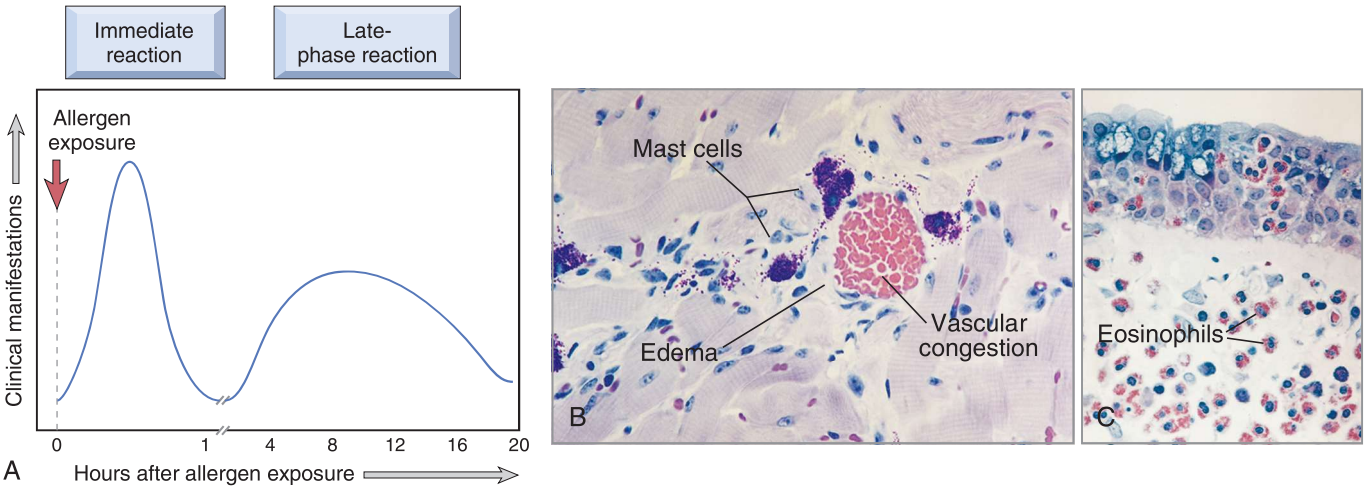

Figure 6.13 Phases of immediate hypersensitivity reactions. (A) Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops 2 to 24 hours later. The immediate reaction (B) is characterized by vasodilation, congestion, and edema, and the late-phase reaction (C) is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Courtesy Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

that act on vessels and smooth muscle and proinflammatory cytokines that recruit inflammatory cells.

- In *antibody-mediated disorders (type II hypersensitivity)*, secreted IgG and IgM antibodies injure cells by promoting their phagocytosis or lysis and injure tissues by inducing inflammation. Antibodies may also interfere with cellular functions and cause disease without tissue injury.
- In *immune complex–mediated disorders (type III hypersensitivity)*, IgG and IgM antibodies bind antigens usually in the circulation, and the antigen-antibody complexes deposit in tissues and induce inflammation. The leukocytes that are recruited (neutrophils and monocytes) produce tissue damage by release of lysosomal enzymes and generation of toxic free radicals.
- In *cell-mediated immune disorders (type IV hypersensitivity)*, T lymphocytes (Th1 and Th17 cells and CD8+ CTLs) are the cause of the tissue injury.

Immediate (Type I) Hypersensitivity

Immediate, or type I, hypersensitivity is a rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells. These reactions are often called *allergy*, and the antigens that elicit them are allergens. Immediate hypersensitivity may occur as a systemic disorder or as a local reaction. The systemic reaction most often follows injection of an antigen into a sensitized individual (e.g., by a bee sting), but can also follow antigen ingestion (e.g., peanut allergens). Sometimes, within minutes the patient goes into a state of shock, which may be fatal. Local reactions are diverse and vary depending on the portal of entry of the allergen. They may take the form of localized cutaneous rash or blisters (skin allergy, hives), nasal and conjunctival discharge (allergic rhinitis and conjunctivitis), hay fever, bronchial asthma, or allergic gastroenteritis (food allergy).

Many local type I hypersensitivity reactions have two well-defined phases (Fig. 6.13). The immediate reaction is characterized by vasodilation, vascular leakage, and, depending on the tissue, smooth muscle spasm or glandular secretions. These changes usually become evident within minutes after exposure to an allergen and tend to subside in a few hours. In many instances (e.g., allergic rhinitis and bronchial asthma), a second, late-phase reaction sets in 2 to 24 hours later without additional exposure to antigen and may last for several days. This late-phase reaction is characterized by infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells, as well as tissue destruction, typically in the form of mucosal epithelial cell damage.

Most immediate hypersensitivity disorders are caused by excessive Th2 responses, and these cells play a central role by stimulating IgE production and promoting inflammation. These Th2-mediated disorders show a characteristic sequence of events (Fig. 6.14), described next.

Activation of Th2 Cells and Production of IgE Antibody

The first step in the generation of Th2 cells is the presentation of the antigen to naïve CD4+ helper T cells, probably by DCs that capture the antigen from its site of entry. For reasons that are still not understood, only some environmental antigens elicit strong Th2 responses and thus serve as allergens. In response to antigen and other stimuli, including cytokines such as IL-4 produced at the local site, the T cells differentiate into Th2 cells. The newly minted Th2 cells produce a number of cytokines on subsequent encounter with the antigen; as mentioned earlier, the signature cytokines of this subset are IL-4, IL-5, and IL-13. IL-4 acts on B cells to stimulate class switching to IgE and promotes the development of additional Th2 cells. IL-5 is involved in the development and activation of eosinophils, which are important effectors of type I hypersensitivity (discussed later). IL-13 enhances IgE production and acts on epithelial cells to stimulate mucus secretion. In addition, Th2 cells (as well as mast cells and epithelial cells) produce chemokines that attract more Th2 cells, as well as other leukocytes, to the reaction site. Patients with chronic atopic diseases such as

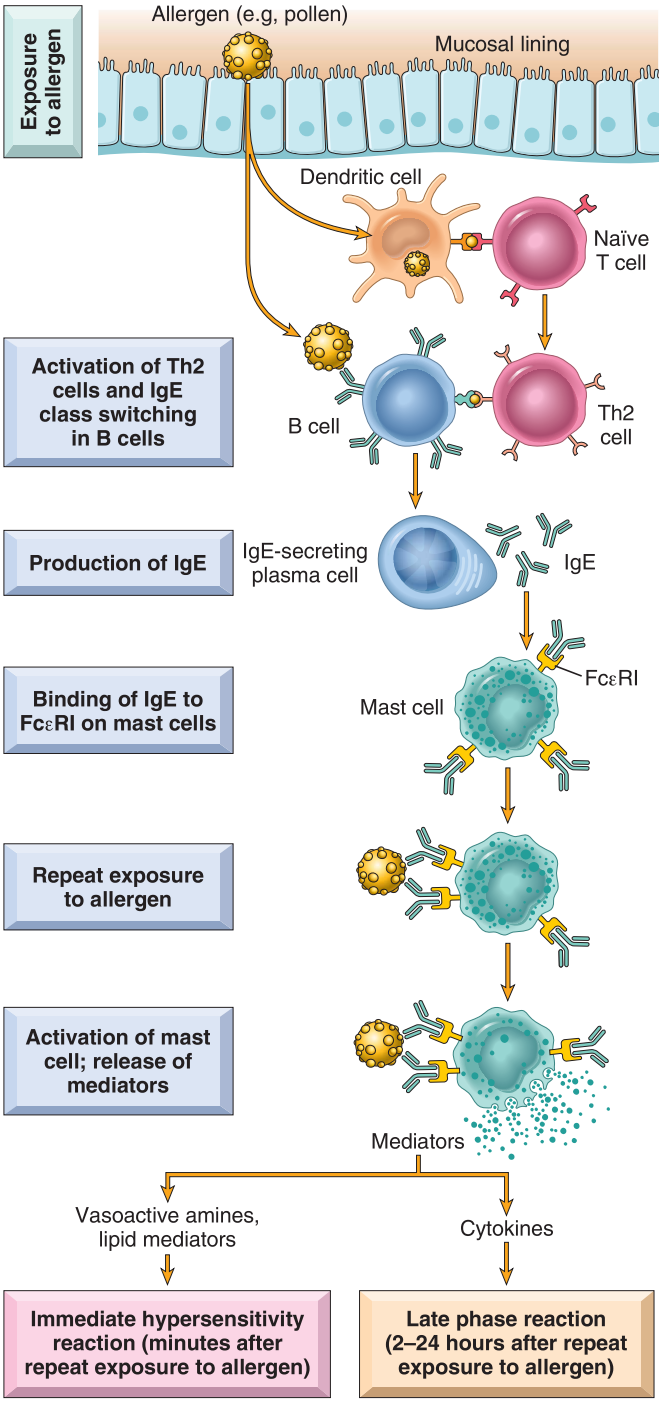

Figure 6.14 Sequence of events in immediate (type I) hypersensitivity. Immediate hypersensitivity reactions are initiated by the introduction of an allergen, which stimulates Th2 responses and IgE production in genetically susceptible individuals. IgE binds to Fc receptors (FcεRI) on mast cells, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic manifestations of immediate hypersensitivity.

asthma and atopic dermatitis are sometimes classified into Th2-high and Th2-low based on biomarkers that reflect the intensity of the pathologic T-cell response in individual patients. This separation may serve as a guide to therapy, as antagonists of Th2 cytokines (IL-4, IL-5) are predictably most effective in the Th2-high group.

Before Th2 responses develop, type 2 ILCs in tissues may respond to cytokines produced by damaged epithelia. These ILCs secrete IL-5 and IL-13 and are thus able to induce the same tissue reactions as the classical Th2 cells. Over time, the Th2 cells become the dominant contributors to the local cytokine response.

Sensitization and Activation of Mast Cells

Because mast cells are central to the development of immediate hypersensitivity, we first review some of their salient characteristics. Mast cells are bone marrow–derived cells that are widely distributed in the tissues. They are abundant near small blood vessels and nerves and in subepithelial tissues, which explains why local immediate hypersensitivity reactions often occur at these sites. Mast cells have cytoplasmic membrane-bound granules that contain a variety of biologically active mediators, described later. The granules also contain acidic proteoglycans that bind basic dyes such as toluidine blue. (*Mast* in German refers to fattening of animals, and the name of these cells came from the erroneous belief that their granules fed the tissue where the cells were located.) As detailed next, mast cells (and their circulating counterpart, basophils) are activated by the cross-linking of high-affinity IgE Fc receptors; in addition, mast cells may also be triggered by several other stimuli, such as complement components C5a and C3a (called anaphylatoxins because they elicit reactions that mimic anaphylaxis), both of which act by binding to receptors on the mast cell membrane. Other mast cell secretagogues include some chemokines (e.g., IL-8), drugs such as codeine and morphine, adenosine, melittin (present in bee venom), and physical stimuli (e.g., heat, cold, sunlight). Basophils are similar to mast cells in many respects, including the presence of cell surface IgE Fc receptors as well as cytoplasmic granules. In contrast to mast cells, however, basophils are not normally present in tissues but rather circulate in the blood in small numbers. Similar to other granulocytes, basophils can be recruited to inflammatory sites.

When a mast cell armed with IgE antibodies previously produced in response to an antigen is exposed to the same antigen, the cell is activated, leading to the release of an arsenal of powerful mediators that are responsible for immediate hypersensitivity reactions. Mast cells and basophils express a high-affinity receptor called FcεRI that is specific for the Fc portion of IgE and avidly binds IgE antibodies. IgE-coated mast cells are said to be sensitized because they are activated by subsequent encounters with antigen. In the first step of activation, the antigen binds to the IgE antibodies on the mast cell surface. Multivalent antigens bind to and cross-link adjacent IgE antibodies, bringing the underlying Fcε receptors together. This triggers signal transduction pathways from the cytoplasmic portion of the receptors that lead to the release of preformed mediators and de novo production of mediators that are responsible for the initial, sometimes explosive, symptoms of immediate hypersensitivity, and they also set into motion the events that lead to the late-phase reaction.

Mediators of Immediate Hypersensitivity

Mast cell activation leads to degranulation, with the discharge of preformed mediators that are stored in the granules, and

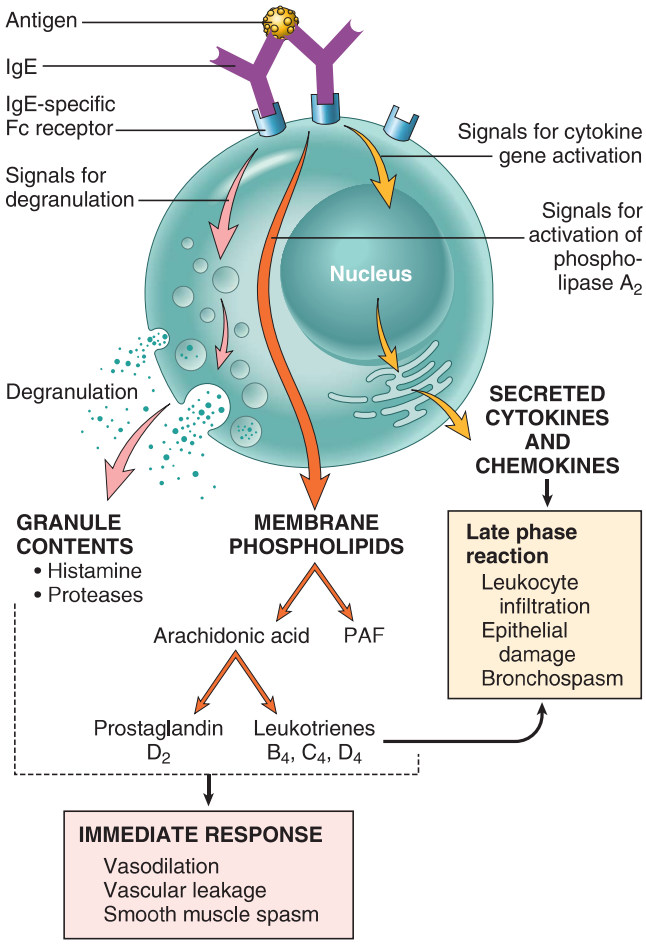

Figure 6.15 Mast cell mediators. On activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. *PAF,* Platelet-activating factor.

de novo synthesis and release of additional mediators including lipid products and cytokines (Fig. 6.15).

Granule contents. Mediators contained within mast cell granules are the first to be released and can be divided into three categories:

- *Vasoactive amines.* The most important mast cell–derived amine is *histamine* (Chapter 3). Histamine causes intense smooth muscle contraction, increases vascular permeability, and stimulates mucus secretion by nasal, bronchial, and gastric glands.
- *Enzymes.* These are contained in the granule matrix and include neutral proteases (chymase, tryptase) and several acid hydrolases. The enzymes cause tissue damage and lead to the generation of kinins and activated components of complement (e.g., C3a) by acting on their precursor proteins.
- *Proteoglycans.* These include heparin, a well-known anticoagulant, and chondroitin sulfate. The proteoglycans serve to package and store the amines in the granules.

Lipid mediators. The major lipid mediators are arachidonic acid–derived products (Chapter 3). Mast cell activation is associated with activation of phospholipase A_2, an enzyme that converts membrane phospholipids to arachidonic acid. This is the parent compound from which leukotrienes and prostaglandins are produced by the 5-lipoxygenase and the cyclooxygenase pathways, respectively.

- *Leukotrienes.* Leukotrienes C_4 and D_4 are the most potent vasoactive and spasmogenic agents known. On a molar basis, they are several thousand times more active than histamine in increasing vascular permeability and causing bronchial smooth muscle contraction. Leukotriene B_4 is highly chemotactic for neutrophils, eosinophils, and monocytes.
- *Prostaglandin D_2.* This is the most abundant mediator produced in mast cells by the cyclooxygenase pathway. It causes intense bronchospasm and increases mucus secretion.
- *Platelet-activating factor (PAF).* PAF (Chapter 3) is a lipid mediator produced by some mast cell populations that is not derived from arachidonic acid. It causes platelet aggregation, histamine release, bronchospasm, increased vascular permeability, and vasodilation. Its role in immediate hypersensitivity reactions is not well established.

Cytokines. Mast cells are sources of many cytokines, which may play an important role at several stages of immediate hypersensitivity reactions. The cytokines include: TNF, IL-1, and chemokines, which promote leukocyte recruitment (typical of the late-phase reaction); IL-4, which amplifies the Th2 response; and numerous others. The inflammatory cells that are recruited by mast cell–derived TNF and chemokines are additional sources of cytokines.

The mediators produced by mast cells are responsible for most of the manifestations of immediate hypersensitivity reactions. Some, such as histamine and leukotrienes, are released rapidly from sensitized mast cells and trigger the intense 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 (see 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, Th2 cells, and mast cells. The Th2 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. Eosniophils contain crystals called Charcot-Leyden crystals composed of the protein galectin-10, which are sometimes released into the extracellular space and can be detected in the sputum of patients with asthma. These crystals promote inflammation and enhance Th2 responses, so they may contribute to allergic reactions. 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