

screening. Until then, women may face an increasing array of complex choices.

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Toward Asthma Prevention — Does All That Really Matters Happen before We Learn to Read?

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Patients with asthma and their caregivers are currently faced with a remarkable paradox. Considerable progress has been made during the past 20 years in the pharmacotherapy, educational tools, and environmental measures available for the control of symptoms of asthma. As a result of these advances, more than 90 percent of patients with asthma now have the potential to lead a normal life. The bad news, however, is the absence of any universally accepted strategy for the prevention of the disease. With the exception, perhaps, of measures for the avoidance of infrequent forms of asthma caused by very specific types of exposure (e.g., occupational or aspirin-induced asthma), no single action has been irrefutably demonstrated to decrease the risk of the development of persistent asthma in persons who do not already have the disease.

The greatest obstacle to the development of approaches for the prevention of asthma has been the lack of a clear understanding of its natural history. In the past, the cross-sectional surveys on which we have relied have proved misleading. These types of surveys are based heavily on patients' recall of

past events, which is particularly susceptible to bias. Most adults, for example, have no direct memory of events that occurred during their preschool years. It is thus not surprising that, until quite recently, it was widely believed that chronic asthma was equally likely to begin at any age. In addition, asthma was considered to be a progressive disease: the longer it lasted, it was thought, the more likely it was that irreversible changes would develop in the structure and function of the lungs.¹

These conceptions had important consequences from the point of view of public health. Asthma is a disease in which both genetic and environmental factors have important roles,² and thus considerable attention was paid to the search for environmental causes of the disease that could affect persons of all ages. On the basis of the results of cross-sectional studies, factors such as environmental tobacco smoke,³ air pollution,⁴ and exposure to common aeroallergens⁵ that were known to trigger asthma symptoms in persons who already had the disease were widely reputed to cause it as well.

The publication in recent years of the results of adequately powered, well-designed longitudinal

studies with follow-up starting during the first years of life has produced a remarkable change in our understanding of asthma, its beginnings, its clinical expression, and its evolution. An article by Sears et al. in this issue of the *Journal*⁶ presents cogent data from one such study conducted in Dunedin, New Zealand.⁶ Of the many new insights that these studies have provided, three are particularly relevant to the prevention of asthma.

First, most persons of any age who have chronic, persistent asthma have their first symptoms during their preschool years.⁷ Although this fact was already well established, the study by Sears et al. provides a new, very important clue: symptoms of asthma appeared much earlier in cases that seemed to remit during adolescence only to relapse during early adulthood than in remitting cases in which a relapse did not occur. These findings provide strong support for the contention that environmental factors, acting during early life and interacting with specific "asthma genes," are crucial for the development of the chronic, persistent form of the disease.² The identification of these factors will thus be crucial for a primary-prevention strategy, which will necessarily be focused on events that occur in infancy and early childhood.

Important advances have recently been made in this area. For years, the strong association between persistent asthma and the development of IgE-antibody responses to certain aeroallergens (house-dust mites, in the case of the study by Sears et al.) suggested the hypothesis that the degree of exposure to these allergens in early life could determine the risk of asthma. However, studies in which the concentration of mite allergen in dust was assessed in the homes of newborn children failed to show an association between mite levels and the subsequent development of asthma symptoms up to the early school years.⁸ Also, the prevalence of asthma in areas where mites are not abundant is not lower than that observed in areas of high mite infestation.⁹ Moreover, almost paradoxically, increased exposure to cat allergen¹⁰ and to indoor dogs¹¹ in early life has been reported to be associated with a marked decrease in the subsequent risk of asthma. Taken together, these data do not support a primary-prevention strategy based on the manipulation of exposure to allergens in early life.

More promising appear observations that early exposure to microbial products, through both the air¹² and the oral-fecal route,¹³ may markedly decrease the risk of the subsequent development of

asthma. In fact, higher levels of microbial products such as endotoxin have been found in the house dust from homes where pets live than in that from homes without pets.¹⁴ The microbial burden in early life is believed to hasten the development of immune responses that do not involve the predominance of type 2 helper T cells that is characteristic of persistent asthma.¹⁵ Although the matter is still controversial, these observations clearly point toward early exposure to innocuous surrogates for these microbial products as a potentially successful strategy for the prevention of asthma.

A second conclusion has to do with the timing of the changes in lung function that are characteristic of the disease. As a group, patients with asthma have lower values than persons without asthma on several measures of lung function, including the ratio of the forced expiratory volume in one second to the forced vital capacity, as reported by Sears et al.⁶ These deficits are strongly associated with the severity of disease and are believed to represent alterations in lung function and structure that contribute to the persistence of symptoms of asthma. Until recently, the origin of these deficits was not well understood. It now appears that lower levels of lung function are already present by the early school years in patients in whom persistent asthma will ultimately develop, with no further deterioration after that age. This has been shown to be true for persons with persistent or relapsing symptoms, as in the study by Sears et al., for schoolchildren with mild-to-moderate asthma, as in the Childhood Asthma Management Program study,¹⁶ and for persons with severe, unremitting asthma, as in the 30-year prospective study from Australia.¹⁷ In all these studies, follow-up began after the first asthma symptoms had developed.

Results of other studies in which children were recruited at birth and lung function was measured shortly thereafter suggest that the deficits in lung function and growth observed in patients with persistent asthma became apparent, to a great extent, after the development of the first symptoms of the disease.¹⁸ It is plausible to surmise that the fast-growing lung of the preschool child may be particularly susceptible to the effects of chronic inflammation associated with persistent asthma. Therefore, and in order to be successful, strategies for the prevention of deterioration of lung function in patients with asthma will also need to be focused on very young children, in whom the disease process is just beginning.

A third but not less important conclusion that may be derived from longitudinal studies is that the most common clinical expression of asthma — namely, episodic wheezing — has a high frequency in developed countries. In the study by Sears et al. three quarters of all subjects reported clinically significant wheezing in at least one survey up to 26 years of age. Most of these subjects had sporadic and mild symptoms, but evidence of chronic recurrence could be observed in up to one third of the population. There is thus an urgent need for tools with which to identify young children with symptoms of asthma who are at high risk for the development of the more persistent forms of the disease, so that potential preventive measures can be targeted to those who will benefit the most.

The results reported by Sears et al. are thus quite compelling: the prevention of asthma will require interventions focused on the types of early environmental exposure that predispose children to or protect them against the onset and progression of the disease. For the first time, there is justifiable hope that a debilitating disease that markedly affects the lives of the young and the old equally can be thwarted before it starts or can be stopped before it causes irreversible harm.

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