

The Natural History of Allergic Disease in Children and Its Intervention

DOUGLAS E. JOHNSTONE, M.D.

ABSTRACT

A familiarity with the expanding body of information on the natural history of allergic diseases in children will help clinicians provide better advice to parents on the care and intervention of allergic disease.

INTRODUCTION

IN THESE DAYS of slick salesmanship, the motto of health maintenance organizations or private hospitals looking for a larger portion of the shrinking patient share—also corporate health goals and labor's demand for better medical care—is “maintenance of good health”—in other words, prevention of disease. For allergic disease in children, before one can discuss prevention, it is necessary to be familiar with how big a problem allergic disease is in the spectrum of all childhood disease. Also, who are these allergic children, and what are their characteristics? In recent years, clinicians have begun to piece together the factors that, it is hoped, will form a scientific basis not only for predicting who is at risk for those conditions but also for formulating a factually based program of prophylaxis.

It is quite disturbing to find how few recent graduates of pediatric and family medicine training programs seem to be aware of or at least make use of what is known about the natural history of allergic disease⁽¹⁾ in children and how this knowledge can be helpful in its intervention. The reasons for this are many. Because the vast majority of patients with allergic disease are seen in an outpatient or private practice setting rather than on university hospital ward rounds, academicians and, thus, medical students and residents in training tend to overlook the magnitude of the problem in the overall list of medical conditions worthy of serious study. They may not know until they have been out in practice for some years the enormity of the scope of allergic problems. Bronchial asthma and other respiratory allergic disorders make up a very significant portion of chronic disease in children. Allergies rank second in order after dental problems and are among the most costly pediatric medical problems.⁽²⁾ The cost in number of

Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York.

deaths, hospital admissions, and loss of full activity is enormous.⁽³⁾ With such an impact on health and on school and work attendance, interest is growing in learning more about the natural history of allergic disease in order to improve treatment and, hopefully, to prevent its development.

CHILDREN AT RISK

What are the characteristics of those children at risk to develop atopic disease?⁽⁴⁾ Table 1 lists these characteristics.

Whereas most humans form IgE immunoglobulins in response to exposure to some foreign proteins, in atopic individuals, the IgE response persists much longer. Kuhns and Pappenheimer⁽⁵⁾ demonstrated this by finding that young college students given injections of diphtheria toxoid developed skin-sensitizing antibodies to this toxoid. However, 6 months later, positive skin tests to the toxoid persisted only in those students with a positive family history of atopic disease.

Injections of acetylcholine and histamine result in some abnormal dermal responses as well as white dermographism.⁽⁶⁾ Varnier and Hahn⁽⁷⁾ found that 11 of 14 children with asthma and eczema showed a positive delayed blanch skin reaction to intradermal injection of methacholine. At room temperature, they found that basal skin temperature was higher than in nonatopic children in their study. Resting heart rates of children with asthma and eczema were significantly higher than in nonatopics. They concluded that their results indicate that abnormal basal and reactivity levels in cardiac and vascular variables in atopic children may represent a nonallergic factor related to atopy. An immediate family history of atopic disorders seems to set the stage for the development of the atopic state.⁽⁸⁾

Most asthmatics and⁽⁹⁾ some nonasthmatic atopics⁽¹⁰⁾ have hyperreactive airways, as demonstrated by abnormal bronchial responses to the inhalation of methacholine, histamine, and pollen extracts. This hyperreactivity is apparently not inborn but acquired.

Ouellette and Reed⁽¹¹⁾ found that 9 of 10 asthmatics given an injection of killed influenza vaccine had a significant increase in the amount of airway obstruction induced by methacholine inhalation whereas nonatopic children had no such response.

Predisposing factors

With this as a background to the characteristics of those children at risk of developing atopic disease, it is helpful to review what is known about some of the factors that seem to predispose to, or turn on, allergic responses. These are listed in Table 2.

Genetic factors

The inheritability of atopic disorders has been confirmed.^(12,13) There is also a trend toward a genetic predisposition to end-organ inheritance.⁽¹⁴⁻¹⁶⁾ Individuals with the HLA phenotype Dw2

TABLE 1. SOME CHARACTERISTICS OF ATOPIC INDIVIDUALS

1. Persistence of the IgE response
2. Abnormal dermal responses
3. Peculiar autonomic responses
4. Exaggerated bronchial reactivity and irritability
5. Different reactivity to some vaccines and viral infections
6. Age-specific factors in childhood asthmatics
7. Susceptibility to nonspecific mucosal irritants, such as cold air, viruses, histamine-releasing drugs, and psychological stimuli

NATURAL HISTORY OF ALLERGIC DISEASE

TABLE 2. FACTORS THAT MAY PREDISPOSE TO OR MODULATE DEVELOPMENT OF ALLERGIC RESPONSES

-
1. Genetic factors
 2. In utero factors
 - a. Drugs administered during pregnancy (progesterone and beta blockers)
 - b. Maternal smoking during pregnancy
 - c. In utero food sensitization
 3. Mother's serum IgE level
 4. Country of birth
 5. Month of birth
 6. Perinatal complications of mother or infant
 7. Possible predictive value of cord blood IgE level; not all at-risk newborns have elevated cord blood IgE
 8. Influence of infant's diet on subsequent development of allergy
 9. The role of breast-feeding
 10. Surgery, general anesthesia, and/or hospitalization in the first year of life
 11. Household exposure to allergens and pollutants
 12. Cigarette smoking in the home
 13. Role of infection in atopic disease
 14. Role of early immunotherapy in pollinosis and asthma
-

are highly likely to become sensitized to ragweed antigen Ra5. Other phenotypes may also prove to be predictive of atopy. If both parents are allergic, the risk of their offspring developing allergy has been shown to be 40–60%.⁽¹⁷⁾ If both parents are atopic with the same manifestation of atopy, the risk is 50–60%. If one parent is atopic, the risk is 20–40%. If one sibling is atopic, the risk is 25–35%. If neither parent nor sibling is atopic, the risk is 5–15%. Magnusson⁽¹⁸⁾ has reported that atopic women have more male offspring. Another recent interesting but not altogether unexpected report on cellular genetics of allergic disease was reported by Agosti et al.,⁽¹⁹⁾ who were able to demonstrate that allergen-specific IgE-mediated hypersensitivity is adoptively transferable by bone marrow transplantation from donor to recipient by B cells with allergen-specific memory. Marsh et al.⁽¹³⁾ have pointed out that there is increasing evidence that atopic disease development is brought on by multifactorial effects of both genetic and environmental origins. In this regard, Falliers et al.⁽²⁰⁾ cited a study of a group of monozygotic twins. One of each pair had moderately severe asthma requiring chronic medication. The other twin, in each case, had one or two bouts of mild wheezing associated with viral infections. Serum levels of IgE, eosinophilia, and number of positive skin tests to allergens were similar in both twins. However, responses to inhaled methacholine were dissimilar. The more symptomatic twin was more reactive to methacholine inhalation challenge, suggesting that the degree of bronchial hyperreactivity is not inborn but is somehow acquired. What are some of the factors that favor acquiring this state?

In utero factors

A history of symptomatic asthma during pregnancy has been shown to be associated with an increased incidence of respiratory disease or jaundice,⁽²¹⁾ as well as decreased birth weight.⁽²²⁾ Prematurity and low birth weight by themselves, however, do not affect the development of allergy.⁽²³⁾

Drugs administered during pregnancy may have some immunoregulatory actions. Progesterone administered during pregnancy was shown to cause a highly significant increase in cord blood serum IgE levels.⁽²⁴⁾ Similarly, a study of the effects of mothers taking a beta-blocker drug during pregnancy resulted in increased cord blood IgE levels, and follow-up⁽²⁵⁾ of the resulting offspring revealed that at 3 years of age, atopic disease developed in the offspring of 9 of 24 mothers

taking metoprolol compared to only 2 of 19 controls not on the drug with a similar atopic family history.

Maternal smoking during pregnancy causes a significant rise in cord blood serum IgE and IgD,⁽²⁶⁾ as well as IgG.⁽²⁷⁾ These findings were most apparent in newborns with a negative biparental family history of atopy. Furthermore, newborns of nonallergic parents had a more than threefold higher risk of developing atopic disease before 18 months of age if the mother smoked than if she did not. These findings suggest that parental smoking in some way affects the fetal immune system.

There is ample evidence of in utero sensitization to milk,⁽²⁸⁾ wheat,⁽²⁹⁾ egg,⁽³⁰⁾ penicillin,⁽³¹⁾ and microfilariae.⁽³²⁾ Michel et al.⁽²³⁾ reported finding three infants with milk-specific RAST IgE antibodies in their cord blood. Their mothers' sera did not contain similar antibodies, strongly suggesting that these newborns had become sensitized to cow's milk prenatally. In view of this, some pediatric allergists have recommended that mothers of at-risk infants should avoid during pregnancy those foods thought to be most allergenic, e.g., egg, milk, fish, nuts, peanuts, and wheat. The role of the maternal diet during pregnancy on the development of allergy was studied in allergic families in Sweden.^(33,34) Atopic pregnant women were randomly either placed on a diet free of milk and egg during the third trimester of pregnancy or were permitted to eat these foods. However, those on the avoidance diet were permitted to consume 65 g per day of Nutramagen. Recent clinical observations have shown that some babies who are exquisitely sensitive to cow's milk may also exhibit allergic symptoms from drinking Nutramagen. The Swedish authors found no difference in cord blood IgE levels and no positive RAST antibodies to milk or egg in cord bloods. However, mothers fed milk and egg during pregnancy did have higher IgG antibodies to these foods. The authors concluded that avoidance of these foods in pregnancy did not prevent in utero sensitization to foods and may be less likely to affect the fetus than previously supposed. However, longer follow-up of these infants may come to another conclusion. Also, the authors admitted that "evidently, a future beneficial effect of maternal diet in pregnancy cannot be excluded by estimation of cord blood IgE only".

In fact, Chandra et al.⁽³⁵⁾ did demonstrate, in a group of women who had already delivered one atopic child and were placed on a diet avoidance program during pregnancy, that there was a significant reduction of occurrence of atopic eczema compared to mothers permitted to consume milk and egg, fish, beef, and peanut. The effect was even more noticeable for mothers on the restricted diet who breast-fed their infants. Among 55 mothers in the food avoidance group, 17 of their offspring developed atopic eczema. Eczema developed in 5 of 35 infants who were breast-fed, and it occurred in 12 of 20 who were not breast-fed. In the group of women in this study who did not avoid allergenic foods, eczema developed in 30 infants. These differences were significant. Even in the group who did not observe dietary avoidance in pregnancy, eczema occurred five times more frequently in formula-fed than in breast-fed babies. Similarly, Zeiger et al.⁽³⁶⁾ reported that maternal allergen avoidance during pregnancy and lactation resulted in a lowered occurrence of atopic eczema.

One of the main reasons why some workers⁽³⁷⁻⁴⁰⁾ in this field have not endorsed allergenic food avoidance during pregnancy for atopic women is the belief that fetal exposure to large amounts of an allergenic food may result in tolerance to it, whereas exposure to minute amounts of the same antigen might result in sensitization to it. This concept came from the work of Jarret and Hall.⁽⁴¹⁾ However, these workers were able to demonstrate these effects only in rats and only if the antigen were injected along with adjuvant. Kjellman et al.⁽³⁹⁾ have speculated that perhaps exposure to tobacco smoke and other sources of indoor or outdoor pollution may constitute adjuvants for atopic infants. A study by Firer et al.⁽⁴²⁾ has been cited by several workers as the human counterpart to Jarret's animal studies. Firer studied two groups of children allergic to milk. One group was exclusively breast-fed, and the other group received cow's milk either in substantial amounts on more than two occasions or small volumes at frequent intervals over a period of months. The median IgA, IgG, and IgM as well as food-specific IgE levels were higher

in the breast-fed group than in the milk-fed and control groups. It should be noted, however, that there were some important differences in the breast-fed and cow's milk-fed groups. In the breast-fed group, 5 of the 10 infants had urticaria or angioedema, suggesting that they were, perhaps, members of a specially and exquisitely milk-sensitive group described by Schwartz et al.⁽⁴³⁾ It might have been helpful if Firer et al. had done their study prospectively, randomly assigning infants to either group based on cord blood IgE and RAST food-specific antibody studies. The cow's milk-fed group in their study developed mainly gastrointestinal symptoms as evidence of cow's milk allergy rather than urticaria and angioedema found in the breast-fed group.

There probably exists a subset of atopic infants destined to develop severe or even life-threatening milk allergy. In Schwartz et al.'s study,⁽⁴³⁾ these infants had high IgE levels and RAST antibodies to milk. One reason this type of severe allergy is not more common was suggested by Jacoby et al.,⁽⁴⁴⁾ who reported that pregnancy is characterized, in some, by a strong suppressor T cell activity, which may explain the low incidence of IgE-specific sensitization in utero.

Glovsky et al.⁽⁴⁵⁾ reported that immunotherapy with grass extract in mothers led to decreased skin test reactivity in their offspring. Similar studies of offspring of mothers undergoing immunotherapy during pregnancy by the same authors found that the offspring of these mothers were less likely to have positive prick tests to Chinese elm, house dust, and mite than were offspring of mothers not receiving such immunotherapy. Settupane et al.⁽⁴⁶⁾ were not able to confirm these results. They reported a long-term follow-up of children of atopic mothers who either did or did not receive immunotherapy during pregnancy. They found no difference in the proportions of either group's giving positive skin tests to pollens or the numbers who developed asthma or rhinitis.

The mother's serum IgE level plays an important role in the subsequent development of atopy in her child. Michel et al.⁽²³⁾ found that, roughly, the more allergic the mothers, the higher the concentrations of IgE in the cord blood of their newborn infants. If a mother had a serum IgE level of more than 100 IU/ml, the serum IgE of her newborn's blood was significantly higher than that of newborns whose mothers' serum IgE level was less than 100 IU/ml. Conversely, they found that the IgE levels of the infants' fathers did not seem to influence the newborns' cord blood IgE levels.

Country of birth or, more precisely, whether a child is born in an urban area or in a rural area, seems an important predictive factor in whether a child is more likely to develop atopic disease. Morrison-Smith⁽⁴⁷⁾ reported that atopy is less common in "developing" countries than in "developed" countries. In a study of immigrants to England, he confirmed a lower incidence of bronchial asthma in children of African origin who were born outside Britain. Offspring of parents of similar origins who were born in England, however, had at least as high a prevalence of atopic disease as non-African children. This finding is in keeping with the reports of Haus⁽⁴⁸⁾ and Van Niekerk et al.,⁽⁴⁹⁾ who found a lower incidence of atopic disease in rural compared to urban South African blacks. Similar findings have been reported in Nigeria⁽⁵⁰⁾ and New Zealand,⁽⁵¹⁾ as well as in inhabitants of the Maldives⁽⁵²⁾ and Tristan de Cunha⁽⁵³⁾ Islanders. These findings suggest that the difference in the prevalence of asthma in these groups was environmental rather than purely genetic.

Month of birth seems to be a predisposing factor in atopic sensitization. Björkstén et al.^(54,55) studied thousands of Finnish conscripts and found that subjects born in March, i.e., 2 months before the birch pollen season, developed birch pollen allergy twice as often as did those born in other months. Also, the degree of exposure, i.e., the birch pollen count in the year of birth, influences the atopic outcome of such newborns. Croner and Kjellman⁽⁵⁶⁾ found that this seasonal influence was confined to babies with an elevated cord blood IgE. Morrison-Smith and Springett⁽⁵⁷⁾ reported increased risk for grass allergy in British children born before the grass pollen season. Kemp⁽⁵⁸⁾ made similar observations about children born before the grass pollen season. In the United States, Settupane and Hagy⁽⁵⁹⁾ found, similarly, that American infants born 2 months

preceding the ragweed pollen season have a twofold increased risk of developing allergy to ragweed compared to infants born in the winter.

Perinatal complications

Certain details of an infant's perinatal history may significantly affect his or her chances of developing bronchial asthma. A group of psychologists at the New York Hospital⁽⁶⁰⁾ examined the perinatal records of a group of asthmatic children and their mothers' delivery. They found a history of greater frequency of neonatal complications of various sorts among the asthmatic children and their mothers than they found in a control group of nonasthmatic children delivered in the same hospital on the same day. Clearly, this study suggests that a stressful birth significantly increases the chances of a child's subsequently developing bronchial asthma. However, prematurity and low birth weight do not affect the development of allergy.⁽²³⁾

Predictive value of cord blood IgE

Although there is ample evidence^(30,61-67) of the predictive value of an elevated cord blood IgE level, not all children destined to develop allergy have elevated cord blood IgE. Kjellman and Croner⁽⁶⁸⁾ measured cord blood IgE in 1,651 newborns and followed them for 7 years. If the cord blood IgE concentration was more than 0.9 kU/L, atopy developed in 52% of the children by 18 months of age, in 69% by 3 years, and in 82% by 6 years of age. They found that an elevated cord blood IgE level or a positive family history of allergic disease accounted for 67% of the obvious allergic disease in infants in their study identified by 6 years of age. However, 33% of obvious allergic infants did not have either elevated cord blood IgE levels or a positive family history of atopy and would thus not have been identified at birth as being at risk for developing atopic disease. Similarly, Zeiger et al.,⁽³⁶⁾ in reporting on follow-up of a group of at-risk children placed on a prophylaxis program, noted that more than 60% of infants treated prophylactically who subsequently developed atopic disease had undetectable cord blood IgE levels. Also, it must be remembered that total IgE levels may be elevated not only in atopic infants but also in apparently healthy individuals. It is not surprising that one often finds low or normal levels in individuals with very serious atopic disease.⁽⁶⁹⁾ In addition, some ethnic influences affect IgE levels. Haus et al.⁽⁷⁰⁾ studied cord blood IgE levels in South African newborns and found that these levels were significantly elevated in these black infants, even if one eliminated from the study those infants with a positive family history and those whose mothers had *Ascaris* infestation. So although finding an elevated cord blood IgE seems predictive of atopic disease in most infants, not all infants destined to develop atopy have elevated levels.

INFLUENCE OF DIET ON SUBSEQUENT DEVELOPMENT OF ALLERGY

Once a child is born, one of the most important factors influencing his or her chance of developing atopic disease is diet. In the 1920s, pediatricians noted that children who were fed egg yolk, either to treat or to avoid iron deficiency anemia, frequently developed classic atopic eczema. They further observed that a majority of these eczematous infants went on to develop major respiratory allergies, such as asthma or allergic rhinitis.⁽⁷¹⁾ They also noted that seven times as many infants fed cow's milk developed atopic eczema as did those who had been exclusively breast-fed.⁽⁷²⁾

Glaser and Hill are credited with the recommendation that one should deliberately withhold from the diet of babies of allergic families those foods suspected of being common allergenic offenders in the development of eczema. These foods include egg, chicken, milk, beef, and wheat. They suggested that these foods be avoided during the first 6-9 months of life as well as during the mother's last trimester of pregnancy.

Trials of dietary prophylaxis

The first reported trials recommended strict avoidance of egg and chicken and cow products and wheat for 9 months, substituting soybean milk for milk formula. Few of these infants were breast-fed. In the first of these trials,⁽⁷³⁾ infants who were fed such a diet showed significantly less atopic eczema. Also, of those who did develop eczema, only 15% went on to develop asthma or rhinitis. By contrast, 60% of their eczematous siblings and controls not on this diet went on to develop major respiratory allergies. In a second, 12-year prospective study of the effects of dietary prophylaxis,⁽⁷⁴⁾ 235 infants of atopic families were randomly assigned either to be on a diet free of milk, beef, egg, chicken, and wheat for the first 9 months of life or to be permitted to have these foods in the first few months of life. Of those on the prophylactic diet, only 10% were breast-fed. The only other formula permitted for this group was soybean-derived formula. The nondiet group received evaporated milk formula. Follow-up data revealed that significantly fewer (9 of 112) in the milk-free diet group developed asthma compared to infants not placed on such a diet (40 of 120), followed for an average of 12 years. Mothers of both groups were advised to avoid consumption of milk in the last trimester of their pregnancies.

Other studies have reported the helpfulness of dietary prophylaxis. Businco et al.⁽⁷⁵⁾ reported that environmental controls and reduced maternal intake of milk and eggs gave promising results in preventing atopic disease. Zeiger et al.⁽³⁶⁾ carried out a study of dietary prophylaxis, making significant efforts to minimize or avoid criticisms of other such studies. They found that in spite of a prophylactic protocol and regimen, availability of professionals to provide nutritional and environmental guidance, and frequent and personal follow-up, atopic sensitization and allergic disease developed in some of these prospectively followed infants of parents with documented IgE-mediated atopy. The "two most obvious factors responsible for the above findings are parental non-compliance and genetic penetrance."⁽³⁶⁾ These authors used a sensitive enzyme-linked immunosorbent assay (ELISA) for cow's milk-specific IgG antibody to document noncompliance by parents or parent surrogates.

In a follow-up of the subjects in their intervention study, Hamburger et al.⁽⁷⁶⁾ found that less than half (47%) of highly motivated families adhered to one of the fundamental precepts of their allergy prophylaxis study, namely, elimination of or marked restriction of the intake of cow's milk during the last trimester of pregnancy and while nursing their infant. Confirmation of this rather surprising poor showing was noted⁽³⁶⁾ during unexpected home visits, where less than half of the families had removed pets or instituted dust and mold control in the home in spite of detailed environmental instructions. Kajoraari and Saarinen⁽⁷⁷⁾ emphasized the importance of total solid food avoidance for infants for 6 months in dietary prophylaxis regimens. Halpern et al.⁽⁷⁸⁾ were unable to confirm the effectiveness of dietary prophylaxis. A detailed critique of the comparison of the studies of Johnstone and Dutton and Halpern et al. has appeared elsewhere.⁽⁷⁹⁾ Two more recent studies^(80,81) have presented impressive evidence to try to refute the prophylactic advantage of soy vs cow's milk in the prevention of allergic disease. In the first of these, Kjellman and Johansson⁽⁸⁰⁾ studied 48 children with a biparental family history of atopy. The soy-fed group was breast-fed for 2–3 months, and the milk-fed group was breast-fed for 1.5–3 months before milk formula was given. In either group, these children might have become sensitized to cow's milk received via their mothers' breast milk. The authors concluded that withholding cow's milk for 9 months did not reduce the incidence of atopic symptoms of cow's milk intolerance. However, they permitted mothers of both groups to drink milk while nursing and did not specify how long or if solid foods were delayed. Obvious allergy developed in 66.7% of both groups. This incidence of allergy inordinately exceeds any previously published frequencies of allergic disease found in other studies^(81–83) of the incidence of atopic disease in the general population. These authors could not reproduce the findings of Dannaus et al.⁽⁶⁶⁾ that a high level of transplacentally received anti-cow's milk IgG antibody protects against the development of atopic disease.

In a more recent report on the use of soybean formula in a dietary prophylaxis program, Merrett et al.⁽⁸¹⁾ reported a 12 month prospective study of 500 Welsh babies born into allergic families. In the intervention group, 238 mothers were assigned to withhold from their children all cow's milk products for 4 months, replacing them with soy formula or breast-feeding with soy complementary feeds. Mothers in this group were advised to restrict their daily milk intake to one-half pint per day. One third of the soy-fed group were breast-fed compared to 43% of the cow's milk-fed group. By 3 months of age, 26% of the soy group had received some cow's milk products. The allergic symptoms reported among the two groups during the first year were similar, but all symptoms were less in infants in either group who had been breast-fed. This would at least suggest, contrary to the findings of Kjellman and Johansson,⁽⁸⁰⁾ that avoidance of cow's milk was helpful in the intervention of atopic disease in the study groups. Few IgE antisoybean antibodies were detected in the sera of the soy-fed group. As in Zeiger's study,⁽³⁶⁾ these authors found problems with compliance with instructions by parents. At 3 months of age, 37% of the soy-fed group infants had demonstrable serum IgG4 milk-specific antibodies in their sera. In both groups, nasal symptoms were related to house dust mite exposure and number of siblings in the home. Mother's smoking, social class, presence in the home of open fires, and being born within the months of August and November increased the risk of wheezing in either group. They also found no cord blood IgE level below which symptoms of asthma or eczema did not occur. They wondered if the really predictive value of cord blood IgE measurements will be in those infants without a positive family history of atopy. It may be that those with an immediate family history will develop atopic symptoms no matter what the level of cord blood IgE is, if the appropriate dietary and environmental factors are at work. Finally, it is of interest that Merrett et al.,⁽⁸¹⁾ in the discussion of their article, state that "it is just possible that the deleterious effects of cow's milk feeding are yet to show and that the ten-year follow-up trial of Johnstone and Dutton [(74)] anticipates this possibility."

In support of the argument against use of soy formula as a substitute for cow's or breast milk in a dietary prophylaxis regimen, several authors^(36,80,84) refer to the allergenicity of soybean. However, a careful review of the references cited by these authors revealed that with the exception of a description of a child with anaphylaxis from ingestion of soy formula,⁽⁸⁵⁾ most of the references⁽⁸⁶⁻⁸⁹⁾ reported either sprue-like or other nonallergic gastrointestinal symptoms. Asthma from occupational inhalation of soybean dust has been reported.^(90,91) Thus, it was not unexpected that Kjellman and Johansson,⁽⁸⁰⁾ in their soy vs milk prophylaxis trial, found no significant IgE antibodies to soybean in their soy-fed group. In fact, in clinical practice, slightly positive skin tests to soybean extract occur not uncommonly, but the incidence of soybean-induced anaphylaxis as a result of an infant's ingesting soy formula is very low if not rare.

Recently, Lindfors and Enocksson⁽⁹²⁾ attempted to refute the desirability of cow's milk avoidance in at-risk newborns by conducting a study in which 216 infants were randomly given during the first few days of life either cow's milk formula or only breast milk. After their mothers' lactation began, both groups were breast-fed. No effort was made to standardize the age at which infants were weaned or given solids. Nursing mothers were not put on an allergen-free diet. More infants in the breast-fed group developed symptoms of allergy than infants in those permitted to have cow's milk in the first few days of life before resuming breast-feeding. Serum IgE from cord bloods of the breast-fed group were higher than the milk-fed group. This may mean that there could have occurred a bias for more truly at-risk infants being in the breast-fed group. If other factors, such as mothers' ingestion of milk, smoking among mothers, and other social and environmental factors, operated, the two groups may not have been truly comparable and thus not equally at risk for atopic disease. Also, their findings are at odds with those of Stintzing and Zietterstrom.⁽⁹³⁾ The delayed introduction of solid feeding has been associated with a significant prevention of atopic diseases in prospective⁽⁹⁴⁻⁹⁶⁾ and retrospective studies.⁽⁹⁷⁾

In the past, the choice for a hypoallergenic formula for at-risk infants as well as those suspected of having milk allergy was evaporated milk, which was tolerated by some children who

NATURAL HISTORY OF ALLERGIC DISEASE

were sensitive only to the heat-labile milk proteins, such as lactalbumin. Goat's milk has significant cross-reactivity with cow's milk. Wilson and Hamburger⁽⁹⁸⁾ have stated that a formula with even less potential for allergy than soybean is a formula whose protein source is enzymatically hydrolyzed casein. Unfortunately, however, these casein hydrolysate formulas have been shown capable of causing anaphylaxis in a subset of infants who were exquisitely sensitive to milk proteins.^(99,100) This is also true for the newer whey protein hydrolysates.^(101,102) Recently, Schwartz⁽¹⁰³⁾ described 20 children who were very sensitive to cow's milk. All 20 gave a positive prick test to cow's milk proteins. He also found that 75% (15/20) of these infants gave significantly positive prick tests to whey hydrolysate (Good Start), 10/20 had positive prick tests to Alfa-Re, another whey hydrolysate formula, 10/20 had positive prick tests to casein hydrolysate (Nutramagen), and 8/20 had a positive prick test to Elementum. Although he has not yet challenged these infants with these hydrolysates by oral feeding of these formulas, he advised that caution be used when considering the use of hydrolysates of casein or whey in children known to have had severe adverse allergic reactions to cow's milk. He found that those infants with the positive prick tests to the hydrolysate formulas had significantly higher antigen-specific serum IgE antibody levels to cow's milk, casein, and beta-lactoglobulin.

The findings of Schwartz⁽¹⁰³⁾ and of Businco et al.⁽¹⁰¹⁾ are not surprising in view of the report of Seban et al.,⁽¹⁰⁴⁾ who pointed out 12 years ago that because hydrolysis of milk proteins may be incomplete and a number of potentially allergenic macromolecules may be present in such formulas, manifestations of milk intolerance may occur in infants with extreme sensitivity if they are fed such formulas. These same authors showed that although manufacturers of casein hydrolysis formulas claimed that they were produced only from casein, injections of these formulas into animals resulted in the production of precipitating antibodies against at least three whey proteins as well as against casein. The manufacturers of such whey hydrolysates in the United States have removed the word "hypoallergenic," which appeared in bold type on the front of their can labels. This announcement⁽¹⁰²⁾ came just weeks after publicity over reports that a small number of infants, who were extremely allergic to cow's milk formulas, suffered serious reactions to these so-called hypoallergenic formulas.

Breastfeeding: Is it protective?

Some of the controversy⁽¹⁰⁵⁾ about the preventive value of breast-feeding in at-risk infants is due to differences in study design.

Evidence that food proteins gain entrance to an infant via breast milk. Donnally⁽¹⁰⁶⁾ and Cogswell and Alexander⁽¹⁰⁷⁾ demonstrated egg allergy in infants whose only source of egg was via their mothers' breast milk. Similar evidence for sensitivity to cow's milk via breast milk has been reported.^(108,109) Jacobsson and Lindberg⁽¹¹⁰⁾ reported the results of a study of 19 breast-fed infants with severe colic. When the mothers of these infants were put on a diet free of cow's milk, the colic disappeared in 13 of the 19 infants. In 12 of the 13, the colic reappeared when the mothers resumed drinking cow's milk. The authors identified cow's milk proteins in the breast milk of these mothers. Warner⁽¹¹¹⁾ reported infants with eczema whose rash was exacerbated when their mothers ate egg. The eczema cleared when the mothers stopped eating egg and recurred when they ate it again.

Studies suggesting that breast-feeding prevents or delays onset of atopic disease. Saarinen et al.⁽⁹⁴⁾ followed 256 infants for 3 years and found that infants solely breast-fed for 6 months had fewer atopic symptoms than those given cow's milk. This was thought to be significant, however, only if there was a positive family history of atopy. Hide and Gueyer⁽¹¹²⁾ followed 843 infants for 2 years. Breast-feeding was associated with reduced incidence of allergy overall as well as asthma in patients with a negative family history. Blair⁽¹¹³⁾ followed 244 children for 20 years and found that those who had been breast-fed for at least 8 weeks had, on average, an appreciably better prognosis than asthmatics who had never been breast-fed. This finding confirms the previous

findings⁽⁷⁴⁾ suggesting that a prolonged follow-up is needed to be sure of the final outcome of a dietary intervention study. Other studies^(70,114-117) have demonstrated similar findings. Kaufman and Frick⁽¹¹⁸⁾ reported that babies who were breast-fed for 6 weeks were less likely to develop bronchial asthma than those who had been given cow's milk formulas. They prospectively followed full-term infants of 92 allergic mothers for 2 years. Only 2 of 38 breast-fed babies developed asthma, whereas 10 of 56 infants who received cow's milk became asthmatic in this study.

On the other hand, there have been some studies^(96,97,119) that suggested that breast-feeding does not help. However, Midwinter et al.,⁽¹²⁰⁾ Blair,⁽¹¹³⁾ and Atherton et al.⁽¹²¹⁾ have appropriately refuted their conclusions and criticized their study designs.

The latest study in this field is that of Hattevig et al.⁽¹²²⁾ They assigned one group of 65 atopic mothers to a diet free of egg, cow's milk, and fish during the first 3 months postpartum, whereas the 65 mothers in the control group consumed their usual diet. The infants were breast-fed. The diet of both groups of infants was similar; i.e., cow's milk was not permitted during the first 6 months of life, and eggs and fish were not permitted until 9 months of age. The incidence of atopic eczema was significantly lower in the group whose mothers avoided milk, egg, and fish (10.8%) compared to infants whose mothers ate these foods (28%). Additional evidence suggesting the importance of breast-feeding was the report of Chen.⁽¹²³⁾ He reported a synergistic effect of passive smoke exposure and artificial feeding on numbers of hospitalizations for respiratory illness in early childhood. Thus, although there seems little doubt that breast-feeding and avoidance of solids for the first 6 months is helpful to prevent or delay allergy symptoms, it is important that the mothers be on a diet strictly free of cow products, egg, chicken, and fish during the lactation period. Early feeding of solids increases risk of allergy in at-risk infants.

Fergusson et al.⁽⁹⁷⁾ followed 1123 infants for 2 years and found that atopic dermatitis was associated with early solid feedings and was proportional to the number of solid foods introduced in the first year of life. Similarly, Murray,⁽¹²⁴⁾ in a survey of Canadian children, found that any child with a positive family history of allergy who was exclusively breast-fed was significantly less likely to have rhinorrhea or nasal eosinophilia.

Additional potential benefits of breast-feeding. Downham et al.⁽¹²⁵⁾ found that breastfeeding protects against respiratory syncytial viral infections. Machtinger and Moss⁽¹²⁶⁾ studied 57 mother-infant pairs with a positive family history of atopy. Eleven infants in the study developed obvious allergic disease. The breast milk from mothers of these 11 infants was found to contain lower total IgA as well as lower IgA antibodies to cow's milk and casein than breast milk from mothers whose infants had few or no allergic symptoms. Inadequate quantities of maternal antibodies to food allergens appear to play a permissive role in the development of allergic disease in at-risk infants who are breast-fed. In this regard, it is of interest that Sloper et al.⁽¹²⁷⁾ reported that atopic eczematous infants have significantly lower IgA plasma cell counts in their jejunal mucosa biopsies than do controls. Also, Schwartz and Buckley⁽¹²⁸⁾ found that children with no serum IgA are more likely to have allergic disease. Taylor et al.⁽¹²⁹⁾ reported that at-risk children of allergic families who had transient lower levels of serum IgA at 3 months of age were more likely to develop eczema and to have positive skin tests to allergens. Juto⁽¹³⁰⁾ described a subset of infants with low T lymphocyte counts in their blood at 1 month of age who were more likely to develop an elevated serum IgE level if fed cow's milk, whether or not breast-fed. These findings suggest that the tendency to develop allergic disease is multifactorial and that some of the determinants act at certain crucial ages in the infant or fetus. When we have a more complete understanding of all of these factors, we can be more specific about intervention suggestions and the times when they should be applied.

NATURAL HISTORY OF ALLERGIC DISEASE

Other dietary factors

Anderson et al.⁽¹³¹⁾ reported the interesting observation of the oral pruritis that occurs when some hay fever patients eat cantaloupe, banana, honeydew melon, or watermelon. Patients with this type of symptom were all highly allergic to ragweed and were more likely to develop pollen asthma than were ragweed-sensitive hay fever patients without itching in their throats from eating melons. Similarly, there has been reported oral itching in birch pollinosis when eating apples.⁽¹³²⁾ Other authors have found a relationship between birch pollinosis and symptoms from ingestion of hazelnut, potato, apple, carrot, and celery.⁽¹³³⁻¹³⁸⁾ Moller⁽¹³⁹⁾ reported on a study of 72 children with birch pollinosis. Of these, 93% reported sensitivity to nuts, apples, and carrots. Their hay fever symptoms improved after immunotherapy. However, neither subcutaneous nor oral immunotherapy resulted in a decrease in their food sensitivities. Dreborg⁽¹⁴⁰⁾ has reviewed the mechanisms involved in these food sensitivity symptoms in pollen-sensitive children.

EARLY SURGERY OR ANESTHESIA AND HOSPITALIZATION IN THE FIRST YEAR OF LIFE

In early infancy, factors other than diet seem to turn on the allergic diathesis. Johnstone et al.⁽¹⁴¹⁾ conducted three studies to follow up the clinical impression of some pediatric allergists that early surgery might increase the risk of developing asthma or hay fever. In the first part of the study, 115 children who had been operated on for pyloric stenosis were traced and found to have had an above-average prevalence of allergic disease. Of those who had undergone such an operation, 20% developed bronchial asthma, 21% developed hay fever, and 36% developed one or both of these conditions. These prevalences were much higher than those found in household interviews in the Rochester Child Health Study investigation⁽⁸³⁾ of a random sample of children 0-17 years of age in Monroe County, New York. That study showed that 3.4% of the random sample of Rochester children had had asthma, 8.5% had had hay fever, and 10.6% had had one or both of these conditions. In the second part of their study, Johnstone et al.⁽¹⁴¹⁾ reported on 47 boys who had had a hernia repair and who were followed with similar results. Of those who had undergone a herniorrhaphy in their first year of life, 34% developed asthma, 21% developed hay fever, and 55% developed either one or both of these conditions. In the third part of the study, 202 children from the Rochester Child Health Study⁽⁸³⁾ whose parents had reported that they had had asthma or hay fever were studied for evidence of early hospitalization or surgery. Their parents reported significantly more hospitalizations. For boys under 2 years of age, there were significantly more operations necessitating general anesthesia than for nonasthmatic children of the same age from the same random population group.

HOUSEHOLD EXPOSURE TO ALLERGENS AND POLLUTANTS

Factors in one's indoor and outdoor environment, which may have an impact on the atopic patient and affect how symptomatic one's condition may be, are numerous, and the number grows each year. Some of them are living organisms or are derived from living creatures, e.g., molds, mites, pollens, animal danders. Some are inanimate factors, such as temperature, humidity, wind, and strong odors. Kjellman et al.⁽³⁹⁾ have proposed that environmental factors, especially cigarette smoking, may act as adjuvants for the process of IgE-type sensitization in humans, much as proposed by Szentivanyi's animal model of *Bordetella pertussis*-induced hypersensitive state of mice and rats.⁽¹⁴²⁾ Climatic factors may influence the availability of allergens. Interest is centering on the influence of air pollution, indoors and outdoors. Samet et al.⁽¹⁴³⁾ called attention to the importance of particles and fumes, especially tobacco smoke, SO₂, and NO₂.

Effect of cigarette smoking

The literature on the health effects of involuntary smoking⁽¹⁴⁴⁾ is vast and expanding. Parental smoking raises children's serum IgE⁽¹⁴⁵⁾ and IgD.⁽¹⁴⁶⁾ It also results in a 60% increase in asthma-related visits to emergency departments of hospitals.⁽¹⁴⁷⁾ Using other criteria for studying the effect of passive smoke of mothers, Murray and Morrison⁽¹⁴⁸⁾ investigated 94 consecutively observed asthmatic children. The 24 children whose mothers smoked, when they were compared with children whose mothers did not smoke, had 47% more symptoms, a 13% lower mean FEV₁ percent, a 23% lower mean FEF₂₅₋₇₅, and a fourfold greater responsiveness to aerosolized histamine. There was a highly significant correlation between the results of the tests and the number of cigarettes the mother smoked while she was in the house. The differences between the children of smoking and nonsmoking mothers were greater in older than in younger children.

Black⁽¹⁴⁹⁾ estimates that 30% of all chronic middle ear effusions in children could be attributed to passive smoking exposure. Also, smoking plays a role in recurrent otitis media.⁽¹⁵⁰⁾ Pukander et al.⁽¹⁵¹⁾ found that exposure to passive smoking increases the frequency of acute otitis even if the patient is not atopic. Exposure to smoke significantly increases the number of episodes of bronchitis⁽¹⁵²⁾ in children of allergic families.^(153,154) Oski,⁽¹⁵⁵⁾ commenting on the article of Murray and Morrison,⁽¹⁴⁸⁾ stated that "A pregnant woman who smokes, smokes for two" and "This form of child abuse should be reportable!"

Indoor household dampness

Andrea et al.⁽¹⁵⁶⁾ demonstrated a synergistic effect of parental smoking and dampness in the home, which increased allergy to animal pets but not to pollen. Outdoor pollution, on the other hand, increased the risk of pollen asthma. The effect of dampness in the home had an effect only among children with a genetic propensity^(39,143) for asthma.

Role of house dust mites

Over the past 20 years, allergists have come to appreciate the importance of house dust mite,⁽¹⁵⁷⁾ which is probably the single most important source of house dust allergens. Since then, reports from around the world have documented the role of mites as an etiologic allergen in asthma⁽¹⁵⁸⁻¹⁶³⁾ as well as in rhinitis and atopic dermatitis.⁽¹⁶¹⁻¹⁶⁴⁾ A committee of the American Academy of Allergy and Immunology⁽¹⁶⁵⁾ reviewed the types and performance characteristics of available domestic air-cleaning devices, the available data on concentration of allergens in indoor air, and the studies on the clinical relevance of the use of indoor air-cleaning devices. They concluded that use of room air-cleaning devices in the absence of other forms of environmental controls was not reasonable. In an effort to elucidate these "other forms of environmental controls," Mosbech et al.⁽¹⁶⁶⁾ carried out a study to demonstrate the importance of heat and humidity control in reducing exposure to dust mites. They studied the mite content of mattress dust in beds covered with electric heating blankets and found significant differences between beds with and without electric blankets within the first month of observation. The amount of dust mite in mattresses of control beds increased by 120% compared to a reduction of 52% in beds supplied with electric blankets. Also, climatic conditions were measured beneath the blanket in a spare bed in the same bedroom. When beds were covered with eiderdown, the temperature was increased by 12°C. and the relative humidity was decreased by 24% within 3 hours. Comparisons of laboratory results with actual measurements in dwellings⁽¹⁵⁷⁾ demonstrated that humidity is usually the decisive limiting factor for mite growth.⁽¹⁶⁶⁻¹⁷⁰⁾ The primary source of food of mites appears to be human skin scales or fungi growing on skin scales. The efficiency of avoidance measures is supported⁽¹⁵⁷⁾ by studies on patients living in mite-free environments, such as high altitude or mite-free rooms, in which patients have demonstrated both improvement of

NATURAL HISTORY OF ALLERGIC DISEASE

asthma and reduced nonspecific bronchial reactivity.^(161,171,172) Two controlled studies^(173,174) have demonstrated the clinical efficacy of cleaning measures in patients' houses. Mothers of mite-sensitive children need to know the importance of removal of bedroom rugs, closing hot air bedroom registers, and frequent hot water laundering of a child's bedding. Miller et al.⁽¹⁷⁵⁾ recently reported on the efficacy of using a 3% tannic acid spray in reducing dust mite concentrations in carpets.

Household pets

One important source of increasing the allergic load in the home is the presence of animal pets. When it is hot, most pets pant and drool saliva to control their body temperatures instead of sweating. When this highly allergenic saliva dries, it becomes an important part of what we call "house dust" in the home. Only in industrialized nations do parents have the necessary room, food, and finances to maintain household pets. In large cities of countries such as China,⁽¹⁷⁶⁾ asthma resulting from allergy to cats, dogs, hamsters, or guinea pigs rarely occurs because cramped housing conditions, the fact that both parents go to work, and limited food availability make the keeping of pet animals in homes impractical. Chinese pediatricians could not believe that Americans not only keep cats and dogs in their homes but often have them sleep in a child's bedroom or even on the bed! Although most allergists agree that the most rational therapy for atopic disease is complete avoidance of the offending allergen, we seem to be waging a losing battle⁽³⁶⁾ to convince parents to remove pets from the home. It is not surprising that even when parents have been convinced to get the cats out of the home, cat antigen Fel d 1 can be demonstrated in dust samples in the homes⁽¹⁷⁷⁾ up to 24 weeks later.

Attempts at hyposensitization through immunotherapy have been made with varying success. Taylor et al.⁽¹⁷⁸⁾ were able to demonstrate that immunotherapy with a potent cat antigen can decrease bronchial reactivity to inhalation challenge with the same cat antigen. Efforts are ongoing to further identify breed-specific dog dandruff antigens.⁽¹⁷⁹⁾ Clinicians have long observed that pet-sensitive children may respond on exposure with allergic symptoms to some cats or dogs while failing to do so to other species of the same animal. This observation, however, is not an excuse for a parent to exchange a child's cat or dog for another pet of the same species for an asthmatic child known to be sensitive to his or her own pet.

ROLE OF INFECTION IN ATOPIC DISEASES

In an effort to separate out the relative roles of genetics vs. environmental factors in the development of allergic disease, Frick et al.⁽¹⁸⁰⁾ studied prospectively 13 infants born to allergic families. Over the 4-year study, all 13 developed some symptoms of allergy. An upper respiratory infection occurred in 11 of the 13 children 1–2 months before the onset of allergic sensitization. Evidence for a viral infection was an increase in complement-fixing antibody titers to viruses, such as parainfluenza, respiratory syncytial, and cytomegalic inclusion viruses. To further evaluate the relationship between viral infections and the development of allergic sensitization, Frick⁽¹⁸¹⁾ conducted studies on inbred allergic dogs. Puppies from litters of dogs with positive skin tests for grass pollens were given injections of pollen extracts, and measurements of IgE antibody were then compared in animals given either live attenuated distemper-hepatitis virus vaccination or placebo injections. Vaccinated puppies produced more IgE antibody to pollen than did unvaccinated littermates. In additional experiments, IgE sensitization was determined in pups who were given an intranasal canine parainfluenza virus vaccine followed by pollen inhalation or in littermates exposed only to inhalation of pollen. More IgE antibody to pollen was produced in parainfluenza-vaccinated dogs than in unvaccinated littermates. Frick concluded that in atopic-prone children as well as in inbred dogs, viral infections can alter immunoregulation of IgE and thereby influence the development of allergic disease. It

is important to keep in mind that it is viral infections and not bacterial infections that cause trouble in atopic children.⁽¹⁸²⁾ For this reason, it was not surprising that bacterial vaccines proved no better than placebo injections in protecting against the allergic effects of respiratory infections.⁽¹⁸³⁾

Welliver et al.⁽¹⁸⁴⁾ discovered a correlation between titers of RSV-IgE antibody and the pattern of respiratory illness. Children with either pneumonia with wheezing or bronchiolitis had higher titers of virus-specific IgE antibody during both acute and convalescent periods compared to infants with upper respiratory RSV illness without wheezing. Welliver et al.⁽¹⁸⁵⁾ also found that the pattern of IgE antibody response to parainfluenza virus was similar to observations with RSV infections. To evaluate further the significance of virus-specific IgE, Welliver et al.⁽¹⁸⁶⁾ followed 38 infants for 48 months after an initial episode of bronchiolitis. They found that 70% of infants with high RSV-IgE antibody titers experienced wheezing on later occasions. Only 28% of infants with undetectable titers of RSV-IgE had subsequent episodes of documented wheezing. The authors concluded that sensitization to antigens other than the viruses can follow damage to bronchial epithelia because antigen permeability increased.

The direct effect of virus infection on allergic subjects as well as the late asthmatic response was studied by Lemanski et al.⁽¹⁸⁷⁾ They studied 10 adult ragweed-allergic rhinitis patients. One month after baseline studies, the patients were inoculated intranasally with live rhinovirus (RV16). During the acute RV illness, there was a significant increase in airway reactivity both to histamine and to ragweed antigen. Before the rhinovirus inoculation, only 1 of 10 subjects had a late asthmatic reaction after antigen challenge. However, during the rhinovirus infection, 8 of 10 patients had a late asthmatic reaction ($p < 0.0085$ compared with baseline). The development of the late asthmatic reactions was independent of changes in airway reactivity and the intensity of the immediate response to antigen. Busse⁽¹⁸⁸⁾ recently reviewed the subject of the relationship of viral infections to the onset of allergic disease and asthma. He notes that during acute rhinovirus infection, leukocyte histamine release to ragweed antigen was significantly enhanced over baseline. The greater the amount of leukocyte histamine release following activation, the greater the degree of bronchial reactivity.

EARLY IMMUNOTHERAPY MAY SIGNIFICANTLY ALTER THE NATURAL HISTORY OF CHILDHOOD POLLINOSIS

Having considered what constitutes being allergic and some of the forces that seem to turn on the process, it seems appropriate to sum up the clinical conditions in which the type and timing of treatment may influence the outcome in children. Immunotherapy, appropriately applied, can be a useful tool in the treatment of respiratory allergies. However, immunotherapy by itself should never be considered the total treatment of these conditions. Four general factors determine how well or poorly an individual child will do. Paying attention to or crediting the success of treatment to only one of them completely misses the point of optimal holistic medical management of the allergic child.⁽¹⁸⁹⁾ Unless all these factors receive equal attention by investigators, the findings may color the validity⁽¹⁹⁰⁾ or creditability of such reports. The first of these factors is the degree of success in lessening or interrupting exposure to offending allergens. The second is judicious use of prophylactic and therapeutic pharmacologic agents. The third factor is appropriate use of immunotherapy. The fourth is general, nonspecific advice, including avoidance of nonspecific irritants, such as tobacco smoke, education of patients and families on the use of therapies, including use of gadgets to monitor severity of asthma, and warning parents not to inadvertently teach children to use their illness for gain. Choice of careers may be an important subject to discuss with patients and parents.

NATURAL HISTORY OF ALLERGIC DISEASE

Immunotherapy in pollinosis and allergic rhinitis

Seasonal allergic rhinitis due to pollen allergy is one of the most common as well as the most undertreated types of allergy in American children.⁽¹⁹¹⁾ In an effort to characterize any benefit from immunotherapy in children with pollinosis, a prospective controlled study was designed in the Allergy Clinic of the University of Rochester School of Medicine.⁽¹⁹²⁾ We started with the thesis that to give immunotherapy for childhood hay fever did not help any child. The object of the study was to prove this thesis or disprove it. Children with a history of August–September hay fever, with a positive family history for atopy and a positive skin test to short ragweed were assigned to receive either immunotherapy injections of extract of short ragweed or placebo injections. Otherwise, their treatments were the same. The fact that an experiment was going on was unknown to the mother, the nurses administering the injections, and the clinic physicians who evaluated the children. The study went on for 5 years. Not all of the children receiving ragweed injections lost all their hay fever symptoms, but none of them developed asthma during the study period. Approximately 40% of the placebo group developed asthma, first in the ragweed season and then at other times of the year. Also, significantly more of the placebo group developed allergic rhinitis symptoms in nonpollen seasons.

In reviewing the study population afterward, it was found that the severity of the hay fever symptoms in either group before the study had nothing to do with whether or not a child went on to develop asthma. We could find no distinguishing features of a single child in the placebo group that would indicate which child was at risk to develop pollen asthma. However, the tendency for a child to do well in this study seemed related to the dose of antigen given in immunotherapy. The higher the dose of ragweed antigen a child was given, the better were the symptom scores and the less likely the child was to develop asthma. None of those who received relatively high doses of ragweed antigen developed asthma during the study period if they had not already had asthma before the study began. We concluded that although we could have prevented asthma in this experimental population in only a portion of the children with hay fever, we thought that children with pollen hay fever should receive immunotherapy regardless of the severity or mildness of their allergic symptoms. This points out a difference in the natural history of hay fever in children compared to adults, where the chances of an untreated adult hay fever patient's developing asthma because of not receiving immunotherapy may be as low as 2–5 per thousand.

Parents of atopic children deserve to know these differences, and if they should decide to defer immunotherapy, they should at least participate in the decision-making. Pediatricians should recall that patients with hay fever but without asthma may show slightly abnormal pulmonary function tests during the pollen season.⁽¹⁹³⁾ Townley et al.⁽¹⁰⁾ demonstrated a significant increase in bronchial sensitivity to inhalation of methacholine, histamine, and pollen extracts in patients with hay fever compared to normals. More recently, Ramsdale et al.⁽¹⁹⁴⁾ reported finding methacholine responsiveness in 10 of 25 rhinitis patients with no history of asthma. These findings suggest that pulmonary function tests should be a routine part of the work-up of new patients with hay fever or perennial allergic rhinitis who have never shown signs of asthma.

Others have reported⁽¹⁹⁵⁾ similar findings on the benefits of early immunotherapy in children with hay fever as well as pointing⁽¹⁹⁶⁾ out that the results were better the shorter the duration of symptoms before immunotherapy began and the longer the duration of therapy.

However, studies of Broder et al.⁽¹⁹⁷⁾ and Smith⁽¹⁹⁸⁾ claimed that they were unable to corroborate the concept that early immunotherapy in children with hay fever prevented the subsequent development of pollen asthma. In a review of these studies,⁽¹⁸⁹⁾ it was pointed out that in these studies, interviews of families were carried out in a small town in Michigan. It is of interest that the authors asked about hay fever and asthma in only a few of the children between the ages of 6 and 8 years. However, “neither asthma nor hay fever were uniformly asked about in the remainder of six and seven year olds and all those under six years of age. This entire

group (under age six) has been excluded from consideration in this report.”⁽¹⁸⁹⁾ As is well known to most pediatricians, the onset of these conditions occurs well before 6 years of age in most allergic children. In the second part of the Tecumseh study,⁽¹⁹⁹⁾ the authors reported on the onset sequence of asthma in hay fever patients. In 23% of their patients, hay fever preceded asthma by at least 1 year. During the period of the study, only 10% of those at risk, however, had actually developed asthma as yet. Four years later, they again surveyed the same population and reported the number of probably allergic as well as “highly suspect” of having asthma and hay fever. Only the probable cases were used in the analysis of the onset sequence of hay fever and asthma. They noted that “methods of ascertaining and diagnosing allergic rhinitis and asthma were different in the first and second surveys.”⁽¹⁹⁹⁾ Thus, it is not surprising that the cumulative prevalence rates increased 60% from the first Tecumseh study to the second one.^(200,201) They found that 25% of the persons who were thought to have probable asthma as well as hay fever had not previously been diagnosed as having either one. When they went back and asked the same patients, “the cumulative prevalence of allergy was higher in twice-examined persons.” Thus, they may have missed some crucial pediatric hay fever patients the first time they surveyed the town. Taking the Tecumseh studies at face value, a lower percentage of children with hay fever in their study were at risk to develop asthma. However, it does not gainsay the principle proposed in our Rochester study.⁽¹⁹²⁾

Fontana et al.⁽²⁰²⁾ reported that they found no benefit from immunotherapy in childhood ragweed hay fever. However, in reviewing this report, Sly⁽²⁰³⁾ pointed out that the symptom scoring system used did not assess severity or duration of symptoms. Also, relatively small doses of pollen extracts were used.^(192,204) It is well known that clinical response to immunotherapy in children is related to the dose of antigen administered in patients with rhinitis as well as bronchial asthma. A study by Sadan et al.⁽²⁰⁵⁾ confirmed the value of immunotherapy in children and detailed the immunologic basis for clinical improvement.

BRONCHIAL ASTHMA: NATURAL HISTORY

A knowledge of the natural history of asthma is essential background information for the assessment of therapeutic measures. Parents frequently ask about the likely outcome of their child's disease. “Will he outgrow it?” One of the problems in evaluating studies of the natural history of asthma is that few have involved following asthmatic children into late adolescence or adulthood. Phalen⁽²⁰⁶⁾ followed 401 asthmatic Australian children from age 7 to 28 years. He found that three quarters of wheezing children had infrequent episodes of asthma and represented only 5% of the childhood population. One in 40 of asthmatic children developed chronic or persistent asthma, and they represented 1 in 200 children. With regard to age of onset of symptoms, Phalen found that the majority with onset of wheezing before the age of 12 months had the pattern of infrequent episodic asthma during childhood, and only 20% developed persistent asthma. Fewer than 5% of those with onset after the age of 3 years developed persistent asthma. Conversely, over half of those with persistent asthma had the onset of wheezing before the age of 2 years and 40% before the age of 12 months. Although many children with infrequent episodic asthma seem to lose their asthma, 50% continued to have episodes of wheezing into late adolescence and early adult life. Most of these patients denied that they had asthma. Phalen listed risk factors for a less favorable course of asthma as eczema and the frequency of episodes of wheezing. He also found that “no subject fell into a group called intrinsic asthma.” He believes that asthma is a very underdiagnosed condition. In his study, only those children with infrequent episodes of wheezing have even a 50% chance of being wheeze-free by early adult life. Even those who seemed to have outgrown their asthma in adolescence have a risk of its recurring in adult life. He stressed the importance of following asthmatic groups over many years, as did Blair.⁽¹¹³⁾

NATURAL HISTORY OF ALLERGIC DISEASE

Anderson et al.⁽²⁰⁷⁾ undertook to follow the outcome of 8806 British children, born in March 1958, at ages 7, 11, and 16 years. By 16 years of age, 11.6% of children in their study had experienced asthma. However, throughout the whole time span studied, the prevalence figure for asthma was 4.2%, which figure comes close to that found in a study of a random population of children in Rochester, New York.⁽⁸³⁾ One interesting finding of the Anderson study was that half of the children who were thought to have outgrown their asthma again had symptoms of bronchospasm in adulthood.

Early immunotherapy may significantly alter the natural history of bronchial asthma and increase the likelihood of a child's outgrowing it

If the natural history of extrinsic bronchial asthma in childhood were the same with and without immunotherapy, there would be no reason to give asthmatic children allergy injection therapy. In each of four long-term studies^(113,208-210) on the follow-up of asthmatic children who had not received immunotherapy, at least 75% of these children persisted with symptoms of asthma into adolescence or early adulthood. By contrast, Rackemann and Edwards⁽²¹¹⁾ reported on a 20-year follow-up study of 688 asthmatic children, all of whom had received immunotherapy. They reported that approximately three fourths of their patients were free of asthma when questioned 20 years after therapy began. Thus, the proportion of asthmatic children expected to outgrow their asthmatic symptoms by late adolescence was almost exactly the opposite, depending on whether or not they had received specific immunotherapy. Blair⁽¹¹³⁾ pointed out that unless follow-up studies of childhood asthmatics extend beyond 18 years of age, a false impression of the natural history of childhood asthma will result. In a Rochester study,⁽²¹⁰⁾ a previous history of seasonal hay fever significantly increased the likelihood of a child's asthma's persisting into adulthood. Buffum and Settiple,⁽²¹²⁾ in reporting on a 10-year follow-up of 518 asthmatic children, found a subset of children, with a strongly positive skin test to egg white and with the onset of asthma before 2 years of age and a history of atopic eczema, who tended to have a persistence of their eczema and asthma. Their asthma often became intractable to usual treatment.

To follow the long-term clinical course of asthmatic symptoms in 210 asthmatic children, Johnstone and Dutton⁽²¹³⁾ randomly assigned 210 asthmatic children to receive either specific immunotherapy or placebo injections and followed their clinical course for 14 years. Twenty-two percent of the placebo-treated children were free of their asthma for at least 1 year by the age of 16 years. Seventy-two percent of the children who had received immunotherapy were free of symptoms by the same age. In the treated group, the chance of clinical improvement in a child's asthma⁽²⁰⁴⁾ or of outgrowing the asthma⁽²¹³⁾ seemed greater the higher the dose of antigen received in immunotherapy. In the treated group who received the maximum tolerable dose of antigen, the percentage of children free of asthma at the end of the study exceeded 80%. In this study, the likelihood of a child's outgrowing the asthma was in no way affected by the age of onset of the asthma, the sex of the child, or the severity of asthma when first seen, providing the child did not have egg-sensitive eczema and onset of asthma before age 2 years.⁽²¹²⁾ A previous history of seasonal hay fever, however, significantly increased the likelihood of a child's asthma persisting into adolescence.

In a study of the effectiveness of immunotherapy for asthma caused by ragweed sensitivity,⁽¹⁹²⁾ we followed a group of asthmatic children for 5 years. Randomly, the children were given either ragweed injections or placebo injections. Over the 5 years of the study, two thirds of the treated group of pollen asthmatics lost their symptoms. There was a 16% increase in the prevalence of asthma in the placebo-treated group.

Aas⁽²¹⁴⁾ demonstrated the positive value of immunotherapy in children with house dust asthma. In 93 children, he substantiated the diagnosis of asthma by bronchial provocation challenges with house dust extract. He then assessed the effectiveness of the treatment by measuring

changes in bronchial sensitivity before and after immunotherapy by means of measuring changes in pulmonary function after bronchial inhalation challenge with the same dust extracts used in immunotherapy. Specific therapy was found to be superior to placebo injections. The differences were statistically significant. Similarly, McAllen et al.⁽²¹⁵⁾ did bronchial challenges before and after injections of grass pollen or placebo in grass-sensitive asthmatics. They reported that in the second year, 80% of the treated group were protected, as evidenced by bronchial inhalation challenge with grass pollen extracts. The controls remained unchanged in their bronchial sensitivity to the same grass extract. Other reports^(216,217) have added to the growing number of studies supporting the value of immunotherapy in childhood asthmatics. A refutation of the arguments of opponents of immunotherapy exists in some detail.⁽²¹⁸⁾

RECURRENT OTITIS MEDIA

Although pediatric allergists have long suspected a relationship between eustachian tube dysfunction caused by underlying allergic rhinitis and recurrent otitis in infants and children,^(219,220) too few pediatricians and primary physicians are quick to recognize this relationship.⁽²²¹⁾ McGovern et al.⁽²²²⁾ summarized the age distribution of this condition together with a description of the aural and allergic manifestations found in 512 children with secretory otitis media seen by them. They maintained that conservative allergic management, consisting of environmental controls, symptomatic medications, and immunotherapy resulted in marked improvement in the majority of these children. Bierman et al.,⁽²²³⁾ in a study of 2,000 allergic children, found that a fourth of them had middle ear dysfunction. The authors made a plea for a team effort on the part of pediatricians, allergists, otologists, surgeons, and school teachers and parents in the total care of children with secretory otitis media. The allergic part of their regimen included advice on environmental controls, appropriate use of symptomatic medicines, dietary restrictions where indicated, and specific immunotherapy.

Further interest in the possible connection between allergy and ear dysfunction in infants has been aroused by the literature pointing to the connection between smoking and subsequent elevation of serum IgE⁽¹⁴⁵⁾ and increase in childhood asthma,⁽¹⁴⁷⁾ as well as significant increase in glue ear.⁽¹⁴⁹⁾ McMahan et al.⁽²²⁴⁾ have suggested that up to 90% of patients with secretory otitis develop it secondary to allergy. Bernstein⁽²²⁵⁾ demonstrated in a series of studies that there is a definite subset of children with allergic problems who develop secretory otitis media. In one of his studies, a third of the children with secretory otitis had associated allergic rhinitis.

The possibility that IgE-mediated allergic reactions participate in the pathogenesis of otitis media with effusion has been suggested⁽²²⁶⁾ by clinical studies showing a higher prevalence of otitis media in patients with allergy. Patients with allergic rhinitis can develop posterior nasopharyngeal mucosal edema, which occludes the proximal portion of the eustachian tube, which, in turn, contributes to the subsequent development of middle ear effusion. When Ackerman et al.⁽²²⁷⁾ challenged patients with allergic rhinitis with pollen allergens intranasally, many of them developed eustachian tube obstruction, as measured by the nine-step pressure-swallowing procedure. In addition to pollens, house dust as a perennial allergen has been shown to provoke eustachian tube obstruction and allergic rhinitis in similar studies. Rhinoscopy performed minutes after antigen challenge revealed profuse edema and watery secretions that enveloped the posterior nasopharynx and obscured the region of the eustachian tube orifice.

Fireman demonstrated in human subjects with allergy, as well as in primates, that aerosolized intranasal histamine not only induced rhinitis but also provoked eustachian tube dysfunction.⁽²²⁸⁾ Walker et al.⁽²²⁹⁾ reported that a single intranasal challenge with histamine provoked eustachian tube obstruction in patients with allergic rhinitis but not in normals. From these studies, it seems that there is little doubt of the relationship between allergic rhinitis and the tendency to develop eustachian tube obstruction.

NATURAL HISTORY OF ALLERGIC DISEASE

SUMMARY AND RECOMMENDATIONS FOR EARLY DETECTION AND POSSIBLE INTERVENTION OF ALLERGIC DISEASE IN CHILDREN

- A. *Genetic counseling* about chances of a child's inheriting atopic tendency
- B. *Season of birth*: Plan pregnancy to end after pollen seasons. If practical, plan first trimester to occur when mother's allergy symptoms are least likely to require symptomatic medications.
- C. *During pregnancy*: Mother should not smoke or drink alcoholic beverages. She should also avoid taking progesterone and beta-blocker drugs. Although not yet proven of importance, mothers should, in the last trimester, avoid milk products and egg.
- D. Consider some or all of the following *theoretical predictive tests*
 - 1. Pregnant mother's serum IgE level
 - 2. In third trimester, measure mother's serum level of IgG antibodies to beta-lactoglobulin
 - 3. Newborn cord blood levels of IgE and food-specific RAST IgE antibody determinations
 - 4. Measure newborn's platelet count⁽²³⁰⁾
 - 5. Measure total IgA and milk-specific IgA antibody levels in colostrum and mother's first milk
 - 6. At 1 month of age, measure infant's total T lymphocyte count
 - 7. At 3 months of age, determine infant's serum IgA level
 - 8. At 6 months of age, determine infant's serum IgE level
- E. *Dietary avoidance*: Withhold cow's milk, egg, wheat, corn, peanut, and fish for first 9–12 months of life. Warn hospital nurses against giving infants any supplemental feeding of cow's milk. Try to delay introduction of solids 9–12 months. Encourage *exclusive breast feeding*, if possible, for 12 months. During nursing, mothers should avoid eating cow's milk products, egg, fish, corn, and peanut. Parents should be warned to prevent grandparents or other surrogate infant caretakers from giving the infant milk or forbidden solids before the indicated age. For complementary feeding when breast feeding is not possible, use soybean, whey, or casein hydrolysate formula.
- F. *Optimal obstetric and perinatal care* to minimize complications in mother or infant during the neonatal period
- G. When practical, *defer elective surgery* in first 2 years of life, especially in boys with a positive family history of atopy.
- H. Because infants have been shown⁽²³¹⁾ to develop specific IgE antibodies to *Bordetella pertussis* after DPT immunization, theoretically one should consider *deferring DPT* immunization of children of allergic families until after 6 months of age, if practical and safe.
- I. *Environmental controls*: No smoking in the home, including during pregnancy. No furry pets in the home. Maintain optimal humidity in the home, including the basement and patient's bedroom. Use dustproof (waterproof) covers on mattresses and pillows. Minimize house dust mite exposure (frequent laundering, including use of dryer, of bedding and night clothes at least twice a week; remove carpets from bedroom). If symptoms are severe in spite of these measures, consider use of a HEPA filter or air conditioner in child's bedroom with bedroom registers and doors closed. In pollen season, use of eyecup and eyedrops as well as rinsing child's hair at bedtime.
- J. *Early recognition of developing atopy in child* by use of multitest skin tests or RAST tests at 4 months, 12 months, and yearly thereafter. This might permit early detection of sensitivities before clinical symptoms begin and permit early further and more aggressive manipulation of the child's allergenic environment.
- K. Begin *early immunotherapy* for pollinosis (even if symptoms are mild) and extrinsically caused atopic bronchial asthma.

Although knowledge of the natural history of atopy in children and familiarity with feasible intervention measures is essential to modern care of children of allergic families, we do not

JOHNSTONE

always succeed in preventing the onset of major allergy in such children. Each year, new findings in clinical and laboratory science add additional information that influences our chance of preventing atopic disease. We must strive to improve compliance by patients in the intervention process to make them succeed. We must continue to educate ourselves, physicians caring for children, and their parents about what is known and what we can accomplish in the early recognition of and prevention of allergic disease in children.

REFERENCES

1. Johnstone D. The natural history of allergic disease. *Ann Allergy* 1977;38:387.
2. Bousquet J, Kjellman N-I. Predictive value of tests in childhood allergy. *J Allergy Clin Immunol* 1986;78:1019.
3. McCombs R., Lowell F., Ohman J. Myths, morbidity, and mortality in asthma. *JAMA* 1979;242:1521.
4. Hamburger R. Allergy and the immune system. *Am Sci* 1976;64:157.
5. Kuhns W, Pappenheimer A. Immunochemical studies of antitoxin products in allergic individuals hyperimmunized with diphtheriatoid. *Am J Exp Med* 1953;95:363.
6. Hillman B. The allergic child. *Ann Allergy* 1967;25:620.
7. Varonier H, Hahn W. Cardiac and vascular reaction in atopic and nonatopic children. *J Allergy* 1966;38:352.
8. Van Arsdel P, Motulsky A. Frequency and heritability of asthma and allergic rhinitis in college students. *Acta Gen* 1959;9:101.
9. Parker C, Bilbo R, Reed C. Methacholine aerosol as a test for bronchial asthma. *Arch Intern Med* 1965;115:452.
10. Townley R, Dennis M, Itkin I. Comparative actions of acetyl-beta-methylcholine, histamine, and pollen antigens in subjects with hay fever and patients with bronchial asthma. *J Allergy* 1965;36:121.
11. Ouelette J, Reed C. Increased response of asthmatic subjects to methacholine after influenza vaccine. *J Allergy* 1965;36:558.
12. DeWeck A. HLA and allergy. *Monogr Allergy* 1977;11:3.
13. Marsh D, Meyes D, Bias W. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551.
14. Gerrard J, Vickers P, Gerrard E. The familial incidence of allergic disease. *Ann Allergy* 1976;36:10.
15. Kjellman N-I. Atopic disease in seven year old children. *Acta Paediatr Scan* 1977;66:465.
16. Sibbald B, Horn M, Brain E, Greeg I. Genetic factors in childhood asthma. *Thorax* 1980;35:671.
17. Bousquet J, Kjellman N-I. Childhood allergy: Predictive value of tests in childhood allergy. *J Allergy Clin Immunol* 1986;78:1019.
18. Magnusson G. Cord serum IgE in relation to family history and as a predictor of atopic disease in early infancy. *Allergy* 88 (in press.)
19. Agosti J, Sprenger J, Lawrence G, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogenic bone marrow transplantation. *N Engl J Med* 1988;319:1623.
20. Falliers C, Cardoso R, Bane H, et al. Discordant manifestations in monozygotic twins: Genetic identity vs. clinical, physiologic, and biochemical differences. *J Allergy* 1971;47:207.
21. Light W, Wortley G. Effect of maternal asthma on the newborn. *J Allergy Clin Immunol* 1980;65:204.
22. Greenberger P, Patterson R. The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 1988;9:539.

NATURAL HISTORY OF ALLERGIC DISEASE

23. Michel F, Bousquet J, Greillier P, et al. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic disease in infancy. *J Allergy Clin Immunol* 1980;65:422.
24. Bousquet J, Menardo J, Viala J, Michel F. Predictive value of cord serum IgE determination in the development of "early onset" atopy. *Ann Allergy* 1983;51:291.
25. Björkstén B, Kjellman N-I. Perinatal factors influencing the development of allergy. *Clin Rev Allergy* 1987;5:339.
26. Magnusson C. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986;78:898.
27. Magnusson C, Johansson S. Maternal smoking leads to increased cord serum IgG3. *Allergy* 1986;41:302.
28. Delepesse M, Sarfati M, Lang F, Sehon A. Prenatal and neonatal synthesis of IgE. *Monogr Allergy* 1983;18:83.
29. Kaufman H. Allergy in the newborn: Skin test reactions confirmed by the Prausnitz-Kustner test at birth. *Clin Allergy* 1971;1:363.
30. Businco L, Marchetti R, Pelligrini G, Perlini R. Predictive value of cord blood IgE levels in "at risk" newborn babies and influence of type of feeding. *Clin Allergy* 1983;13:505.
31. Levin S, Altman Y, Sela M. Penicillin and dinitrophenyl antibodies in newborns and mothers detected with chemically modified bacteriophage. *Pediatr Res* 1971;5:87.
32. Weil G, Hussain R, Kumaraswami V. Prenatal allergic sensitization to helminth antigens in offspring of parasite-infected mothers. *J Clin Invest* 1983;71:1124.
33. Lilja G, Dannaeus A, Fälth-Magnusson K, et al. Immune response of the atopic woman and fetus, effects of high and low dose food allergen intake during late pregnancy. *Clin Allergy* 1988;18:131.
34. Fälth-Magnusson K, Oman J, Kjellman N-I. Maternal abstention from cow's milk and egg in allergy risk pregnancies: Effect on antibody production in the mother and newborn. *Allergy* 1987;42:64.
35. Chandra R, Puri R, Suraiya C, Cheema P. Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in infants. *Clin Allergy* 1986;16:563.
36. Zeiger R, Heller S, Mellon M, et al. Effectiveness of dietary manipulation in the prevention of food allergy in infants. *J Allergy Clin Immunol* 1986;78:224.
37. Gerrard J. Allergy in breast-fed babies to ingredients in breast milk. *Ann Allergy* 1979;42:69.
38. Ahlstedt S, Björkstén B. Specific IgE antibody responses in rats and mice after daily immunization without adjuvant. *Int Arch Allergy Appl Immunol* 1983;71:293.
39. Kjellman N-I, Andrae S, Croner S, et al. Epidemiology and prevention of allergy. *Immunol Allergy Pract* 1988;10:393.
40. Johansson S, Lilj G, Nordvall S. IgE-mediated allergy during infancy. *Int Pediatr* 1988;3:209.
41. Jarrett E, Hall E. The development of IgE-suppressive immunocompetence in young animals: Influence of exposure to antigen in the presence and absence of maternal immunity. *Immunology* 1984;53:365.
42. Firer M, Hosking C, Hill D. Effect of antigen load on development of milk antibodies in infants allergic to milk. *Med J* 1981;283:693.
43. Schwartz R, Kubicka M, Dreyfuss E, Nikaein A. Acute urticarial reactions to cow's milk in infants previously fed breast milk or soy milk. *Pediatr Asthma Allergy Immunol* 1987;1:81.
44. Jacoby E, Olding L, Gladstone M. Immunologic regulation of fetal-maternal balance. *Adv Immunol* 1984;35:157.
45. Glovsky M, Marsh D, Shatz M, et al. Further studies on tolerance induction to allergens in utero in man. *J Allergy Clin Immunol* 1983;71:92.
46. Settiple R, Chafee F, Settiple G. Pollen immunotherapy during pregnancy: long-term follow-up of offspring. *Allergy Proc* 1988;9:555.
47. Morrison-Smith J. Skin tests and atopic allergy in children. *Clin Allergy* 1973;3:269.

JOHNSTONE

48. Haus M. Genetic and environmental influences on cord blood atopic markers and on atopic sensitization in infancy. M.D. Thesis 1988. University of Cape Town, South Africa.
49. Van Niekerk C, Weinberg E, Shore S, et al. Prevalence of asthma: A comparative study of urban and rural Xhosa children. *Clin Allergy* 1979;9:319.
50. Warrell D, Fawcett D, Harrison D. Bronchial asthma in the Nigerian Sarauna region: A clinical and laboratory study of 106 patients with a review of the literature on asthma in the tropics. *J Med* 1975;45:325.
51. Waite D, Eyles E, Tonkin L, O'Donnell T. Asthma prevalence in Tokelauan children in two environments. *Clin Allergy* 1980;10:71.
52. Wolstenholme R. Bronchial asthma in the southern Malives. *Clin Allergy* 1979;9:325.
53. Mantle J, Pepys J. Asthma amongst Tristan de Cunha Islanders. *Clin Allergy* 1974;4:161.
54. Bjorksten F, Suoniemi I, Koski V. Neonatal birch pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980;10:585.
55. Bjorksten F, Suoniemi I, Koski V. Neonatal birch pollen contact and subsequent allergy to birch pollen. *Allergy* 1986;41:68.
56. Croner S, Kjellman N-I. Predictions of atopic disease: Cord blood IgE and month of birth. *Allergy* 1986;41:68.
57. Morrison-Smith J, Springett V. Atopic disease and month of birth. *Clin Allergy* 1979;9:153.
58. Kemp A. Relationship between time of birth and the development of immediate hypersensitivity to grass-pollen antigens. *Med J Aust* 1979;1:263.
59. Settupane R, Hagy G. Effect of atmospheric pollen on the newborn. *RI Med J* 1979;62:477.
60. Salk L, Brelling B, Strauss W, Dietrich J. Perinatal complications in the history of asthmatic children. *Am J Dis Child* 1974;127:30.
61. Hamburger R, Lenoir M, Groshong R, et al. Development of IgE and allergy during the first year of life: Preliminary data. *J. Allergy Clin Immunol* 1974;53:94.
62. Kjellman N-I. Predictive value of high IgE levels in children. *Acta Paediatr Scan* 1976;65:465.
63. Bousquet J, Menardo J, Viala J, Michel F. Predictive value of cord serum IgE determination in the development of "early onset" atopy. *Ann Allergy* 1983;51:291.
64. Casimer G, Verleyev D, Duchateau J. Concentrations seriques en IgE: Prediction des manifestations atopiques. Avantages de l'allaitement maternel. *Rev Med Brux* 1983;4:323.
65. Croner S, Kjellman N-I, Eriksson B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982;57:364.
66. Dannaeus A, Johansson S, Foucard T. Clinical and immunological aspects of food allergy. II. Development of allergic symptoms and humoral immune response in infants of atopic mothers during the first twenty-four months of life. *Acta Paediatr Scan* 1978;67:497.
67. Magnusson C. Immunoglobulin E in cord serum as predictor of allergy in early infancy (abstract). Presented at the International Symposium on Prevention of Allergic Diseases. Florence, Italy, June 1984.
68. Kjellman N-I, Croner S. Cord blood IgE determination for allergy prediction—A follow-up to seven years of age in 1651 children. *Ann Allergy* 1984;53:167.
69. Platts Mills R, Snajdr M, Ishizaka K, Frankland A. Measurements of IgE antibody by an antigen-binding assay: Correlation with PK activity and IgG and IgA antibodies to allergens. *J Immunol* 1978;120:1201.
70. Haus M, Heese D, Weinberg E, et al. The influence of ethnicity, an atopic family history, and maternal ascaris on cord blood serum IgE concentrations. *J Allergy Clin Immunol* 1988;82:179.
71. Ratner B, Collins-Williams C, Untracht S. Allergic dermal respiratory syndrome in children. *Am J Dis Child* 1951;82:666.

NATURAL HISTORY OF ALLERGIC DISEASE

72. Grulee C, Sanford H. The influence of breast feeding and artificial feeding on infantile eczema. *J Pediatr* 1936;9:223.
73. Glaser J, Johnstone D. Prophylaxis of allergic disease in children. *JAMA* 1953;253:620.
74. Johnstone D, Dutton A. Dietary prophylaxis of allergic disease in children. *Engl J Med* 1966;274:715.
75. Businco L, Cantania A, Bruno, G. Prevention of atopy. Results of a long-term (7 months to 8 years) follow-up. *Ann Allergy* 1987;59(2):183.
76. Hamburger R, Casilla R, Johnston R, et al. Long-term studies in prevention of food allergy: Patterns of IgG anti cow's milk antibody responses. *Ann Allergy* 1987;59:175.
77. Kajoraari M, Saarinen U. Prophylaxis of atopic disease by six months' total solid food elimination. *Acta Paediatr Scand* 1983;72:411.
78. Halpern S, Sellars W, Johnson R, et al. Development of childhood allergy in infants fed breast, soy, or cow's milk. *J Allergy Clin Immunol* 1973;51:139.
79. Johnstone D. Year Book of pediatrics, Chicago: Year Book Medical Publishers, 1974, pp 82-83.
80. Kjellman N-I, Johansson S. Soy versus cow's milk in infants with a parental history of atopic disease: Development of atopic disease and immunoglobulins from birth to four years of age. *Clin Allergy* 1979;9:347.
81. Merrett T, Burr M, Burlant B, et al. Infant feeding and allergy: 12 month prospective study of 500 babies born into allergic families. *Ann Allergy* 1988;61:13.
82. U.S. Public Health Survey. Chronic respiratory conditions reported in interviews: Health statistics for U.S. Health Survey. Dept. of Health, Education, and Welfare. Series B, No 1a, p 2, 1959.
83. Haggerty R, Roghmann K, Pless I. Child health and the community. New York: Wiley & Sons, 1975, p 346.
84. Michel F, Bousquet J, Dannaeus A, et al. Preventive measures in early childhood allergy. *J Allergy Clin Immunol* 1986;78:1022.
85. Mortimer E. Anaphylaxis following ingestion of soybean. *J Pediatr* 1977;58:730.
86. Peters G. Bronchial asthma due to soybean allergy. *Ann Allergy* 1965;23:1970.
87. Whittington P, Gibson R. Soy protein intolerance: Four patients with concomitant cow's milk intolerance. *Pediatrics* 1977;59:730.
88. Ahmet M, Rubin C. Soy proteins—Another cause of flat intestinal lesions. *Gastroenterology* 1972;62:227.
89. Mendoza J, Meyes J. Soybean sensitivity: Case report. *Pediatrics* 1970;46:774.
90. Bush R, Cohen M. Immediate and late-onset asthma from occupational exposure to soybean dust. *Clin Allergy* 1977;7:369.
91. Anto J, Sunyer J, Rodriguez-Roisson R, et al. Community outbreaks of asthma associated with inhalation of soybean dust. *N Engl J Med* 1989;320:1097.
92. Lindfors A, Enocksson E. Development of atopic disease after early administration of cow's milk formula. *Allergy* 1988;43:11.
93. Stinzing G, Zetterstrom R. Cow's milk allergy, incidence, and pathogenic role of early exposure to cow's milk formula. *Acta Paediatr Scand* 1979;68:383.
94. Saarinen U, Kajosaari M, Blackman A, Sumes M. Prolonged breast feeding as prophylaxis for atopic disease. *Lancet* 1977;2:163.
95. Kajosaari M, Saarinen U. Prophylaxis of atopic disease by six months total solid food elimination. *Acta Paediatr Scand* 1983;72:411.
96. Kramer S, Moroz B. Do breast-feeding and delayed introduction of solid foods protect against subsequent atopic eczema? *J Pediatr* 1981;98:546.
97. Fergusson D, Horwood I, Beautrais A, et al. Eczema and infant diet. *Clin Allergy* 1981;2:325.

98. Wilson N, Hamburger R. Allergy to cow's milk in the first year of life and its prevention. *Ann Allergy* 1988;61:323.
99. Haddad Z, Kobra V, Verma S. IgE antibodies to peptic and peptic-tryptic digests of betalactoglobulin: Significance of food hypersensitivity. *Ann Allergy* 1979;42:368.
100. Lifschitz E, Hawkins H, Guerra C, Byrd N. Case report: Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. *J Pediatr Gastroenterol Nutr* 1988;7:141.
101. Businco L, Cantini A, Longhi A, Giampietro P. Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Re, Nestlé) in infants with cow's milk allergy. *Ann Allergy* 1989;62:333.
102. Nestlé to drop claim on label of its formula. *The Wall Street Journal*, March 13, 1989, p B-5.
103. Schwartz R. Skin testing with hydrolyzed cow's milk protein formulas in children with IgE-mediated cow's milk allergy: A spectrum of allergenicity and an indication for caution (Abstract). Allergy Section Meeting, American Academy of Pediatrics, October 1989.
104. Seban L, Konjin A, Freier S. Chemical and immunological properties of protein hydrolysate formula. *Am J Clin Nutr* 1977;30:840.
105. Kramer M. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. *J Pediatr* 1988;112:181.
106. Donnally H. The question of elimination of foreign protein (egg white) in woman's milk. *J Immunol* 1930;19:15.
107. Cogswell J, Alexander J. Breast-feeding and eczema-asthma (Letter) *Lancet* 1982;1:910.
108. Kaplon M, Soli N. Immunoglobulin E to cow's milk in breast-fed atopic children. *J Allergy Clin Immunol* 1979;64:122.
109. Gerrard J. Allergy in breast-fed babies to ingredients in breast milk. *Allergy* 1983;41:69.
110. Jacobsson I, Lindberg R. Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet* 1978;1:437.
111. Warner J. Food allergy in fully breast-fed infants. *Clin Allergy* 1980;10:133.
112. Hide D, Gueyer B. Clinical manifestations of allergy related to breast and cow's milk feeding. *Arch Dis Child* 1981;56:172.
113. Blair H. Natural history of asthma: 20 year follow-up. *Arch Dis Child* 1977;52:613.
114. Matthew D, Norman A, Taylor V, Turner M. Prevention of eczema. *Lancet* 1977;1:321.
115. Juto P, Moller C, Enberg S, Björkstén B. Influence of type of feeding on lymphocyte function and development of infant allergy. *Clin Allergy* 1982;12:409.
116. Jacobsson I, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853.
117. Chandra R. Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediatr Scand* 1979;68:691.
118. Kaufman H, Frick O. Prevention of asthma. *Clin Allergy* 1981;11:549.
119. Gordon R, Noble D, Ward A, Aller R. Immunoglobulin E and the eczema-asthma syndrome in early childhood. *Lancet* 1982;1:72.
120. Midwinter R, Moore W, Soothill J, et al. Letter. *Lancet* 1982;1:339.
121. Atherton D, Sewell M, Soothill J, Wells R. A double blind controlled crossover trial of an antigen avoidance diet in atopic eczema. *Lancet* 1978;1:401.
122. Hattevig F, Kjellman B, Sigurs M, et al. The effect of maternal avoidance of eggs, cow's milk, and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989;19:27.
123. Chen Y. Synergistic effect of passive smoking and artificial feeding on hospitalization for respiratory illness in early childhood. *Chest* 1989;95:1004.
124. Murray A. Infant feeding and respiratory allergy (Letter). *Lancet* 1971;1:497.

NATURAL HISTORY OF ALLERGIC DISEASE

125. Downham M, Scott R, Sims D, et al. Breast feeding protects against respiratory syncytial virus infections. *Br Med J* 1976;2:274.
126. Machtinger S, Moss R. Cow's milk allergy in breast-fed infants: The role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986;77:341.
127. Sloper K, Brook C, Kingston D, et al. Eczema and atopy in early childhood: Low IgA plasma cell counts in the jejunal mucosa. *Arch Dis Child* 1981;56:939.
128. Schwartz D, Buckley R. Serum IgE concentrations and skin reactivity to anti-IgE antibody in IgA-deficient patients. *N Eng J Med* 1971;284:13.
129. Taylor B, Norman A, Orgel H, et al. Transient IgA deficiency and pathogenesis of infantile atopy. *Lancet* 1973;2:111.
130. Juto P. Elevated serum immunoglobulin E in T-cell-deficient infants fed cow's milk. *J Allergy Clin Immunol* 1980;66:402.
131. Anderson L, Dreyfuss E, Logan J, et al. Melon and banana sensitivity coincident with ragweed pollenosis. *J Allergy* 1970;45:310.
132. Juhlin-Dannfeldt C. About the occurrence of different types of pollens and its implications for diagnosis and therapy. *Nord Med* 1943;20:2328.
133. Berlin L. Immunological analysis of birch pollen antigens with special reference to the allergic components. *Int Arch Allergy Appl Immunol* 1972;42:300.
134. Calkhoven P, Aalbers M, Hoste V, et al. Cross-reactivity among birch pollen, vegetables, and fruits as detected by IgE antibodies is due to at least three distinct cross-reactive substances. *Allergy* 1987;42:382.
135. Dreyberg S, Foucard T. Allergy to apple, carrot, and potato in children with birch pollen allergy. *Allergy* 1983;38:167.
136. Ericksson M. Food hypersensitivity reported by patients with asthma and hay fever. *Allergy* 1978;33:189.
137. Halmepuro L, Vountela K, Kalimo K, et al. Cross-reactivity of IgE antibodies with allergens in birch pollen, fruits, and vegetables. *Int Arch Allergy Appl Immunol* 1984;74:235.
138. Halmepuro L, Lowenstein H. Immunological investigations of possible structural similarities between pollen antigens and antigens in apple, carrot, celery tuber. *Allergy* 1985;40:264.
139. Moller C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. *Ann Allergy* 1989;62:343.
140. Dreborg S. Food allergy in pollen-sensitive patients. *Ann Allergy* 1988;61:41.
141. Johnstone D, Roghmann K, Pless I. Factors associated with the development of asthma and hay fever in children: The possible risks of hospitalization, surgery, and anesthesia. *Pediatrics* 1975;56:398.
142. Szentivanyi A. The beta-adrenergic theory of the atopic abnormality in bronchial asthma. *J. Allergy* 1968;42:203.
143. Samet J, Marbury M, Spencler J. Respiratory effects of indoor air pollution. *J Allergy Clin Immunol* 1987;79:685.
144. Fielding J, Phenow K. Health effects of involuntary smoking. *N Eng J Med* 1988;319:1452.
145. Kjellman N-I. Effect of parental smoking on IgE levels in children. *Lancet* 1981;1:993.
146. Ownby D, McCullough J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *J Allergy Clin Immunol* 1988;82:634.
147. Evans D, Levinson M, Feldman H, et al. The impact of passive smoking on emergency room visits of urban children with asthma. *Am Rev Respir Dis* 1987;135:567.
148. Murray A, Morrison B. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 1986;77:575.
149. Black N. The etiology of glue ear—A case control study. *Int J Pediatr Otorhinolaryngo* 1965;9:121.

JOHNSTONE

150. Stahlberg M, Ruuskanen O, Virolainen E. Risk factors for recurrent otitis media. *Pediatr Infect Dis* 1986;5:30.
151. Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2-3 year old urban children. *Acta Otolaryngol (Stockh)* 1985;100:260.
152. McConnochie K, Righmann K. Parental smoking, presence of older siblings, and family history of asthma increases risk of bronchitis. *Am J Dis Child* 1986;140:806.
153. Cogswell J, Mitchell E, Alexander J. Parental smoking, breast feeding, and respiratory infection in development of allergic disease. *Arch Dis Child* 1987;62:338.
154. Burchfield C, Higgins M, Keller J, et al. Passive smoking in childhood. *Am Rev Respir Dis* 1986;133:966.
155. Oski F. Comment. Year book of pediatrics. Chicago: Year Book Medical Publishers, 1988, p255.
156. Andrea S, Axelsson O, Bjorksten B, et al. Symptoms of bronchial hyperactivity and asthma in relation to environmental factors. *Arch Dis Child* 1988;63:473.
157. Report of International Workshop, Bad Kreuznach, September 1987. Dust mite allergens and asthma—A worldwide problem. *J Allergy Clin Immunol* 1989;83:416.
158. Van Bronswijk J, Sinha R. Pyroglyphid mites (acar) and house dust mite allergy: A review. *J Allergy* 1971;47:31.
159. Miyamoto T, Oshima S, Ishizaki T, Sano S. Allergenic identity between the common flor mite (*Dermatophagoides farinae* Hughes 1961) and house dust as a causative agent in bronchial asthma. *J Allergy* 1968;42:14.
160. Turner K. Epidemiology of atopic disease. In: Lessor M, Lee T, Kemeny D, eds. The international textbook of allergy. New York: John Wiley, 1987, pp 337-345.
161. Platts-Mills T, Chapman M. Dust mites: Immunology, allergic disease, and environmental control. *J Allergy Clin Immunol* 1987;80:755.
162. Smith J. Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis (eczema). In: Middleton E, Reed C, Ellis E, eds. Allergy: Principles and practice. St. Louis: C.V. Mosby, 1983, p 771.
163. Bullock J, Frick O. Mite sensitivity in house dust-allergic children: Evaluation by clinical and laboratory methods. *Am J Dis Child* 1972;123:222.
164. Mitchell E, Crow J, Rowntree S, et al. Cutaneous basophil hypersensitivity to inhalant allergens: Local transfer of basophil accumulation with immune serum but not IgE antibody. *J Invest Dermatol* 1984;83:290.
165. Nelson H, Hirsch R, Ohman J, et al. Recommendations for the use of residential air cleaning devices in the treatment of allergic respiratory diseases. *J Allergy Clin Immunol* 1988;82:661.
166. Mosbech H, Korsgaard J, Lind P. Control of house dust mites by electric heating blankets. *J Allergy Clin Immunol* 1988;81:706.
167. Korsgaard J. Mite asthma and residency: A case-control study on the impact of exposure to house dust mites in dwellings. *Am Rev Respir Dis* 1983;128:231.
168. Green W, Woolcock A, Stuckey M, et al. House dust mites and skin tests in different Australian localities. *Aust NZ J Med* 1986;16:639.
169. Platts-Mills T, Hyden M, Chapman M, Wilkins S. Seasonal variations in dust mite and grass-pollen allergens in dust from houses of patients with asthma. *J Allergy Clin Immunol* 1986;79:781.
170. Arlian L. Humidity as a factor regulating feeding and water balance of the house dust mites *Dermatophagoides farinae* and *D. pteronyssinus* (Acari: Pyroglyphidae). *J Med Entomol* 1977;14:484.
171. Platts-Mills T, Tovey W, Mitchell E, et al. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;2:675.
172. Vervloet D, Penaud A, Razzouk H, et al. Altitude and house dust mites. *J Allergy Clin Immunol* 1982;69:290.

NATURAL HISTORY OF ALLERGIC DISEASE

173. Murray A, Fergusson A. Dust-free bedrooms in the treatment of asthmatic children with house dust mite allergy. *Pediatrics* 1983;71:418.
174. Walshaw M, Evans C. Allergen-avoidance in house dust mite-sensitive adult asthma. *Medicine* 1986;58:199.
175. Miller J, Miller A, Luczynska C, et al. Effect of tannic acid spray on dust mite antigen levels in carpets. *J Allergy Clin Immunol* 1989;83:262.
176. Johnstone D, Ghory J. Two pediatric allergists' sojourn to the People's Republic of China. *Ann Allergy* 1979;42:5.
177. Wood R, Chapman M, Adkinson N, Eggleston P. The effect of cat removal on allergen content in household dust samples. *J Allergy Clin Immunol* 1989;83:730.
178. Taylor W, Ohman J, Lowell F. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of bronchial response to cat allergen and histamine. *J Allergy Clin Immunol* 1978;61:283.
179. Lingren S, Belin L, Dreborg S, et al. Breed-specific dog dandruff allergens. *J Allergy Clin Immunol* 1988;82:196.
180. Frick O, German D, Mills J. Development of allergy in children with virus infection. *J Allergy Clin Immunol* 1979;63:228.
181. Frick O. Effect of respiratory and other virus infections on IgE immunoregulation. *J Allergy Clin Immunol* 1986;78:1013.
182. McIntosh K, Ellis E, Hoffman L, et al. The association of viral and bacterial respiratory infection with exacerbation of wheezing in young asthmatic children. *J Pediatr* 1973;82:578.
183. Johnstone D. Study of the value of bacterial vaccines on the treatment of bronchial asthma associated with respiratory infections. *Pediatrics* 1959;24:427.
184. Welliver R, Wong D, Sun M, et al. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N Engl J Med* 1981;305:841.
185. Welliver R, Wong D, Middleton E, et al. Role of parainfluenza virus-specific IgE in pathogenesis of croup and wheezing subsequent to infection. *J Pediatr* 1982;101:889.
186. Welliver R, Sun M, Rinaldo D, Ogra P. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J Pediatr* 1986;109:776.
187. Lemanski R, Dick E, Swenson C, et al. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. *J Clin Invest* 1989;83:1.
188. Busse W. The relationship between viral infections and onset of the allergic diseases and asthma. *Clin Exp Allergy* 1989;19:1.
189. Johnstone D. Immunotherapy in children: Past, present and future. A historical review and look into the future. *Ann Allergy* 1981;46:1.
190. Johnstone D. The natural history of allergic disease in children. *Adv Pediatr Allergy*, October 23, 1982; *Excerpta Medica Suppl.*
191. Appel S, Szanton V, Rapaport H. Survey of allergy in a pediatric population. *Penn Med* 1961;64:621.
192. Johnstone D. Study of the role of antigen dosage in the treatment of pollenosis and pollen asthma. *Am J Dis Child* 1957;94:1.
193. Brown E, Nobili C, Sannel T. Dyspnea and diminished vital capacity as a symptom and sign of hay fever. *Dis Chest* 1946;12:205.
194. Ramsdale E, Morris M, Roberts R, Hargreave F. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;75:573.
195. Pedvis S, Fox Z, Bacall H. Long-term follow-up of ragweed hay fever in children. *Ann Allergy* 1962;20:596.
196. Schuster R, Quassem A, Thal W. Results of specific hyposensitization in children with pollenosis. *Allergie Immunol (Annales Europeennes d'Allergie et d'Immunologie Clinique)* May 1989;Suppl 5:43.

JOHNSTONE

197. Broder I, Barlow P, Norton R. The epidemiology of asthma in a total community, Tecumseh, Michigan. I. Description of study and general findings. *J Allergy* 1962;33:513.
198. Smith J. Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis. In: Middleton E, Reed C, Ellis E, eds. *Allergy principles and practice*. St. Louis: C.V. Mosby Co., 1978, p 52.
199. Broder I, Barlow P, Norton R. The epidemiology of asthma in a total community, Tecumseh, Michigan. II. The relationship between asthma and hay fever. *J Allergy* 1962;33:524.
200. Broder I, Higgins M, Matthews K, Keller K. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. III. Seasonal survey of the community. *J Allergy Clin Immunol* 1974;53:127.
201. Broder I, Higgins M, Matthews K, Keller K. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. IV. Natural history. *J Allergy Clin Immunol* 1974;54:69.
202. Fontanna V, Holt L, Mainland D. Effectiveness of hyposensitization in ragweed hay fever in children. *JAMA* 1966;195:985.
203. Sly M. *Pediatric allergy*. Flushing, NY: Medical Examination Publishing Company, 1977, p 310.
204. Johnstone D, Crump L. The value of hyposensitization therapy in perennial bronchial asthma in children. *Pediatrics* 1961;27:39.
205. Sadan N, Rhyne M, Mellits M. et al. Immunotherapy of pollenosis in children: Investigation of the immunologic basis of clinical improvement. *N Engl J Med* 1969;280:623.
206. Phalen S. The natural history of childhood asthma into adult life. *Immunol Allergy Pract* 1988;10:334.
207. Anderson H, Bland J, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Commun Health* 1986;40:121.
208. Flensburg E. Prognosis for bronchial asthma arising in infancy after nonspecific therapy hitherto applied. *Acta Paediatr* 1945;33:4.
209. Ryzzing E. Continued follow-up investigation concening the fate of 298 asthmatic children. *Acta Paediatr* 1959;48:255.
210. Johnstone D. A study of the natural history of bronchial asthma in children. *Am J Dis Child* 1968;115:213.
211. Rackemann E, Edwards MD. Asthma in children: A follow-up study of 688 patients after an interval of 20 years. *N Eng J Med* 1952;246:858.
212. Buffum W, Settipane G. Prognosis in asthma in children. *Am J Dis Child* 1968;112:214.
213. Johnstone D, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: A 14-year study. *Pediatrics* 1968;42:7983.
214. Aas K. Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation on the effect on bronchial sensitivity to house dust. *Acta Paediatr Scand* 1971;60:264.
215. McAllen J, Heaf P, McInroy P. Depot grass pollen injections: Effect of repeated treatment on clinical response and measured bronchial sensitivity. *Br Med J* 1967;1:22.
216. Zychowicz C, Nowacka W, Wicinski M, et al. The influence of Bencard HDM vaccine on the clinical course of the atopic bronchial asthma in children. *Allergie Immunol* May 1989; Suppl 5:44.
217. Gadjiev K. Influence of specific hyposensitization on remote outcome of bronchial asthma in children. *Allergie Immunol* May 1989;Suppl 5:41.
218. Johnstone D. Immunotherapy in children: Past, present and future (Part II). *Ann Allergy* 1981;46:60.
219. Glaser J. *Allergy in children*. Springfield, IL: Charles C Thomas, 1956, p 229.
220. Szanton V, Szanton W. Hearing disturbances in allergic children. *Ann Allergy* 1961;19:1177.
221. Gellis S. *The year book of pediatrics*. Chicago: Year Book Medical Publishers, 1960–1961, p 143.
222. McGovern J, Haywood T, Fernandez A. Allergy and secretory otitis media. *JAMA* 1967;200:124.

NATURAL HISTORY OF ALLERGIC DISEASE

223. Bierman C, Pierson W, Donaldson J. The evaluation of middle ear function. *Am J Dis Child* 1970;120:233.
224. McMahan J, Calenoff E, Croft D, et al. Chronic otitis media with effusion and allergy: Modified RAST analysis in 119 cases. *Otolaryngol Head Neck Surg* 1981;89:427.
225. Bernstein J. Recent advances in otitis media with effusion. *Ann Allergy* 1985;55:544.
226. Fireman P. Otitis media and nasal disease: A role for allergy. *J Allergy Clin Immunol* 1988;82:917.
227. Ackerman M, Friedman R, Doyle W, et al. Antigen-induced eustachian tube obstruction: An intranasal provocative challenge test. *J Allergy Clin Immunol* 1984;73:604.
228. Doyle W, Ingram A, Fireman P. Histamine-induced eustachian tube obstruction in monkeys. *J Allergy Clin Immunol* 1985;76:551.
229. Walker S, Shapiro G, Bierman C, et al. Induction of eustachian tube dysfunction with histamine nasal provocation. *J Allergy Clin Immunol* 1985;76:158.
230. Magnusson C, deVeck A. Does thrombocytopenia in cord blood predict atopy? *Ann Allergy* 1985;55:267.
231. Haus M, Weinberg E, Malherbe D. The development of specific IgE antibodies to *Bordetella pertussis* following immunisation in infancy. *Lancet* 1985;1:711.

Address reprint requests to:
Douglas E. Johnstone, M.D.
360 White Spruce Blvd.
Rochester, NY 14623

This article has been cited by:

1. ROBERT A. HOEKELMAN. 1991. A Department Chairman's View of Allergy in ChildhoodA Department Chairman's View of Allergy in Childhood. *Pediatric Asthma, Allergy & Immunology* 5:4, 287-296. [[Citation](#)] [[PDF](#)] [[PDF Plus](#)]
2. ERIC M. DREYFUSS. 1991. The Rochester, New York Tradition: Allergy and AllergistsThe Rochester, New York Tradition: Allergy and Allergists. *Pediatric Asthma, Allergy & Immunology* 5:4, 283-286. [[Citation](#)] [[PDF](#)] [[PDF Plus](#)]