1. Introduction and Social Aspects

Herpes simplex viruses (HSVs) are among the most common infectious agents of man. There are two distinct serotypes (HSV-1 and HSV-2), and they usually have different modes of transmission. HSV-1 is transmitted chiefly via a nongenital route, whereas HSV-2 is most often transmitted venereally or from a mother’s genital infection to the newborn. The mode of spread of each of the two virus types is reflected by its relative prevalence at different ages and by its pattern of clinical distribution within the host. Thus, HSV-1 infections occur most frequently during childhood and usually affect body sites above the waist. HSV-2 infections, on the other hand, occur most often during adolescence and young adulthood and involve body sites below the waist, primarily the genitals. Most infections in newborns are also caused by HSV-2.

Although infections in persons without prior exposure to either virus (primary infections) may often be subclinical, they tend to be more severe than infections that occur in persons previously exposed to HSV-1 or HSV-2 or both. The clinical manifestations of either virus may also be more severe in certain types of hosts, e.g., the newborn or immunocompromised patient, and with involvement of certain sites, e.g., the central nervous system.

Although not ubiquitous in all populations studied, infection with these viruses represents a socially significant problem for which no effective vaccine is yet available. HSV-2 infection is becoming appreciated as a common venereal disease in several countries, and more cases of neonatal HSV infections with fatal or severe sequelae are being recognized. HSV infections of the central nervous system are also often fatal or debilitating, and ocular infections may endanger normal vision. Recurrent HSV infections are very common and are often physically and psychologically distressing. With the greater usage of immunosuppressive and cytotoxic drugs, iatrogenic HSV infections of varying clinical severity are more commonly recognized. Because of incompleteness of information, the total impact of the relationship of HSVs to human cancers, abortions, birth defects, and chronic neurological diseases cannot be ascertained at present.

2. Evolutionary and Historical Background

HSVs belong to a family of DNA viruses that includes more than 60 other viruses affecting a wide...
range of species from fungi to man.\textsuperscript{62} The other human viruses are cytomegalovirus (CMV), varicella–zoster virus (VZV), and Epstein–Barr virus (EBV). All these viruses have the capacity to persist in their natural host, either in neural cells, e.g., HSV and VZV, or in nonneural cells, e.g., CMV and EBV. The high prevalence in primitive societies of antibodies to the human herpesviruses, in contrast to the low prevalence of antibodies to other nonpersistent viruses,\textsuperscript{10} emphasizes the survival advantage conveyed by viral persistence and suggests an early origin for viruses in the herpes family.

Many of the vertebrate herpesviruses have very similar clinicoepidemiological patterns, such as venereal transmission and the ability to cause encephalitis, keratitis, skin or genital lesions, and disseminated neonatal disease.\textsuperscript{59} Despite the presence of common antigens among many of the herpesviruses and other common phenotypic expression, such as intranuclear inclusions in the infected cell, genetic similarities have been demonstrated with current technology primarily between HSV-1 and HSV-2. It therefore appears likely that one of these viruses evolved from the other; however, the origin of the HSVs from progenitors in lower species cannot be ruled out. Thus, the human viruses share common nucleotide sequences with the bovine mammilitis herpesvirus and common antigens with the B virus of macaques, which can produce an almost invariably fatal encephalitis in humans.

The term \textit{herpes} (\textit{επεμω}, “to creep”) has been used since the earliest epoch of Greek medicine to include spreading cutaneous lesions of varied etiology.\textsuperscript{55} The “herpetic eruptions which appear about the mouth at the crisis of simple fevers” were first described around 100 A.D. by a Roman physician, Herodotus. About 1600 years later, herpetic of the genital tract in both men and women was first reported by a French physician, Astruc. By the 19th century, the generally accepted use of the term \textit{herpes} was restricted to certain diseases associated with vesicular eruptions; by the latter part of that century, a further distinction was made on the basis of cytopathological differences between infections of the pox and herpes groups. In the early part of the 20th century, herpes zoster was differentiated on clinical and epidemiological grounds from “herpes febrilis” and “herpes genitallis.” This distinction was further supported by the studies of Gruter and other European workers who showed that specimens obtained from zoster lesions could not be transmitted to the rabbit cornea, in contrast to those obtained from the two herpetic conditions. Around 1920, a German physician, Lipschütz, maintained that, although herpes febrilis and herpes genitalis were biologically related, they were etiologically different; however, this idea was not confirmed until recent years.

Over the next 40 years, the experimental host range of HSVs was widened to include other laboratory animals, chick embryos, and ultimately cell cultures. The clinical spectrum of HSV infections was augmented to include gingivostomatitis, encephalitis, meningitis, Kaposi’s varicelliform eruption, and neonatal disease. It also became appreciated that HSV infections could recur in the presence of demonstrable levels of serum antibodies.

In the early 1960s, Schneweis\textsuperscript{86} in West Germany and Plummer\textsuperscript{72} in England found antigenic differences among HSV strains. By 1967, Nahmias and Dowdle\textsuperscript{55} had demonstrated that the large majority of genital and newborn infections are caused by HSV-2 and that most nongenital infections are caused by HSV-1, relating these clinical findings with the usual mode of transmission of the two virus types. In more recent years, strain differences within each of the two HSV types have been demonstrated in their polypeptides and by restriction endonuclease analysis of their viral DNAs.\textsuperscript{11–13,71} The application of modern biochemical and immunological technology, together with the broadening clinicopathological and epidemiological observations in more recent times, has thus provided new approaches to laboratory diagnosis, prevention, and therapy.\textsuperscript{65}

3. Methodology Involved in Epidemiological Analysis

3.1. Mortality

HSV infections are not reported nationwide in the United States, other than the few fatal cases of HSV encephalitis (around 20 a year) that are reported to the Center for Disease Control (CDC).

Mortality from HSV infection occurs primarily in three types of hosts: newborns, older persons with encephalitis, and those who are compromised by immunological or skin defects or by severe malnu-