immediate reactions characterized by edema, mucus secretion, and smooth muscle spasm; others, exemplified by cytokines, including chemokines, set the stage for the late-phase response by recruiting additional leukocytes. Not only do these inflammatory cells release additional waves of mediators (including cytokines), but they also cause epithelial cell damage. Epithelial cells themselves are not passive bystanders in this reaction; they can also produce soluble mediators, such as chemokines.

Late-Phase Reaction

In the late-phase reaction, leukocytes are recruited that amplify and sustain the inflammatory response without additional exposure to the triggering antigen. *Eosinophils* are often an abundant leukocyte population in these reactions (Fig. 6-13C). They are recruited to sites of immediate hypersensitivity by chemokines, such as eotaxin, and others that may be produced by epithelial cells, T_H2 cells, and mast cells. The T_H2 cytokine IL-5 is the most potent eosinophil-activating cytokine known. Upon activation, eosinophils liberate proteolytic enzymes as well as two unique proteins called major basic protein and eosinophil cationic protein, which damage tissues. It is now believed that the late-phase reaction is a major cause of symptoms in some type I hypersensitivity disorders, such as allergic asthma. Therefore, treatment of these diseases requires the use of broad-spectrum antiinflammatory drugs, such as steroids, rather than anti-histamine drugs, which are of benefit in the immediate reaction as occurs in allergic rhinitis (hay fever).

Development of Allergies

Susceptibility to immediate hypersensitivity reactions is genetically determined. An increased propensity to develop immediate hypersensitivity reactions is called *atopy*. Atopic individuals tend to have higher serum IgE levels and more IL-4–producing T_H2 cells than does the general population. A positive family history of allergy is found in 50% of atopic individuals. The basis of familial predisposition is not clear, but studies in patients with asthma reveal linkage to polymorphisms in several genes. Some of these genes are located in the chromosome 5q31 region; these include genes encoding the cytokines IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF. This locus has attracted great attention because of the known roles of many of these cytokines in the allergic reaction, but how the disease-associated polymorphisms influence the development of allergies is not known. Linkage has also been noted to 6p, close to the HLA complex, suggesting that the inheritance of certain HLA alleles permits reactivity to certain allergens.

Environmental factors are also important in the development of allergic diseases. Exposure to environmental pollutants, which is common in industrialized societies, is an important predisposing factor for allergy. In fact, it is known that dogs and cats diverged from humans about 95 million years ago and chimpanzees only about 4-5 million years ago, suggesting that chimps share more genes with us than do dogs and cats. Nevertheless, dogs and cats, who live in the same environment as humans, develop allergies and chimps do not. This simple observation suggests that environmental factors may be more important in the development of allergic disease than genetics. Viral infections of the airways are important triggers for bronchial asthma, an allergic disease affecting the lungs (Chapter 15). Bacterial skin infections are strongly associated with atopic dermatitis.

It is estimated that 20% to 30% of immediate hypersensitivity reactions are triggered by non-antigenic stimuli such as temperature extremes and exercise, and do not involve T_H2 cells or IgE; such reactions are sometimes called *nonatopic allergy*. It is believed that in these cases mast cells are abnormally sensitive to activation by various nonimmune stimuli.

The incidence of many allergic diseases is increasing in developed countries, and seems to be related to a decrease in infections during early life. These observations have led to an idea, sometimes called the *hygiene hypothesis*, that early childhood and even prenatal exposure to microbial antigens educates the immune system in such a way that subsequent pathologic responses against common environmental allergens are prevented. Thus, too much hygiene in childhood may increase allergies later in life. This hypothesis, however, is difficult to prove, and the underlying mechanisms are not defined.

With this consideration of the basic mechanisms of type I hypersensitivity, we turn to some clinically important examples of IgE-mediated disease. These reactions can lead to a wide spectrum of injury and clinical manifestations (Table 6-2).

Systemic Anaphylaxis

Systemic anaphylaxis is characterized by vascular shock, widespread edema, and difficulty in breathing. It may occur in sensitized individuals in hospital settings after administration of foreign proteins (e.g., antisera), hormones, enzymes, polysaccharides, and drugs (e.g., the antibiotic penicillin), or in the community setting following exposure to food allergens (e.g., peanuts, shellfish) or insect toxins (e.g., those in bee venom). Extremely small doses of antigen may trigger anaphylaxis, for example, the tiny amounts used in skin testing for various forms of allergies. Because of the risk of severe allergic reactions to minute quantities of peanuts, U.S. agencies are considering a ban on peanut snacks served in the confined quarters of commercial airplanes. Within minutes after exposure, itching, hives, and skin erythema appear, followed shortly thereafter by a striking contraction of respiratory bronchioles and respiratory distress. Laryngeal edema results in hoarseness and further compromises breathing. Vomiting, abdominal

Table 6-2 Examples of Disorders Caused by Immediate Hypersensitivity

Clinical Syndrome	Clinical and Pathologic Manifestations
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) cause by vascular dilation; airway obstruction due to laryngeal edema
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury caused by late-phase reaction
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles