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The natural history of asthma in adults: The problem of irreversibility

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Asthma is common, affecting 5% to 10% of adults; asthma is progressive, leading to irreversible obstruction in 80% of elderly patients; and asthma is complex, often complicated by coexisting lung diseases. This loss of lung function results from 4 independent pathologic conditions: (1) airway remodeling, especially in the small airways, from the lymphocytic-eosinophilic inflammation that characterizes asthma; (2) bronchiectasis; (3) postinfectious pulmonary fibrosis; and (4) emphysema and chronic bronchitis from tobacco smoke. Deterioration in lung function develops faster in nonallergic patients with intrinsic asthma during the period shortly after onset of asthma and in older patients. About 4% of patients die of asthma, and most are elderly. Death most often results from complications of irreversible obstruction or cardiotoxicity of bronchodilator therapy. More research is needed to improve therapy for preventing remodeling of small airways, to confirm the frequency of bronchiectasis and postinfectious fibrosis and to determine their causes, and to develop diagnostic criteria to identify these complications. Meanwhile, clinicians treating adult asthmatic patients need to be aggressive in preventing the damage from cigarette smoke; in immunizing for influenza and pneumococcus infection and identifying and treating respiratory infections, particularly at times of acute exacerbations; in diagnosing and managing bronchiectasis; and in objectively confirming the efficacy of asthma therapy to prevent illness from overtreatment with glucocorticoids and bronchodilators. (*J Allergy Clin Immunol* 1999;103:539-47.)

Key words: Asthma, adults, natural history, cause of death, treatment, smoking, lung function, airway remodeling, bronchiectasis, emphysema

Abbreviation used

COPD: Chronic obstructive pulmonary disease

Weich and Samet¹ have recently reviewed asthma from the epidemiologic perspective. This article will review the natural history of asthma in adults from the clinical perspective, paying particular attention to the problem of development of irreversible airway obstruction. Epidemiologic study has largely focused on children and young adults because recorded diagnoses of "asthma" are most accurate in this age group. Less information has been published about the epidemiology of asthma in middle-aged and elderly individuals, yet the experience of physicians whose practice includes older people is that these patients are often more severely impaired than younger asthmatic subjects.^{2,3}

Two main problems that have hampered a more complete understanding of the course of the disease in adults are (1) the erroneous, but widely accepted, concept that airway obstruction can develop in any particular patient from only a single pathologic process and (2) the difficulties in identifying asthma for epidemiologic purposes. Barbee,⁴ in his review of the epidemiology and natural history of asthma in the elderly, has called attention to the problems of the semantics and diagnostic labeling of patients with chronic airflow obstruction. In reality, many of our adult patients, particularly older patients, have more than one airway disease (ie, diseases that are brought about by distinctly separate pathways of inflammation). Of course, the concept that asthma, chronic bronchitis, and emphysema should be considered as manifestations of one disease entity in which both endogenous and exogenous factors play a role in pathogenesis is not new. Long ago, this concept, introduced by Orie and his colleagues⁵ in Groningen, The Netherlands, became known as the "Dutch Hypothesis." If the aim of the investigation is to compare the frequency of acute asthma as a specific cause of death at different times and

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places, it is appropriate to limit the study to young patients. But if the aim is to understand the course of the disease throughout a lifetime, it is essential to consider co-existing diseases and other confounding events. The Dutch Hypothesis effectively describes the clinical situation of older patients with chronic airway obstruction.

Although a recent Expert Panel Report⁶ has summarized a firm international consensus about the definition of asthma, this definition is not as useful for epidemiologic studies as it is for clinical purposes. Most epidemiologic studies, both cross-sectional and longitudinal, rely heavily on physician diagnosis. But unfortunately, physician patterns of diagnostic labeling have changed over the years, following fashions not unlike those that govern the length of skirts or the width of neckties. Mostly, these fashions have been set by the concept of the "cause" of asthma in vogue at the time—psychogenic in the middle of the century, bronchospasm and airway hyperresponsiveness in the 1970s and 1980s, and lymphocytic-eosinophilic airway inflammation in the present. Also, a physician's decision to record a diagnosis of asthma has been influenced by the efficiency of available treatments and by socioeconomic concerns. Thus physician-diagnosed or patient-recorded "asthma" is not necessarily consistent between communities or at different times in the same community.⁷ The objective physiologic component of the recent Expert Panel definition relies on serial spirometry that is often not available to the epidemiologist, especially retrospectively. In research studies the pathologic component of desquamation of the epithelium and bronchial infiltration by lymphocytes and eosinophils is best identified by biopsy or bronchoalveolar lavage, but it can be determined in a less invasive manner by careful analysis of sputum samples.^{8,9} Unfortunately, in the practice setting such sputum analysis is rarely performed, and the diagnostic presence of eosinophils in the sputum or circulation is easily suppressed by glucocorticoid treatment. Therefore epidemiologists have found it necessary to rely on physician diagnoses supplemented by questionnaires, spirometry, and tests of airway hyperresponsiveness and to define explicitly their criteria for case selection.¹⁰ These criteria often vary with the aim of the study and the information that is available. Different questionnaires provide different information of varying degrees of reliability.¹¹ Unfortunately, bronchial hyperresponsiveness to methacholine or histamine is neither sufficiently sensitive nor specific to be an absolute criterion of mild asthma in subjects with normal spirometry, and the geometric effect of airway narrowing causes hyperresponsiveness in all patients with chronic airway obstruction of any cause.^{4,12,13} These reservations about methodology aside, considerable useful information is available about the natural history of asthma in adults, even though the numbers derived from epidemiologic studies can be considered only approximate.

INCIDENCE AND PREVALENCE

The incidence of asthma is far greatest in young children, about 3000 in 100,000 individuals in the first year

and 900 in 100,000 in years 1 to 4. After the age of 20 years, the incidence rate remains at about 100 in 100,000 throughout the rest of the life span.^{3,14} In young children asthma is more common in boys, but in young adults the incidence is higher in women.^{14,15} Late in life it again becomes higher in men³; reasons for these differences between the sexes are unknown. In any event, an asthmatic adult may have had the symptoms consistently since childhood or have recovered from the disease in childhood only to relapse or have acquired the disease recently. Although asthma in children is frequently mild and often remits, if it is severe, it usually persists or recurs in young adulthood.¹⁶⁻²¹ Several publications have identified the following factors that correlate with persistence or recurrence of childhood asthma: (1) onset before 3 years of age; (2) female sex; (3) presence of infantile eczema or allergic rhinitis; (4) positive skin test responses to airborne allergens and IgE level; (5) severity of the disease and amount of impairment of pulmonary function; and (6) cigarette smoking, both active and passive.

Factors responsible for the *de novo* development of asthma in adults have not been fully defined. Unlike asthma beginning in childhood, there is no familial correlation. Occupational exposures are important during the working years. Although the prevalence of occupational asthma in the general community is uncertain and presumably varies in different localities, it may account for as many as 5% of cases.²²⁻²⁴ The epidemics of asthma from soybean dust in Barcelona, Spain, which affected only adults, illustrate 2 important points.^{25,26} Allergens can escape from the workplace to affect the nearby community, and allergens encountered for the first time as an adult can sensitize and cause asthma. Otherwise, the common environmental allergens become less important with increasing age. Apparently those who are capable of becoming sensitized will have done so by the time they become adults. Asthma is associated with elevated serum IgE levels from childhood into old age, but skin test or specific IgE antibody test responses are often negative in adult-onset asthma.^{15,27-31} Often asthma begins with a respiratory viral infection.³ Also, a history of frequent respiratory infections in childhood or early adult life is associated with adult-onset asthma.³² The role of air pollution in the incidence of adult asthma is controversial.^{33,34}

Smoking increases the incidence of both occupational and nonoccupational asthma.^{20,23,25,35-39} Smoking also increases bronchial responsiveness to methacholine, but only in nonallergic subjects.^{40,41} The molecular and cellular mechanisms of the effect of cigarette smoking on the incidence, severity, and progression of asthma have not been fully determined. Some effects seem relevant, but their precise function is obscure. Cigarette smokers have increased serum IgE levels and numbers of eosinophils circulating in the blood.^{40,42} However, smokers do not have increased eosinophils in lung tissue or bronchoalveolar lavage fluid; instead, neutrophils and macrophages predominate.⁴³

Asthma is common. The prevalence of asthma in the adult population varies between communities and with

race and socioeconomic status. In the United States in the years 1976 to 1980, the Second National Health and Nutrition Examination Survey estimated the prevalence of asthma in adults at about 7% to 10%. Worldwide, both the incidence and prevalence of asthma have increased during the past 20 years, but this increase seems to have affected children and adolescents more than adults.^{14,44} The prevalence in adults has remained constant at about 5% to 10%.^{7,45-48} Asthma is more prevalent in women, in part because of their increased longevity and in part because of diagnostic labeling. Women are more often admitted to the hospital.⁴⁹ Also, asthma is somewhat more prevalent in the elderly than in young adults, presumably because the incidence rate exceeds the remission rate.^{4,50}

COURSE OF THE DISEASE

Although as many as 20% of older asthmatic subjects enter a period of remission at least for a time, the remission rate is much less than it is for children in the second decade of life.² Asthma beginning after the age of 50 years is more severe and less reversible than asthma in children.⁵¹ Rackemann and Edwards,⁵² who introduced the term *intrinsic asthma*, reported that only 20% of his nonallergic asthmatic patients enjoyed a remission during a 15- to 30-year follow-up period. Samter and Beers⁵³ reported similar outcomes in aspirin-sensitive adults. The Tucson community-based longitudinal study of the course of respiratory diseases over the past 25 years provides uniquely valuable information about the course of asthma. Remission was not observed in patients with long-standing disease or reduced FEV₁ values at the time of diagnosis.² If a remission does occur, the probability of a relapse increases with increasing age.^{2,45,54}

Indeed, rather than enjoying a period of remission, adult patients with asthma often have declining pulmonary function over the years.^{27,30,55-59} The Tucson group have reported that FEV₁ declines rapidly shortly after the diagnosis of asthma in older patients but then remains fairly stable.^{2,27} The rate of decline increases with increasing age, and a diagnosis of "asthmatic bronchitis" is associated with faster decline.^{57,60} The importance of this diagnostic association will become more apparent in the section below that discusses the anatomic basis of the deterioration of lung function. Greater response to bronchodilators is also associated with faster decline in FEV₁, perhaps because patients with lower baseline FEV₁ have greater room for improvement after use of the bronchodilator.⁶⁰ The rate of decline is associated with elevated total serum IgE and with peripheral blood eosinophilia, although the rate of decline is greater in nonallergic patients with intrinsic asthma than in allergic patients with extrinsic asthma.^{56,57,59,61-63} However, patients who continue to be exposed to allergens to which they are sensitized may experience progressive and poorly reversible disease.⁶⁴ This declining outcome resulting from continued exposure is particularly apparent in patients with occupational asthma.⁶⁵⁻⁷¹

Smoking doubles the severity of asthma symptoms.³⁵ However, published prospective studies about the effect of smoking on the rate of decline of asthma are conflicting.^{30,57} It is clear, unfortunately, that many adults with asthma, particularly young adults, do smoke.^{21,30,57,63} In any case, regardless of the semantic issues about the terms *asthma*, *asthmatic bronchitis*, *chronic bronchitis*, and *chronic obstructive pulmonary disease* (COPD), it is obvious that asthmatic patients who smoke will have a greater rate of decline in lung function. In 1989, O'Connor et al⁷² reviewed the role of allergy and nonspecific hyperresponsiveness in the pathogenesis of COPD. Ten years later, most of the questions that they suggested for future research remain unanswered. What is the mechanism of the relationship of smoking to IgE, eosinophilia, and airway hyperresponsiveness? Is the excessive decline in pulmonary function associated with eosinophilia without IgE-mediated allergy associated with progressive airway obstruction? To what extent is asthma a risk factor for the development of obstructive lung disease from cigarette smoking? Their final comment is still highly pertinent: "Potential interrelationships between smoking-related inflammation, allergic inflammation, airway hyperresponsiveness, and proteolytic destruction of lung tissue should be explored."⁷² Matsuse et al¹³ have shown that chronic adenovirus infection of the airways is associated with the development of COPD. The airway inflammation of asthma may well have the same effect as inflammation from latent adenovirus infection.

To estimate the magnitude of the problem of irreversible airway obstruction in elderly asthmatic patients, I reviewed every fourth record of the more than 1200 patients 65 years of age or older who were treated for asthma at Mayo Clinic in 1993. After eliminating those who had not had spirometry performed or whose records did not contain information to substantiate a diagnosis of asthma, 242 records were available for analysis. The criteria for the designation of definite asthma were those of the Rochester community-based study of the epidemiology of asthma in the years 1964 to 1983.¹⁴ It is of interest that 10 years later, in 1993, physician diagnosis of asthma had become much less specific. About 5% of patients receiving such a diagnosis had dyspnea only on exertion, no eosinophilia, and fixed airway obstruction. Another 5% of patients had symptoms limited to daytime cough, and their spirometry results were normal. Because of possible bias introduced by the fact that the Mayo Clinic is a tertiary care center, the data of local patients receiving primary care were compared with those of referred patients. Referred patients did have more severe obstruction than local patients, but the difference was not great, and the conclusions were similar. The majority of these elderly patients with asthma had severe, poorly reversible obstruction. Fig 1 displays the greatest postbronchodilator FEV₁ values recorded during the year. Despite clear evidence from longitudinal studies cited above that the average FEV₁ declines over a period of years, the data from these patients shows no correlation between the FEV₁ value and the duration of

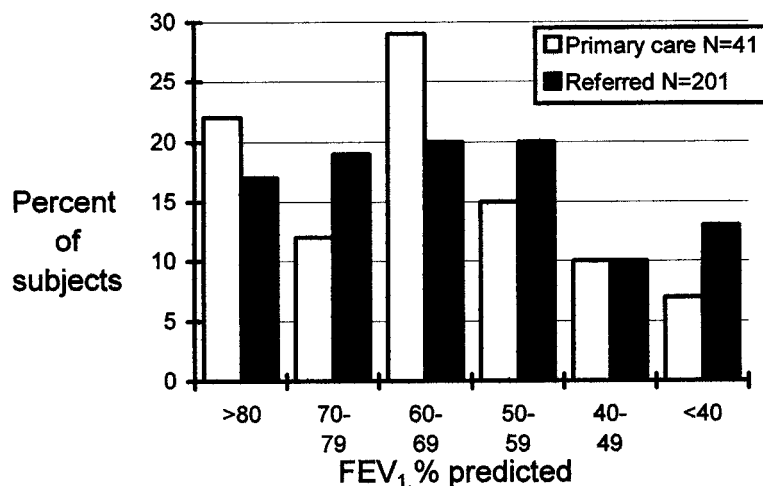


FIG 1. These patients are a random selection of a quarter of the total of approximately 1200 patients 65 years of age and older given a diagnosis of asthma at the Mayo Clinic in Rochester, Minnesota, in 1993. The plotted values are those measured after inhalation of adrenergic bronchodilator. For the patients referred to the Mayo Clinic from other cities, spirometry was performed at the time of the outpatient visit when the patients were in their usual state of health, but these values do not necessarily represent the maximal values that could be obtained with optimum doses of prednisone. However, if spirometry had been recorded on several visits, the highest value was plotted. In this setting about 20% of the patients had FEV₁ values of less than 50% of their age-, sex-, and race-adjusted predicted value. The primary care patients lived in the Rochester area. Many of them had been followed for many years, and the most recent result is shown. The patients referred from other areas had somewhat more severe asthma than the local patients. Reprinted with permission from Reed CE. The role of allergy and inflammation. In: Barbee RA, Bloom JW, editors. *Asthma in the elderly*. New York: Marcel Dekker, Inc; 1997. p. 33-52.

the disease (Fig 2). Many severely obstructed elderly asthmatic patients had symptoms for only a few months or years. In contrast, a few patients with a history of asthma since childhood had normal spirometry results. Others have reported similar results.^{2,59} Because it is this subgroup of elderly asthmatic subjects with long-standing disease who more often have positive skin test responses and a history of allergic asthma, it is not surprising that Almind et al³⁰ reported that asthmatic subjects with positive skin test responses retained reversibility; those with negative test responses did not.

ANATOMIC BASIS FOR IRREVERSIBILITY

At least 4 different abnormalities contribute to irreversible impairment of FEV₁ in asthma: (1) airway remodeling; (2) bronchiectasis; (3) linear postinfectious pulmonary fibrosis; and (4) emphysema and chronic bronchitis.

Airway remodeling consists of deposition of collagen beneath the epithelial basement membrane, hypertrophy of bronchial wall smooth muscle, and hyperplasia of mucus glands and goblet cells. Edema, vascular dilatation, and increased numbers of blood vessels also contribute to the thickening of the airway wall. These changes affect the entire airway from mainstem bronchi to bronchioles.⁷³⁻⁷⁶ Whether there is loss of bronchial wall elastic fibers is controversial.^{77,78} The cellular biologic mechanisms of these changes have not yet been clarified. Presumably growth factors like transforming

growth factor- β and platelet-derived growth factor released from leukocytes or damaged epithelium are involved.⁷⁹

The eosinophilic pneumonitis and central saccular bronchiectasis of allergic bronchopulmonary aspergillosis are well known.⁸⁰ Patients with this uncommon granulomatous complication of asthma typically have progressive irreversible loss of lung function. Untreated, it causes pulmonary fibrosis, particularly of the upper lobes. Allergic bronchopulmonary aspergillosis can serve as an illustration of more common development of bronchiectasis and fibrosis in adult asthmatic subjects. Paganin et al^{81,82} studied 57 subjects with chronic asthma using high-resolution computerized tomography. They reported varicose bronchiectasis in 4 subjects and cylindrical bronchiectasis in 32. Park et al⁸³ reported that high-resolution computerized tomography abnormalities correlate with duration and severity of asthma. Sequellar linear shadows of pulmonary fibrosis are also common in subjects with severe asthma, more so in nonallergic cases.⁸² Bronchiectasis and linear pulmonary fibrosis presumably result from the complex inflammation of infections rather than from the direct effect of the lymphocytic-eosinophilic inflammation of asthma. Pneumonia is more frequent in asthmatic than normal subjects.⁸⁴

Centrilobular and paraseptal emphysema has been demonstrated in nonsmoking asthmatic subjects, but not unexpectedly, they are considerably more common in smokers, occurring in up to 20%. The frequency increases with age.^{82,85,86}

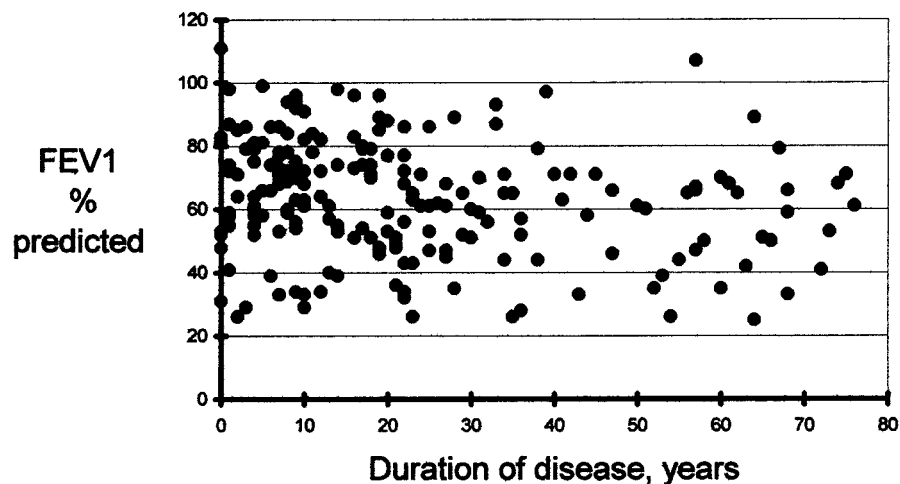


FIG 2. FEV₁ as a function of the duration of asthma in the patients 65 years of age and older included in Fig 1. The duration of asthma was dated from the first physician's diagnosis of asthma or the first symptoms of wheezing and shortness of breath, whichever came first. Many severely obstructed elderly asthmatic patients had symptoms for only a few months or years. In contrast, a few patients with a history of asthma since childhood had normal spirometry results.

Figure not available

FIG 3. The effect of aerosol beclomethasone dipropionate on the decline in lung function of patients with moderate-to-severe asthma. Twenty-six patients with asthma who had at least an 80 mL/y decline in FEV₁ and at least 2 exacerbations a year were followed for 4 years. During the first 2 years, they were treated with bronchodilators alone; during the second 2 years aerosol beclomethasone dipropionate, 400 mg twice daily, was added. During the first 2 years, mean prebronchodilator FEV₁ declined about 350 mL; the mean postbronchodilator FEV₁ declined about 200 mL. During the first 6 months of glucocorticoid treatment, FEV₁ improved as expected, but then the decline resumed. During the last 18 months of observation, the prebronchodilator FEV₁ declined 150 mL; the postbronchodilator FEV₁ declined 200 mL. Reprinted with permission from *Ann Intern Med* 1993;118:770-8.

FATAL ASTHMA

Most of the epidemiologic studies of death from asthma have concentrated on the 15- to 35-year-old age group because the death certificate is more reliable at this age. However, death from asthma, like death from all causes, increases with age. Most deaths from asthma occur in the elderly.^{2,87-89} In the Rochester community-based study of 2499 patients with asthma followed for 14 years, there were 140 deaths, 4% of which were caused by asthma.⁹⁰ Although the survival of all patients with asthma was the same as the general population, patients whose disease began after the age of 35 years had a higher mortality rate. Others have reported that asthma does increase mortality rate.^{30,90,91} In the Rochester community-based study, a death certificate diagnosis of asthma as the underlying cause of death was found to have a low sensitivity (42%) but high specificity (99%).⁹² Other investigators have commented on the poor reliability of the death certificate.⁹³⁻⁹⁷ In Rochester death from acute asthma was uncommon. More often the death was caused by complications of irreversible lung disease (frequently a respiratory infection) or by coexisting cardiac disease often associated with cardiotoxic effects of adrenergic agonists and theophylline enhanced by hypoxemia.^{90,98} Smoking is an additional risk factor for death.⁹⁹

EFFECT OF TREATMENT ON COURSE OF DISEASE

Glucocorticoids effectively control the airway inflammation of asthma, and aerosol glucocorticoids retard the decline in FEV₁.⁵⁹ Therefore the data from a prospective study by Dompeling et al⁵⁸ in Nijmegen, The Netherlands, are particularly disquieting. Beclomethasone dipropionate improved FEV₁ but did not prevent continued decline (Fig 3). Half of these asthmatic patients smoked, and the data do not permit distinction between the possibilities that the continued decline was the result of continued exposure to cigarette smoke or that the decline was the result of the failure of the glucocorticoid delivered by a metered-dose inhaler to reach the peripheral airways in a dose sufficient to prevent the continued remodeling of small airways. The small airways are the site of a major component of chronic obstruction.^{12,76}

Aerosol glucocorticoids reduce the amount of subepithelial fibrosis and numbers of goblet cells in the central airways accessible to endoscopic biopsy.¹³ However, in as much as improvement in asthmatic symptoms, changes in FEV₁, and biopsy all preferentially reflect changes in the central airways, the available data supporting the efficacy of aerosol glucocorticoids cannot be extrapolated to the small airways with complete confidence. Aerosols delivered by metered-dose inhalers deposit most of the intrapulmonary dose in the central airways,¹⁰⁰ and therefore it is possible that aerosol glucocorticoids will not prevent the airway remodeling of peripheral airways. This is a question that can be

addressed when aerosol delivery systems that provide a better deposition in small airways become available. No studies of the effect of oral glucocorticoids on the progression of obstruction have been reported, but systemic delivery would be expected to be more effective in the lung periphery than aerosol delivery.

CONCLUSIONS AND RECOMMENDATIONS

Particularly when it begins later in life, asthma in adults is often a slowly progressive irreversible disease. By age 65 years, the majority of older patients have a substantial degree of irreversible impairment of lung function that results from a combination of pathologic changes. These changes include airway remodeling from the chronic lymphocytic-eosinophilic inflammation, bronchiectasis and patchy fibrosis from repeated infections, and chronic bronchiolar damage and emphysema from cigarette smoking. Most deaths from asthma occur in the elderly and result from complications of these chronic irreversible anatomic changes more often than from acute attacks. The cardiotoxic effects of β -adrenergic agonists and theophylline amplified by hypoxemia contribute to death from coronary artery disease.

More data about the course of asthma in adults are needed from long-term prospective studies. The role of repeated or chronic bronchopulmonary infections by bacteria or fungi, as well as viruses, has not received sufficient attention. The etiology of intrinsic, nonallergic asthma is as much a mystery now as it was in 1916. The cell biology of airway remodeling needs clarification so that more effective preventive treatment can be devised. More efficient systems for delivering glucocorticoids to the small airways and methods of evaluation of their efficacy in preventing remodeling of peripheral airways are needed.

In the meantime several practical points in management can be emphasized. Some are obvious. Others will need validation by long-term prospective studies before final acceptance. They are as follows:

- Asthmatic subjects must not smoke.
- Sensitivity to environmental allergens, especially occupational allergens, should be identified and controlled.
- Except in very mild cases, adults with chronic asthma should receive aerosol glucocorticoid treatment. Close attention to proper inhalation technique is critical for success. Outcome should be monitored by appropriately timed spirometry, paying more attention to changes in FEF₂₅₋₇₅ as an indicator of small airway function than is conventional. Peak flow can be "normal," even though substantial obstruction persists. If normal FEV₁ and substantially improved FEF₂₅₋₇₅ are not achieved, reversibility with oral glucocorticoids should be determined. Another reasonable outcome goal of glucocorticoid therapy as a means of preventing airway remodeling is to maintain peripheral blood eosinophils below 100/mm³.
- Assure immunization against influenza for all adult

asthmatic subjects and pneumococcus for older patients.

- A chest radiograph should be obtained at times of acute exacerbations in older adults because the probability of pneumonitis is high.
- If there is a substantial degree of irreversibility, the reason should be determined by high-resolution computerized tomography, and management should be planned accordingly. If there is bronchiectasis, appropriate antimicrobial therapy should be given. Toxicity from excessive oral glucocorticoids can be avoided if the irreversibility is shown to a pathologic basis that is not responsive to anti-inflammatory therapy.
- The dose of β -adrenergic agonists should be kept low in patients at risk of heart disease, especially during acute episodes when hypoxemia is present. Ipratropium is a suitable bronchodilator for many patients, but its efficacy needs to be confirmed by spirometry.

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