undetectable plasma virus for years, develop active infection if they stop the treatment.

Despite these dramatic improvements, several new complications associated with HIV infection and its treatment have emerged. Some patients with advanced disease who are given antiretroviral therapy develop a paradoxical clinical deterioration during the period of recovery of the immune system. This occurs despite increasing CD4+ T-cell counts and decreasing viral load. This disorder has been called the *immune reconstitution inflammatory syndrome*. Its basis is not understood but is postulated to be a poorly regulated host response to the high antigenic burden of persistent microbes. Perhaps a more important complication of long-term HAART pertains to adverse side-effects of the drugs. These include lipoatrophy (loss of facial fat), lipoaccumulation (excess fat deposition centrally), elevated lipids, insulin resistance, peripheral neuropathy, premature cardiovascular kidney and liver disease. Finally, non-AIDS morbidity is far more common than classic AIDS-related morbidity in long-term HAART-treated patients. Major causes of morbidity are cancer, and accelerated cardiovascular, kidney, and liver disease. The mechanism for these non-AIDS related complications is not known, but persistent inflammation and T-cell dysfunction may be playing a role.

MORPHOLOGY

The anatomic changes in the tissues (with the exception of lesions in the brain) are neither specific nor diagnostic. Common pathologic features of AIDS include opportunistic infections, KS, and B cell lymphomas. Most of these lesions are discussed elsewhere, because they also occur in individuals who do not have HIV infection. Lesions in the central nervous system are described in Chapter 28.

Biopsy specimens from enlarged lymph nodes in the early stages of HIV infection reveal a marked hyperplasia of B cell follicles. The follicles are enlarged and often take on unusual, serpiginous shapes. The mantle zones that surround the follicles are attenuated, and the germinal centers impinge on interfollicular T cell areas. This hyperplasia of B cells is the morphologic reflection of the polyclonal B-cell activation and hypergammaglobulinemia seen in HIV-infected individuals.

With disease progression, the frenzy of B-cell proliferation subsides and gives way to a pattern of severe lymphoid involution. The lymph nodes are depleted of lymphocytes, and the organized network of follicular dendritic cells is disrupted. The germinal centers may even become hyalinized. During this advanced stage viral burden in the nodes is reduced, in part because of the disruption of the follicular dendritic cells. These "burnt-out" lymph nodes are atrophic and small and may harbor numerous opportunistic pathogens, often within macrophages. Because of profound immunosuppression, the inflammatory response to infections both in the lymph nodes and at extranodal sites may be sparse or atypical. For example, mycobacteria may not evoke granuloma formation because CD4+ cells are deficient. In the empty-looking lymph nodes and in other organs, the presence of infectious agents may not be readily apparent without special stains. As might be expected, lymphoid involution is not confined to the nodes; in later stages of AIDS, the spleen and thymus also are converted to "wastelands" that are virtually devoid of lymphocytes.

Despite spectacular advances in our understanding of HIV infection, the long-term prognosis of patients with AIDS remains dismal. Although with effective drug therapy the mortality rate has declined in the United States, the treated patients still carry viral DNA in their lymphoid tissues. Can there be a cure with persistent virus? Although a considerable effort has been mounted to develop a vaccine, many hurdles remain to be crossed before vaccine-based prophylaxis becomes a reality. Molecular analyses have revealed an alarming degree of variation in viral isolates from patients; this renders the task of producing a vaccine extremely difficult. Recent efforts have focused on producing antibodies against relatively invariant portions of HIV proteins. The task of developing an effective vaccine is complicated by the fact that the correlates of immune protection are not fully understood. At present, therefore, prevention, public health measures, and antiretroviral drugs remain the mainstays in the fight against AIDS.

KEY CONCEPTS

Pathogenesis and Course of HIV Infection and AIDS

- Virus entry into cells: requires CD4 and co-receptors, which are receptors for chemokines; involves binding of viral gp120 and fusion with the cell mediated by viral gp41 protein; main cellular targets are CD4+ helper T cells, macrophages, and DCs
- Viral replication: provirus genome integrates into host cell DNA; viral gene expression is triggered by stimuli that activate infected cells (e.g., infectious microbes, cytokines produced during normal immune responses)
- Progression of infection: acute infection of mucosal T cells and DCs; viremia with dissemination of virus; latent infection of cells in lymphoid tissue; continuing viral replication and progressive loss of CD4+ T cells
- Mechanisms of immune deficiency:
  - Loss of CD4+ T cells: T-cell death during viral replication and budding (similar to other cytopathic infections); apoptosis as a result of chronic stimulation; decreased thymic output; functional defects
  - Defective macrophage and DC functions
  - Destruction of architecture of lymphoid tissues (late)
- Clinical manifestations of AIDS include opportunistic infections, tumors such as B-cell lymphomas, and CNS abnormalities.

Amyloidosis

Amyloidosis is a condition associated with a number of inherited and inflammatory disorders in which extracellular deposits of fibrillar proteins are responsible for tissue damage and functional compromise. These abnormal fibrils are produced by the aggregation of misfolded proteins (which are soluble in their normal folded configuration). The fibrillar deposits bind a wide variety of proteoglycans and glycosaminoglycans, including heparan sulfate and dermatan sulfate, and plasma proteins, notably serum amyloid P component (SAP). The presence of