long-term nonprogressors have varied considerably over the years, and so such individuals constitute a heterogeneous group. Long-term nonprogressors were first described in the 1990s. Originally, individuals were considered to be long-term nonprogressors if they had been infected with HIV for a long period (≥10 years), their CD4+ T cell counts were in the normal range, and they remained stable over years without receiving cART. Approximately 5–15% of HIV-infected individuals fell into this broader nonprogressor category. However, this group was rather heterogenous and over time a significant proportion of these individuals progressed and ultimately required therapy. From this broader group, a much smaller subgroup of "elite" controllers or nonprogressors was identified, and they constituted less than 1% of HIV-infected individuals. These elite controllers, by definition, have extremely low levels of plasma viremia and normal CD4+ T cell counts. It is noteworthy that certain of their HIV-specific immune responses are robust and clearly superior to those of HIV-infected progressors. In this group of elite controllers certain HLA class I haplotypes are overrepresented, particularly HLA-B57-01 and HLA-B27-05. Outside of the subgroup of elite controllers, a number of other genetic factors have been shown to be involved to a greater or lesser degree in the control of virus replication and thus in the rate of HIV disease progression (see "Genetic Factors in HIV-1 and AIDS Pathogenesis," below).

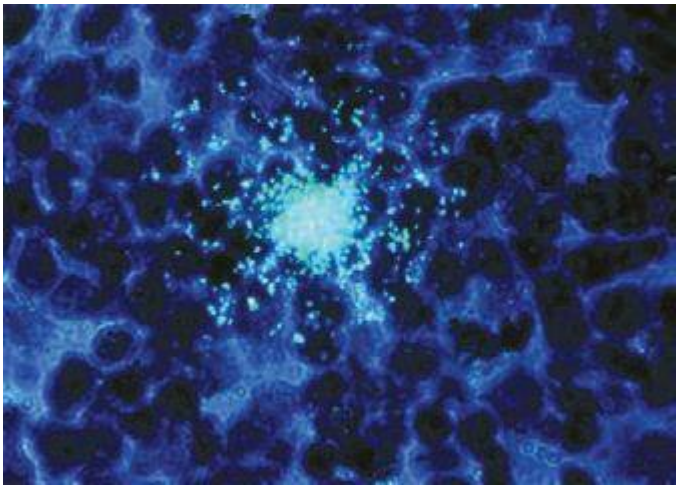

FIGURE 226-23 HIV in the lymph node of an HIV-infected individual. An individual cell infected with HIV shown expressing HIV RNA by in situ hybridization using a radiolabeled molecular probe. Original ×500. *(Adapted from G Pantaleo, AS Fauci et al: Nature 362:355, 1993.)*

LYMPHOID ORGANS AND HIV PATHOGENESIS

Regardless of the portal of entry of HIV, lymphoid tissues are the major anatomic sites for the establishment and propagation of HIV infection. Despite the use of measurements of plasma viremia to determine the level of disease activity, virus replication occurs mainly in lymphoid tissue and not in blood; indeed, the level of plasma viremia directly reflects virus production in lymphoid tissue.

Some patients experience progressive generalized lymphadenopathy early in the course of the infection; others experience varying degrees of transient lymphadenopathy. Lymphadenopathy reflects the cellular activation and immune response to the virus in the lymphoid tissue, which is generally characterized by follicular or germinal center hyperplasia. Lymphoid tissue involvement is a common denominator of virtually all patients with HIV infection, even those without easily detectable lymphadenopathy.

Simultaneous examinations of lymph tissue and peripheral blood in patients and monkeys during various stages of HIV and SIV infection, respectively, have led to substantial insight into the pathogenesis of HIV disease. In most of the original human studies, peripheral lymph nodes have been used predominantly as the source of lymphoid tissue. More recent studies in monkeys and humans have also focused on the GALT, where the earliest burst of virus replication occurs associated with marked depletion of CD4+ T cells. In detailed studies of peripheral lymph node tissue, using a combination of polymerase chain reaction (PCR) techniques for HIV DNA and HIV RNA in tissue and HIV RNA in plasma, in situ hybridization for HIV RNA, and light and electron microscopy, the following picture has emerged. During acute HIV infection resulting from mucosal transmission, virus replication progressively amplifies from scattered lymphoid cells in the lamina propria to draining lymphoid tissue, leading to high levels of plasma viremia. The GALT plays a major role in the amplification of virus replication, and virus is disseminated from replication in the GALT to peripheral lymphoid tissue. A profound degree of cellular activation occurs (see below) and is reflected in follicular or germinal center hyperplasia. At this time copious amounts of extracellular virions (both infectious and defective) are trapped on the processes of the follicular dendritic cells (FDCs) in the germinal centers of the lymph nodes. Virions that have bound complement components on their surfaces attach to the surface of FDCs via interactions with complement receptors and likely via Fc receptors that bind to antibodies that are attached to the virions. In situ hybridization reveals expression of virus in individual cells of the paracortical area and, to a lesser extent, the germinal center (Fig. 226-23). The persistence of trapped virus after the transition from acute to chronic infection likely reflects a steady state whereby trapped virus turns over and is replaced by fresh virions that are continually produced. The trapped virus, either as whole virion or shed envelope, serves as a continual activator of CD4+ T cells, thus driving further virus replication.

During early and chronic/asymptomatic stages of HIV disease, the architecture of lymphoid tissues is generally preserved and may even be hyperplastic owing to an increased presence of B cells and specialized CD4+ T cells called follicular helper CD4+ T cells (TF_H) in prominent germinal centers. Extracellular virions can be seen by electron microscopy attached to FDC processes. The trapping of antigen is a physiologically normal function for the FDCs, which present antigen to B cells and, along with the action of TF_H cells, contribute to the generation of B cell memory. However, in the case of HIV, persistent cellular activation, resulting in the secretion of proinflammatory cytokines such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, IFN-γ, and IL-6, which can induce viral replication (see below) and diminish the effectiveness of the immune response against the virus. In addition, the CD4+ TF_H cells that are recruited into the germinal center to provide help to B cells in the generation of an HIV-specific immune response are highly susceptible to infection by virus either trapped on FDC or propagated locally. Thus, in HIV infection, a normal physiologic function of the immune system that contributes to the clearance of virus, as well as to the generation of a specific immune response, can also have deleterious consequences.

As the disease progresses, the architecture of lymphoid tissues begins to show disruption. Confocal microscopy reveals destruction of the fibroblastic reticular cell (FRC) and FDC networks in the T cell zone and B cell follicles, respectively, and an incapacity to replenish naïve cells. The mechanisms of destruction are not completely understood, but they are thought to be associated with collagen deposition causing fibrosis and loss of production of cytokines such as IL-7 and lymphotoxin-α, which are critical to the maintenance of lymphoid tissues and their lymphocyte constituents. As the disease progresses to an advanced stage, there is complete disruption of the architecture of the lymphoid tissues, accompanied by dissolution of the FRC and FDC networks. At this point, the lymph nodes are "burnt out." This destruction of lymphoid tissue compounds the immunodeficiency of HIV disease and contributes both to the inability to control HIV replication (leading usually to high levels of plasma viremia in the untreated or inadequately treated patient) and to the inability to mount adequate immune responses against opportunistic pathogens. The events from primary infection to the ultimate destruction of the immune system are illustrated in Fig. 226-24. Recently, nonhuman primate studies and some human studies have examined GALT at various stages of HIV disease. Within the GALT, the basal level of activation combined with virus-mediated cellular activation results in the infection and elimination of an estimated 50–90% of CD4+ T cells in the gut. The extent of