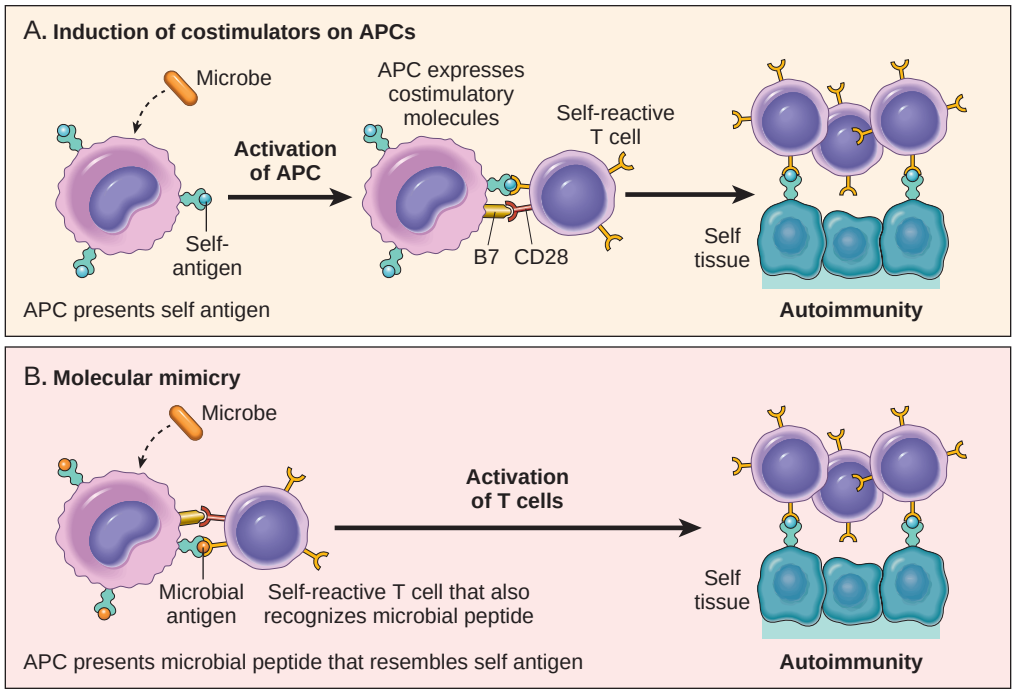

Figure 6-23 Postulated role of infections in autoimmunity. Infections may promote activation of self-reactive lymphocytes by inducing the expression of costimulators **(A),** or microbial antigens may mimic self antigens and activate self-reactive lymphocytes as a cross-reaction **(B).**

KEY CONCEPTS

Immunologic Tolerance and Autoimmunity

- Tolerance (unresponsiveness) to self antigens is a fundamental property of the immune system, and breakdown of tolerance is the basis of autoimmune diseases.
- Central tolerance: immature lymphocytes that recognize self antigens in the central (generative) lymphoid organs are killed by apoptosis; in the B-cell lineage, some of the self-reactive lymphocytes switch to new antigen receptors that are not self-reactive.
- Peripheral tolerance: mature lymphocytes that recognize self antigens in peripheral tissues become functionally inactive (anergic), or are suppressed by regulatory T lymphocytes, or die by apoptosis.
- The factors that lead to a failure of self-tolerance and the development of autoimmunity include (1) inheritance of susceptibility genes that may disrupt different tolerance pathways, and (2) infections and tissue injury that may expose self antigens and activate APCs and lymphocytes in the tissues.
- Autoimmune diseases are usually chronic and progressive, and the type of tissue injury is determined by the nature of the dominant immune response.

General Features of Autoimmune Diseases

Diseases caused by autoimmunity have some important general features.

- **Autoimmune diseases tend to be chronic, sometimes with relapses and remissions, and the damage is often progressive.** One reason for the chronicity is that the immune system contains many intrinsic amplification loops that allow small numbers of antigen-specific lymphocytes to accomplish their task of eradicating complex infections. When the response is inappropriately directed against self tissues, the same amplification mechanisms exacerbate and prolong the injury. Another reason for the persistence and progression of autoimmune disease is the phenomenon of *epitope spreading*, in which an immune response against one self antigen causes tissue damage, releasing other antigens, and resulting in the activation of lymphocytes by these newly encountered epitopes.
- **The clinical and pathologic manifestations of an autoimmune disease are determined by the nature of the underlying immune response.** Some of these diseases are caused by autoantibodies, whose formation may be associated with dysregulated germinal center reactions. Most chronic inflammatory diseases are caused by abnormal and excessive T_H1 and T_H17 responses; examples of these diseases include psoriasis, multiple sclerosis, and some types of inflammatory bowel disease. CD8+ CTLs contribute to killing of cells, such as islet β cells in type 1 diabetes. In some autoimmune diseases, such as rheumatoid arthritis, both antibodies and T cell–mediated inflammation may be involved.

With this background we can proceed to a discussion of specific autoimmune diseases. Table 6-6 lists both systemic and organ-specific autoimmune disorders. The systemic diseases tend to involve blood vessels and connective tissues, and therefore, they are often called *collagen vascular diseases* or *connective tissue diseases*. Our focus here is on selected systemic autoimmune diseases; organ-specific disorders are covered elsewhere in the book.