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 T_H2 responses and these cells play a central role by stimulating IgE production and promoting inflammation. These T_H2-mediated disorders show a characteristic sequence of events (Fig. 6-14), described next.

Activation of T_H2 Cells and Production of IgE Antibody

The first step in the generation of T_H2 cells is the presentation of the antigen to naive CD4+ helper T cells, probably by dendritic cells that capture the antigen from its site of entry. For reasons that are still not understood, only some environmental antigens elicit strong T_H2 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 T_H2 cells. The newly minted T_H2 cells produce a number of cytokines upon 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 T_H2 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, T_H2 cells (as well as mast cells and epithelial cells) produce chemokines that attract more T_H2 cells, as well as other leukocytes, to the reaction site.

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 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 is 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 extremely small numbers. Similar to other granulocytes, basophils can be recruited to inflammatory sites.

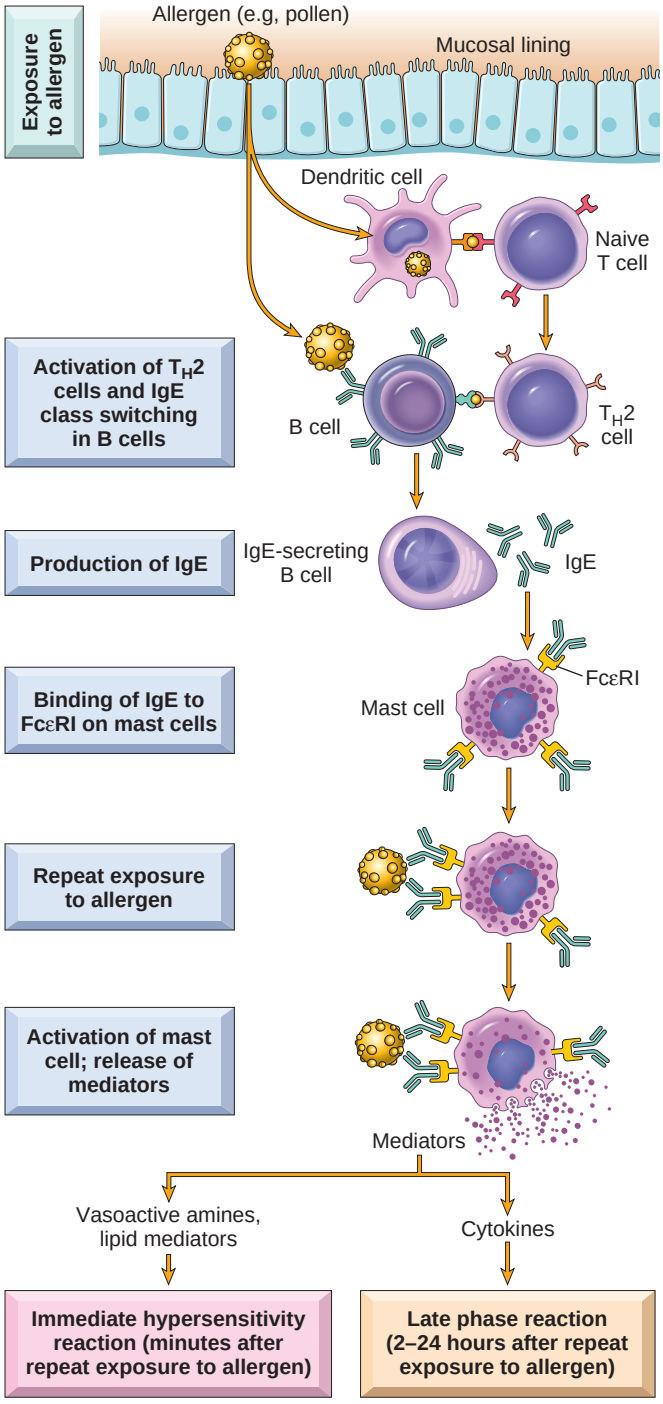

Figure 6-14 Sequence of events in immediate (type I) hypersensitivity. Immediate hypersensitivity reactions are initiated by the introduction of an allergen, which stimulates T_H2 responses and IgE production in genetically susceptible individuals. IgE binds to Fc receptors (FcεRI) on mast cells, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic manifestations of immediate hypersensitivity. See text for abbreviations.