The infants who survive usually have permanent deficits, including intellectual disability, hearing loss, and other neurologic impairments. The congenital infection is not always devastating, however, and may take the form of interstitial pneumonitis, hepatitis, or a hematologic disorder. Most infants with this milder form of cytomegalic inclusion disease recover, although a few develop intellectual disability later. Uncommonly, a totally asymptomatic infection may be followed months to years later by neurologic sequelae, including delayed-onset intellectual disability and deafness.

Perinatal Infections. Infection acquired during passage through the birth canal or from breast milk is usually asymptomatic due to protective maternal anti-CMV antibodies, which are transmitted to the fetus across the placenta. Despite the lack of symptoms, many of these infants continue to excrete CMV in their urine or saliva for months to years. Subtle effects on hearing and intelligence later in life have been reported in some studies. Much less commonly, infected infants develop interstitial pneumonitis, failure to thrive, rash, or hepatitis.

Cytomegalovirus Mononucleosis. In healthy young children and adults the disease is nearly always asymptomatic. In surveys around the world, 50% to 100% of adults have antibodies to CMV, indicating previous exposure. **The most common clinical manifestation of CMV infection in immunocompetent hosts beyond the neonatal period is an infectious mononucleosis-like illness, with fever, atypical lymphocytosis, lymphadenopathy, and hepatitis, marked by hepatomegaly and abnormal liver function tests.** The diagnosis is made by serology. Most people recover without any sequelae, but the virus may continue to be excreted in body fluids for months to years. Irrespective of the presence or absence of symptoms, infected individuals remain seropositive for life and the virus is never cleared, persisting in latently infected leukocytes.

CMV in Immunosuppressed Individuals. **Immunocompromised individuals (e.g., transplant recipients, HIV-infected individuals) are susceptible to severe CMV infection;** these may be either primary infections or reactivation of latent CMV. In the past, CMV was the most common opportunistic viral pathogen in AIDS , but the frequency of serious CMV infection in HIV-positive people has been greatly reduced by antiretroviral treatment. Recipients of solid-organ transplants (heart, liver, kidney) also may contract CMV from the donor organ.

In all these settings, serious, even life-threatening, disseminated CMV infections in immunosuppressed people primarily affect the lungs (pneumonitis) and gastrointestinal tract (colitis). In the pulmonary infection an interstitial mononuclear infiltrate with foci of necrosis develops, accompanied by the typical enlarged cells with inclusions. The pneumonitis can progress to full-blown acute respiratory distress syndrome. Intestinal necrosis and ulceration can develop and be extensive, leading to the formation of pseudomembranes and debilitating diarrhea. Diagnosis of CMV infections is made by demonstration of characteristic morphologic alterations in tissue sections, viral culture, rising antiviral antibody titer, detection of CMV antigens, and PCR-based detection of CMV DNA. The antigen-detection and PCR-based assays have revolutionized the approach to monitoring CMV infection in people after transplantation.

Chronic Productive Infections

In some infections the immune system is unable to eliminate the virus, and continued viral replication leads to persistent viremia. The high mutation rate of viruses such as HIV and HBV may contribute to their escape from control by the immune system. HIV and HBV infection are described in Chapters 6 and 18, respectively.

Transforming Viral Infections

Some viruses can transform infected cells into benign or malignant tumor cells. Oncogenic viruses can stimulate cell growth and survival by a variety of mechanisms, as discussed in Chapter 7. Several viruses have been implicated in the causation of human cancer, including EBV, HPV, HBV, and HTLV-1. EBV is discussed here; others are discussed in later chapters.

Epstein-Barr Virus (EBV)

EBV causes infectious mononucleosis, a benign, self-limited lymphoproliferative disorder, and is associated with the pathogenesis of several human tumors, most commonly certain lymphomas and nasopharyngeal carcinoma. Infectious mononucleosis is discussed here and EBV-associated neoplasms are discussed in Chapter 7.

Infectious mononucleosis is characterized by fever, sore throat, generalized lymphadenopathy, splenomegaly, and the appearance in the blood of atypical activated T lymphocytes (mononucleosis cells). Some people develop hepatitis, meningoencephalitis, and pneumonitis. Infectious mononucleosis occurs principally in late adolescents or young adults among upper socioeconomic classes in developed nations. In the rest of the world, primary infection with EBV occurs in childhood and is usually asymptomatic.

Pathogenesis. EBV is transmitted by close human contact, frequently through the saliva during kissing. EBV infects B cells and possibly epithelial cells of the oropharynx. It has been hypothesized that EBV initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue (tonsils and adenoids), where mature B cells are infected (Fig. 8-13). Of note, people with X-linked agammaglobulinemia, who lack B cells, do not become latently infected with EBV or shed virus, suggesting that B cells are the main reservoir of infection. An EBV envelope glycoprotein binds CD21 (CR2), the receptor for the C3d component of complement (Chapter 3), which is present on B cells. Infection of B cells may take one of two forms. In a minority of B cells, infection is lytic, leading to viral replication and eventual cell lysis accompanied by release of virions, which may infect other B cells. In most B cells, however, EBV establishes latent infection, during which the virus persists as an extrachromosomal episome.

A small number of EBV-encoded proteins are believed to be particularly important in the establishment of latency, as follows: