Drug-Induced Asthma. Several pharmacologic agents provoke asthma. *Aspirin-sensitive asthma* is an uncommon type, occurring in individuals with recurrent rhinitis and nasal polyps. These individuals are exquisitely sensitive to small doses of aspirin as well as other nonsteroidal anti-inflammatory medications, and they experience not only asthmatic attacks but also urticaria. Aspirin (and other non-steroidal anti-inflammatory drugs) triggers asthma in these patients by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism, leading to a rapid decrease in prostaglandin E_2. Normally prostaglandin E_2 inhibits enzymes that generate proinflammatory mediators such as leukotrienes B_4, C_4, D_4 and E_4, which are believed to have central roles in aspirin-induced asthma.

Occupational Asthma. This form of asthma may be triggered by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), or other chemicals (formaldehyde, penicillin products). Only minute quantities of chemicals are required to induce the attack, which usually occurs after repeated exposure. The underlying mechanisms vary according to stimulus and include type I reactions, direct liberation of bronchoconstrictor substances, and hypersensitivity responses of unknown origin.

Pathogenesis. **Atopic asthma is caused by a T_H2 and IgE response to environmental allergens in genetically predisposed individuals.** Airway inflammation is central to disease pathophysiology and causes airway dysfunction partly through the release of potent inflammatory mediators and partly through remodeling of the airway wall. As the disease becomes more severe, there is increased local secretion of growth factors, which induce mucus gland hypertrophy, smooth muscle proliferation, angiogenesis, fibrosis and nerve proliferation. Varying combinations of these processes help explain the different asthma subtypes, their response to treatment and their natural history over a person's lifetime.

The contributions of the immune response, genetics and environment are discussed separately below, although they are closely intertwined.

T_H2 Responses, IgE and Inflammation. **A fundamental abnormality in asthma is an exaggerated T_H2 response to normally harmless environmental antigens** (Fig 15-10). T_H2 cells secrete cytokines that promote inflammation and stimulate B cells to produce IgE and other antibodies. These cytokines include IL-4, which stimulates the production of IgE; IL-5, which activates locally recruited eosinophils; and IL-13, which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells. The T cells and epithelial cells secrete chemokines that recruit more T cells and eosinophils, thus exacerbating the reaction. As in other allergic reactions (Chapter 6), IgE binds to the Fc receptors on submucosal mast cells, and repeat exposure to the allergen triggers the mast cells to release granule contents and produce cytokines and other mediators, which collectively induce the *early-phase (immediate hypersensitivity) reaction* and the *late-phase reaction*.

The early reaction is dominated by bronchoconstriction, increased mucus production, variable degrees of vasodilation, and increased vascular permeability. Bronchoconstriction is triggered by direct stimulation of subepithelial vagal (parasympathetic) receptors through both central and local reflexes triggered by mediators produced by mast cells and other cells in the reaction. The late-phase reaction is dominated by recruitment of leukocytes, notably eosinophils, neutrophils, and more T cells. Although T_H2 cells are the dominant T cell type involved in the disease, other T cells that contribute to the inflammation include T_H17 (IL-17 producing) cells, which recruit neutrophils.

Many mediators produced by leukocytes and epithelial cells have been implicated in the asthmatic response. The long list of "suspects" in acute asthma can be ranked based on the clinical efficacy of pharmacologic intervention with antagonists of specific mediators.

- Mediators whose role in bronchospasm is clearly supported by efficacy of pharmacologic intervention are: (1) *leukotrienes C_4, D_4,* and *E_4*, which cause prolonged bronchoconstriction as well as increased vascular permeability and increased mucus secretion, and (2) *acetylcholine*, released from intrapulmonary parasympathetic nerves, which can cause airway smooth muscle constriction by directly stimulating muscarinic receptors.
- A second group includes agents present at the "scene of the crime" but whose actual role in acute allergic asthma seems relatively minor on the basis of lack of efficacy of potent antagonists or synthesis inhibitors: (1) *histamine*, a potent bronchoconstrictor; (2) *prostaglandin D_2*, which elicits bronchoconstriction and vasodilatation; and (3) *platelet-activating factor*, which causes aggregation of platelets and release of serotonin from their granules. These mediators might yet prove important in certain types of chronic or nonallergic asthma.
- Finally, a large third group comprises the "suspects" for whom specific antagonists or inhibitors are not available or have been insufficiently studied as yet. Several promising focused therapies for asthma that target the IL-13/IL-4 signal transduction pathways are in development, including anti-IL-13 monoclonal antibodies and IL-4 receptor antagonists. Other targets include IL-1, TNF, IL-6, chemokines (e.g., eotaxin, also known as CCL11), neuropeptides, nitric oxide, bradykinin, and endothelins.

It is thus clear that multiple mediators contribute to the acute asthmatic response. Moreover, the composition of this "mediator soup" might vary among individuals or different types of asthma. The appreciation of the importance of inflammatory cells and mediators in asthma has led to greater emphasis on anti-inflammatory drugs, such as corticosteroids, in its treatment.

Genetic Susceptibility. **Susceptibility to atopic asthma is multigenic and often associated with increased incidence of other allergic disorders, such as allergic rhinitis (hay fever) and eczema.** The genetic polymorphisms linked to asthma and other allergic disorders were described in Chapter 6. Suffice it to say here that many of these are likely to influence immune responses and the subsequent inflammatory reaction. Some of the stronger or more interesting associations include the following: