Typically, a primary infection with herpes simplex virus (HSV) is followed by the establishment of latent infection in the sensory ganglia of the affected dermatome. At the site of inoculation, the virus replicates in epithelial cells and then travels by retrograde axonal transport to the local sensory ganglia. There the virus causes a productive infection, which is followed in several days by the establishment of a latent infection. The virus persists asymptotically in this latent state for the life of the host, but may periodically reactivate and travel down the neuron back to the epithelial surface to cause the typical recurrent herpetic lesion [1,2].

The molecular state of the HSV genome during latency is still unknown. Some investigators believe the virus exists in an episomal form, whereas others believe that the viral DNA is integrated into the host cell genome [3]. It is also uncertain whether limited transcription of the viral genome occurs during latency [3], and the precise mechanism of reactivation of latent virus has also not been established [4]. Substantial information, however, has accumulated about the immune response to HSV and its antigenic components. HSV codes for at least 50 proteins, including several glycoproteins which are expressed in the viral envelope and on the surface of infected cells. HSV-1 and HSV-2 have five glycoproteins designated gB, gC, gD, gE, and gG. While each HSV-1 glycoprotein (except possibly gG) has immunologic cross-reactivity with the respective glycoprotein of HSV-2, gD and gB appear to share the most type-common antigenic determinants. In addition, gB and gD appear to be major targets for neutralizing antibodies, and antibodies to these glycoproteins appear during the course of natural infection [5]. Humoral and cellular immunity play critical, but distinct, roles in controlling HSV infections. Humoral immunity is important in protection against the acquisition of primary disease, but reactivation occurs even in the presence of
high antibody titers [6]. This may be due to the fact that HSV spreads directly from cell-to-cell, thereby avoiding neutralization by antibody in the extracellular space. Cellular immunity and interferon are probably the most important factors in limiting the cell-to-cell spread of the infection [7]. Patients with cellular immune dysfunction suffer more severe and frequent recurrences than immunocompetent individuals. No specific cellular, humoral, or nonspecific host defense defect, however, has been identified in immunocompetent patients with frequently recurrent disease [8].

Information on the pathogenesis of infection with HSV is making it possible to formulate rational intervention directed at the different stages of the infectious cycle. This includes (a) prevention of latent infection by vaccination, (b) treatment of established symptomatic infection by chemotherapy, and (c) limiting reactivation of the virus by identification and abrogation of precipitating factors.

Prevention of Latent Infection

To be effective, a herpes vaccine not only must limit the symptoms of primary infection, but must prevent the establishment of a latent infection. This means that the virus must be neutralized prior to entry into the nerve ending. Once inside the nerve, the virus is protected from the host immune response and may establish a latent infection which has the potential to periodically reactivate.

Our understanding of the pathogenesis of latency and reactivation in humans is based in large part on research carried out in experimental animals. A mouse model of HSV infection has been adapted to study the efficacy of various HSV vaccines in protecting against the development of latent infection with wild-type virus [9]. In this model, vaccinated mice are challenged with HSV by a variety of routes, including lip, eye, ear, or footpad. After several weeks, the local sensory ganglia are explanted onto indicator cells and observed for reactivation of HSV. Studies with several HSV vaccines have demonstrated substantial but not complete protection against the development of latent ganglionic infection. In some cases, latent infection developed despite high levels of neutralizing antibody [9, 10]. This suggests that the immunogenicity of a vaccine may not be the only factor that determines the degree of protection afforded by vaccination. For example, there is some evidence that the degree of protection correlates with the amount of serum exudate at the site of inoculation of the challenge virus [9]. Vaccinated mice challenged by the relatively avascular footpad route, which induced little bleeding or serum exudate, showed much less protection against the development of latent infection than identically vaccinated mice challenged by the more vascular lip route. This may be due to the fact that the serum exudate contains antibody, and the more antibody at the site of viral chal-