

Focusing on childhood asthma: The Childhood Asthma Management Program (CAMP)

During the last 2 decades, much insight has been gained into the pathogenesis of asthma. Among these insights has been a renewed appreciation of the consequences of the inflammatory nature of this process. Although it has been known for some time that inflammation characterizes symptomatic and fatal disease,¹ we now know that even mild disease that is clinically quiescent is associated with airways inflammation.^{2,3} This information has helped guide clinical research into the therapy of asthma and had a significant impact on guidelines for therapy.⁴ In this respect investigations have demonstrated that use of corticosteroids will decrease airways inflammation while also decreasing the clinical severity of disease and the level of airway responsiveness.^{5,6} Unfortunately, a recent study in adults has also demonstrated that discontinuation of this class of drug often leads to increased symptoms, as well as deterioration in lung function and airway responsiveness.⁷ Furthermore, although 10 years of therapy with inhaled corticosteroids decreased inflammation and reduced epithelial damage in one study of adults with severe asthma, airway hyperresponsiveness persisted.⁸

Much of the insight into the inflammatory nature of asthma noted above has been achieved through studies involving bronchoalveolar lavage, biopsy, or both. Because of the invasive nature of these studies, most investigations have used adults as subjects. Although this is understandable and totally appropriate, it is also important to note potential limitations of this approach. One limitation is that investigators are usually characterizing the disease long after onset of the process. It has been estimated that a significant proportion of asthma present in adults had an onset during the childhood years. In addition, if one looks at childhood asthma alone, the onset of the process is usually before age 5 years.^{9,10} Thus studies in adults have assessed disease pathogenesis and its response to therapy several years to decades after onset. This has led to speculation that persistence of airway hyperresponsiveness, as well as our inability to produce protracted remissions with corticosteroids, is due to remodeling of airways. The most likely stimulus for

remodeling is the inflammatory response, which is presumed to be present early in the evolution of the disease.¹¹

Recently, the importance of trying to expand our understanding of asthma closer to the early development of the disease has been stressed.¹² In addition, the potential importance of understanding this disease in terms of growth and maturation of airways and immune responses has also been addressed.¹³ The observation that the incidence of asthma in a defined population increased only in children and adolescents¹⁰ also speaks to the need to focus on asthma early in life.

The article entitled "Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP)" by Zeiger et al,¹⁴ which appears in this issue of *The Journal*, is an important study that adds to the expanding literature about childhood asthma. Using the extensive CAMP baseline cross-sectional data, which includes information on asthma duration, lung function (including airway responsiveness to methacholine), and symptoms, Zeiger and colleagues argue that asthma severity is related to the duration of the disease. Although there is controversy in how best to quantitate asthma severity,¹⁵ this study largely circumvents that issue by showing relationships between several variables that reflect severity and time of physician-diagnosed asthma to entry into CAMP. For example, after controlling for potential explanatory variables (atopy, household Der p 1 levels, and anti-inflammatory medication use among others), regression models revealed that duration of asthma was significantly and independently associated with lower lung function (prebronchodilator percent predicted FEV₁ and prebronchodilator and postbronchodilator FEV₁/forced vital capacity), greater methacholine responsiveness (expressed as ln FEV₁PC₂₀), more asthma symptoms, and greater use of albuterol on an as-needed basis during a 4-week screening period. In addition, duration was significantly associated with physician/nurse assessments of asthma severity and other historical measures of medication use. Thus a relationship with duration of disease was found with multiple criteria that together reflect severity of disease.

It might be argued that the changes in lung function reported by Zeiger et al¹⁴ are small and thus not clinically significant. Yet a few points are worthy of consideration. First, a similar decline in percent predicted FEV₁ was reported in children by Agertoft and Pedersen¹⁶ in an untreated control group that was followed for 5 years.

More concerning was the observation in this latter study,¹⁶ as well as other studies (reviewed by Zeiger et al), that delays in initiating inhaled corticosteroid therapy led to blunted improvements in lung function when anti-inflammatory therapy was eventually introduced. Indeed, Haahtela et al⁷ found that as little as a 2-year delay in starting inhaled corticosteroids was associated with a blunted improvement in lung function in adults with mild-to-moderate asthma. Second, the current study did not enroll children with severe disease. In all likelihood, severe asthma has even greater adverse effects on lung function.¹⁷ Third, as noted previously, the association between duration of asthma and disease severity was demonstrated for several indices other than lung function, including the subjective opinions of those caring for the children before entry into this study. Thus although the changes in lung function were small, the overall course of the disease was judged more severe by those that best knew these children. Fourth, Lange et al¹⁸ recently reported in a sample from the general population in Copenhagen that adults who identified themselves as having asthma had substantially greater declines in FEV₁ over time than those without the disease. They concluded that long-term studies should evaluate whether treatment can postpone the accelerated decline of lung function that occurs in people with asthma. This observation potentially confirms some previous reports on decline in lung function in asthma and prompts us to follow lung function over time in a manner similar to that used to follow patients with cystic fibrosis or chronic obstructive pulmonary disease. Knowing that this decline in asthma starts in childhood implies that younger subjects must be included in prospective studies that address this issue. The CAMP experience will help address this and other important concerns in years to come. For example, this multicenter study, with its large database, will more clearly determine whether declines in lung function noted with increasing duration of disease (as reported in this issue of *The Journal*¹⁴) can be partially or completely corrected once chronic anti-inflammatory therapy is initiated. Although the cross-sectional nature of the study by Zeiger et al¹⁴ has limitations, it is important to remember the core of this program is a prospective study comparing the safety and efficacy of 3 treatment arms. The 3 arms are inhaled nedocromil, inhaled budesonide, and as-needed albuterol used alone over 4 to 5 years in children who entered the program between the ages of 5 and 12 years. Thus additional information will be forthcoming regarding the utility of early institution of anti-inflammatory therapy in terms of preserving lung function and decreasing disease morbidity. The potential adverse effects of long-term anti-inflammatory therapy will also be addressed.

One speculation advanced by Zeiger et al¹⁴ is that earlier diagnosis and more aggressive intervention may be necessary to diminish the adverse effects of chronic asthma. In other words, we may once again need to focus on even younger subjects in our attempts to understand the disease's pathogenesis and to develop effective therapies.

Unfortunately, this is easier said than done. Wheezing in infants and toddlers is quite common and may be self-limited with early resolution or remain a recurring problem, eventually leading to a diagnosis of asthma.^{19,20} That different pathogenic processes underlie wheezing illnesses in this younger population is suggested in both epidemiologic studies^{19,21} and early studies assessing bronchoalveolar lavage findings in wheezing children.²² Unfortunately, the differing wheezing phenotypes are not easily sorted out under most clinical situations. For example, the equipment for assessing lung function that might help distinguish between groups of wheezing infants and aid in establishing a diagnosis of asthma are neither easily nor routinely used. Use of bronchoscopy with bronchoalveolar lavage/biopsy remains investigational. In addition, more easily obtained markers of disease that may eventually differentiate asthma from other illnesses with wheezing are just now being explored and characterized.²³ Their applicability to the general care of infants and toddlers with respiratory disease remains to be established. Even when a diagnosis of asthma is made in this age group, there are several technical difficulties and controversies associated with the use of inhaled corticosteroids.²⁴ Included among the various issues is determining the appropriate dose of medication, as well as monitoring for potential adverse effects of therapy. Thus delving into this younger population is a formidable challenge, and yet the importance of this approach in terms of understanding disease pathogenesis and eventually intervening in ways that effect morbidity/mortality appears essential. One of the major contributions of the CAMP program may prove to be the model it is establishing for studying childhood asthma. A similar effort with a large database and multiple study sites will likely be needed as we explore the disease ever closer to its usual time of onset.

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