

The natural history of asthma

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Our understanding of the natural history of asthma is improving through the establishment of a more precise definition of asthma linked with information from large-scale longitudinal studies. Risk factors for the development of childhood asthma including sex, atopic status, genetic and familial factors, respiratory infections, and outdoor and indoor pollution are now more clearly understood. New information on the relation of viral wheezing episodes in infancy to later childhood asthma is evolving. We now know that children who start wheezing early in life and continue to wheeze at age 6 years are more likely to have a maternal history of asthma, elevated serum IgE levels, and normal lung function in the first year of life. However, at age 6 years they have both elevated serum IgE levels and diminished lung function. Approximately 50% of adults who report having had childhood asthma no longer have symptoms. Airway responsiveness in childhood tends to predict airway responsiveness in adulthood and to be greater in asthmatics with persistent symptoms. Studies of the natural history of asthma support the hypothesis that early therapeutic intervention in mild disease may lead to an improved clinical outcome. Adults exposed to specific occupational environments are at additional risk for the development of asthma. As we learn more about the natural history of asthma, we will have a better understanding of the effect of early diagnosis, environmental control, and therapy on the outcome of the disease. (*J Allergy Clin Immunol* 1998;102:S65-S72.)

Key words: Natural history, asthma, risk factors, atopic hypersensitivity, air pollution, prevalence, occupational diseases

A determination of the natural history of any disease is predicated on satisfying 3 primary criteria: first, a precise definition that allows identification of the subjects with the disease and excludes those with similar symptoms; second, longitudinal data that allow one to trace the disease throughout its course, from onset to either death or remission; and finally, a clear understanding of the effect therapy has on the course of disease and its outcome. The data that are currently available fall far short of satisfying these criteria.

Although the definition of asthma has been made more specific by the inclusion of its pathologic features, the clinical manifestations are nonspecific. Because of this lack of specificity, asthma is often referred to as a clinical syndrome rather than a specific disease. Longitudinal

Abbreviations used

BHR: Bronchial hyperresponsiveness

FEV₁: Forced expiratory volume (in 1 second)

asthma studies have commonly been either repeated cross-sectional analyses with different subject cohorts or cohort studies of relatively short duration. In studies of older adults it has been difficult to separate subjects with asthma from those with chronic obstructive pulmonary disease. Finally, none of the long-term asthma studies thus far have addressed the issue of therapy and its effect on the course of disease. Despite these major limitations, an increasingly well-documented database exists that allows us to at least reach tentative conclusions concerning many aspects of the natural history of asthma.

WHAT IS ASTHMA?

For a disease that is more than 2000 years old and affects millions of people worldwide, attempts to define asthma have met with little success until very recently. In the 1950s the routine use of lung function testing was introduced into clinical practice. At the end of that decade, a prestigious Ciba symposium was held in London for the primary purpose of redefining the airway obstructive diseases, specifically, emphysema, asthma, and chronic bronchitis. What emerged was a definition of asthma that emphasized the reversibility of airflow obstruction, either spontaneously or as a result of therapy.¹ In 1962 a second criterion, the presence of bronchial hyperresponsiveness (BHR), was added to the definition.²

In the 1970s knowledge of the pathologic anatomic characteristics of the asthmatic airway was limited to autopsy studies of patients who had died in status asthmaticus. As a terminal event, bronchial inflammation, edema, epithelial sloughing, and mucous plugging were present.³ Virtually nothing was known, however, about the pathologic condition of the airway in patients with mild disease.

In the mid-1980s protocols were developed that permitted bronchoscopic evaluation of patients with asthma. In rapid succession a number of investigators described an intense inflammatory lesion characterized by the presence of eosinophils and mucosal sloughing in patients with newly diagnosed asthma who had mild disease. Details of these reports and the complexity of the inflammatory process that is involved are addressed by Dr. Busse in this issue. As a result of these studies, asthma is now defined as an inflammatory disease of the airways.^{4,5} Reversibility of airflow obstruction and BHR continue to be important components of this definition.

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The clinical manifestations of asthma, however, are characterized by symptoms that are relatively nonspecific. As a result, infants and young children with asthma are still given diagnoses of wheezy bronchitis and allergic bronchitis, and older patients continue to have chronic obstructive pulmonary disease with an "asthmatic" component and "reversible" emphysema.

WHAT ARE THE RISK FACTORS FOR CHILDHOOD ASTHMA?

Sex

Male sex has been noted in many studies to be a risk factor for asthma in children before the age of 14 years⁶ and female sex to be a risk factor for asthma in adults. However, sex does not appear to affect the course of the disease. In the early studies by Rackemann and Edwards⁷ and Blair,⁸ the clinical course was comparable over 20-year follow-up intervals in male and female patients. McNicol and Williams⁹ studied Australian asthmatics and reported that between ages 21 and 28 years, significantly more men than women had moved to a more severe asthma group. Furthermore Weiss et al¹⁰ demonstrated apparent sex-related differences in the relation between asthma and lung function: male patients had a higher incidence rate of asthma, but female patients had a greater deficit in pulmonary function.

Atopic status

Burrows et al¹¹ investigated the association between atopy and asthma in a random population sample ($n = 2657$) with skin tests as the marker of atopy. They found that in children aged 3 to 14 years, atopy was strongly associated with attacks of wheezing and dyspnea. In a later follow-up study in the same geographic region, these investigators found that increases in total serum IgE were strongly associated with the prevalence of asthma.¹²

Atopy is also associated with a poorer prognosis of asthma. Children with eczema and positive skin tests have more severe asthma,¹³ and the persistence of eczema has been associated with persistence of asthma.⁸ Atopy was associated with persistent wheezing in a cohort of babies at high risk for allergic diseases¹⁴ and was also associated with an increased risk for both early and later childhood onset of wheezing. In a follow-up of a 1958 birth cohort,¹⁵ subjects who had asthma or wheezy bronchitis by age 16 years were twice as likely to have a report of wheezing during the preceding year if they had hay fever, allergic rhinitis, or eczema.

Genetic/familial factors

A potential genetic component of asthma has been hypothesized based on the initial observations that asthma tended to cluster in families. Further analyses of familial aggregation, twin, linkage, and association studies now support this initial hypothesis. More recent studies have used genetic linkage analysis as a method to find chromosomal locations of disease susceptibility genes. A recent screen of the entire human genome carried out by

the Collaborative Study on the Genetics of Asthma confirmed the importance of chromosomal regions 5q, 6p, 11q, 12q, 13q, and 14q and suggested new regions including 2q, 5p, 11p, 17p, 19q, and 21q.¹⁶

Respiratory infections

Viral infections occur frequently in children and often cause wheezing in children both with and without asthma. Children with past hospitalizations for viral respiratory infections have been shown to have abnormal lung function and increased airway reactivity after infections.¹⁷ In addition, a population-based study of children in Boston found that a history of bronchiolitis or croup in early childhood (ie, between ages 5 and 9 years) was a predictor of increased bronchial responsiveness at follow-up 5 years later.¹⁸ However, the role of viral respiratory infections in the cause of asthma remains unclear.

Outdoor air pollution

Significant evidence links outdoor air pollution to exacerbations of asthma. For example, experimental studies have shown that the oxidant pollutants such as nitrogen dioxide¹⁹ and ozone²⁰ may enhance the effects of allergens, possibly by increasing airway permeability. In addition, through the study of geographically clustered outbreaks of asthma, investigators have linked the release of airborne allergens (eg, soybean dust) to the occurrence of epidemic asthma.²¹

Indoor air pollution

As children and adults spend increasing amounts of time indoors, interest in indoor sources of pollution as a cause of asthma has increased. There is evidence that the degree of allergen exposure may affect the incidence of asthma and wheezing.

A prospective cohort study in the United Kingdom by Sporik et al¹⁴ demonstrated that the risk of asthma may be related to the level of childhood exposure to house-dust mite. Levels of house-dust mite measured in the home were predictive of the development of asthma. Children with higher levels of house-dust mite also tended to start wheezing at an earlier age.

Cigarette smoking

There are substantial data showing that active smoking has the effect of increasing nonspecific airway responsiveness, perhaps by inducing airway inflammation. Maternal smoking is associated with increased risk for both the onset and exacerbation of asthma. Furthermore in utero exposure to tobacco may affect airway responsiveness and result in an initial decrease in the infant's airway function after birth.²² In 1992, the U.S. Environmental Protection Agency reviewed the data on environmental tobacco smoke and found sufficient evidence to link parental smoking and childhood asthma. The California Environmental Protection Agency reviewed their evidence through 1996. They identified 37 relevant investigations that found an approximately 50% increased risk for clinically diagnosed asthma associated with parental smoking.

WHEN DOES ASTHMA START?

The relation of viral wheezing episodes to later childhood asthma has been incompletely understood. The association of asthma in older children with increased serum IgE levels¹² is not evident in early childhood wheezing.²³

In a recent prospective study, Martinez et al²⁴ assessed the factors that affect wheezing before age 3 years and their relation to wheezing at age 6 years. A total of 1246 newborns were enrolled; follow-up data were available at ages 3 and 6 years for 826 of these children. Assessments in infancy included measurement of cord serum IgE levels, pulmonary function testing before the occurrence of any lower respiratory tract illness, measurement of serum IgE levels at age 9 months, and completion of a questionnaire by the children's parents when the children were 1 year old. Measurements at age 6 years included assessment of lung function, skin allergy testing, and determination of serum IgE levels.

At age 6 years 51.5% of children had never wheezed, 19.9% had at least 1 lower respiratory tract illness with wheezing during the first year of life but had no wheezing at age 6 years, 15% had no wheezing before age 3 years but had wheezing at age 6 years, and 13.7% had wheezing both before age 3 years and also at age 6 years.

The children who had wheezing before age 3 years but not at age 6 years had diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity) both before age 1 year and at age 6 years. They also were more likely than the other children to have had mothers who smoked but not mothers with asthma and did not have elevated serum IgE levels or skin-test reactivity.

By comparison, children who started wheezing in early life and continued to wheeze at age 6 years were more likely than the children who never wheezed to have the following characteristics: a maternal history of asthma ($P < .001$), elevated serum IgE levels ($P < .01$), normal lung function in the first year of life, and elevated serum IgE levels ($P < .001$) but diminished lung function ($P < .01$) at age 6 years. It is important to note that the children with persistent wheezing had the lowest levels of lung function of all the groups.

The Martinez study shows that one third of all children age 3 years or younger had lower respiratory tract illnesses with wheezing, but almost 60% of these children had stopped wheezing by age 6 years. There was a significant, direct relation between the risk of persistent wheezing and the serum IgE level at age 9 months. No relation was found between the risk of persistent wheezing at age 6 years and cord serum IgE levels, however, suggesting that some form of IgE-mediated sensitization may occur during the first year of life in children with persistent wheezing. This sensitization to allergens in very young children may contribute to early wheezing just as it does in older children with asthma.

Children with persistent wheezing had significantly reduced lung function at the age of 6 years. This lower airway function is consistent with findings reported by

other investigators.¹⁰ The data of Martinez et al²⁴ support the conclusion that among children with persistent wheezing, deficits in pulmonary function are not caused by lower initial lung function but may occur as a result of the chronic inflammation inherent in asthma.

WHAT HAPPENS TO THE CHILD WITH ASTHMA?

"Will my child outgrow asthma?" This very frequently asked question is posed to health care providers by parents of asthmatic children, and it needs to be answered. Fortunately, study data are now becoming available that help clarify the determinants of persistent asthma. Initial information on the natural history of childhood asthma came from cohort studies of children attending specialized practices or clinics that began in the 1930s. However, patients in these studies had more severe asthma than would be expected in the general population, thus adding a potential bias to the studies.

A better understanding of the natural history of childhood asthma is possible now through prospective cohort studies^{15,25-32} of population-based groups of children who have been monitored over time (Table I).³³ Park et al²⁷ collected information at birth and at ages 5 and 10 years on a national cohort of 11,465 children in the United Kingdom. A history of wheezing was obtained through questionnaires administered to the parents. Of the children who had at least 1 wheezing attack before age 5 years, only 20% had 1 or more wheezing attacks at age 9 years. The number of attacks before age 5 years was a strong predictor of prognosis at age 10 years. Fifty percent of the children with a diagnosis of asthma at age 5 years no longer had a diagnosis of asthma at age 10 years.

Results from studies that spanned the years from childhood to adulthood are now available. McNicol and Williams⁹ reported on a study population that was enrolled in 1964 at age 7 years for which 21 years of follow-up have been completed.³⁴ Forty-three percent of subjects who wheezed at age 7 years were no longer wheezing at age 28 years, and 32% had wheezing at least weekly. It is important that the subjects with more severe wheezing at age 28 years tended to have lower lung function and greater airway responsiveness. Over time, some asthmatics improved, and an approximately equal number worsened.

Members of a 1958 birth cohort in the United Kingdom have now been monitored up to age 33 years.^{15,30,35} Parents of the participants were interviewed when the children were ages 7, 11, and 16 years. The participants themselves were interviewed at ages 23 and 33 years. Of children with a report of asthma or wheezy bronchitis before age 7 years, only 10% had wheezing within the preceding year when questioned at age 23 years. However, at age 33 years, 27% reported wheezing in the preceding year.³⁰ For subjects who reported continued wheezing at age 33, forced expiratory volume in 1 second (FEV₁) was reduced by approximately 10% compared with the control group.

TABLE I. Selected recent studies of the natural history of childhood asthma

Study	Study population	Follow-up	Findings
Kelly 1987 ²⁵ Kelly 1988 ²⁶	401 Australian children, age 7 yr on enrollment	5 follow-up evaluations until age 28 yr	<i>Wheezing:</i> Tended to abate in pts with less severe wheezing on enrollment and to persist in those with more initial wheezing. <i>Lung function:</i> At age 28 yr, tended to be lower in those with more severe wheezing.
Park 1986 ²⁷	11,486 U.K. children in a 1970 birth sample	Questionnaire completed by parents when children reached ages 5 and 10 yr	<i>Wheezing:</i> 80% of 2345 children with wheezing before age 5 yr had no wheezing at age 10 yr. <i>Asthma:</i> 50% of 238 children with a diagnosis of asthma at age 5 yr were asthma-free at age 10 yr.
Godden 1994 ²⁸	455 Scottish children ages 9–15 yr on enrollment: 121 with asthma; 167 with wheezing; 167 controls	Evaluation after 25-yr follow-up	<i>Clinical features in former asthmatic patients:</i> More likely to wheeze Lower lung function Greater BHR
Sporik 1991 ²⁹	67 U.K. infants at risk for atopic disorder	Annual evaluation through age 5 yr and again at age 11 yr	<i>Wheezing:</i> Of 21 children with wheezing at age <2 yr, 76% were wheeze-free 61% did not have BHR at age 11 yr Of 21 children with wheezing at age >2 yr, 17 were wheezing 12 had BHR at age 11 yr
Strachan 1996 ^{15,30}	1335 U.K. children in a 1958 birth sample	Periodic evaluation in subjects up to age 35 yr	<i>Wheezing:</i> Of 302 children with wheezing by age 16 yr, ~40% still had asthma or wheezing in the last study evaluation year (at ages 34–35 yr)
Kokkonen and Linna 1993 ³¹	108 Swedish children with a diagnosis of asthma by age 15 yr	Evaluation at ages 20–24 yr	<i>Symptom-free:</i> 28% <i>Symptoms at least weekly:</i> 22% <i>BHR:</i> 48%
Roorda 1994 ³²	406 children, ages 8–12 yr on enrollment, referred for treatment to a clinic in The Netherlands	Mean follow-up 14.8 yr, or to mean age of 24.7 yr	<i>BHR:</i> Decreased over time <i>FEV₁:</i> Increasing % predicted over time

BHR, Bronchial hyper-responsiveness; FEV₁, forced expiratory volume (in 1 second).

Adapted from Murphy SJ. Pediatric Asthma. New York: Marcel Dekker, Inc.; (in press) by courtesy of Marcel Dekker, Inc.

Several smaller studies^{6-9,13,36,37} are summarized in Table II³⁸ and show similar results. It appears that approximately 50% of adults who reported having childhood asthma no longer have symptoms. Airway responsiveness in childhood, however, tends to predict airway responsiveness in adulthood,³⁹ to be greater in asthmatics with persistent symptoms,²⁸ and not to improve over time.⁴⁰ These studies support the hypothesis that early therapeutic intervention in mild asthma may lead to an improved clinical outcome.

IS THE PREVALENCE OF ASTHMA INCREASING?

Since the development of the British Medical Council respiratory questionnaire in 1960, a large number of epidemiologic studies designed to determine the prevalence of asthma have been completed. In most studies estimates of prevalence have been dependent on partici-

pants' responses to standardized questionnaires. Virtually all published reports have been handicapped by the lack of a diagnostic gold standard for asthma.⁴¹ Allergy skin-test reactivity and total and specific IgE measurements have sometimes been added to increase the specificity of the diagnostic database. Woolcock et al^{42,43} added measurements of nonspecific bronchial responsiveness. Even the addition of this clinical tool, however, met with only modest success.^{44,45}

Despite these limitations, asthma prevalence rates have been investigated in many parts of the world. Reported numbers have been presented as both the prevalence of wheeze as a specific symptom and the prevalence of an asthma diagnosis. In 1969 Williams and McNicol⁴⁶ studied 10-year-old Australian schoolchildren and found the point prevalence of asthma to be 3.7%, with a cumulative prevalence rate of 11.7%. The prevalence of wheeze was considerably higher.

TABLE II. Selected studies describing the clinical course of childhood asthma

Study	Study population	Average duration of follow-up (yr)	Outcome (%)			
			Asymptomatic or improved	Symptomatic		Death of asthma
				Mild	Chronic/severe	
Rackemann and Edwards 1952 ⁷	688 children, asthma onset before age 13 yr, from private practice	20	66	14	17	1.5
Dees 1957 ³⁶	236 children, age <14 yr, from pediatric allergy clinic	5	44	36	20	1.0
Ogilvie 1962 ³⁷	1000 children, referred to investigator for care, after 1935	11	48	26	19	7
Buffum and Settignano 1966 ¹³	518 children, from private practice, before 1956	10	41	52	6	1
Blair 1977 ⁸	244 children, age <12 yr, from group practice, 1948–1952	20	27	49	21	1
McNicol 1973 ⁹	314 children, age 7 yr, from public schools, beginning in 1964	7	48		52	—
Schachter 1984 ⁶	25 children, ages 7–17 yr, from general population sample, beginning in 1972	7	72		28	—

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Significant variations in asthma prevalence rates have been reported from different countries with different climates and environments. The lowest rates, less than 2%,^{47,48} have been found in Scandinavia; the highest rates, frequently more than 10%,^{42,45} have been documented in Australia and New Zealand. Prevalence rates in North America^{49,50} and the United Kingdom have generally been somewhere between these extremes.⁵¹

Studies designed to determine whether there has been a recent increase in asthma prevalence rates are difficult to interpret. They have relied almost exclusively on repeated cross-sectional surveys of different populations living under similar conditions. In their initial survey, Auerbach et al⁵² determined the point prevalence of asthma among 17-year-old Israeli males (examined for military service) to be 5.0%, with a cumulative prevalence of 7.9%. When the survey was repeated 4 years later, the percentages for these variables were 5.9% and 9.6%, respectively. Ninan and Russell⁵³ conducted a similar study in Finland with a 25-year interval and found the prevalence of asthma had increased from 4% to 10%.

Rather than accept that these changes were solely related to an increase in asthma prevalence, Magnus and Jaakkola⁵⁴ addressed the question of diagnostic labeling and the effect that changes may have on asthma prevalence data. They analyzed 16 studies, all of which were conducted with the repeated cross-sectional survey

method. Despite the fact that the reports almost universally indicated an increase in asthma prevalence, the authors were skeptical. In their view the added attention given to asthma in recent years including both public and professional information campaigns has led to an increase in and possible overuse of the asthma diagnostic label. Whether the reported increases are real or just a reflection of changes in diagnostic labeling is not clear. In many cases symptoms have increased less than the asthma diagnosis, suggesting that the increased symptom prevalence accounts for only a portion of the reported increase in asthma diagnoses.

WHAT ARE RISK FACTORS FOR THE ONSET OF ASTHMA IN ADULTS?

For many years studies of risk factors for the development of asthma have focused primarily on early childhood, the age at which the incidence of asthma is highest. Most of these studies have been concerned with early allergen exposure and genetic factors. Adult-onset asthma has received much less attention.

In 1977 Burrows et al⁵⁵ reviewed retrospective historical data obtained in the Tucson study of airway obstructive disease and found that a history of respiratory symptoms during childhood was a major risk factor for wheezing after age 20 years. Among subjects with a childhood history, the combination of a reduced FEV₁ and a smok-

ing history was associated with a higher incidence of adult airway obstructive disease. This was attributed to an increased susceptibility to the damaging effects of environmental irritants and infections. In essence, airways that are damaged during childhood are more susceptible to disease later.

Additional insight into the impact of childhood respiratory symptoms on adult-onset disease has been provided by Martin et al⁵⁶ and subsequently by Kelly et al.³⁴ Both reports provide follow-up data on the cohort of asthmatic children initially described by Williams and McNicol.⁴⁶ Martin et al⁵⁶ found that 55% of those whose wheezing had started before age 7 years and had stopped before the onset of adolescence were without wheezing at age 21 years. When Kelly et al re-examined the same cohort 7 years later, they found that 31% of those who had no wheezing at age 21 years were again wheezing at age 28 years.³⁴ The data suggest that a major risk factor for the occurrence of adult asthma is a history of even mild asthma during childhood.

A number of investigators have attempted to identify other factors that appear to be causally related to the onset of asthma during adulthood, especially in adult patients with no history of childhood respiratory disease. Most reports have related asthma onset to the presence of BHR. Peat et al⁵⁷ found the best correlate with BHR to be atopy. Positive correlations were also noted with female sex and a smoking history. In a Canadian study, Jaakkola et al⁵⁸ monitored several hundred subjects between the ages of 15 and 40 years for an 8-year period. The onset of asthma in this study was related to an increase in the slope of the decline in FEV₁, suggesting the presence of airway hyperresponsiveness and subclinical asthma before a diagnosis of full-blown asthma. In 1980 Dodge and Burrows⁵⁹ found that asthma onset before age 40 years had a significant relation with atopy; over age 40 years, however, allergic factors were not associated with disease onset.

Despite the absence of an allergic background in older adult asthma resulting from an absolute decrease in both allergen skin-test reactivity and total serum levels of IgE,^{60,61} Burrows et al¹² concluded that an allergic relation does exist. In the Tucson study levels of IgE were corrected for age. When this correction was complete, the odds ratios for the development of asthma correlated with IgE levels, even in older adults. With this correlation the authors questioned whether it is appropriate to divide asthma into extrinsic and intrinsic types. A number of other reports⁶²⁻⁶⁴ describing longitudinal studies in patients of various ages would appear to support these findings. In some of these reports smoking and socioeconomic status also played a role but almost always in association with BHR, atopy, or both. What remains unanswered is whether these factors play a role in *causing* asthma or are the result of the disease itself.

Occupational asthma

Adults exposed to specific occupational environments may be at additional risk for the development of asthma.

At present, several hundred such exposures have been identified, accounting for between 15% and 20% of adult asthma in the United States. Venables and Chan-Yeung⁶⁵ recently classified the pathologic mechanisms involved in occupational asthma into 3 groups. The first group includes those exposures that induce specific IgE responses. These compounds may be high-molecular-weight allergens or low-molecular-weight compounds that act as haptens, combining with body proteins to form complete allergens. A second exposure category includes agents that appear to cause asthma by non-IgE immunologic mechanisms, the precise nature of which is not known. Finally, a number of inherently toxic substances appear to induce an asthmatic response on the basis of their irritative capacity.⁶⁶

The importance of nonspecific BHR as a feature of occupational asthma was stressed in a report by Lam et al.⁶⁷ Patients with occupational asthma had the same degree of responsiveness as those with nonoccupational asthma. During a period of 2 to 4 years after removal from the offending agent, BHR decreased; however, it returned to previous levels if re-exposure occurred. Lam et al concluded that BHR was a consequence of, rather than a predisposing factor in, occupational asthma.

Thus asthma that results from occupational exposure differs little in its clinical or pathologic features from nonoccupational asthma. Bronchial hyperresponsiveness is present and is frequently severe. The pathologic condition of the airway is also similar. Atopy is a significant risk factor for those agents that induce specific IgE antibodies. In occupational asthma that is related to low-molecular-weight compounds, nonsmokers and nonatopic individuals are at greater risk. Again, a genetic predisposition may be present.⁶⁸

CONCLUSION

The definition of asthma has continued to evolve into the late 1990s. Asthma is now defined as an inflammatory disease of the airway, with reversible airflow obstruction and airway hyperresponsiveness as important components of this definition. The importance of risk factors for the development of childhood asthma continues to be clarified. Young males are more likely to have asthma, but young females may have a greater deficit in pulmonary function. Atopy continues to be strongly associated with the development of persistent asthma. The observation that asthma tends to cluster in families has led to genetic studies with linkage analysis which, it is hoped, will lead to a greater understanding of the genetics of asthma. Viral respiratory infections are a common trigger of wheezing in children; however, their exact role in the cause of asthma remains to be defined. Clearer evidence of the environment in the cause of asthma can be seen through clusters of asthma occurring with soybean dust released into the atmosphere; however, the role of outdoor air pollution is less clear. In the indoor environment levels of house-dust mites appear to be predictive of the development of asthma in an at-risk population. For children with persistent wheezing, defects in pulmonary

function are not caused by initial lower lung function but, rather, may occur as the result of chronic inflammation inherent in asthma. We know that airway responsiveness in childhood tends to predict airway responsiveness in adulthood, is greater in asthmatics with persistent symptoms, and does not improve over time. These data support the hypothesis that mild asthma and early therapeutic intervention may lead to an improved clinical course.

Occupational asthma has given us a snapshot view into the possible natural history of asthma. Asthma that results from occupational exposure differs little in its clinical or pathologic features from nonoccupational asthma. In addition, BHR is present, atopy is a significant risk factor, and the airway pathologic characteristics are similar.

The natural history of asthma continues to evolve, aided by clarification of the definition of this disease and large-scale longitudinal studies and research into the genetics of asthma. A once blurry picture is becoming clearer. Asthma that starts in childhood has a high probability of continuing into adulthood and may be modified by therapeutic intervention.

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