blood is filtered at high pressure to form other fluids, like urine and synovial fluid, are sites where immune complexes become concentrated and tend to deposit; hence, immune complex disease often affects glomeruli and joints.

3. **Inflammation and tissue injury.** Once immune complexes are deposited in the tissues, they initiate an acute inflammatory reaction. During this phase (approximately 10 days after antigen administration), clinical features such as fever, urticaria, joint pains (arthralgias), lymph node enlargement, and proteinuria appear. Wherever complexes deposit the tissue damage is similar. The mechanisms of inflammation and injury were discussed above, in the discussion of antibody-mediated injury. The resultant inflammatory lesion is termed *vasculitis* if it occurs in blood vessels, *glomerulonephritis* if it occurs in renal glomeruli, *arthritis* if it occurs in the joints, and so on.

It is clear that complement-fixing antibodies (i.e., IgG and IgM) and antibodies that bind to leukocyte Fc receptors (some subclasses of IgG) induce the pathologic lesions of immune complex disorders. The important role of complement in the pathogenesis of the tissue injury is supported by the observations that complement proteins can be detected at the site of injury and, during the active phase of the disease, consumption of complement leads to a decrease in serum levels of C3. In fact, serum C3 levels can, in some cases, be used to monitor disease activity.

MORPHOLOGY

The principal morphologic manifestation of immune complex injury is acute vasculitis, associated with necrosis of the vessel wall and intense neutrophilic infiltration. The necrotic tissue and deposits of immune complexes, complement, and plasma protein appear as a smudgy eosinophilic area of tissue destruction, an appearance termed **fibrinoid necrosis** (see Fig. 2-15). When deposited in the kidney, the complexes can be seen on immunofluorescence microscopy as granular lumpy deposits of immunoglobulin and complement and on electron microscopy as electron-dense deposits along the glomerular basement membrane (see Figs. 6-31 and 6-32).

If the disease results from a single large exposure to antigen, such as *acute serum sickness*, the lesions tend to resolve as a result of catabolism of the immune complexes. A form of *chronic serum sickness* results from repeated or prolonged exposure to an antigen. This occurs in several diseases, such as systemic lupus erythematosus (SLE), which is associated with persistent antibody responses to autoantigens. In many diseases, the morphologic changes and other findings suggest immune complex deposition but the inciting antigens are unknown. Included in this category are membranous glomerulonephritis and several vasculitides.

Local Immune Complex Disease (Arthus Reaction)

The *Arthus reaction* is a localized area of tissue necrosis resulting from acute immune complex vasculitis, usually elicited in the skin. The reaction can be produced experimentally by intracutaneous injection of antigen in a previously immunized animal that contains circulating antibodies against the antigen. As the antigen diffuses into the vascular wall, it binds the preformed antibody, and large immune complexes are formed locally. These complexes precipitate in the vessel walls and cause fibrinoid necrosis, and superimposed thrombosis worsens the ischemic injury.

KEY CONCEPTS

Pathogenesis of Diseases Caused by Antibodies and Immune Complexes

- Antibodies can coat (opsonize) cells, with or without complement proteins, and target these cells for phagocytosis by phagocytes (macrophages), which express receptors for the Fc tails of IgG and for complement proteins. The result is depletion of the opsonized cells.
- Antibodies and immune complexes may deposit in tissues or blood vessels, and elicit an acute inflammatory reaction by activating complement, with release of breakdown products, or by engaging Fc receptors of leukocytes. The inflammatory reaction causes tissue injury.
- Antibodies can bind to cell surface receptors or other essential molecules and cause functional derangements (either inhibition or unregulated activation) without cell injury.

T Cell–Mediated (Type IV) Hypersensitivity

The cell-mediated type of hypersensitivity is caused by inflammation resulting from cytokines produced by CD4+ T cells and cell killing by CD8+ T cells (Fig. 6-18). CD4+ T cell–mediated hypersensitivity induced by environmental and self antigens is the cause of many chronic inflammatory diseases, including autoimmune diseases (Table 6-5). CD8+ cells may also be involved in some of these autoimmune diseases and may be the dominant effector cells in certain reactions, especially those that follow viral infections.

CD4+ T Cell–Mediated Inflammation

In CD4+ T cell–mediated hypersensitivity reactions, cytokines produced by the T cells induce inflammation that may be chronic and destructive. The prototype of T cell–mediated inflammation is *delayed-type hypersensitivity (DTH)*, a tissue reaction to antigens given to immune individuals. In this reaction, an antigen administered into the skin of a previously immunized individual results in a detectable cutaneous reaction within 24 to 48 hours (hence the term *delayed*, in contrast to immediate hypersensitivity). Both T_H1 and T_H17 cells contribute to organ-specific diseases in which inflammation is a prominent aspect of the pathology. The inflammatory reaction associated with T_H1 cells is dominated by activated macrophages, and that triggered by T_H17 cells has a greater neutrophil component.

The inflammatory reactions stimulated by CD4+ T cells can be divided into sequential stages.

Activation of CD4+ T Cells. As described earlier, naive CD4+ T cells recognize peptides displayed by dendritic cells and secrete IL-2, which functions as an autocrine growth factor to stimulate proliferation of the antigen-responsive T cells. The subsequent differentiation of