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Airway remodeling and persistent airway obstruction in asthma

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There is growing recognition that some patients with long-standing asthma may possess a component of irreversible airflow obstruction despite optimal therapy. This persistent airflow obstruction is thought to be the result of structural changes in the airways that occur as a result of airway remodeling. The structural changes that lead to chronic obstruction are not known, nor are the intricacies of the remodeling process. Hence airway remodeling and its role in the evolution of irreversible airflow obstruction remain conceptual. Much work has been carried out to better define the histopathologic characteristics of asthma, including the characteristic features of airway inflammation. However, attempts to delineate the physiologic consequences of specific histologic findings are at an early stage of development. The thesis that airway remodeling is driven by chronic inflammatory processes has important implications for the way we make treatment decisions, especially in the patient with mild asthma. Abounding interest in airway remodeling has led to a growing literature on the subject, a literature that is largely speculative and perhaps too tautologic in the sense that remodeling is frequently defined by any observed histologic change, irrespective of its physiologic consequences. Careful attempts to link histologic observations with clinical, demographic, and physiologic findings will be necessary to unravel the causes of remodeling and identify who is at risk for development of irreversible airway obstruction. (*J Allergy Clin Immunol* 1999;104:509-16.)

Key words: Airway remodeling, persistent airflow obstruction, irreversible airflow obstruction, asthma, airway inflammation

Airway remodeling is a term applied to describe the dynamic processes that lead to structural changes in the airways in asthma. These structural changes are thought to result in an irreversible component of the airway obstruction seen in asthma and perhaps also in the development of airway hyperresponsiveness. The dynamic processes underlying these structural changes are viewed as injury-repair processes driven by airway inflammation.

Abbreviations used

BAL: Bronchoalveolar lavage
ECP: Eosinophil cationic protein
EGF: Epidermal growth factor
mRNA: Messenger RNA
PDGF: Platelet-derived growth factor
TGF: Transforming growth factor

Although the concept of airway remodeling and its role in chronic persistent airflow obstruction is widely accepted, it should be recognized that airway remodeling is still just a concept. Numerous histopathologic abnormalities have been described in asthmatic airways, and yet the functional consequences of these abnormalities and their role in the natural history of asthma remain unknown. In this article we describe the potential clinical importance of airway remodeling, how various histopathologic alterations in asthma relate to airway remodeling, the role of airway inflammation in airway remodeling, and the evidence that therapeutic interventions may alter the remodeling process.

CLINICAL SIGNIFICANCE OF AIRWAY REMODELING

We have long recognized that reversible airflow obstruction is one of the unique features of bronchial asthma. During an acute episode, smooth muscle constriction, mucus secretion, and airway wall edema are the chief pathophysiologic alterations, all of which are potentially reversible processes. In many patients treatment of the acute episode can lead to restoration of normal lung function. Recently, however, there has been a growing appreciation that a significant degree of airflow obstruction may persist in some asthmatic patients who have never smoked and who have received aggressive therapy.

Several investigators have demonstrated that the longitudinal decline in FEV₁ is more than 80% greater in asthmatics than in nonasthmatic subjects.^{1,2} Moreover, this accelerated decline in function appears linked to increased airway lability or abnormal airway responsiveness, not only in asthma but in chronic obstructive lung disease as well.³⁻⁵ With a more rapid loss of function, an asthmatic patient might be expected to demonstrate a

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persistently abnormal FEV₁ over time. This prediction has been confirmed in several cross-sectional studies reporting the presence of persistent lung function abnormalities in patients with long-standing asthma despite aggressive therapy.⁶⁻⁸ Although the duration of asthma appears to be an important risk factor for persistent obstruction, other factors may also play a role. For example, Roorda et al⁹ followed up a large cohort of 8- to 12-year-old children for a follow-up of 14.8 years and found that the FEV₁ (percent predicted) in childhood was the best predictor of the adult FEV₁ level. Persistent airflow obstruction may be a problem for some asthmatic patients, but it is not the inevitable outcome for all. In our experience, many elderly individuals with life-long asthma have normal or near-normal function with optimal therapy. In addition, we are not aware of large numbers of patients with severe respiratory disability who have asthma alone as the causative factor. So who is at risk for development of persistent obstruction? And, is this pathologic consequence of airway remodeling a problem for the majority or the minority of asthmatic patients? These and a number of other important questions remain to be answered.

PATHOPHYSIOLOGY OF AIRWAY REMODELING

To the extent that asthma is characterized by inflammation, it is reasonable to speculate that airway remodeling is an injury-repair response driven by inflammatory process. How inflammation leads to remodeling, however, is unknown. Likewise, the precise structural changes of a remodeled airway that result in chronic persistent airflow obstruction are also unknown. Huber and Knessler¹⁰ recognized long ago that the asthmatic airway was characterized by increased bronchial wall thickness. More recently, other investigators have used mathematic models to demonstrate that an increase in wall thickness between the epithelium and the smooth muscle layer (inner airway wall) may alter airway mechanics, potentiating the level of resistance changes for a given degree of smooth muscle shortening.¹¹ How increased wall thickness per se, in the absence of active smooth muscle constriction, could result in irreversible airflow obstruction is unclear, however, because small changes in wall thickness appear to have little influence on baseline resistance.¹² Nevertheless, it is notable that chronic airflow obstruction is generally defined on the basis of spirometric measurements, and the effects of changes in wall thickness on maximum airflow during forced expiratory maneuvers is not addressed in such models.

Macklem¹³ examined the effects of airway-parenchymal interactions in developing another model for estimating maximum airway narrowing. In his model the outer airway wall is also taken into account. The outer airway wall is the adventitial tissue extending from the outer perimeter of airway smooth muscle to the parenchymal interface. The lung parenchyma normally acts as an elastic load on airway smooth muscle. This

load is reflected by the peribronchial pressure, which varies inversely with lung volume. Accordingly, as lung volume increases, the load on smooth muscle increases, thus limiting airway narrowing. According to Macklem, inflammation and edema of the outer airway wall would diminish the elastic load by expanding the peribronchial space, unlinking the parenchyma from the airway. Although this model was used to explain differences in the degree of airway narrowing induced by smooth muscle agonists in asthmatic versus healthy individuals, the principles of the model have relevance as a potential explanation for chronic persistent airway obstruction in some asthmatic patients. For example, loss of parenchymal-airway interdependence would diminish the effects of increasing lung volumes on increasing airway diameter. Thus, with forced expiratory maneuvers initiated from total lung capacity, decreases in maximal flow would be observed throughout the vital capacity maneuver. Alternatively, thickening of the inner airway wall or submucosa could decrease airway compliance and act as an increased elastic load on lung parenchyma, thus limiting the increase in airway diameter at higher lung volumes.

PATHOLOGIC FINDINGS

Several elements contribute to airway wall thickening, most of which have been identified in earlier reports of pathologic changes that occurred in patients dying from acute asthma.¹⁴⁻¹⁷ These included airway wall infiltration with inflammatory cells, thickening of the basement membrane, increased airway smooth muscle mass, and exudation of plasma with edema of the airway wall. Our appreciation of the spectrum of pathologic findings in asthma has grown recently because of the use of fiberoptic bronchoscopy to sample tissues from asthmatic patients with varying degrees of disease severity and also because of the use of newer techniques, particularly morphometry and immunohistochemistry.

The major components of the cellular infiltrate are mast cells, eosinophils, and lymphocytes. Although mast cells are found in the submucosa, their numbers are not increased in comparison with those of healthy subjects.¹⁸⁻²² However, the demonstration of cytoplasmic vacuolization suggests that mast cells in asthmatic patients differ by virtue of their state of activation and participation in active inflammation.²¹ Increased numbers of eosinophils are found both in the epithelium and submucosa of asthmatic airway tissue and appear to be in an activated state on the basis of staining with EG2 mAb that recognizes the cleaved and activated forms of eosinophil cationic protein (ECP).^{18,20,21,23} The increased presence of ECP and major basic protein in bronchoalveolar lavage (BAL) samples from asthmatic patients is also indicative of eosinophil activation.²⁴

Both lymphocytes and plasma cells are increased in the asthmatic airway wall compared with those of nonasthmatic airways.^{18,25} Moreover, immunohistochemical studies have shown that in asthma there is an

TABLE I. Factors derived from bronchial epithelium of potential importance in asthma

CSFs	Cytokines	Growth factors	Receptors, antagonists, other factors	Chemokines	
				C-X-C/ α	C-C/ β
GM-CSF	TNF- α	TGF- β	TNF receptor type 1	IL-8	RANTES
Granulocyte-CSF	IL-1	TGF- α	IL-1 receptor antagonist type 1	GRO- α	MCP-1
Macrophage-CSF	IL-6	SCF	Endothelins	GRO- γ	MCP-4
CSF-1	IL-11	bFGF	NO		Eotaxin
	IL-10	Fibronectin	Lipids (15-HETE, PGE ₂ , PGF _{2α})		
	IL-16	PDGF	PGE ₂ , PGF _{2α}		
		EGF			

CSF, Colony-stimulating factor; TGF, transforming growth factor; MCP, monocyte chemoattractant protein; SCF, stem cell factor; bFGF, basic fibroblast growth factor; NO, nitric oxide; 15-HETE, 15-eicosatetraenoic acid; PDGF, platelet-derived growth factor; EGF, epidermal growth factor. (Adapted and modified from Polito AJ, Proud D. Epithelial cells as regulators of airway inflammation. *J Allergy Clin Immunol* 1998;102:714-8; Raeburn D, Webber SE. Proinflammatory potential of the airway epithelium in bronchial asthma. *Eur Respir J* 1994;7:2226-33; and Vignola AM, Chanez P, Chiappara G, Gagliardo R, Bonsignore G, Bousquet J. Growth factors in the remodelling of asthma. *Allergy Clin Immunol Int* 1998;10:149-53.)

increase in the number of activated T lymphocytes as demonstrated by CD25 expression.²⁰ T lymphocytes recovered in BAL samples from asthmatic patients have shown increased expression of IL-1, IL-3, IL-4, IL-5, and GM-CSF but not of IFN- γ , indicating that they are of the TH₂ subclass of CD4⁺ lymphocytes.²⁶

The apparent thickening of the basement membrane represents subepithelial fibrosis with hyalinization and thickening of the lamina reticularis. The lamina rara and lamina densa, "true" basement membrane structures, are of normal dimensions.²⁷ Deposition of collagen types III and V as well as fibronectin has been shown to account for the thickening.²⁸ Other work has demonstrated that tenascin, a glycoprotein, is also abundant in the reticular basement membrane in patients with chronic and seasonal asthma but not in healthy subjects.²⁹ An approximately 2-fold increase in basement membrane thickness has been reported in patients with mild asthma,^{28,30,31} and the thickness appears to correlate with the number of matrix cells in the submucosa but not with the number of eosinophils or lymphocytes.^{29,31}

The airway epithelium may play a role in subepithelial fibrosis and perhaps other aspects of airway remodeling as well. The airway epithelium is a rich source of growth factors, cytokines, chemokines, and other mediators (Table I).³²⁻³⁴ An important target for these products appears to be the myofibroblast, which is considered responsible for the synthesis and deposition of many of the matrix components found in the enlarged subepithelial layer.³⁵

GM-CSF, a hematopoietic growth factor, has been found to be overexpressed in the epithelium of airways in even mild asthma and may be of particular importance.³⁵ Recent evidence from animal models suggests that GM-CSF could have a direct role in producing fibrotic reactions in the lung.³⁶ Moreover, it could indirectly promote remodeling through its well-established effects in eosinophil activation and survival.³⁴ The importance of GM-CSF in IgE-mediated airway inflammation is supported by our own recent observation that, among the eosinophil-active cytokines (ie, IL-3, IL-5, and GM-CSF), GM-CSF is pro-

duced for a prolonged period (1-2 weeks) after antigen challenge in ragweed allergic asthmatic patients.³⁷ Further, we have recently found that the airway epithelium is an important source of this GM-CSF production (unpublished observations).

Transforming growth factor- β (TGF- β) has received particular attention as a potentially important factor in airway remodeling in asthma. Found not only in epithelium but also in eosinophils, macrophages, and fibroblasts, TGF- β possesses complex immunoregulatory properties, including a direct effect on growth of certain cell types (eg, stimulation of fibroblast growth and inhibition of epithelial cell growth) and regulation of the synthesis of matrix components.^{34,38} Numbers of TGF- β messenger RNA (mRNA)-positive cells have been shown to correlate with EG2⁺ eosinophils, both of which were increased in asthmatic patients with more severe physiologic impairment.³⁸ However, the role of TGF- β and other growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and endothelins remains controversial. Both EGF and PDGF play important roles in the repair of bronchial epithelium after injury, and bronchial fibroblasts from asthmatic patients show enhanced responsiveness to PDGF.³⁹ However, either increased levels have not been observed in asthmatic patients or increased levels have not been found to correlate with airway fibrosis.^{31,34} In addition to their potent vasoconstrictor and bronchoconstrictor properties, endothelins such as endothelin-1 have the ability to activate fibroblasts, and they have been found in increased levels in bronchial biopsy specimens from asthmatic patients.⁴⁰ However, their role in airway remodeling has not been elucidated.

Other histopathologic findings that relate to airway wall thickening and potential structural changes in asthmatic patients include increased smooth muscle mass and increased vascularity. Morphometric studies reveal that the increase in smooth muscle mass is usually located in larger airways where bronchoconstriction is most prominent, whereas increases in smooth muscle mass involving the entire length of the tracheobronchial tree,

including the bronchioles, is less common.⁴¹ Additional analyses have shown that the increased smooth muscle mass in the larger airways is caused by hyperplasia, whereas increases in smaller airways are more likely to reflect hypertrophy.⁴² Although the mechanisms responsible for smooth muscle proliferation remain unknown, recent *in vitro* studies have shown that the inflammatory mediator histamine, as well as interactions between airway smooth muscle cells and T lymphocytes, may induce smooth muscle cell proliferation.^{43,44} The role of T-cell-derived cytokines in these responses is unclear.

An increase in both the number and size of vessels was reported in biopsy specimens taken from fifth-generation airways in asthmatic patients compared with control subjects.⁴⁵ By contrast, studies comparing postmortem specimens taken from patients with fatal asthma, asthmatics who died of other causes, and nonasthmatics showed no differences in total cross-sectional vascular area, although in fatal asthma an increase in the number and size of large vessels was observed with a reduction in the number and size of small vessels.⁴⁶ Because airway wall edema appears to be an important feature of severe asthma, further investigations into the mechanisms of angiogenesis and its physiologic importance in asthma are warranted.

Airway plugging with viscid mucus, although not a structural change, is a well-established finding in patients with fatal asthma and in acute episodes of status asthmaticus.^{16,47} Moreover, mucus gland hypertrophy and goblet cell metaplasia in the epithelium are common findings in histopathologic specimens.^{18,48} In our experience, however, mucus production is seldom seen in stable asthma, even when chronic persistent airflow obstruction is present. Thus we are skeptical of its role in remodeling and as a cause of persistent obstruction.

Most recent histologic studies have focused on large or medium airways (ie, second- to fifth-generation airways) that are accessible by bronchoscopy. Tissues obtained by this technique are limited to the inner airway wall or the area bounded by the surface epithelium and the smooth muscle layer. Hence most of the investigation of remodeling in the context of the histopathologic features of asthma has focused on epithelial damage, subepithelial fibrosis, and submucosal cellular infiltrates and edema in proximal airways. Less well appreciated are the potential roles of structures not obtained during bronchoscopy, namely, small peripheral airways and the outer wall of airways of all sizes.

With use of resected lung tissue from stable asthmatic patients and from nonasthmatic control subjects undergoing cancer surgery, Hamid et al²² compared the cellular characteristics of airways larger and smaller than 2-mm diameter. Compared with control subjects, stable asthmatics had increased numbers of eosinophils and T lymphocytes in airways of all sizes. In the asthmatic group, the authors found that airways <2 mm in diameter had increased numbers of EG2+ (activated) eosinophils compared with larger airways, although there was no increase in total number of eosinophils. Lymphocytic and

eosinophilic infiltration of small airways has also been reported in postmortem specimens from asthmatic patients dying from other causes as well as those dying from asthma, although fatal asthma appears to be associated with a greater profusion of eosinophilic infiltration.^{25,49}

Interest in the role of small airways and their surrounding parenchymal structures in asthma has grown, with reports that in fatal asthma inflammation extends beyond the smooth muscle layer to involve the outer airway wall.⁴⁷ The intense infiltration and thickening of the outer airway wall in a case of fatal asthma shown in Fig 1 is illustrative of the alterations that can occur in the peribronchial space. The importance of the outer airway wall as a site of important events that could lead to airway remodeling is supported by studies showing greater eosinophil infiltration in the outer versus the inner airway wall in small but not large airways in fatal episodes of asthma⁵⁰ and by studies demonstrating that inflammation at the interface between small airways and lung parenchyma may be an important cause of asthma morbidity in nocturnal asthma.⁵¹

HISTOPATHOLOGY AND ASTHMA SEVERITY

Although the pathologic characteristics of asthma are well known, the association between these features and physiologic impairment is less certain. Studies designed to examine associations between pathologic findings and measures of severity as assessed by spirometry and airway responsiveness have yielded widely discordant results (Table II). This discordance is related to the substantial variability in measurement of inflammatory markers in airway mucosal biopsies, to the narrow range of severity studied because of the invasive nature of bronchoscopy, and to variations in treatment taken by volunteers.⁵² Correlations between FEV₁ alterations and tissue infiltration with eosinophils are difficult to establish, although it is noteworthy that Crimi et al⁵³ found an inverse correlation between FEV₁ and numbers of eosinophils in sputum and BAL fluid but not in biopsy samples. Associations between FEV₁ alterations and subepithelial fibrosis have been reported by some investigators^{38,54} but not by others.^{28,55,56}

Discordancies are also evident in studies attempting to relate pathologic findings to airway responsiveness to methacholine or histamine. For example, although significant correlations between tissue eosinophilia and airway hyperresponsiveness have been reported by several investigators,^{20,57-59} other investigators have failed to confirm these findings.^{21,53,60} It is important to note, however, that some studies have involved small numbers of subjects with limited power to perform valid correlation analyses.

Perhaps the most consistently reported finding is a correlation between the thickness of the reticular basement membrane and airway responsiveness.^{31,54,55,59} The significance of this finding is not clear, however. The correlation itself does not imply a causal relation because both

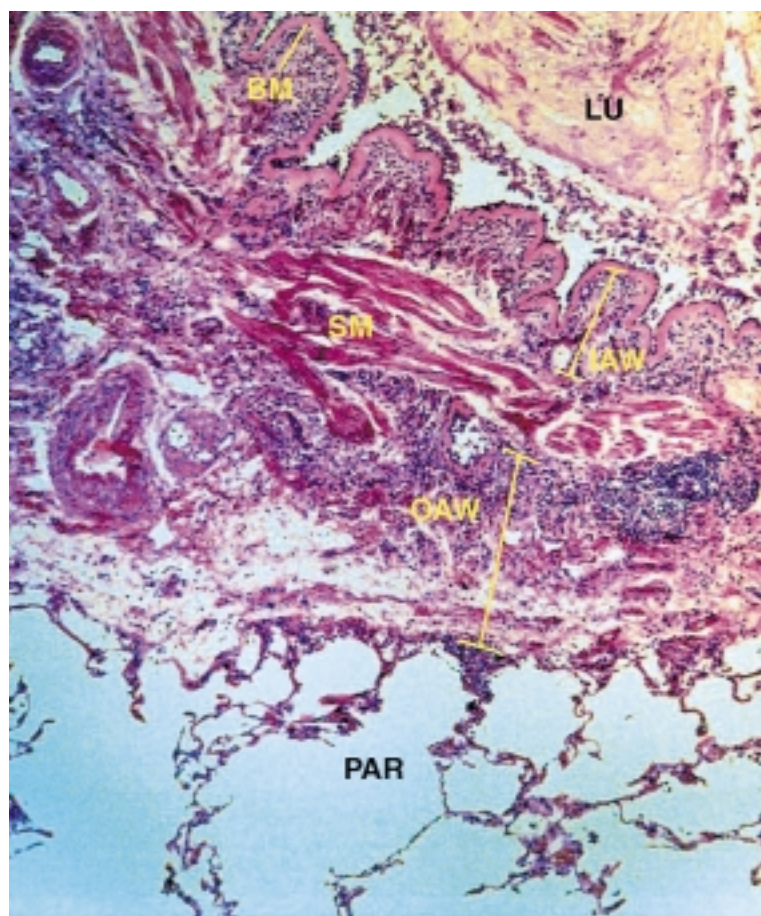


FIG 1. Section of airway in 70-year-old patient with long-standing asthma showing intense inflammation of both inner (IAW) and outer airway wall (OAW). SM, Smooth muscle; PAR, parenchyma; LU, lumen; BM, basement membrane.

TABLE II. Relationship between histopathologic findings and physiologic characteristics

Clinical variable	Histologic variable	Correlation found	No correlation found
FEV ₁	Tissue eosinophils		Reference No. 21, 53, 56, 58
	Basement membrane thickening	Reference No. 38, 54	Reference No. 28, 55
Airway responsiveness*	Tissue eosinophils	Reference No. 21, 57, 58, 59	Reference No. 21, 53, 60
	Basement membrane thickening	Reference No. 31, 55, 54, 59	Reference No. 28

*Measured by methacholine-histamine challenge.

findings may be unrelated consequences of airway inflammation. Although epidemiologic studies indicate that abnormal airway responsiveness and increased airway lability are risk factors for an accelerated decline in FEV₁ in asthma,^{4,5} the role of subepithelial fibrosis remains circumstantial. In fact, histopathologic studies have shown that basement membrane thickening may be demonstrated in newly diagnosed asthmatic patients.^{28,31,54} If basement membrane thickening can be found in newly diagnosed asthmatic patients and persistent obstruction is correlated with disease duration,⁶⁻⁸ subepithelial fibrosis would appear to have a limited role in remodeling. Similarly notable is the observation that cellular infiltrates in airways of subjects with newly diagnosed asthma are com-

parable to those found in patients with long-standing asthma.¹⁸

TREATMENT IMPLICATIONS

The prospect of developing persistent airflow obstruction as a consequence of long-standing airway inflammation has significant implications with respect to therapy, especially in patients with mild asthma, who comprise the largest fraction of the asthmatic population. Current treatment guidelines recommend use of inhaled β -agonists alone for patients with mild intermittent asthma and the use of several alternatives, some with uncertain anti-inflammatory properties, in patients with mild

TABLE III. Effects of corticosteroids on histopathologic characteristics in asthma

Decreased cellularity usually resulting from decreases in eosinophils, mast cells, and lymphocytes ^{29,62-70}
Decreased numbers of dendritic cells and HLA-DR expression ⁷¹
Decreased numbers of cells expressing mRNA for IL-4 and IL-5 ⁷⁰
Increased numbers of cells expressing mRNA for IFN- γ ⁷⁰
Increased area of ciliated epithelium ⁶²
Decreased thickness of basement membrane ⁷²
Decreased tenascin in basement membrane ²⁹

persistent asthma.⁶¹ Corticosteroids are perhaps the most extensively studied asthma medications in relation to their effects on markers of airway inflammation. Various investigators have reported beneficial effects in terms of reducing cellular infiltrates, decreasing subepithelial fibrosis, increasing ciliated epithelial cells, and other effects (Table III).^{29,62-72}

In separate studies involving children and adults, an inverse relationship between the duration of asthma before treatment with inhaled corticosteroids and the level of improvement in lung function achieved after treatment has been observed.^{73,74} The authors of these studies concluded that corticosteroids should be instituted very early in the course of the disease, implying that corticosteroids can prevent irreversible airway obstruction from occurring. Neither study, however, was designed to address this issue. Haahtela et al⁷⁵ randomized newly diagnosed patients to 3 years of corticosteroid therapy or to 2 years of scheduled β -agonist treatment followed by corticosteroids in the third year. Patients in whom corticosteroid therapy was delayed for 2 years had significantly lower lung function at the end of the third year of treatment. Because this was a randomized study, it is reasonable to assume that the duration of asthma was approximately the same for both groups. Thus these data would support the thesis that inhaled corticosteroids may prevent or lessen permanent loss of function over several years. By contrast, other investigators have shown that delayed versus early introduction of inhaled corticosteroids resulted in similar increases in FEV₁, although early introduction resulted in greater improvement in histamine responsiveness.⁷⁶

Because it is clear that persistent airflow obstruction will develop in all patients, future studies should be designed to help identify who is at risk for the physiologic consequences of remodeling. It is increasingly accepted that asthma is not a single nosologic entity but rather a heterogeneous disorder with multiple nosologies and natural histories. Long-term prospective studies designed to assess not only the effects of corticosteroids, but leukotriene antagonists and placebo as well, on irreversible lung function decline will be helpful in identifying populations who are at risk as well as the benefits of therapy. Further studies comparing histologic features of those with accelerated decline in lung function and those with normal rates of decline may help elucidate much needed information on pathologic and physiologic correlations.

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Correction

The following correction applies to the review article by Fish and Peters entitled "Airway remodeling and persistent airway obstruction in asthma," which appeared in volume 104, number 3, part 1, p 509-16, 1999, of the Journal.

The first sentence of the last paragraph should read, "Because it is clear that persistent airflow obstruction will not develop in all patients, future studies should be designed to help identify who is at risk for the physiologic consequences of remodeling."