which stimulates proliferation of B cells. Despite the presence of spontaneously activated B cells, patients with AIDS are unable to mount antibody responses to newly encountered antigens. This could be due, in part, to lack of T-cell help, but antibody responses against T-independent antigens are also suppressed, and hence there may be other intrinsic defects in B cells as well. Impaired humoral immunity renders these patients prey to disseminated infections caused by encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae*, both of which require antibodies for effective opsonization and clearance.

Pathogenesis of Central Nervous System Involvement

The pathogenesis of neurologic manifestations deserves special mention because, in addition to the lymphoid system, the nervous system is a major target of HIV infection. Macrophages and microglia, cells in the central nervous system that belong to the macrophage lineage, are the predominant cell types in the brain that are infected with HIV. It is believed that HIV is carried into the brain by infected monocytes. In keeping with this, the HIV isolates from the brain are almost exclusively M-tropic. The mechanism of HIV-induced damage of the brain, however, remains obscure. Because neurons are not infected by HIV, and the extent of neuropathologic changes is often less than might be expected from the severity of neurologic symptoms, most workers believe that the neurologic deficit is caused indirectly by viral products and by soluble factors produced by infected microglia. Included among the soluble factors are the usual culprits, such as IL-1, TNF, and IL-6. In addition, nitric oxide induced in neuronal cells by gp41 has been implicated. Direct damage of neurons by soluble HIV gp120 has also been postulated.

Natural History of HIV Infection

Virus typically enters through mucosal epithelia. The subsequent pathologic and clinical manifestations of the infection can be divided into several phases: (1) an acute retroviral syndrome; (2) a middle, chronic phase, in which most individuals are asymptomatic; and (3) clinical AIDS (Figs. 6-41 and 6-42).

Primary Infection, Virus Dissemination, and the Acute Retroviral Syndrome

Acute (early) infection is characterized by infection of memory CD4+ T cells (which express CCR5) in mucosal lymphoid tissues, and death of many infected cells. Because the mucosal tissues are the largest reservoir of T cells in the body, and a major site of residence of memory T cells, this local loss results in considerable depletion of lymphocytes. Few infected cells are detectable in the blood and other tissues. Mucosal infection is often associated with damage to the epithelium, defects in mucosal barrier functions, and translocation of microbes across the epithelium.

Mucosal infection is followed by dissemination of the virus and the development of host immune responses. Dendritic cells in epithelia at sites of virus entry capture the virus and then migrate into the lymph nodes. Once in lymphoid tissues, dendritic cells may pass HIV on to CD4+ T cells through direct cell-cell contact. Within days after the first exposure to HIV, viral replication can be detected in

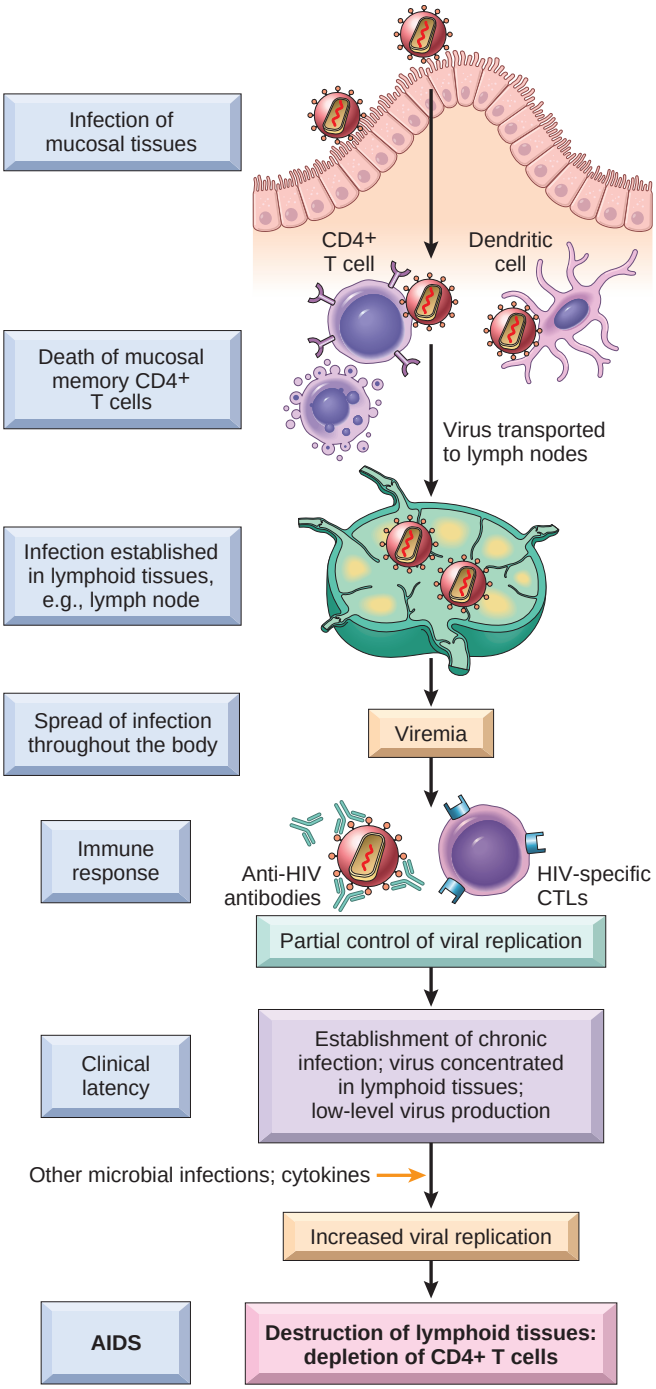

Figure 6-41 Pathogenesis of HIV-1 infection. The initial infection starts in mucosal tissues, involving mainly memory CD4+ T cells and dendritic cells, and spreads to lymph nodes. Viral replication leads to viremia and widespread seeding of lymphoid tissue. The viremia is controlled by the host immune response, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages continues unabated, but there is some immune containment of virus (not illustrated). There continues a gradual erosion of CD4+ cells and ultimately, CD4+ T-cell numbers decline, and the patient develops clinical symptoms of full-blown AIDS. CTL, Cytotoxic T lymphocyte.