Peters T. The epidemiology of childhood eczema, I: a population based study of associations. *Paediatr Perinat Epidemiol* 1987;1:67-79.
 89. Taylor B, Wadsworth M, Golding J, Butler N. Breast feeding, eczema, asthma and hay fever. *J Epidemiol Commun Health* 1983;37:95-9.
 90. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. *BMJ* 1994;308:692-5.
 91. Strachan DP, Harkins LS, Johnston IDA, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;99:6-12.
 92. Nowak D, Heinrich J, Jörres R, Wassmer G, Berger J, Beck E, et al. Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: West and East Germany. *Eur Respir J* 1996;9:2541-52.
 93. Forastiere F, Agabiti N, Corbo GM, Dell'Orco V, Porta D, Pistelli R, et al. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. *Epidemiology* 1997;8:566-70.
 94. Matricardi PM, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionne P, et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997;314:999-1003.
 95. Matricardi PM, Franzinelli F, Franco A, Caprio G, Murru F, Cioffi D, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 1998;101:439-44.
 96. Sunyer J, Anto JM, Kogevinas M, Barcelo MA, Soriano JB, Tobias A, et al. Risk factors for asthma in young adults. *Eur Respir J* 1997;10:2490-4.
 97. Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997;99:454-60.
 98. Crane J, Pearce N, Shaw R, Fitzharris P, Mayes C. Asthma and having siblings. *BMJ* 1994;309:272.
 99. Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995;8:349-56.
 100. Price JF. Acute and long-term effects of viral bronchiolitis in infancy. *Lung* 1990;168(Suppl):414-21.
 101. Long CE, McBride JT, Hall CB. Sequelae of respiratory syncytial virus infections: a role for intervention studies. *Am J Respir Crit Care Med* 1995;151:1678-81.
 102. Sims D, Downham M, Gardner P, Webb J, Weightman D. Study of 8 year old children with a history of RSV bronchiolitis in infancy. *BMJ* 1978;1:11-4.
 103. Pullen CR, Hey EN. Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ* 1982;284:1665-9.
 104. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5.
 105. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland S. Frequency of infections in the first years of life and risk of asthma, atopy and airway hyperresponsiveness among schoolage children. *Eur Resp J* 1999;14:4-11.
 106. Anderson HR. The epidemiological and allergic features of asthma in the New Guinea Highlands. *Clin Allergy* 1974;4:171-83.
 107. Flynn MGL. Respiratory symptoms, bronchial responsiveness, and atopy in Fijian and Indian children. *Am J Respir Crit Care Med* 1994;150:415-20.
 108. Flynn MGL. Respiratory symptoms of rural Fijian and Indian children in Fiji. *Thorax* 1994;49:1201-4.
 109. Shaheen SO, Aaby P, Hall AJ, Barker DJP, Heyes CB, Shiell AW, et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996;347:1792-6.
 110. Matricardi PM, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionne P, et al. Cross sectional retrospective study of prevalence of atopy among

- Italian military students with antibodies against hepatitis A virus. *BMJ* 1997;314:999-1003.
111. Krämer U, Heinrich J, Wjst M, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. *Lancet* 1998;352:450-4.
112. Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M, GHM Associates. Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Thorax* 1995;50:1067-72.
113. Wold AE. The hygiene hypothesis revisited: is the rising frequency of allergy due to changes in the intestinal flora? *Allergy* 1998;53(46 Suppl):20-5.
114. Holt PG. Mucosal immunity in relation to the development of oral tolerance/sensitization. *Allergy*. 1998;53(46 Suppl):16-9.
115. Braun-Fahrlander CH, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, et al. Prevalence of hay fever and allergic sensitization in farmers' children and their peers living in the same rural community. *Clin Exp Allergy* 1999;29:28-34.
116. von Ehrenstein O, von Mutius E, Illi S, Baumann L, Böhm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 1999. In press.
117. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitisation. *Clin Exp Allergy* 1999. In press.
118. Martinez FD. Maturation of immune responses at the beginning of asthma. *J Allergy Clin Immunol* 1999;103:355-61.
119. Holt PG, Sly PD, Björkstén B. Atopic versus infectious diseases in childhood: a question of balance? *Pediatr Allergy Immunol* 1997;8:53-8.
120. Baldini M, Lohman IC, Halonen M, Erickson RP, Holt PG, Martinez FD. A polymorphism in the 5'-flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum IgE. *Am J Respir Cell Mol Biol* 1999;20:976-83.
121. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997;275:77-9.
122. Strannegard IL, Larsson LO, Wennergren G, Strannegard O. Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. *Allergy* 1998;53:249-54.
123. Alm JS, Lilja G, Pershagen G, Scheynius A. Early BCG vaccination and development of atopy. *Lancet* 1997;350:400-3.
124. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children, prospective cohort study: the Longitudinal Study of Pregnancy and Childhood Team. *BMJ* 1999;318:1173-6.
125. Nilsson L, Kjellman NI, Björkstén B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc Med* 1998;152:734-8.
126. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998;53:927-32.
127. Kemp T, Pearce N, Fitzharris P, Crane J, Fergusson D, St George I, et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997;8:678-80.
128. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999;353:1485-8.
129. Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *Lancet* 1997;350:85-90.