INTRODUCTION

Several definitions of asthma have been proposed since the Ciba Foundation Symposium held in 1959 (1). The Global Strategy for Asthma Management and Prevention report (2) stated that the definition of asthma may be based on pathology and its functional consequences, i.e., “Asthma is a chronic inflammatory disease of the airways in which many cell types play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough particularly at night and/or early morning. These symptoms are usually associated with widespread but variable airflow obstruction that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.” The definition is still imperfect because some patients with asthma show poor reversibility, whereas some chronic bronchitics have an apparent reversibility of their airflow obstruction, which recently has been linked to features of asthma (3).

For many years, the basic alterations of asthma were considered to be bronchospasm, edema, and hypersecretion. Evidence of bronchial inflammation arose from the studies of nonspecific bronchial hyperresponsiveness, bronchoalveolar lavage (BAL) (4), bronchial biopsies (5), and induced sputum (6) and observations made postmortem of patients with asthma who died from an attack of asthma (Figures 1 and 2) or from other causes (5, 7).

The genetic predisposition to develop asthma is now well recognized (8) and the IgE-mediated response to common allergens represents the most common form of the disease in childhood and early adulthood (9). However, even in nonallergic asthma, an immunologic basis for the condition may be considered because the pathological features and the nature of inflammation are largely similar (10, 11) as are high-affinity IgE receptor (FceRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma (12).

The treatment of asthma is internationally agreed upon and guidelines have been developed for the management of asthma (2, 13, 14). All guidelines focus on the treatment of inflammation although there are differences between them. Management should take into account that asthma is a condition associated with the following: acute symptoms that can be quickly reversed by bronchodilators; exacerbations caused by chronic inflammation which can be prevented or more slowly reversed by anti-inflammatory drugs; and the process of airway wall remodeling, for which there is no defined treatment yet fully validated. Thus, asthma should be seen as a continuum from symptoms to airway wall remodeling, but the sequence and/or the severity of these events is highly variable from patient to patient.

This report describes the acute inflammation of asthma and its symptoms; the nature of chronic inflammation, its consequences, and how it might be controlled; and the remodeling process, for which less is currently known, and possibilities for altering the process and its reversal.

ACUTE INFLAMMATION AND BRIEF SYMPTOMS

Precipitous symptomatic attacks of asthma may be caused by several known or unknown factors such as exposure to allergens (9), viruses (15), or indoor and outdoor pollutants (16) and each may induce an acute inflammatory response.

Mechanisms: Experimentally Induced Allergic Reactions

Inhaled allergen challenge may be used as a model to understand acute inflammation in asthma.

Early-phase reaction. Inhaled allergen challenge in allergic patients leads to an early allergic inflammatory allergic reaction and in some cases, this may be followed by a late-phase reaction. The early-phase reaction is initiated after the activa-
tion of cells bearing allergen-specific IgE. It is characterized by the rapid activation of airway mast cells (Figure 3) (17, 18) and macrophages (19, 20). Cell types other than basophils and mast cells that bear the high-affinity IgE receptor FcεRI (21) may also participate, but it is not known whether they can be activated directly by allergens. The activated cells rapidly release proinflammatory mediators such as histamine (22), eicosanoids (23), and reactive oxygen species which induce contraction of airways smooth muscle, mucous secretion, and vasodilatation. The bronchial microcirculation has a central role in this inflammatory process (24). Inflammatory mediators induce microvascular leakage with exudation of plasma into the airways (25, 26). Acute plasma protein leakage induces a thickened engorged and edematous airway wall and a resultant narrowing of the airway lumen. In addition, plasma may also traverse the epithelium, pass through the tight junctions, and collect in the airway lumen. Plasma exudation may compromise epithelial integrity, and its presence in the lumen may reduce clearance of mucus (27). Plasma proteins may also promote the formation of viscid luminal plugs of exudate mixed with mucus and inflammatory and epithelial cells. Together, these effects contribute to airflow obstruction.

Late-phase reaction: Cellular events and release of proinflammatory mediators. The late-phase inflammatory reaction occurs between 6 to 9 h after allergen provocation and involves the recruitment and activation of eosinophils (28), CD4+ T cells...
There is selective retention of airway T cells (34), the expression of adhesion molecules (35–37), and the release of selected proinflammatory mediators (18, 38) and cytokines involved in the recruitment and activation of inflammatory cells (22, 39). The activation of T cells after allergen challenge leads to the release of T helper cell, type 2 (Th2)-like cytokines which may be a key mechanism of the late-phase response (40), but it is unlikely that there is sufficient time within the first phase of the late-phase reaction (2 to 4 h) for allergen to stimulate cytokine gene transcription, translation, and protein production in sensitized T cells. However, the release of preformed cytokines by mast cells is the likely initial trigger for the early recruitment of cells (41). This cell type may recruit and induce the more persistent involvement by T cells. Twenty-four hours after allergen challenge, an increase of activated interleukin-2 (IL-2)-positive T cells and of interleukin-5 (IL-5) or granulocyte-macrophage colony-stimulating factor (GM-CSF) messenger RNA (mRNA) expression are observed in bronchial biopsies (42), suggesting the involvement of T cells, possibly in the more chronic phase of the response.

The enhancement of nonspecific bronchial hyperresponsiveness can usually be demonstrated after the late-phase reaction but not after the early-phase reaction following allergen or occupational challenge (43, 44).

Recruitment of inflammatory cells into the airways. The late-phase reaction is considered to be a model system to study the mechanisms of the chronic inflammation of asthma (45, 46). Inflammatory cells mature and are released by bone marrow and traffic in the circulation before being recruited into the airway wall. However, hematopoietic cells are also present in the airways (47). Asthma is associated with increased levels of hematopoietic progenitor cells in bone marrow (48, 49). Cell recruitment rather than replication of preexisting inflammatory cell precursors appears to be the predominant means (Figure 5) but the precise mechanisms are still not clearly defined, and a tissue-directed component may also be underestimated (50).

The recruitment of peripheral blood cells including eosinophils, lymphocytes, and monocytes into inflamed airways is the result of adhesive interactions between circulating inflammatory and microvascular endothelial cells via the production of proinflammatory mediators, cytokines, and chemokines, and the expression of cell surface adhesion molecules. Upregulation of distinct adhesion molecules such as CD 11a, CD 11b, CD 18, or Very Late Antigen (VLA-4) on blood cells and intercellular adhesion molecule-1 (ICAM-1) or vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells is a critical step for the induction of the inflammatory response (36, 51, 52). The ligand VLA-4 is not present on neutrophils (53), which may, in part, explain the selective recruitment of eosinophils in asthma (54). An increase of such airway vascular adhesion molecules has been observed in asthma (55, 56).

Recruitment of cells into the airways wall is associated with their priming and activation (57) and is also dependent on cytokines such as IL-5 (58) and GM-CSF acting to enhance eosinophil recruitment, terminal maturation (59), and expression of their adhesion molecules (53, 60). Chemokines such as R A N T E S (regulated upon activation, normal T-cell expressed and secreted) (61, 62) and eotaxin (63, 64) also act on eosinophils and T cells to enhance markedly their recruitment and possibly their activation. R A N T E S (66) and IL-16, a lymphocyte chemoattractant factor, and macrophage inflammatory protein 1α (MIP-1α) are found in B A L fluid (B A L F) of antigen-challenged asthmatics (67) and may also participate in the process.

Clinical Consequences and Treatment
This bronchoconstrictive response associated with acute inflammation is characterized by brief symptoms including...
In the bronchial tree, the major site of the airways inflammation is still controversial. It is accepted that both central and peripheral airways are inflamed, but a recent paper has focused on the importance of bronchial and alveolar as well as peripheral tissue inflammation (80) whereas two other studies have shown that inflammation is not more prominent in the peripheral than in the central airways (81, 82). Differences between these studies may relate to the sampling procedure because Kraft and coworkers used transbronchial biopsies (80) whereas the other investigators studied excised lung specimens (81). The site of the airways inflammation is of importance for the optimal target delivery of anti-inflammatory drugs.

Cell Survival in Airway Tissues

The survival of inflammatory cells in airway tissues depends on survival factors. A apoptosis, a dynamic process involved in the control of the “tissue load” of cells at inflamed sites, tends to limit inflammatory tissue injury and promote resolution rather than progression of inflammation (83, 84). Because apoptosis attempts to terminate the inflammatory process by reducing the number of viable inflammatory cells within the bronchial mucosa, the persistence of inflammation may be due to alterations in the regulation of cell apoptosis leading to a chronic and self-perpetuating inflammatory cell survival and accumulation. Once at the site of airways inflammation, their survival as activated cells is increased (85) as a consequence of reduced apoptosis (86, 87) and possibly by increased expression of adhesion molecules on epithelial cells (77, 88). Increased eosinophil survival in asthma is associated with reduced apoptosis (86, 89). Several cytokines and chemokines may also promote cell survival, among them, GM-CSF, IL-3, IL-5, and RANTES, which are overexpressed in asthmatic airways (90–95). Antiasthmatic treatments may resolve inflammation by causing apoptosis (96). Glucocorticoids (97–99) and to a lesser extent theophylline (100, 101) reduce the survival of inflammatory cells including eosinophils.

Characteristics of Chronic Inflammation

Inflammation in chronic asthma appears to be far more complex than a simple eosinophilic inflammation alone (102). All cells of the airways, including T-cells, eosinophils, mast cells, macrophages, epithelial cells, fibroblasts, and even bronchial smooth muscle cells are involved in asthma and become activated. Nonetheless, eosinophils play an effector role by release of proinflammatory mediators (103–106), cytotoxic mediators (107), and cytokines (108–113), resulting in vascular leakage, hypersecretion of mucus, smooth muscle contraction, and epithelial shedding and bronchial hyperresponsiveness. These cells are also involved in the regulation of the airways inflammation and initiate the process of remodeling by the release of cytokines (108–112) and growth factors.

Epithelium: Epithelial cell shedding. For many years bronchial epithelial cells were considered to act mainly as a barrier participating in mucociliary clearance and removal of noxious agents. More recently epithelial cells have been found to participate in inflammatory reactions by the release of eicosanoids, peptidases, matrix proteins, cytokines, and nitric oxide (NO) as well as performing an immune function by their capacity to express human leukocyte-associated antigen-DR (HLA-DR) and present antigen.

In asthma, epithelium is partly shed (Figure 6), ciliated cells appear swollen, vacuolized and there is often loss of cilia (114, 115). When epithelium is reconstituted there are greater numbers of goblet cells than normal. In fatal asthma, extensive epithelial shedding is commonly observed (7). Epithelial cells

- wheezing, dyspnea, and shortness of breath which usually do not persist for more than a day or so.

The treatment of these brief symptoms is based on quick-relief medications (2) among which short-acting inhaled β2-agonists are the most effective (68–70).

Prevention of these brief symptoms can be achieved by long-acting β2-agonists (71) such as salmeterol (71, 72) or formoterol (73). There are phenotypic allelic variations in the structure of the β2-adrenergic receptor expressed in lung cells (74) which may be an important factor in the ultimate physiologic response to β2-agonists (75).

CHRONIC INFLAMMATION

Airways inflammation has been widely demonstrated in all forms of asthma, and an association between the extent of inflammation and the clinical severity of asthma has been demonstrated in some (76, 77) but not all studies (78).

Site of the Inflammation in Asthma

The whole mucosal immune system appears to be involved in bronchial asthma. Although devoid of gastrointestinal symptoms, asthmatics and asymptomatic allergic individuals have duodenal pathologic abnormalities mimicking those observed in the bronchial mucosa (79). The reasons for the preferential involvement of the airways in asthma are not known but may be related to the route and dose of allergen exposure or early injury to the airways.
of asthmatics are also significantly less viable than those of normal subjects (116).

The mechanisms underlying epithelial shedding in asthma are still a matter of debate (117). Epithelial shedding can be caused by plasma exudation (118), toxic inflammatory mediators such as eosinophil granule proteins (119, 120), oxygen free radicals, tumor necrosis factor-alpha (TNF-α) (121), mast cell proteolytic enzymes (103), or metalloproteinases from epithelial cells (122) or macrophages (123). Furthermore, the increased epithelial fragility and shedding may also be caused by a weakened attachment of superficial epithelial cells to basal cells or to their basement membrane; this probably reflecting a disturbance in cell–cell adhesion (124).

The functional consequences of epithelial shedding are still unclear. Eosinophil damage may lead to heightened airways responsiveness (125, 126), a failure to metabolize agonists (127), the destruction of a diffusion barrier altering permeability of the airway mucosa (128), the depletion of epithelial-derived relaxant factors (129) and loss of enzymes (neutral endoproteases) responsible for degrading proinflammatory neutrophil products including substance P (130). The integrity of airway epithelium may influence the sensitivity of the airways to provocative stimuli by liberating a variety of bronchoactive mediators, e.g., lipoxigenase and cyclooxygenase products (116, 131) and NO (132).

Epithelial cell activation. Activated epithelial cells release a wide array of mediators including 15-hydroxyeicosatetraenoic acid (15-HETE) (116), cytokines (133), eotaxin (134), growth factors (135, 136), extracellular matrix (ECM) proteins (116, 137), and metalloproteinases (138) which can induce bronchial obstruction, inflammation, and airways remodeling (139).

In asthma, epithelial cells are activated releasing greater amounts of 15-HETE, prostaglandin E2 (PG E2), fibronectin, cytokines, growth factors, and endothelin spontaneously or after stimulation (116, 140). There is an increased expression of membrane markers such as adhesion molecules (77, 141, 142), endothelin (143), NO synthase (132), cytokines (144, 145) or chemokines (146). Epithelial cells can be activated by IgE-dependent mechanisms (147), viruses, pollutants (148), or proinflammatory mediators such as histamine (149).

Epithelial cells in airway remodeling. In asthma, epithelial cells are likely to be important in repair processes. They release ECM proteins (116) including fibronectin (137, 150) which appears to be of importance in cell regeneration. Bronchial epithelial cell–derived cytokines may amplify ongoing inflammatory processes via the recruitment and activation of specific subsets of inflammatory cells, as well as by prolonging their survival in the airway microenvironment (151). Bronchial epithelial cells represent targets for paracrine acting cytokines and growth factors, which may then modulate bronchial epithelial cell functions. They may be important in the regulation of airway remodeling and fibrosis as they release fibrogenic growth factors such as insulin growth factor (IGF) (135, 152) and transforming growth factor-beta (TGF-β) (153), they regulate fibroblast proliferation (154), and they release metalloproteinases (155).

Inflammatory cells. Increased numbers of inflammatory cells are found among the epithelial cells. These include intact and degranulated eosinophils, lymphocytes, activated macrophages and partly degranulated mast cells (114, 156–158). Recently, it has been demonstrated that goblet cell hyperplasia precedes the inflammatory infiltrate and persists even after the number of inflammatory cells decreases, indicating that some of the phenotypic changes in airway epithelium are not caused by inflammation (159).

Mixed inflammatory infiltrate in the subepithelial layers: Eosinophils. Tissue eosinophilia is a characteristic of asthma but it is not necessarily specific to asthma (160). Eosinophils found in the airways of symptomatic asthmatics are activated (161, 162). Most allergic and nonallergic asthmatics, including those with mild asthma, have a bronchial eosinophilia and there is a significant association between eosinophil activation and asthma severity (76) as well as bronchial hyperresponsiveness (163). Tissue eosinophilia was found to be significantly greater in fatal asthma (164) than in patients with chronic asthma (165). Eosinophils are recruited and found to be activated during segmental allergen challenge (33, 166, 167). Soluble vascular cell adhesion molecule-1 (sVCAM-1) levels after segmental antigen challenge correlate with eosinophil influx, IL-4 and IL-5 production, and the late-phase response (39).

The biological properties of eosinophils include the release of toxic granule proteins, oxygen free radicals, eicosanoids (sulfido-peptide leukotrienes) (168), Th2-like cytokines (169, 170), and growth factors (107, 171). Once activated, products from eosinophils contract human bronchial smooth muscle (172), increase vascular permeability (173), and induce airway hyperresponsiveness (174). Eosinophils are deleterious in asthma by the release of highly toxic products (major basic protein [MBP]; eosinophil cationic protein [ECP]; eosinophil-derived neurotoxin [EDN]; oxygen free radicals) which induce the shedding of the surface epithelium in keeping with the hypothesis of eosinophil-induced damage of the bronchi (107).

Eosinophils can be important cells of airways remodeling. Eosinophils can release growth factors (175, 176), elastase (177), and metalloproteinases (178) involved in the process of tissue remodeling and fibrosis. Eosinophil products stimulate fibroblasts (179). Eosinophilia has long been associated with endomyocardial fibrosis (180) but the involvement of eosinophils in the fibrotic process is not completely understood. Eosinophils appear to be involved in pulmonary fibrosis (181) or in tropical pulmonary eosinophilia (182). Moreover, in an extensive study, MBP deposition was found to be present in some, but not all, cases of pulmonary fibrosis at the site of the fibrotic lesions (183).

Lymphocytes. Increased numbers of T lymphocytes are found in the airways mucosa of patients with fatal asthma (164) or in asthmatics of variable asthma causation including occupational asthma (163, 165, 184, 185). The majority of lymphocytes bear CD4-receptors whereas CD8-positive cells are...
tryptase, histamine, and PGD₂ appear to be prominent (200). There are increased levels of these soybean dust–induced asthma as an activation of mast cells are often degranulated in the airways of asthmatics in both normal subjects and asthmatics (158, 163, 197, 198). They inhibit the growth of epithelial cells.

CD40 expression has been shown to have anti-inflammatory properties. Besides their activity as anticoagulants, heparin and heparan sulfate possess many biological activities that include the ability to modulate tissue homeostasis, wound healing, cell differentiation, cell proliferation (209), and inflammation (210, 211). Prevention of bronchoconstriction in exercise-induced asthma was observed with inhaled heparin (212). Heparin was shown to inhibit the immediate response to allergens in both stable phase and after allergen challenge (114, 199). In fatal soybean dust–induced asthma an activation of mast cells appears to be prominent (200). There are increased levels of tryptase, histamine, and PGD₂ in the BALF (161, 199, 201–203). The importance of mast cell activation remains to be fully understood because association between the severity of asthma and concentrations of histamine or tryptase in the BALF has been inconsistently observed (203, 204). A irway basophil and mast cell density in patients with bronchial asthma was associated in one study to bronchial hyperresponsiveness (198).

Mast cells appear to be critical “trigger” cells during episodes of acute asthma (161) eliciting acute bronchoconstriction, edema, and mucus secretion by the release of histamine and other vasoactive mediators such as PGD₂ and cysteinyl leukotrienes. However, the role of mast cells is not confined to acute asthma and they may release neutral proteases including tryptase (103) and chymase. Tryptase has proinflammatory mast cell function (205) and potentiates histamine-induced contraction in human sensitized bronchus (206), whereas chymase exhibits procollagen proteinase activity (207, 208).

Mast cell products may have anti-inflammatory properties. Besides their activity as anticoagulants, heparin and heparan sulfate possess many biological activities that include the ability to modulate tissue homeostasis, wound healing, cell differentiation, cell proliferation (209), and inflammation (210, 211). Prevention of bronchoconstriction in exercise-induced asthma was observed with inhaled heparin (212). Heparin was shown to inhibit the immediate response to allergens in the lungs of allergic subjects (213, 214) and to reduce bronchial hyperresponsiveness (215).

Basophils and mast cells store preformed Th2-like cytokines which can be released during activation (41, 216–218). Mast cells and basophils can be induced to express CD40L. These studies suggest that mast cells and basophils can induce the synthesis of IgE, independently of T cells. The widespread expression of CD40 in normal epithelial cells suggests that the CD40–CD40L interaction has important, additional influences beyond that of regulating immune responses (219). The CD40 pathway may be important in the regulation of chronic inflammatory diseases. It has been suggested that the restricted basal epithelial cell expression of CD40 is associated with the cycling nature of these cells. CD40 expression has been shown to inhibit the growth of epithelial cells.

Mast cells may be involved in airways remodeling because they appear to have an important role in pulmonary fibrosis (220–222). Mast cells are potential sources of products stimulating migration and proliferation of fibroblasts, (223, 224). Mast cell lines can release components of basement membranes such as laminin and collagen IV (225) and angiogenic growth factors (226). Human mast cells activate fibroblasts, and tryptase is a fibrogenic factor stimulating collagen messenger ribonucleic acid synthesis and fibroblast chemotaxis (227) and is a mitogen for epithelial cells (228).

Macrophages. Mononuclear phagocytes have a fundamental role in specific immunity via their accessory cell function and are metabolic cells which play a major role in chronic inflammation. The spectrum of their biologic activity is vast, and while many of the products released are involved in inflammation, they also take part in healing and repair. Mononuclear phagocytes are likely to be involved in the pathogenesis of asthma because macrophages are among the cells present in the airways inflammatory infiltrate (157, 163, 229, 230), particularly in asthma of the nonatopic form (230). However, the increase in the numbers of macrophages in the airways is far greater in chronic bronchitis than in asthma or control subjects, particularly in bronchioles and surrounding alveoli (189, 191).

Alveolar macrophages (A M) recovered by B A L have been extensively studied in asthma, and most studies have revealed their increased activation (4, 231–235) and shown a significant correlation between their activation and the severity of asthma (236, 237). Endobronchial challenge with allergen has induced the activation of A M (19, 20, 33, 238); they are also activated during the late-phase reaction after allergen challenge (239). Cytokines that usually downregulate A M, such as IL-4, are less effective in asthmatic patients than in control subjects (234, 235).

Macrophages may also be involved in the generation of the airways obstruction and the regulation of the airways inflammation through release of enzymes (231), eicosanoids (240), platelet-activating factor (PAF) (241), oxygen free radicals and cytokines (233, 234), and mucus secretagogues (242) that are likely to be deleterious for the bronchi. M acrophages can also modulate the immune response (243, 244).

Macrophages may also be involved in the regulation of the airway remodeling through the secretion of growth-promoting factors for fibroblasts, cytokines, and growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), or TGF-β possibly involved in fibrosis (245). In interstitial lung diseases, A M were found to be activated and to release cytokines, plasminogen activator, and a fibrinolytic inhibitor (246–248) as well as M IP-1α, a peptide with leukocyte-activating and chemotactic properties (249). In lung inflammation, an increased expression of PDGF β chain is expressed in A M of patients suffering from interstitial pulmonary fibrosis (250–253). By comparison to normal subjects, A M from asthmatics release increased amounts of TGF-β and fibronectin, but to a lesser extent than those of chronic bronchitis patients (254). They also express PDGF-β mRNA in vivo in asthma (255). M acrophages can also synthesize and secrete a group of matrix metalloproteinases (M M P) having the capacity to degrade various ECM macromolecules including elastin. M M P-9 release by A M is increased in asthmatics by comparison to control subjects and chronic bronchitics (123). It is likely that macrophages participate in most processes in healing from acute and chronic inflammation through angiogenesis (256), proliferation of endothelial and mesenchymal cells, and the regulation of ECM synthesis and degradation possibly leading to fibrosis (257).

Polymorphonuclear neutrophils. The role of neutrophils in
stable asthma remains unclear. Although recovered in the sputum of asthmatics (258), neutrophils are usually found in low numbers in BAL (160) and bronchial biopsies (125, 160, 163) from asthmatic subjects. However, neutrophils are increased in the airways during the late-phase reaction after an allergen challenge (31, 32), in some patients who died within hours after an asthma exacerbation (259, 260), in nocturnal asthma (261), in some patients with long-standing asthma (262), or in patients with corticosteroid-dependent asthma (263).

Dendritic cells. There is a network of dendritic cells within the epithelium of the conducting airways of humans that constitutively express major histocompatibility complex (MHC). Dendritic cells may be critically important to the induction of immune responses within the airways as they are specialized in antigen processing and presentation. In animals, the dendritic cell population in the airway epithelium is renewed every 48 to 72 h (264). It appears that dendritic cell number can be altered after exposure to topical and systemic corticosteroids (265). Dendritic cells in normals and asthmatics express the FcεRI (266); their numbers are greater in the airways of asthmatics compared with those of control subjects (267, 268); but their role in asthma is still a matter of debate (269).

Fibroblasts and myofibroblasts. Fibroblasts are frequently found in connective tissue. They are responsible for the production of collagen, reticular and elastic fibers as well as for the synthesis of proteoglycans and glycoproteins of the amorphous intercellular substance (270). Human lung fibroblasts may behave as inflammatory cells upon activation by IL-4 and IL-13 (271). Although they are regarded as fixed cells of connective tissue origin, they retain the capacity for growth and proliferation and are a pluripotent cell. They may be precursors for various cell types including smooth muscle cells (272). Cell cultures from media obtained from bronchial subepithelial myofibroblasts enhances eosinophil survival in vitro (273). The myofibroblast may potentially contribute to the regulation of bronchial inflammation via the release of cytokines (274) and to tissue remodeling by its release of ECM components such as elastin, fibronectin, and laminin (275). In pulmonary fibrosis there is an increased production of ECM components by myofibroblasts (276). During the late-phase reaction after allergen challenge, myofibroblasts increase from the normal of 2% of cells to approximately 15% within a day, and ultrastructural forms of cells between fibroblast and bronchial smooth muscle have been found (272). Restoration of normal tissue structure after injury often coincides with the loss of the myofibroblast phenotype and the reappearance of normal-appearing fibroblasts (275).

In asthma, myofibroblasts are increased in numbers beneath the reticular basement membrane (Figure 7), and there is an association between their numbers and the thickness of reticular basement membrane (277, 278).

Platelets. The importance of platelets in asthma remains unconfirmed (279, 280). They have been described at sites of epithelial sloughing together with fibrin in cases of mild symptomatic asthma (125). They are activated in aspirin-induced asthma (281) and nocturnal asthma (282).

Neurogenic inflammation. Neural mechanisms and their interaction with inflammatory cells are likely to be important in the pathophysiology of asthma. Inflammatory mediators may influence the release of neurotransmitters or may activate afferent nerves leading to bronchoconstrictive reflexes and the release of mucins at sites distant to the initiating event. This
spread of inflammatory effects along the airways is referred to as a neurogenic inflammation (283-286). Neurogenic inflammation is probably not relevant to mild asthma, however, but it may be more important in severe disease such as brittle asthma (287). Inflammation upregulates neurotrophins in asthma, possibly contributing to airway hyperresponsiveness (288).

Eicosanoids. No single mediator is responsible for the clinical and pathologic events in bronchial asthma, but there is now substantial evidence that the cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) play an important role in the pathophysiology of asthma (104, 289-291). Cysteinyl leukotrienes are released by most cells involved in the airways inflammation and particularly by eosinophils (292). Cysteinyl leukotrienes are potent in eliciting bronchoconstriction (293, 294), increase endothelial membrane permeability leading to airway edema, enhance secretion of mucus (295), and may increase bronchial hyperresponsiveness (296, 297). Cysteinyi leukotrienes may also be of importance in inflammation because inhalation of LTE₄ (298) or LTD₄ (299) induces the recruitment of eosinophils in the airways, possibly in part by inducing P-selectin expression on endothelial cells (300), and they have been shown to have an important role in airway eosinophilia in an animal model of asthma (301).

However, cysteinyi leukotrienes may also alter remodeling because they increase proliferation of airway smooth muscle (302, 303) and airway epithelial cells (304) and LTC₄ was shown to upregulate collagenase expression in human lung fibroblasts (305).

Several lines of evidence support the central role of the cysteinyl leukotrienes in aspirin-sensitive asthma (306, 307). There is a profound overexpression of leukotriene C4 synthase in bronchial biopsies from aspirin-intolerant asthmatic patients (308).

The response of patients to drugs may vary depending on genetic factors. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that may modify transcription factor binding and reporter gene transcription have been reported (309), and this may explain the response of patients to 5-lipoxygenase inhibitors.

Other proinflammatory and anti-inflammatory mediators: Enothelins (ETs). Enothelins are a family of 21 amino-acid regulatory peptides which appear to have a role in the regulation of pulmonary functions. ET immunoreactivity was found to be expressed at a higher level in bronchial biopsies of asthmatic patients (143), and levels of ET are elevated in BALF (310) and bronchial biopsies (311) of asthmatics compared with normal subjects. Moreover, endothelin levels are increased in BALF in nocturnal asthma (312). Enothelins are released from macrophages (235), endothelial and epithelial cells (313). The potent bronchoconstrictor and mitogenic actions of ET-1 on airway smooth muscle may contribute significantly to the increased muscle mass and bronchial obstruction observed in asthma (314). ET also possess proinflammatory properties (315) and oxygen free radicals (316).

Nitric oxide (NO). NO is an intercellular transmitter, both in the central and in the peripheral nervous system. In addition to nerve cells, NO is also produced by epithelial cells and by the endothelium. NO plays a key role as a vasodilator, neurotransmitter, and inflammatory mediator in the airways and is produced in increased concentrations in asthma (317). It may be the major bronchodilator of airways normally (318). However, NO may have deleterious effects on the airways as a vasodilator, by increasing plasma exudation, and may also amplify the asthmatic inflammatory response. Proinflammatory cytokines and oxidants increase the expression of an inducible form of NO synthase (iNOS) in airway epithelial cells in asthma (132), and this may be the explanation for the increased concentrations of NO found in exhaled air of asthmatic patients (319).

**Chronic Inflammation in the Different Forms of Asthma**

Inflammation can be demonstrated in allergic (163), nonallergic (11, 94, 230), occupational (185, 320, 321) and aspirin-induced asthma (307, 322). The profile of inflammatory cells and cytokine gene expression appears to be similar in allergic and nonallergic asthma, although the presence or absence of IL-4 protein in nonallergic asthma has been debated (11, 94, 184, 230, 323–325). Chronic inflammation may be induced or acutely increased by exposure to allergens (326), occupational agents (327, 328), pollutants (329–331), or a virus infection (332–334).

Inflammation occurs early in the course of asthma process (335), in patients with mild intermittent asthma (336) and during remissions (262). The severity of asthma has been correlated with many inflammatory indices such as epithelial denudation (125) and activation (77, 116, 337), eosinophil number and activation (76, 187, 338), T-cell activation (230), macrophage activation (236, 339), or cytokine expression (144). However, inflammation does not explain all the components of asthmatic phenotype (78).

In nocturnal asthma, several studies have shown increased airway eosinophils and neutrophils (261, 340, 341), superoxide (342), and cytokine concentrations (112) as well as activation of lymphocytes and macrophages (343) when bronchoscopy with BAL or mucosal biopsies were performed during the night. Histamine (344, 345) and ECP concentrations (346) were increased in the peripheral blood during the night. These findings are of importance because asthma is an inflammatory process which worsens at night in some patients (343, 347). However, other mechanisms may also be responsible for nocturnal asthma. The Gly16 polymorphism of the β2 adrenergic receptor, which imparts an enhanced downregulation of receptor number, is overrepresented in nocturnal asthma and appears to be an important genetic factor in the expression of this asthmatic phenotype (348).

**Clinical Consequences**

Chronic inflammation is associated with nonspecific bronchial hyperresponsiveness and induces exacerbations. Exacerbations are characterized by symptoms or worsening of asthma over a period of days or even weeks (349-351). A though exacerbations need to be better characterized, they are usually separated into mild and severe. In a recent study (352), mild exacerbations were defined as a reduction in morning peak flow rates under 20% baseline values or an increased need for rescue β2-agonists or of nocturnal asthma. However, single isolated days were not considered as exacerbations. In the same study, severe exacerbations were defined as ones requiring treatment with oral glucocorticoids, as judged by the investigator, or a decrease in the peak flow rates as measured in the morning to > 30% below the baseline value on two consecutive days.

Nonspecific bronchial hyperresponsiveness may be defined as an increase in the ease in degree of airway narrowing in response to a wide range of bronchoconstrictor stimuli (353, 354). Several mechanisms have been identified in bronchial hyperresponsiveness which has a heritable component and is closely related to serum IgE levels and airway inflammation (355). Reduced airway caliber, increased bronchial contractility, dysfunctional neural regulation, altered permeability of the bronchial mucosa, proinflammatory humoral and cellular mediators (356), and cytokines such as GM-CSF (144) and
TNF-α (357) are critical factors for bronchial hyperresponsiveness. Non-specific bronchial hyperresponsiveness has been associated with epithelial injury (125, 126, 358), increased airway microvascular permeability (359, 360), inflammatory cells in the airways (28, 46, 126, 144, 244, 361), and features of remodeling (362). However, not all studies have found an association between inflammation and non-specific bronchial hyperresponsiveness (363). Moreover, the degree of airway inflammation was shown to correlate with the magnitude of bronchial hyperresponsiveness (125, 188, 361).

Treatment of Exacerbations
The treatment of exacerbations is based on long-term control medications including corticosteroids, cromoglycate, and nedocromil, long-acting β2 agonists, methylxanthines, and leukotriene modifiers (2, 13, 14).

Although the inflammatory nature of asthma is not completely understood (364), corticosteroids remain the most potent anti-inflammatory drugs for use in the treatment of asthma (365–367). Glucocorticoids have an inhibitory effect on inflammatory and immune responses primarily through the modulation of transcription factors binding to DNA such as activator protein-1 (A P-1), nuclear factor kappa B (NF-κB) (368), and cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB). The effects of glucocorticoids in asthma are widespread but they can reduce cytokines that are involved in cell recruitment and the survival of inflammatory cells including eosinophils, basophils, and lymphocytes (369). In most but not all studies, inhaled corticosteroids (90, 145, 146, 370–380) and oral corticosteroids (186, 381–388) have been shown to reverse many of these inflammatory indices. Moreover, a temporal association between the reduction of inflammatory indices and clinical and physiologic improvement has been observed (384). In patients with mild to moderately severe asthma, inhaled corticosteroids significantly reduce exacerbations, improve pulmonary function, and reduce non-specific hyperreactivity. Inhaled corticosteroids are, however, poorly effective in preventing virus-induced exacerbations (389). There is, however, a very small but still clinically important subset of asthmatics who may not respond favorably to oral corticosteroids (390, 391).

Asthma exacerbations can be treated or reversed to a lesser extent by cromones (392) and theophylline. Nedocromil sodium in studies of bronchial biopsy was not found to alter airways inflammation (393, 394) but did reduce the eosinophil influx into airways after segmental antigen challenge (395). Disodium cromoglycate was also found to reduce inflammation and adhesion molecules in the airways in a biopsy study (396). Theophylline (397–400) has been found to reduce airways inflammation.

Cysteinyl leukotriene antagonists (401, 402) and 5-lipoxygenase inhibitors (403, 404) are effective in the treatment of asthma but their exact roles are currently under investigation. Zileuton, a 5-lipoxygenase inhibitor (405) and cysteinyl leukotriene antagonists (406) have been found to reduce airways inflammation.

Salmeterol was not found to reduce airways inflammation (407, 408) although it reduces basophil hyperreactilascibility in peripheral blood (409) and eosinophil activation in vitro (410). However, although it is very difficult to compare the relative anti-inflammatory activities of drugs because they are not compared in the same study, nonsteroidal drugs appear to be less potent than corticosteroids.

Because asthma often presents with association of symptoms and exacerbations, treatment that combines inhaled corticosteroids and long-acting β2-agonists has been shown to control optimally chronic asthma (352, 411–413). However, other treatment options may be taken such as combination of theophylline (414) or leukotriene antagonists (402) with inhaled steroids.

Onset and Duration of Treatment
Inflammation is an early feature of asthma (335, 415) and it has been proposed that anti-inflammatory treatment should begin as soon as asthma is diagnosed (416). Even patients with mild intermittent asthma present an airways inflammation suggesting that anti-inflammatory drugs should be administered in mild asthma (2, 417). Moreover, it has been observed clinically that patients relapse within days or weeks after cessation of inhaled corticosteroid treatment (418, 419). It is therefore considered essential to continue anti-inflammatory treatment over a prolonged period.

REMODELING OF THE AIRWAYS
A cute inflammation is a beneficial, non-specific response of tissues to injury and generally leads to repair and restoration of the normal structure and function. In contrast, asthma represents a chronic inflammatory process of the airways followed by healing whose end result may be an altered structure referred to as a remodeling of the airways (420). Repair usually involves two distinct processes: regeneration, which is the replacement of injured tissue by parenchymal cells of the same type; and replacement by connective tissue and its eventual maturation into scar tissue. In many instances both processes contribute to the healing response and inflammation. In asthma the processes of cell dedifferentiation, migration, differentiation, and maturation as well as connective tissue deposition can be followed either by complete or altered restitution of airways structure and function, the latter often seen as fibrosis and increase in smooth muscle and mucus gland mass (421) (Figure 8).

Characteristics of Airways Remodeling in Asthma
Structural changes in the airways of asthmatics. In addition to other inflammatory features, the airway wall of patients with asthma is usually characterized by an increased thickness involving an increase in muscle mass and mucus glands, and increased vessel area leading to a thickened airway wall and a markedly and permanently reduced airways caliber (Figures 9 and 10). These changes were observed as well using computed tomographic (CT) scans (422, 423) and result in an increased resistance to airflow, particularly when there is bronchial contraction and bronchial hyperresponsiveness (422, 424). The effect on airflow is compounded by the presence of increased mucus secretion and inflammatory exudate, which not only blocks the airway passages but causes an increased surface tension favoring airway closure.

**Figure 8.** Mechanisms of acute and chronic inflammation in asthma and remodeling processes.
Hypertrophy and hyperplasia of airway smooth muscle. Smooth muscle mass is usually increased in large and/or small airways in both fatal and nonfatal cases of asthma (425–429). The increase in muscle mass is often not seen in chronic bronchitis and chronic obstructive pulmonary disease (COPD), and, if present is increased in the small airways (426, 427). There is a 3- to 4-fold increase in muscle volume in asthmatic airways by comparison to normal subjects (430). In some patients the muscle may occupy up to 20% of the bronchial wall (425). However, while an increase in smooth muscle in the major bronchi has been reported in asthmatic subjects (425), an increased smooth muscle thickness was also found in the peripheral airways (428, 429). Interestingly, in a study of asthmatic patients who died from other causes no hyperplasia or hypertrophy were observed (431). More recent studies have indicated some degree of heterogeneity of the smooth muscle thickening (432, 433). In most patients the increase in muscle mass was most pronounced in large bronchi but some patients had increased muscle mass which involved the entire airway tree including bronchioles.

Smooth muscle cells are multifunctional mesenchymal cells capable of expressing considerable phenotypic plasticity (434). Increases in smooth muscle mass may be due to several factors, including the following: proliferation of smooth muscle induced by inflammatory mediators (435), cytokines (436), and growth factors (437, 438); a “work hypertrophy” resulting from repeated episodes of bronchospasm; or reduced inhibitory control resulting in myogenic activity and hypertrophy. The accumulation of enriched plasma in the environment surrounding airway smooth muscle may also promote smooth muscle mitogenesis and hyperplasia (439). It has been suggested that an intrinsic abnormality of smooth muscle may underlie asthma severity, but data are lacking to support this hypothesis.

In addition to contractile responses and mitogenesis, airway smooth muscle cells have synthetic and secretory potentials with the release of R A N T E S (440). They may participate in chronic airway inflammation by interacting with both Th1- and Th2-derived cytokines to modulate chemoattractant activity for eosinophils, activated T lymphocytes, and monocytes/macrophages. Smooth muscle also has the potential to alter the composition of the ECM environment and orchestrate key events in the process of chronic airway remodeling (441).

There are many functional consequences of the increase in bronchial smooth muscle mass. It has been proposed that the same degree of muscle shortening may cause considerably greater lumenal narrowing in an airway with a thick wall than in a normal airway (442, 443). This has been confirmed by computer modeling of the tracheobronchial tree that examines the interaction between airway smooth muscle shortening, airway wall thickening, and changes in pulmonary resistance (444–446). Unlike the human lung, the model is based on the symmetrical dichotomous branching tracheobronchial tree. The model has shown (446) that the marked increase in airway wall thickness equivalent to that seen in asthma does not reduce the airways caliber if the airway smooth muscle remains at its resting length. A s bronchoconstriction occurs, there is a marked increase in airway resistance (444, 447), and studies of human lungs have shown that the smooth muscle in asthmatic airways needs to shorten by only 40% of its resting length to completely occlude the airway lumen (445). The model also shows that resistance, particularly in the small airways, tends to reach a plateau in normal airways, whereas it increases progressively in asthma because of airways closure (445, 446). These calculations are consistent with observations made during bronchial challenges where, in normal subjects, the reduction in FEV₁ reaches a plateau, whereas in asthmatics, the FEV₁ continues to decrease without a plateau occurring (448).

Increase in mucous glands. Mucous glands are distributed throughout the cartilaginous airways in the normal and in asthma where they may be even present in peripheral bronchioles where normally they are absent. Hypertrophy of the submucosal gland mass is thought to contribute to the excessive mucus production in fatal asthma. The glands make up a higher proportion of the submucosa in fatal asthma compared with normal subjects (425, 429, 449). A nother feature of the glands is dilatation of the secretory ducts that lead into the bronchial lumen, a condition referred to as bronchial gland duct ectasia (450, 451). This may be associated with the interstitial emphysema observed in some asthmatic patients using CT scan (452). The increase in the number of epithelial goblet cells also contributes to the excess of mucus secretion into the lumen (453, 454) and the secretions present in large airways may be aspirated to smaller airways.
Mucous plugs occur in airways of all sizes, from the second generation airways to bronchioles (455). Although some patients may die from cardiac arrhythmia or overwhelming smooth muscle spasm without mucus hypersecretion (456), most patients have an excessive mucus production (457–459) leading to endobronchial mucous suffocation. Over 50% of the airways may be occluded by mucus during a fatal attack of asthma (428). The greater mucous viscosity may significantly reduce mucociliary clearance (460). Large and small airways become plugged with secretions and inflammatory exudate which are so viscous that patients are poorly responsive to high-dose inhaled bronchodilators (456), and the mucus may need to be removed by bronchoscopy and lavage.

Thickening of the reticular basement membrane (i.e., lamina reticularis). The basement membrane of surface epithelium is composed of several layers: the basal lamina (referred to as the “true” basement membrane) and the lamina reticularis. The thickening of the lamina reticularis is a characteristic early typical feature of the asthmatic bronchus (425) which is caused by deposition of reticulin (461). By light microscopy, this is homogeneous and hyaline in appearance. Ultrastructurally, it appears to consist of a plexiform arrangement of the fibrils in an amorphous matrix. The basal lamina is of normal thickness in asthma, whereas the reticular layer is thickened associated with deposition of immunoglobulins and/or collagen I and III and fibronectin but not collagen types V and VII (462) nor laminin (463). The additional reticulin is likely produced after activation of myofibroblasts (277) leading to a so-called “fibrosis” of the airways. The thickening has not been related to the severity, duration, or origins of asthma in some studies (125, 464) whereas a correlation with the severity of the disease has been observed in another one (465). Patients with rhinitis also present with subepithelial fibrosis of the bronchi with a deposition of type I and III collagen and fibronectin. However, these features are less marked than in asthma (466). In contrast, there is a lack of such thickening in COPD (160, 191, 467). The connective tissue of the airways forms a “scaffold” for the replicating parenchymal cells, and its abnormal structure in asthmatic airways may result in several defects and induce a remodeling of the airways which is detrimental to airflow (422).

Blood vessels. There is a rich network of systemic capillaries running immediately beneath the surface lining from central airways to peripheral bronchioles. The subepithelial tracheobronchial capillaries converge and extend to a deeper plexus of larger sinuses which anastomose with the pulmonary capillaries drained by pulmonary veins. Transmission electron microscopy (TEM) demonstrates that the bronchial vessels are adjacent to the epithelial basement membrane, and do not lie in the epithelium itself. These vessels are critical to chronic inflammatory process when they dilate and possibly proliferate. New vessels originate by budding or sprouting of preexisting vessels, a process called angiogenesis (468). Wherever angiogenesis has been studied, the newly generated vessels have been found to be hyperpermeable and increase edema.

In asthma, there is an increase in vessel area (428, 469) leading to a thickened airway wall (445). Bronchial biopsies from patients with mild asthma are more vascular than those of normal control subjects, there are more vessels in asthmatic airways, and asthmatic bronchial vessels are larger than that of control subjects (470). Moreover, in asthma there are endothelial gaps in the bronchial mucosal microvasculature whereas they are not detected in tissue from normal healthy individuals (471).

Various endothelial growth factors have been described (472) and include vascular endothelial growth factor (VEGF) (473), bFGF, platelet-derived endothelial cell growth factor (PD-ECGF) and hepatocyte growth factor (HGF). A number of putative angiogenic factors including small molecules (e.g., prostaglandins, adenosine) as well as many cytokines and growth factors (e.g., TGF-α, bFGF, TGF-β, TNF-α, PDGF) have all been shown to upregulate VEGF expression. The inhibitory effect of corticosteroids on VEGF expression could explain the clinically well-known antiinflammatory potency of corticosteroids at a molecular level (474).

ECM components. Connective tissue cells produce and secrete an array of macromolecules forming a complex network filling the extracellular space of the airway wall called the ECM. The macromolecules that constitute the ECM are secreted locally by all cells present. The composition of the matrix secreted depends on the cell types, their state of differentiation, and their metabolic status. Molecules comprising ECM consist of fibrous proteins (collagen, elastin), structural or adhesive proteins (fibronectin and laminin) embedded in a hydrated polysaccharide gel containing several glycosaminoglycans including hyaluronic acid or hyaluronic (HA). The glycosaminoglycans, proteoglycans, and structural proteins entrap water molecules to form a highly hydrated gel-like “ground substance” in which the insoluble fibrous proteins are embedded, giving the matrix strength, rigidity, and resilience. Until recently, the ECM was thought to be an inert scaffolding having a mechanical role in supporting and maintaining tissue structure. However, it has been shown that the ECM also modulates a multitude of cell functions such as development, migration, and proliferation (475, 476). ECM abnormalities in asthma are still poorly understood but may be of major importance (477).

Collagen is a major protein of the ECM (478). In some asthmatics hyperplasia of collagen fibers can be observed. These fibers may be irregularly disposed but the exact nature of collagen is not completely characterized. The subepithelial tissues of asthmatics contain significantly more collagen type I and III than that of normal control subjects (479) and such “scar formation” may have greater functional implications than the increase in thickness of the reticular basement membrane.

Tenascin and fibronectin are ECM glycoproteins expressed during morphogenesis and tissue repair. An increase in tenascin immunoreactivity was observed in the bronchial subepithelial reticular basement membrane layer in patients with chronic asthma and in those with seasonal asthma compared with control subjects (480). The tenascin immunoreactivity, appearing as an intense wide subepithelial band in asthma, was seen only occasionally in the basement membrane of control specimens. Instead, a diffuse immunoreaction against both total fibronectin and locally produced extradomain A fibronectin was similarly visible in the airway mucosa of both patients and control subjects. There was no correlation between the number of eosinophils or lymphocytes and level of tenascin expression, suggesting that the higher amount of tenascin reflects disease activity in asthma and may be an indicator of a remodeling process rather than of injury itself.

Elastin is a cross-linked protein that gives tissues their elastic recoil and is a requirement for tissues that bend, twist, and stretch reversibly. Subepithelial elastic fibers of the airways are fragmented. In the deeper layer, fibers are often patchy, tangled, and thickened (481) but the total amount of elastic fiber appears to be unchanged (482).

Glycosaminoglycans form an important component of ECM binding to water and cations (483). HA is normally found in adult tissues in small amounts but is present in higher amounts during wound healing (484). It confers important physical properties, notably viscoelasticity, and facilitates cell migration and proliferation during injury and repair (485). HA levels are increased in the BALF of asthmatics, and their level is associated with the severity of the disease (204).
The ECM is a dynamic structure, and an equilibrium between synthesis (486) and controlled degradation of ECM components is required for the maintenance of its homeostasis. Three major elements are involved: proteases and protease inhibitors (487, 488), cell receptors recruiting intracellular and secreted proteases to the cell surface, and integral membrane proteases activating a protease cascade. Eosinophils (178) and macrophages act as a source of MMP-9 in asthmatic airway inflammation (123). Elastase was found to be released in increased amounts in the sputum of asthmatic patients by comparison to control subjects, and elastase concentrations were significantly correlated with FEV₁ (489).

Structural changes in the parenchyma of asthmatics. In the pathologic examination of asthmatic lungs, mild emphysema, a destructive process focusing on the acinus, was described in some cases (431, 490) but is not a usual feature (425, 449). Fibrogenic growth factors. Growth factors interact with the ECM (491) and can be divided into fibrogenic and hematopoietic (245). TGF-β is considered to be a major fibrogenic cytokine (492, 493). The TGF-β family comprises several isoforms of TGF-β which can be generated by several cells including macrophages, epithelial cells, fibroblasts, and eosinophils (175, 492). In a normal lung, bronchial epithelium expresses TGF-β (493). PDGF can be produced by most inflammatory cell types of the airways inflammation and appears to be involved in tissue repair via the induction of migration and proliferation of connective tissue cells and proliferation of smooth muscle (494, 495). On the other hand, epidermal growth factor (EGF), which promotes healing by stimulating the proliferation and migration of epithelial cells and increasing the synthesis of proteins such as fibronectin (496), is not considered a fibrogenic cytokine per se (245) although it was found to have some fibrogenic properties (497). GM-CSF, an important hematopoietic growth factor involved in eosinophil and macrophage accumulation in tissues, is considered a nonfibrotic growth factor (245).

TGF-β expression was found to be increased in asthma in some (498) but not all studies (499, 500), and its compartmentalization is altered (501). TGF-β is even more highly expressed in chronic bronchitis (498). TGF-β was also found in increased concentrations in the BALF of asthmatics by comparison with control subjects and these levels increase further in response to allergen exposure (502). In asthma, bronchial eosinophils express increased levels of TGF-β (498, 503). The increased expression of TGF-β was significantly correlated with two markers of remodeling, the thickness of the reticular basement membrane and the number of fibroblasts both in asthma and chronic bronchitis (498). The expression of EGF is also increased in asthma and chronic bronchitis, but there is no correlation with fibrosis patterns. PDGF expression is not increased in the airways of asthmatics (500, 504, 505) although PDGF (506) mRNA transcripts are found in eosinophils in asthmatics patients. IGF-1 expression is not increased in the airways of asthmatics (500). These results in asthma may explain, in part, why the remodeling of the airways in asthma is a slow process whereas fibrotic diseases of the lung in which PDGF or IGF appear to be involved, may rapidly evolve toward severe fibrosis (507).

Clinical Consequences
Irreversible component of the airways obstruction. For decades, asthma has been considered as a condition of reversible airflow obstruction, and, in the majority of patients, complete reversibility of long-standing abnormal spirometric measurements, such as FEV₁ may be observed after bronchodilators and/or a course of corticosteroids. However, many asthmatic patients, both children and adults, have evidence of residual airflow obstruction (508–512) which may be detected in asymptomatic patients (513) and may be observed months after cessation of asthmatic symptoms in perfectly asymptomatic patients (508, 513, 514). Studies in which lung function changes have been examined have shown that the FEV₁ is decreased mainly in subjects with persistent asthma but objective measures of the small airways are usually not performed (513, 515, 516). It has been shown that peripheral lung resistance is increased in asymptomatic asthmatics with normal FEV₁ (517). However, this irreversible component of the airways obstruction is more prominent in severe patients (512) and persists in some patients even after a long-term treatment with inhaled corticosteroids (518). Asthmatic children or adults are heterogeneous with regard to the degree of reversibility of airflow limitation. A thorough study is difficult to compare, it appears that irreversible airways obstruction is usually associated with the frequency of wheezing and the ongoing presence of asthma (519, 520). Moreover, patients with severe asthma are those who more commonly develop an irreversible airflow obstruction (521).

During adult life, asthma is often associated with an increase in the rate of decline in FEV₁ (519, 522–526). However, symptoms may remain unchanged while lung function deteriorates (527). In middle-aged and elderly smokers it is difficult, in some patients, to separate chronic bronchitis and asthma by means of FEV₁ (528, 529) and responses to bronchodilators (530). Bronchial hyperresponsiveness appears to be constantly associated with an increase in the rate of decline of lung function (515, 524). A topy (531) and smoking are also associated with an increased decline of lung function (519, 531). However, the effect of asthma is variable and not all subjects with asthma have steep rates of decline. It appears that asthma starting after the age of 50 yr elicits a steeper rate of decline than asthma with an earlier onset (532). It has also been shown in some (526, 533) but not all studies (525) that nonallergic asthmatics have a steeper rate of decline of FEV₁. However, there is no prospective study showing that structural changes, pulmonary function parameters, and indices of inflammation are related longitudinally.

The prognostic implications of the incomplete reversibility, observed in some asthmatics, remain to be determined but chronic sequelae of asthma may lead to complications including severe symptomatology and work disability (534). Whether residual irreversible air flow limitation in individuals with asthma or a history of asthma could have been prevented either by early and aggressive pharmacologic treatment or by limitation of exposure to smoke or other noxious environmental agents is another question which needs more data to be fully answered (518, 535–538).

Loss of elastic recoil. In asthma, most studies of moderately severe asthmatic patients in the stable state have found some loss of the elastic recoil and lung elasticity (539–543). These abnormalities may be related to the combined effects of reduced elastic recoil per se and airways obstruction, but the inhalation of isoproterenol has been shown to decrease airways obstruction and is associated with a further decrease of elastic recoil (541). These findings favor an intrinsic abnormality.

Conclusions. Taken together, these studies indicate that many asthmatics have physiologic abnormalities even when they are asymptomatic and under symptomatic control with anti-inflammatory treatment (Figure 11). This may be due to persistent underlying bronchial inflammation and/or the degree of airway remodeling shown to be present in most patients even when they are asymptomatic.
The efficacy of anti-inflammatory treatment on the natural course of asthma is still debated as the longest prospective studies available do not exceed 5 yr. In childhood, lung growth and the effect of alveolar wall attachments to small airways suggest that the early use of anti-inflammatory treatment is favored. It seems that inhaled corticosteroids can reduce the accelerated decline of the pulmonary function or bronchial hyperresponsiveness both in children and adults (536, 537, 558–561) but the effects appear to be incomplete (518). However, there is no evidence that undertreatment of asthma would induce deterioration in the long term. Moreover, it is not known whether very long courses of treatment with inhaled steroids (for 20 to 30 yr) may induce bronchial and systemic side effects, especially when the treatment is started very early in life. These considerations emphasize the need to develop more specific and incisive treatment for the asthmatic condition.

CONCLUSIONS

Studies of airways in chronic asthmatics by bronchoscopic methods and induced sputum have provided much helpful and insightful data. Within the past 20 yr such studies have led to a better understanding of the mechanisms of inflammation and pathogenesis of asthma. Experiments such as the bronchial challenge with allergen provide valuable insights into the allergic inflammatory response but we still do not understand how this may influence or lead to a remodeling process. The recent availability of genetically altered animals lacking genes for selected cytokines and growth factors, so-called transgenic mice, and those whose genes have been enhanced, so-called transgenic overexpressor mice, may prove useful in the elucidation of the role of individual factors in the overall inflammatory cascade and the remodeling process.

Asthma involves acute mechanisms including bronchospasm and edema and the production of mucus which can be altered by the use of bronchodilators. However, in chronic airways inflammation, guidelines have highlighted the importance of anti-inflammatory treatment (Figure 12). Is remodeling of the airways a proven clinical concept? Is it clear that changes in the ECM have the capacity to influence airway function in asthma. However, it is not known how each of the

# Table 1

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<tr>
<th>Research Needs to Better Understand Remodeling in Asthma</th>
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<td>1. Need for a standardized consensus definition of airways remodeling that incorporates information from histology, morphometry, and immunohistochemistry using samples from intrinsic versus extrinsic asthmas as well as appropriate controls (including those with other lung diseases).</td>
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<td>2. To what extent is this remodeling process a normal response to an abnormal injury, or is the response itself abnormal?</td>
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<td>3. What perpetuates the remodeling process?</td>
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<td>4. Does the heterogeneity in time and extent reflect genetic variation or environmental factors?</td>
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<td>5. How early does remodeling begin?</td>
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<td>6. How does remodeling progress?</td>
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<td>7. Is remodeling reversible?</td>
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<td>8. Can the remodeling process be altered and do any of the current anti-inflammatory strategies make any difference to the long-term outcome?</td>
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<td>10. Can a useful and relevant marker (or markers) of remodeling be found?</td>
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many changes that occur in the airway wall contribute to altered airway function in asthma. In asthma, remodeling is almost always present in biopsies, as shown by collagen deposition on the reticular basement membrane, but is not always clinically demonstrated. Destruction and subsequent remodeling of the normal bronchial architecture are manifested by an accelerated decline in FEV1. This irreversible component of the airway obstruction is more prominent in severe patients and even persists after an aggressive anti-inflammatory treatment. There are other clinical consequences of remodeling. The increase in smooth muscle mass can lead to a severe bronchial obstruction during an asthma attack. Mucous glands are sometimes enlarged and may induce an excessive mucus production. The ongoing inflammation and subepithelial fibrosis are linked with the persistence of exacerbations and non-specific bronchial hyperresponsiveness. Degradation and/or reorganization of elastin and cartilage may result in decreased airway wall stiffness and increased airway narrowing for a given amount of force generated by the smooth muscle. Thus, the process of airway wall remodeling is still not understood and requires investigation into its mechanisms and the role of drugs in its reversal and prevention (Table 1).

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