severity and may even be found in atopic patients without asthma symptoms. This inflammation is usually reduced by treatment with ICS. There are also structural changes in the airways (described as remodeling). A characteristic finding is thickening of the basement membrane due to subepithelial collagen deposition. This feature is also found in patients with eosinophilic bronchitis presenting as cough who do not have asthma and is, therefore, likely to be a marker of eosinophilic inflammation in the airway as eosinophils release fibrogenic mediators. The epithelium is often shed or friable, with reduced attachments to the airway wall and increased numbers of epithelial cells in the lumen. The airway wall itself may be thickened and edematous, particularly in fatal asthma. Another common finding in fatal asthma is occlusion of the airway lumen by a mucous plug, which is comprised of mucous glycoproteins secreted from goblet cells and plasma proteins from leaky bronchial vessels (Fig. 309-1). There is also vasodilation and increased numbers of blood vessels (angiogenesis). Direct observation by bronchoscopy indicates that the airways may be narrowed, erythematous, and edematous. The pathology of asthma is remarkably uniform in different phenotypes of asthma, including atopic (extrinsic), nonatopic (intrinsic), occupational, aspirin-sensitive, and pediatric asthma. These pathologic changes are found in all airways, but do not extend to the lung parenchyma; peripheral airway inflammation is found particularly in patients with severe asthma. The involvement of airways may be patchy, and this is consistent with bronchographic findings of uneven narrowing of the airways.

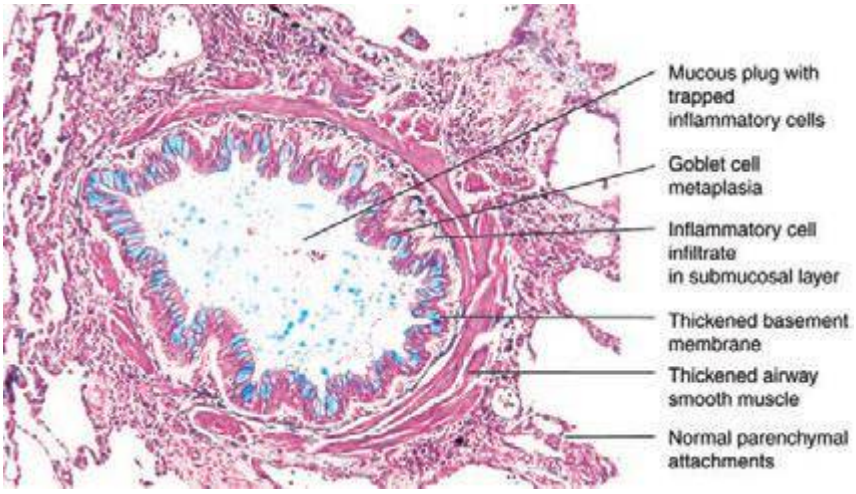

FIGURE 309-1 Histopathology of a small airway in fatal asthma. The lumen is occluded with a mucous plug, there is goblet cell metaplasia, and the airway wall is thickened, with an increase in basement membrane thickness and airway smooth muscle. *(Courtesy of Dr. J. Hogg, University of British Colombia.)*

Airway Inflammation There is inflammation in the respiratory mucosa from the trachea to terminal bronchioles, but with a predominance in the bronchi (cartilaginous airways); however, it is still uncertain as to how inflammatory cells interact and how inflammation translates into the symptoms of asthma (Fig. 309-2). There is good evidence that the specific pattern of airway inflammation in asthma is associated with airway hyperresponsiveness (AHR), the physiologic abnormality of asthma, which is correlated with variable airflow obstruction. The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis. However, an indistinguishable pattern of inflammation is found in intrinsic asthma, and this may reflect local rather than systemic IgE production. Although most attention has focused on the acute inflammatory changes seen in asthma, this is a chronic condition, with inflammation persisting over many years in most patients. The mechanisms involved in persistence of inflammation in asthma are still poorly understood. Superimposed on this chronic inflammatory state are acute inflammatory episodes, which correspond to exacerbations of asthma. Although the common pattern of inflammation in asthma is characterized by eosinophil infiltration, some patients with severe asthma show a neutrophilic pattern of inflammation that is less sensitive to corticosteroids. However, many inflammatory cells are involved in asthma with no key cell that is predominant (Fig. 309-3).

MAST CELLS Mast cells are important in initiating the acute bronchoconstrictor responses to allergens and several other indirectly acting stimuli, such as exercise and hyperventilation (via osmolality changes), as well as fog. Activated mucosal mast cells are found at the airway surface in asthma patients and also in the airway smooth-muscle layer, whereas this is not seen in normal subjects or patients with eosinophilic bronchitis. Mast cells are activated by allergens through an IgE-dependent mechanism, and binding of specific IgE to mast cells renders them more sensitive to activation by physical stimuli such as osmolality. The importance of IgE in the pathophysiology of asthma has been highlighted by clinical studies with humanized anti-IgE antibodies, which inhibit IgE-mediated effects, reduce asthma symptoms, and reduce exacerbations. There are, however, uncertainties about the role of mast cells in more chronic allergic inflammatory events. Mast cells release several bronchoconstrictor mediators, including histamine, prostaglandin D_2, and cysteinyl-leukotrienes, but also several cytokines, chemokines, growth factors, and neurotrophins.

MACROPHAGES AND DENDRITIC CELLS Macrophages, which are derived from blood monocytes, may traffic into the airways in asthma and may be activated by allergens via low-affinity IgE receptors ($Fc_{\varepsilon}RII$). Macrophages have the capacity to initiate a type of inflammatory response via the release of a certain pattern of cytokines, but these cells also release anti-inflammatory mediators (e.g., IL-10), and thus, their roles in asthma are uncertain. Dendritic cells are specialized macrophage-like cells in the airway epithelium, which are the major antigen-presenting cells. Dendritic cells take up allergens, process them to peptides, and migrate to local lymph nodes where they present the allergenic peptides to uncommitted T lymphocytes to program the production of allergen-specific T cells. Immature dendritic cells in the respiratory tract promote T_H2 cell differentiation and require cytokines, such as IL-12 and tumor necrosis factor α (TNF-α), to promote the normally preponderant T_H1 response. The cytokine thymic stromal lymphopoietin (TSLP) released from epithelial cells in asthmatic patients instructs dendritic cells to release chemokines that attract T_H2 cells into the airways.

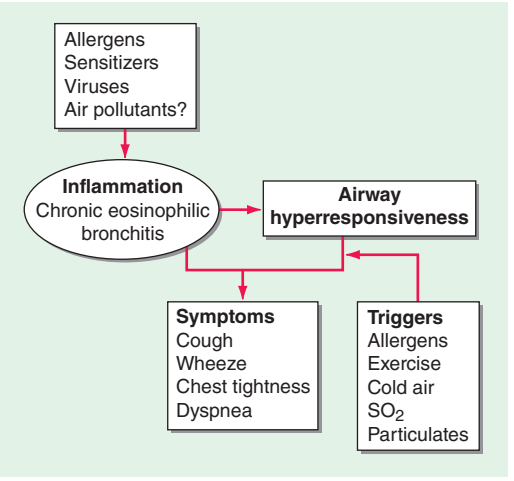

FIGURE 309-2 Inflammation in the airways of asthmatic patients leads to airway hyperresponsiveness and symptoms. So_2, sulfur dioxide.