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The natural history of asthma

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Asthma begins most often in infants as wheezing with respiratory infections. If these episodes are mild and infrequent, asthma does not usually persist into the school years. However, if they are more frequent and severe, the asthma is likely to persist. After infancy, incidence falls and continues at about 100/100,000 for the rest of the lifespan. Allergic asthma develops most often in the second decade of life and frequently persists into adult years, but young patients with allergic asthma often enjoy a transient or even a permanent remission. More severe disease and continued allergen exposure cause persistence. Some patients with occupational asthma continue to have asthma long after exposure ceases. Asthma beginning after the fourth decade is usually intrinsic and may include the aspirin triad. Its severity tends to increase with time. Many middle-aged and elderly adults have a persistent decline in lung function that is retarded but not completely prevented by aerosol glucocorticoids. This loss of lung function is often the result of coexisting lung diseases, particularly bronchiectasis and COPD. Patients with asthma have the same overall rate and age of death as the general population, but are more likely to die of lung diseases, including cancer. (J Allergy Clin Immunol 2006;118:543-8.)

Key words: *Asthma, natural history, epidemiology, adults, children, allergy, occupational asthma, cause of death, lung function, airway remodeling, bronchiectasis, emphysema, smoking*

Abbreviation used
UK: United Kingdom

Physicians who treat patients with asthma are well aware that there is considerable variability in the course of the disease. Some of our patients seem to recover completely. Others have long remissions with occasional mild relapses. Most of them seem to continue about the same for many years. Unfortunately, however, some get worse and develop irreversible airway obstruction. A few even die.

Treatment of our patients would be improved if we understood the reasons for this variability. One barrier for applying the results of population-based studies of natural history to improve our understanding is that there are variations in the criteria for the diagnosis.[1] Over the years, and also in different communities, physicians have used different criteria, so studies in which the subjects are included based solely on physicians' diagnosis may be difficult to interpret. Furthermore, patients' recollections of diagnoses and details of their illness may be faulty. A second barrier to predicting the natural history of asthma is the effect of the highly individualized environment with different exposure to irritants, allergens, and microbial products like endotoxin. A third and perhaps the most important barrier to our understanding of the natural history of asthma is whether we should consider asthma a disease like juvenile diabetes with a single basic underlying etiology but with different complex outcomes, or whether we should consider it a syndrome like hypertension with many etiologies that affect the outcome differently. The identification of many genetic variations affecting airway hyperresponsiveness and pathways of inflammation suggests that we should consider asthma a syndrome, but information about these genetic variations is still too primitive to be applied to large-scale prospective studies or to our individual patients. Discussion of the details of these 3 barriers is outside the scope of this review. Rather, the purpose of this review is to summarize the available information about the natural history of asthma, with the assumption that this information will aid us in treating our patients and telling them or their parents what to expect.

ASTHMA IN CHILDREN

Asthma most commonly begins in infants. A community-based study in Rochester, Minn, found that in the first year of life, 5% of babies had at least 1 physician visit for wheezing.[2] The yearly incidence of definite and probable asthma in the first year of life was 3%. The incidence rate dropped to 0.9% in the age group 1 to 4 years and was stable at about 0.1% after the age of 15 years. Thus, it is

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TABLE I. Melbourne Epidemiological Study of Childhood Asthma: outcome at age 42 years of the 4 groups classified by severity at age 7 years (% of group)

	Condition at enrollment			
Condition at age 42 years	**Mild wheezy bronchitis**	**Wheezy bronchitis**	**Asthma**	**Severe asthma**
No recent asthma	68	58	32	10
Infrequent asthma	18	15	18	13
Frequent asthma	17	17	26	27
Persistent asthma	0	10	24	50

Adapted from Fig 1.[3]

not surprising that many studies of the natural history of asthma have concentrated on children.

In 1964, physicians at the Royal Children's Hospital in Melbourne, Australia, initiated a community-based study of a group of children born in 1957. This cohort has been followed to the present.[3] Because of the policy that treatment was to be left entirely in the hands of the treating physicians, the authors of the most recent report considered that their results reflect the natural history of asthma from childhood into adult life little influenced by what would currently be considered optimal therapy. Children enrolled at age 7 years were divided into 5 groups: (1) control, never wheezed; (2) mild wheezy bronchitis, fewer than 5 episodes; (3) wheezy bronchitis, 5 or more episodes; (4) asthma, not associated with infection; and (5) severe asthma, onset before age 3 years and persistent symptoms. This classification represents the uncertainty about whether infants who wheeze with respiratory infections really do have asthma. These subjects were reviewed at ages 10, 14, 21, 28, 35, and 42 years. Over the years, the symptoms and FEV_1 in each of these groups continued reflect the differences in initial severity. The overall severity increased between the age of 7 and 10 years, but then improved until age 28 years, after which it remained stable. Only 1 subject died of asthma. By age 42 years, some of the subjects in each group were free of asthma, and some had frequent or persistent asthma. The more severe the asthma at age 7 years, the more likely it was to persist to age 42 years (Table I). Reduced lung function at age 7 years was associated with continuing symptoms in adult life, and the lung function continued to be reduced, but did not appear to decline more rapidly than the control or mild groups with normal FEV_1. Presence of hay fever, eczema, or positive skin test results increased the risk of more severe asthma in adult life. Several conclusions seem reasonable. The severity of asthma in early childhood substantially determines the severity of the symptoms in later years. The severity of the symptoms and loss of lung function usually does not progress and on average tends to improve during adolescence. However a few of the children who wheeze only with respiratory infections and whose lung function is normal at other times do have persistent asthma as adults. Children with atopy have more severe and persistent asthma than children whose episodes are provoked only by respiratory infection.

The Tucson Children's Respiratory Study initiated in 1980 is another community-based prospective longitudinal investigation that provides important information about the natural history of asthma beginning in infancy.[4,5] The study population was a birth cohort of 826 children classified into 4 phenotypes on the basis of at least 1 physician-diagnosed wheezing respiratory illness in the first 3 years of life or parent-reported wheeze at age 6 years: (1) never wheeze; (2) transient early wheeze; (3) late-onset wheeze reported first at age 6 years; and (4) persistent wheeze. Follow-up data at ages 8, 11, 13, and 16 years included questionnaire, spirometry, skin testing, and measurement of serum IgE. The transient early wheezers started life with lower lung function and continued to have lower lung function until at least age 16 years, but these children had no more wheezing episodes as they grew older than the never-wheeze control group. In other respects, the presence of episodes of wheezing as the children grew up was remarkably similar to those from Melbourne. The late-onset wheezing and the persistent wheezing groups had more episodes of wheezing in late childhood and adolescence than the other 2 groups. The frequency of wheezing increased until age 11 years and then declined. The Tucson study evaluated several genetic factors for possible influence on the outcome, but as yet, none have been found to correlate. At age 11 and 16 years, there was no difference between these 4 phenotypes in the frequency of positive skin test results to grass pollen, the major allergen responsible for hay fever in Tucson, Ariz, but reactions to *Alternaria* were more common in the children with physician-diagnosed asthma.[6] Also, the persistent wheezing group had a modest elevation of serum IgE concentration.

A third birth cohort study is in progress in Dunedin, New Zealand. The study group consists of 613 children born in 1972 or 1973 and followed through age 26 years. The children were seen every 2 years between 3 and 15 years and then at 18, 21, and 26 years. At age 9 years, 27% of all children had a history of at least 1 episode of wheezing, and 4.2% were receiving antiasthma treatment.[7] By the age of 26 years, half of the cohort had reported wheezing at 1 or more of these assessment visits. Fifteen percent of the cohort had persistent wheezing from onset, and 12% had remission only to relapse. Fifteen percent of the cohort remained in remission. Although these numbers of children who presumably had asthma are high, they are similar to those in the Tucson study. Two factors present at age 9 years that predicted the persistence of asthma at age 26 years were a bronchodilator response (or a positive methacholine test) and a positive skin test result to mite or cat.[8]

One hundred newborn children in Poole, United Kingdom (UK), were selected if at least 1 parent had asthma or hay fever.[9] They were followed yearly until age 6 years and then at ages 11 and 22 years with a symptom questionnaire, skin tests, total serum IgE assay, and airway hyperresponsiveness to histamine. The age of the first reported wheeze was similar to the data from Rochester, Melbourne, and Tucson, greatest in the first year and leveling off in the teens. By age 22 years, 40% of the subjects had had at least 1 episode of wheezing in the past year. However, only 25% were considered to have asthma, and this was generally mild. Remission was most common in

subjects whose first episode of wheezing was before age 5 years or who had infrequent wheezing. Of the 12 children with asthma at age 11 years, 5 had remitted by age 22 years. Conversely, 5 subjects developed asthma between the ages of 11 and 22 years. Four percent of the subjects had a positive skin prick test result at age 1 year, and this percentage increased yearly, reaching 37% at age 22 years. The development of asthma was associated with early sensitization and bronchial hyperresponsiveness, and also with wheezing that persisted from infancy or began after age 5 years.

All children (N = 1456) born on the Isle of Wight, UK, in 1989 were enrolled in a study of the natural history of allergic disease.[10] They were divided into 4 groups according to results of skin tests at ages 4 and 10 years: (1) never atopic, (2) early childhood atopic (positive skin test results only at age 4 years), (3) delayed childhood atopic (positive skin test results only at age 10 years), and (4) chronic childhood atopic (positive skin test results at both ages). The chronic atopics had higher cord blood IgE than the other 3 groups, and all 3 of the atopic groups had elevated IgE at age 10 years. The delayed and chronic atopic groups had a higher percentage of asthma than the other 2 groups, but pulmonary function was normal, indicating that the asthma was mild. The never atopic group, being larger, actually had more children with asthma than any of the other 3. The study has not yet continued long enough to evaluate possible differences in persistence and duration of asthma in adult years.

An analysis of the influence of early life exposures on the incidence and remission of asthma throughout life that included 18,156 subjects in the European Community Respiratory Health Study confirmed many of these points about incidence and remission of asthma.[11,12] Incidence was higher in boys than girls, but higher in women than men. Incidence was higher at all ages in offspring of parents with asthma or allergies. Frequent respiratory infections increased the incidence in children, whereas contact with older children reduced it, and this early contact provided protection that lasted into adult life. The remission rate of asthma beginning before 10 years of age was 43%, dropping to 30% for asthma beginning at ages 10 to 20 years, and to 15% for asthma beginning at ages 20 to 40 years. Contact with older children was associated with higher remission rates in childhood. Although contact with pets reduced the incidence in children, it had no effect on overall remission rates. Remission at all ages was less if the parents had asthma or allergies.

The National Jewish Medical and Research Center in Denver enrolled 150 children at birth on the basis that their mothers had asthma, and followed 145 of them for 8 years.[13] This study included socioeconomic and psychological data. Forty (28%) of these children had asthma between the ages of 6 and 8 years. The disease was severe enough in 22 of them to require at least 1 course of oral corticosteroids. Three factors from the first year of life predicted asthma between ages 6 and 8 years: (1) higher number of respiratory infections, and more importantly, (2) global ratings of parenting difficulties, and (3) elevated serum IgE. Paternal asthma was not a risk factor for asthma at age 3 years, but it was between the ages of 6 and 8 years. Eczema increased early-onset asthma, but not asthma between ages 6 and 8 years. Factors present at age 6 years that predicted asthma between ages 6 and 8 years were (1) elevated IgE, (2) number of positive skin test results, and (3) greater childhood psychological risk. Maternal smoking and duration of breast-feeding were not related to the development of asthma.

Similar results have been reported from East London,[14] Abredeen,[15] and Germany.[16]

The strong probability that inherited differences increase the incidence and affect the course of asthma has been part of our teaching since the 1920s. As Taussig et al in Tucson have written,[4] the great variability and complexity of asthma suggest that the disease is not under the control of a typical mendelian monogenic 2–allele locus, but that several major and minor loci are involved. Furthermore, the expression of these genes is likely to be influenced by multiple diverse environmental exposures. Heredity is one of the factors that determine bronchial hyperresponsiveness.[17] A study of β_2-adrenoreceptor polymorphism in a birth cohort at the Brompton Hospital in London, UK, reported that Gln^{97} or Arg^{16} alleles were associated with reduced VmaxFRC at infancy, but had no effect on FEV_1 at age 10 years or development of asthma.[18] The study did, however, confirm the Tucson report that neonatal bronchial hyperresponsiveness was associated with early transient wheezing and predicted later reduced lung function, but was not related to the later development of asthma. Laprise et al[19] at McGill University conducted a much more extensive investigation of genes expressed in bronchial biopsies of 4 subjects with allergic asthma. They identified 79 genes of known function that were differently expressed in asthma and normal controls, including 21 genes that had been previously described. At least 18 of these genes have a potential biological role in the pathogenesis of the inflammation of asthma. Inhaled corticosteroid therapy corrected the expression of a third of these gene transcripts. Although this study included only 4 subjects, it signals the direction of our future understanding of both the pathogenesis and the natural history of asthma.

These longitudinal studies did not include information about environmental exposures. However, the similarity of results reported from Melbourne, Dunedin, Tucson, Denver, London, the Isle of Wight, and continental Europe indicates that climate itself is not a factor in the natural history of asthma. However, persistence of asthma was associated with positive skin tests to the allergens most commonly causing asthma in the region. Cross-sectional studies have associated exposure to allergens (especially mites) with asthma in infants, children, and adolescents.[20] On the other hand, exposure to animals, including household pets, and to endotoxin in infancy protects against the progression of wheezing with respiratory infection to persistent asthma (the hygiene hypothesis).[21-24]

In summary, infrequent mild wheezing in infants rarely persists to become diagnosed as asthma by the time the child is in school. Furthermore, the severity of chronic persistent asthma is generally stable through adolescence,

TABLE II. Predictors of persistence and severity of childhood asthma

More severe and frequent wheezing episodes during preschool age
Onset during school age
Family history of asthma and allergy
Elevated serum IgE
Early development of positive skin test results
Early development of bronchial hyperresponsiveness
Frequency of respiratory infections
Lack of contact with older children
Parenting difficulties
Greater childhood psychological risk

rarely increasing, but often remitting. The factors that predict persistence of asthma are listed in Table II. It is not clear whether elevated IgE and positive skin tests are separate factors or simply reflect the same biological event. The fact that some individuals with asthma may have elevated IgE but negative skin tests strongly suggests that they should be considered separately.

ASTHMA IN ADULTS

Asthma may persist from childhood or have its onset in adult life. The primary variable for persistence and severity of asthma identified in longitudinal studies is the severity in childhood (Table I). However, common sense and everyday experience tell us that continued exposure to relevant indoor allergens such as mites, cockroaches, and cats is also important. Also, the studies hint that sensitization and exposure to outdoor allergens, especially *Alternaria*, result in more persistent and severe asthma.

The presence of atopy increases the incidence of asthma in children and may also increase the incidence of asthma in young adults. A study in Spain reported that sensitization to allergens, particularly *Alternaria*, is associated with reduced FEV_1, even in the absence of asthma symptoms.[25] A cohort of college students evaluated for hay fever or asthma were followed up 23 years later.[26] At the age of 40 years, about half of subjects who had asthma as freshmen continued to have asthma. Of these subjects, half (a quarter of the entire group) reported that they continued to have about the same frequency and severity of symptoms; very few were worse. During these 23 years, 5.2% of subjects who did not have asthma as freshmen developed asthma subsequently; the yearly incidence rate was 0.23%. In contrast with the data from Spain, the presence of positive skin test results or hay fever as freshmen did not affect the incidence of new cases of asthma as these subjects grew older. Unfortunately, skin tests were not performed at the 23-year follow-up of middle-aged adults, so it is not possible to know whether these new case of asthma were allergic or intrinsic.

Francis Rackemann, who introduced the concept of intrinsic asthma in the 1920s, reported in 1958 a follow-up study of his patients with adult-onset nonallergic asthma.[27] Only about 20% had a remission. More recently, Bronnimann and Burrows reported that data from the Tucson study showed remissions were uncommon after the second decade, and were especially uncommon in subjects 30 to 60 years old. Relapses of asthma that began at any age were common and increased until age 70 years.[28] A study in Sweden reported similar results.[29]

The aspirin triad is an important category of adult asthma. A cross-sectional study from the Scripts Institute in La Jolla, Calif, found that the average age of onset was 34 years, and like all adult-onset asthma, was more common in women.[30] Retrospectively, the severity of the disease progressed from the time of onset to the time of the evaluation. A multicenter study in Europe reported that persistent rhinitis appeared first at a mean age of 29.7 years, followed by asthma, aspirin reactivity, and finally nasal polyps.[31] The disease was more common, started younger, and was more severe in women that men. One third of the patients were atopic; these patients had earlier onset of rhinitis and asthma, but not aspirin sensitivity. One half of the patients were steroid-dependent. In a multicenter study of severe or difficult-to-treat asthma (Epidemiology and the Natural History of Asthma: Outcomes and Treatment Regimens [TENOR]), aspirin-sensitive patients with asthma had a lower mean postbronchodilator FEV_1 compared with nonaspirin-sensitive patients with asthma.[32] This effect was considered to be a result of airway remodeling.

Lung function of some, but no means all, adult patients with asthma declines over the years.[33-35] Doubtless, decline in FEV_1 varies with the severity. One study of the decline of FEV_1 reported that although aerosol glucocorticoid treatment improved FEV_1, it did not prevent continued deterioration.[36] Patients in the Third National Health and Nutrition Examination Survey of 1063 adults 20 years of age or older with lifelong history of asthma had deterioration of lung function; not only did airway obstruction increase, but also a restrictive abnormality developed.[37] There are many reasons for this deterioration of lung function. Airway remodeling from persistent severe inflammation certainly is one.[38] Many patients with asthma smoke and have the consequential lung problems including COPD and cancer of the lung. Allergic bronchopulmonary aspergillosis frequently causes permanent loss of lung function because of bronchiectasis and segmental fibrosis.[39] α-1 Antitrypsin deficiency is another uncommon cause of irreveribility.[40]

OCCUPATIONAL ASTHMA

The natural history of occupational asthma not only is of interest for itself but also can serve as a model for asthma beginning in the adult years. Chan-Yeung et al[41] reported follow-up studies of subjects with asthma from Western Red Cedar. Individuals who remained on the job continued to have symptoms, and their lung function declined. Half of the subjects who quit working with cedar lost their symptoms; the other half continued to have attacks of asthma. This latter group had been exposed

TABLE III. Predictors of persistence and severity of adult asthma

Continued exposure to allergens including occupational agents
Older age of onset
Presence of aspirin sensitivity
Socioeconomic status
Smoking
Coexisting diseases, including COPD, bronchiectasis, and (rarely) α-1 antitrypsin deficiency or allergic bronchopulmonary aspergillosis

longer after symptoms started, were older, had poorer lung function and greater methacholine response, and tended to have dual immediate and late phase response rather than just late phase response to bronchial challenge with Western Red Cedar extract. Different occupational agents have different natural histories.[42] In particular, asthma from diisocyanates can persist for years after exposure ceases, and the airways are remodeled, leading to a degree of irreveribility.[43,44] In summary, a more intense and longer exposure causes a more severe and persistent disease.

ASTHMA IN THE ELDERLY

The incidence of asthma continues the same in patients age 65 to 84 years as it is in younger adults, about 100/100,000.[45] However the disease may be more likely to persist and progress in severity. A cross-sectional study of 242 patients with asthma age 65 and older found that 80% had irreversible obstruction; 20% of them were unable to achieve an FEV_1 greater than 50% predicted.[46] Only a part of this irreversibility is the result of airway remodeling from asthmatic inflammation. More of it is the result of coexisting lung diseases, including bronchiectasis with segmental fibrosis and COPD with emphysema. Asthma increases the risk of lung cancer.[47] This complexity of coexisting lung diseases in older adults not only makes epidemiologic studies difficult but also adds to the problems of diagnosis and treatment[48] (Table III).

DEATH

Being human, everyone with asthma will die. The questions are, when and why? The age of death of patients with asthma does not differ from the population as a whole and is usually caused by the same diseases as the general population.[49] Fatal or near-fatal asthma is extremely rare in young children. In adolescents and young adults, it tends to be sudden. Risk factors for this younger age group include allergy to *Alternaria*, low socioeconomic status, black race, and substance abuse.[50-53] In older adults, death from acute severe asthma remains relatively uncommon. However, older adults with asthma die of respiratory diseases more often than individuals in the general population.[45,49] Also, they are a risk of the cardiac complications of treatment with theophylline and β-adrenergic agonists. Epidemiologic studies of the cause of death are somewhat uncertain because of coexistence of other lung diseases and the inaccuracy of death certificates.[54]

CONCLUSION

Application of the results of these extensive studies about the natural history of asthma to our treatment of individual patients might be simplified by considering asthma a syndrome rather than as a single disease. Extending the Tucson and Melbourne classifications of phenotypes in children into adult years, these asthma syndromes could be (1) intermittent wheezing with respiratory infection in infants; (2) IgE-mediated asthma, predominantly developing in the first 2 decades; (3) intrinsic asthma developing at all ages; and (4) asthma associated with other chronic lung diseases. Infants with only occasional episodes of wheezing with respiratory infection generally do not have asthma as they mature. However, older children and adults with allergic asthma often have attacks provoked by respiratory viral infections. Asthma mediated by IgE reactions to airborne allergens usually begins in the second decade of life. As a rule, older individuals develop allergy only to allergens they did not encounter as children, such as occupational exposures or allergies that develop after moving to a different climate. Allergic asthma is usually not severe and does not progress. Its severity is determined by the amount and duration of exposure; acute heavy exposure can cause acute severe or even fatal reactions.

Intrinsic asthma can begin at any age, but its incidence appears to be higher in middle-aged and older adults. It is more persistent and more likely to progress in severity and to develop a component of irreversibility. It is associated with elevated IgE, even though skin tests are negative. Of course, intrinsic and allergic asthma are not mutually exclusive and can coexist. Unfortunately, criteria for this coexistence are not easily applicable to epidemiologic studies.

Epidemiologic studies designed to investigate the natural history of asthma often include only subjects who meet strict criteria for the diagnosis and exclude subjects who have coexisting lung diseases. One area of considerable practical importance is to establish criteria for recognition and evaluation of the course of concomitant lung diseases, both in children and especially in the elderly. Future studies will also include correlations of the natural history of asthma with specific genotypes and the effect that the environment has on the expression of these genotypes.

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