of humans. In these reactions, the drug (often a reactive chemical) alters self proteins, including MHC molecules, and the "neoantigens" are recognized as foreign by T cells, leading to cytokine production and inflammation. These often manifest as skin rashes.

CD4+ T cell–mediated inflammation is the basis of tissue injury in many organ-specific and systemic autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, as well as diseases probably caused by uncontrolled reactions to bacterial commensals, such as inflammatory bowel disease (Table 6-5).

CD8+ T Cell–Mediated Cytotoxicity

In this type of T cell–mediated reaction, CD8+ CTLs kill antigen-expressing target cells. Tissue destruction by CTLs may be an important component of some T cell–mediated diseases, such as type 1 diabetes. CTLs directed against cell surface histocompatibility antigens play an important role in graft rejection, to be discussed later. They also play a role in reactions against viruses. In a virus-infected cell, viral peptides are displayed by class I MHC molecules and the complex is recognized by the TCR of CD8+ T lymphocytes. The killing of infected cells leads to the elimination of the infection, but in some cases it is responsible for cell damage that accompanies the infection (e.g., in viral hepatitis). Tumor-associated antigens are also presented on the cell surface, and CTLs are involved in the host response to transformed cells (Chapter 7).

The principal mechanism of T cell–mediated killing of targets involves *perforins* and *granzymes*, preformed mediators contained in the lysosome-like granules of CTLs. CTLs that recognize the target cells secrete a complex consisting of perforin, granzymes, and other proteins which enters target cells by endocytosis. In the target cell cytoplasm, perforin facilitates the release of the granzymes from the complex. Granzymes are proteases that cleave and activate caspases, which induce apoptosis of the target cells (Chapter 2). Activated CTLs also express Fas ligand, a molecule with homology to TNF, which can bind to Fas expressed on target cells and trigger apoptosis.

CD8+ T cells also produce cytokines, notably IFN-γ, and are involved in inflammatory reactions resembling DTH, especially following virus infections and exposure to some contact sensitizing agents.

KEY CONCEPTS

Mechanisms of T Cell–Mediated Hypersensitivity Reactions

- Cytokine-mediated inflammation: CD4+ T cells are activated by exposure to a protein antigen and differentiate into T_H1 and T_H17 effector cells. Subsequent exposure to the antigen results in the secretion of cytokines. IFN-γ activates macrophages to produce substances that cause tissue damage and promote fibrosis, and IL-17 and other cytokines recruit leukocytes, thus promoting inflammation.
- The classical T cell–mediated inflammatory reaction is delayed type hypersensitivity.
- T cell–mediated cytotoxicity: CD8+ cytotoxic T lymphocytes (CTLs) specific for an antigen recognize cells expressing the target antigen and kill these cells. CD8+ T cells also secrete IFN-γ.

Now that we have described how the immune system can cause tissue damage, we turn to diseases in which normal control mechanisms fail. The prototypes of such diseases are autoimmune disorders, which are the result of failure of tolerance to self antigens.

Autoimmune Diseases

Immune reactions against self antigens—*autoimmunity*—are an important cause of certain diseases in humans, estimated to affect at least 1% to 2% of the US population. A growing number of diseases have been attributed to autoimmunity (Table 6-6). It should be noted, however, that the mere presence of autoantibodies does not indicate an autoimmune disease exists. Autoantibodies can be found in the serum of apparently normal individuals, particularly in older age groups. Furthermore, innocuous autoantibodies are sometimes produced after damage to tissues and may serve a physiologic role in the removal of tissue breakdown products. How, then, does one define *pathologic autoimmunity*? Ideally, at least three requirements should be met before a disorder is categorized as truly caused by autoimmunity: (1) the presence of an immune reaction specific for some self antigen or self tissue; (2) evidence that such a reaction is not secondary to tissue damage but is of primary pathogenic significance; and (3) the absence of another well-defined cause of the disease. Similarity with experimental models of proven autoimmunity is also often used to support this mechanism in human diseases. Disorders in which chronic inflammation is a prominent component are sometimes grouped under *immune-mediated inflammatory diseases*; these may be autoimmune, or the immune

Table 6-6 Autoimmune Diseases

Organ-Specific	Systemic
Diseases Mediated by Antibodies	
Autoimmune hemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pernicious anemia	
Myasthenia gravis	
Graves disease	
Goodpasture syndrome	
Diseases Mediated by T Cells*	
Type 1 diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma)† Sjögren syndrome†
Diseases Postulated to Be Autoimmune	
Inflammatory bowel diseases (Crohn disease, ulcerative colitis)‡	
Primary biliary cirrhosis†	Polyarteritis nodosa†
Autoimmune (chronic active) hepatitis	Inflammatory myopathies†

*A role for T cells has been demonstrated in these disorders, but antibodies may also be involved in tissue injury.
†An autoimmune basis of these disorders is suspected but the supporting evidence is not strong.
‡These disorders may result from excessive immune responses to commensal enteric microbes, autoimmunity, or a combination of the two.