with cellular receptors (CD4 molecules and chemokine receptors) to deliver potent activation signals resulting in calcium flux, the phosphorylation of certain proteins involved in signal transduction, colocalization of cytoplasmic proteins including those involved in cell trafficking, immune dysfunction, and, under certain circumstances, apoptosis. From an immunologic standpoint, chronic exposure of the immune system to a particular antigen over an extended period may ultimately lead to an inability to sustain an adequate immune response to the antigen in question. In many chronic viral infections, including HIV infection, persistent viremia is associated with "functional exhaustion" of virus-specific T cells, decreasing their capacity to proliferate and perform effector functions. It has been demonstrated that this phenomenon may be mediated, at least in part, by the upregulation of inhibitory receptors on HIV-specific T cells, such as PD-1 shared by both CD4+ and CD8+ T cells, as well as CTLA-4 on CD4+ and Tim-3, 2B4, and CD106 on CD8+ T cells. Furthermore, the ability of the immune system to respond to a broad spectrum of antigens may be compromised if immunocompetent cells are maintained in a state of chronic activation.

The deleterious effects of chronic immune activation on the progression of HIV disease are well established. As in most conditions of persistent antigen exposure, the host must maintain sufficient activation of antigen (HIV)-specific responses but must also prevent excessive activation and potential immune-mediated damage to tissues. Certain studies suggest that normal immunosuppressive mechanisms that act to keep hyperimmune activation in check, particularly CD4+, FoxP3+, CD25+ regulatory T cells (T-regs), may be dysfunctional or depleted in the context of advanced HIV disease.

MEDICAL CONDITIONS ASSOCIATED WITH PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION IN HIV DISEASE It has become clear, as the survival of HIV-infected individuals has increased, that a number of previously unrecognized medical complications are associated with HIV disease—and that these complications relate to chronic immune activation and inflammation (Table 226-4). These complications can appear even after patients have experienced years of adequate control of viral replication (plasma viremia below detectable levels) for several years. Of particular note are endothelial cell dysfunction and its relationship to cardiovascular disease. Other chronic conditions that have been reported include bone fragility, certain cancers, persistent immune dysfunction, diabetes, kidney and liver disease, and neurocognitive dysfunction, thus presenting an overall picture of accelerated aging.

Apoptosis *Apoptosis* is a form of programmed cell death that is a normal mechanism for the elimination of effete cells in organogenesis as well as in the cellular proliferation that occurs during a normal immune response (Chap. 372e). Apoptosis is largely dependent on cellular activation, and the aberrant cellular activation associated with HIV disease is correlated with a heightened state of apoptosis. HIV can trigger both Fas-dependent and Fas-independent pathways of apoptosis, the former of which is generally referred to as activation-induced cell death through an extrinsic pathway and involves the upregulation of the death receptor Fas and Fas ligand. Fas-independent pathways can be either extrinsic with different death receptors or intrinsic due to the downregulation of the antiapoptotic proteins such as Bcl-2. More recently, the phenomenon of *pyroptosis*, an inflammatory form of cell death involving the upregulation of the proinflammatory enzyme caspase-1 and release of the proinflammatory cytokine IL-1 β, has been linked to a bystander effect of HIV replication on CD4+ T cells. Certain viral gene products have been associated with enhanced susceptibility to apoptosis; these include Env, Tat, and Vpr. In contrast, Nef has been shown to possess antiapoptotic properties. A number of studies, including those examining lymphoid tissue, have demonstrated that the rate of apoptosis is elevated in HIV infection and that apoptosis is seen in "bystander" cells such as CD8+ T cells and B cells as well as in uninfected CD4+ T cells. The intensity of apoptosis correlates with the general state of activation of the immune system and not with the stage of disease or with viral burden. It is likely that nonspecific apoptosis of immunocompetent cells related to immune activation contributes to the immune abnormalities in HIV disease.

Autoimmune Phenomena The autoimmune phenomena that are common in HIV-infected individuals reflect, at least in part, chronic immune activation and the dysregulation of B and T cells. Although these phenomena usually occur in the absence of autoimmune disease, a wide spectrum of clinical manifestations that may be associated with autoimmunity have been described (see "Immunologic and Rheumatologic Diseases," below). Autoimmune phenomena include antibodies against autoantigens expressed on intact lymphocytes and other cells, or against proteins released from dying cells. Antiplatelet antibodies have some clinical relevance in that they may contribute to the thrombocytopenia of HIV disease (see below). Antibodies to nuclear and cytoplasmic components of cells have been reported, as have antibodies to cardiolipin and phospholipids; CD4 molecules; CD43 molecules; C1q-A; variable regions of the T cell receptor α, β, and γ chains; Fas; denatured collagen; and IL-2. In addition, autoantibodies to a range of serum proteins, including albumin, immunoglobulin, and thyroglobulin, have been reported. Molecular mimicry, either from opportunistic pathogens or from HIV itself, is also a trigger or co-factor in autoimmunity. Antibodies against the HIV envelope proteins, especially gp41, often cross-react with host proteins; the best known examples are antibodies directed against the membrane-proximal external region of gp41 that also react with phospholipids and cardiolipin. The phenomenon of polyreactive HIV-specific antibodies may be beneficial to the host (see "Immune Response to HIV," below).

The increased occurrence and/or exacerbation of certain autoimmune diseases have been reported in HIV infection; these diseases include psoriasis, idiopathic thrombocytopenic purpura, Graves' disease, antiphospholipid syndrome, and primary biliary cirrhosis. The majority of these manifestations were described prior to the advent of cART and have decreased in frequency since its widespread use. However, with increasing availability of cART, an *immune reconstitution inflammatory syndrome* (IRIS) has become increasingly common in infected individuals, particularly those with low CD4+ T cell counts. IRIS is an autoimmune-like phenomenon characterized by a paradoxical deterioration of clinical condition, which is usually compartmentalized to a particular organ system, in individuals in whom cART has recently been initiated. It is associated with a decrease in viral load and at least partial recovery of immune competence, which is usually associated with increases in CD4+ T cell counts. The immunopathogenesis is felt to be related to an increase in immune response against the presence of residual antigens that are usually microbial and is commonly seen with underlying *Mycobacterium tuberculosis* and cryptococcosis. This syndrome is discussed in more detail below.

CYTOKINES AND OTHER SOLUBLE FACTORS IN HIV PATHOGENESIS

The immune system is homeostatically regulated by a complex network of immunoregulatory cytokines, which are pleiotropic and redundant and operate in an autocrine and paracrine manner. They are expressed continuously, even during periods of apparent quiescence of the immune system. On perturbation of the immune system by antigenic challenge, the expression of cytokines increases to varying degrees (Chap. 372e). Cytokines that are important components of this immunoregulatory network are thought to play major roles in HIV disease, during both the early and chronic phases of infection. A potent pro-inflammatory "cytokine storm" is induced during the acute phase of HIV infection, likely a response by inflammatory cells recruited to mucosal tissues where the virus initially replicates at very high levels. Cytokines that are induced during this early phase include IFN-α, IL-15, and the CXC chemokine IP-10 (CXCL10), followed by IL-6, IL-12, and TNF-α, and a delayed peak of the anti-inflammatory cytokine IL-10. Soluble factors of innate immunity are also induced shortly after infection, including neopterin and β-microglobulin. Several of these early-expressed cytokines and factors are not downregulated following the early phase of HIV infection, as seen in self-resolving viral infections, and persist during the chronic phase of infection and contribute to maintaining high levels of immune activation. Among the cytokines and factors associated with early innate immune responses, they are intended to contain viral replication, although most are potent inducers of HIV expression/replication