made by serology, but viral culture and PCR-based tests are also used.

Viral Hemorrhagic Fever

Viral hemorrhagic fever (VHF) is a severe life-threatening multisystem syndrome in which there is vascular dysregulation and damage, leading to shock. VHF is caused by enveloped RNA viruses belonging to four different genera: Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. These viruses can produce a spectrum of illnesses, ranging from a mild acute disease characterized by fever, headache, myalgia, rash, neutropenia, and thrombocytopenia to severe, life-threatening disease in which there is sudden hemodynamic deterioration and shock. All these viruses pass through an animal or insect host during their life cycles and therefore their ranges are restricted to areas in which their hosts reside. Humans are incidental hosts who are infected when they come into contact with infected hosts (typically rodents) or insect vectors (mosquitoes and ticks). Some viruses that cause hemorrhagic fever (Ebola, Marburg, Lassa) also can spread from person to person.

The pathogenesis of the infection and its complications vary among the different viruses but there are some common features. Damage to blood vessels is often prominent. It may be caused by direct infection of and damage to endothelial cells, or infection of macrophages and dendritic cells leading to production of inflammatory cytokines. There may be hemorrhagic manifestations, including petechiae, caused by a combination of thrombocytopenia or platelet dysfunction, endothelial injury, cytokine-induced disseminated intravascular coagulation, and deficiency of clotting factors because of hepatic injury. Hemorrhages may be prominent in some infections (e.g. Congo-Crimean fever) but are rarely life-threatening. Necrosis of tissues secondary to the vascular lesions and hemorrhages may be seen and varies from mild and focal to massive, but the attendant inflammatory response is usually minimal.

Latent Infections (Herpesvirus Infections)

Latency is defined as the persistence of viral genomes in cells that do not produce infectious virus. Dissemination of the infection and tissue injury stem from reactivation of the latent virus. The viruses that most frequently establish latent infections in humans are *herpesviruses*. These are large encapsulated viruses with double-stranded DNA genomes that encode approximately 70 proteins. Herpesviruses cause acute infection followed by latent infection in which the viruses persist in a noninfectious form with periodic reactivation and shedding of infectious virus.

There are eight types of human herpesviruses, belonging to three subgroups that are defined by the type of cell most frequently infected and the site of latency: α-group viruses, including HSV-1, HSV-2, and VZV, which infect epithelial cells and produce latent infection in neurons; lymphotropic β-group viruses, including CMV, human herpesvirus-6 (which causes exanthem subitum, also known as roseola infantum and sixth disease, a benign rash of infants), and human herpesvirus-7 (a virus without a known disease association), which infect and produce latent infection in a variety of cell types; and the γ-group viruses EBV and KSHV/HHV-8, the cause of Kaposi sarcoma, which produce latent infection mainly in lymphoid cells. In addition, herpesvirus simiae (monkey B virus) is an Old World monkey virus that resembles HSV-1 and can cause fatal neurologic disease in animal handlers, usually resulting from an animal bite.

Herpes Simplex Viruses

HSV-1 and HSV-2 differ serologically but are closely related genetically and cause a similar set of primary and recurrent infections. Both viruses replicate in the skin and the mucous membranes at the site of entry of the virus (usually oropharynx or genitals), where they produce infectious virions and cause vesicular lesions of the epidermis. The viruses spread to sensory neurons that innervate these primary sites of replication. Viral nucleocapsids are transported along axons to the neuronal cell bodies, where the viruses establish latent infection. In immunocompetent hosts, primary HSV infection resolves in a few weeks, although the virus remains latent in nerve cells. During latency the viral DNA remains within the nucleus of the neuron, and only latency-associated viral RNA transcripts (LATs) are synthesized. No viral proteins appear to be produced during latency. LATs may contribute to latency by conferring resistance to apoptosis, silencing lytic gene expression through heterochromatin formation, and serving as precursors for microRNAs that downregulate expression of critical HSV lytic genes. Reactivation of HSV-1 and HSV-2 may occur repeatedly with or without symptoms, and results in the spread of virus from the neurons to the skin or to mucous membranes. Reactivation can occur in the presence of host immunity, because HSVs have developed ways to avoid immune recognition. For example, HSVs can evade antiviral CTLs by inhibiting the MHC class I recognition pathway, and elude humoral immune defenses by producing receptors for the Fc domain of immunoglobulin and inhibitors of complement.

In addition to causing cutaneous lesions, HSV-1 is the major infectious cause of corneal blindness in the United States. Corneal epithelial disease is thought to be due to direct viral damage, while corneal stromal disease appears to be immune-mediated. HSV-1 is also the major cause of fatal sporadic encephalitis in the United States. When the infection spreads to the brain, it usually involves the temporal lobes and orbital gyri of the frontal lobes. Inherited mutations in TLR3 or components of its signaling pathway increase the risk of HSV encephalitis. In addition, neonates and individuals with compromised cellular immunity (e.g., secondary to HIV infection or chemotherapy) may suffer disseminated herpesvirus infections. HSV-2 infection increases the risk of HIV transmission by four-fold and increases the risk of HIV acquisition by two- to three-fold.

MORPHOLOGY

HSV-infected cells contain large, pink to purple **intranuclear inclusions** (Cowdry type A) that consist of viral replication proteins and virions at various stage of assembly that push the host cell chromatin out to the edges of the nucleus (Fig. 8-9). Due to cell fusion, HSVs also produces inclusion-bearing multinucleated syncytia.