

# Herpes Simplex Virus Epidemiology and Ocular Importance

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**Purpose.** To review the changing epidemiology of herpes simplex disease and correlate it with the epidemiology of ocular herpes simplex disease. **Method.** A review of pertinent reports in the world literature about the epidemiology of herpes simplex and specifically about ocular herpes simplex. **Results.** In developed countries, many individuals are reaching adolescence and adulthood without prior herpesvirus infection. Herpes simplex genital infection is increasing at a rapid rate in sexually active adolescents and adults, with about one in six adults now infected in the United States. Similar statistics are confirmatory worldwide in developed countries. Active herpes simplex infection is a risk factor for acquisition of human immunodeficiency virus. The Herpetic Eye Disease Study, as well as prior studies from Moorfields Eye Hospital and the Mayo Clinic in Rochester, Minnesota, provides us with the epidemiology of ocular herpes simplex. Recent studies suggest an older age of onset and perhaps overall more severe ocular disease as compared with the older literature. **Conclusions.** Herpes simplex is a significant health concern at present with genital infections increasing in epidemic proportions. This is also reflected in a rise in the incidence of neonatal herpes. Herpes simplex virus type 1 (HSV-1) infection is being acquired for the first time in an older age group. A significant and increasing proportion of genital herpes is caused by HSV-1. Serologic studies are no longer as useful in distinguishing orofacial herpes from genital herpes. More acute retinal necrosis syndrome cases are associated with HSV-2. Speculation about the future of ocular herpes is made based on this changing epidemiology.

**Key Words:** Herpes simplex—Epidemiology herpes—Ocular herpes simplex—Genital herpes—Congenital herpes—Neonatal herpes—Acute retinal necrosis—HSV-1—HSV-2.

## HERPESVIRUSES

There are now eight recognized human herpesviruses: herpes simplex virus type 1 (HSV-1), HSV-2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 (associated with roseola infantum), human herpesvirus 7 (associated with roseola infantum and febrile convulsions), and human herpesvirus 8 (associated with Kaposi sarcoma and lymphomas) (Table 1).<sup>1</sup> HSV is now a major health concern, confirmed by the epidemic of genital HSV and the enhanced acquisition of human immunodeficiency virus (HIV) infections in association with HSV infections. This perspective will focus on HSV-1 and HSV-2, with emphasis

on the implications of the epidemiologic changes for ocular disease.

All human herpesviruses probably diversified from a common ancestor a million years ago. There is a host-linked evolution of the human herpesviruses such that the mediation of the cospeciation of these human herpesviruses occurred through these species-specific latent infections.<sup>2</sup> HSV is endemic in virtually every human society throughout the world, from urban to remote native tribes. Humans are the only natural reservoirs for HSV and there are close associations recognized between HSV-1 strains and historical human populations. Different ethnic populations can have specific DNA polymorphisms to the extent that HSV-1 may be used as a marker for human populations.<sup>2</sup>

HSV can be detected by polymerase chain reaction (PCR) in the trigeminal ganglia of 18.2% of cadavers of people up to 20 years of age, which increases to reach almost 100% in cadavers of people at least 60 years of age.<sup>3</sup> HSV-1 is more likely to inhabit the trigeminal ganglia and HSV-2 the sacral ganglia, explaining the clinical pictures of orofacial and genital herpes infections. A recent study, however, refutes this concept because HSV-1 and -2 were detected by PCR and in situ hybridization in 207 of 262 spinal ganglia from the cervical to the sacral ganglia.<sup>4</sup> HSV-1 and -2 were found equally in each, indicating no ganglion site preference and suggesting that there must be local host factors characterizing the frequency of recurrence of HSV-1 in the facial area and HSV-2 in the genital area. Other studies support the concept that local factors strongly influence reactivation.<sup>5</sup>

The spectrum of disease caused by HSV includes primary and recurrent infections of mucous membranes (e.g., gingivostomatitis, herpes labialis, and genital infections), neonatal and congenital HSV infection, eczema herpeticum in patients with underlying atopic dermatitis or Darier's disease or Sézary syndrome, visceral HSV infections in immunocompromised hosts, HSV encephalitis, and an association with erythema multiforme. Ocular complications include lid, conjunctival, corneal, intraocular infections, and retinitis. Patients undergoing chemotherapy, organ or bone marrow transplant recipients, and patients with HIV infection can develop multiple and extensive lesions and in some cases, visceral spread may occur.<sup>6–8</sup>

The different manifestations of HSV infections appear related to host populations and the age of acquisition of the infection.<sup>9</sup> Each HSV-1 genome has distinct restriction endonuclease fingerprints, but no consistent biologic differences have been documented; the same is true for HSV-2. Additionally, there is no evidence of differing racial or sexual susceptibility to HSV nor significant seasonal or sexual variation in the incidence of overt disease. The incubation period of primary HSV infection ranges from 1 to 28

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**TABLE 1.** *Features of herpesvirus*


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Eight human herpesviruses recognized
HSV-1
HSV-2
VZV
Cytomegalovirus
Epstein-Barr virus
Human herpesvirus 6 (associated with roseola)
Human herpesvirus 7 (associated with exanthem subitum, pityriasis rosea)
Human herpesvirus 8 (associated with Kaposi sarcoma, lymphoma)
Diversified from common ancestor 1 million years ago
Ethnic populations have similar HSV DNA (possibly a marker)
At least 33% of world with clinically recurrent HSV infections
Almost entire population with serologic evidence of infection by middle age
HSV detected in almost 100% of trigeminal ganglions by age 60 y
HSV-1 and -2 reside equally in almost all ganglia; local host factors control expression
Primary infections clinically recognized only about 1–6% of the time
Symptomatic patients have greater viral load and higher risk of transmission
Asymptomatic patients more common and the usual mode of transmission
Oropharyngeal shedding at least 1% of days
Prevalence of HSV-1 antibodies decreasing in developed countries
Newly recognized syndrome of herpetic pharyngotonsillitis in adolescents

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VZV indicates varicella-zoster virus.

days. HSV is infectious during asymptomatic shedding and for the 5 to 10 days it takes for the skin or mucous membrane lesions to heal.<sup>10</sup>

Latency with HSV is prevalent, with at least 33% of the world with clinically evident recurrent HSV infections.<sup>11</sup> Fifteen to forty-five percent of adults have herpes labialis, which has a tendency to decrease with age.<sup>9</sup> Persons with a history of HSV labialis comprise only 30 to 70% of people with HSV-1 antibodies. The clinical surveys greatly underestimate the incidence and prevalence of HSV infection because more than two thirds of initial HSV-1 and -2 infections are asymptomatic or unrecognized.<sup>9</sup> In some series, primary infections with HSV manifest clinically only 1 to 6% of the time.<sup>2</sup> HSV-1 and -2 may be shed asymptotically at the time of primary, initial, or recurrent infection.

Geographic location, socioeconomic status, and age influence HSV-1 prevalence. Because HSV-1 is transmitted principally by contact with infected oral secretions or lesions, the incidence and prevalence are influenced by factors that affect the degree of exposure to these sources of infection, such as crowding, poor hygiene, and age. Seropositive children and adults, including those with no history of HSV labialis, periodically shed HSV in saliva and are the major source of transmitting HSV infections. The proportion of the population with positive serology for HSV-1 that sheds ranges from 1 to 10%, but it may be greater in children or in the first 2 years after the primary infection and is also markedly increased in the immunosuppressed patient.<sup>9</sup> The risk of infection is directly proportional to the titer of virus shed, which is usually more in a symptomatic patient. Because the number of people with asymptomatic disease far exceeds the number with symptomatic disease, however, asymptomatic shedding of HSV is the most common mode of transmission. Asymptomatic shedding of HSV-1 in oropharyngeal secretions occurs intermittently in about 80% of infected persons; at a single time, the rate of shedding is 3 to 5%<sup>12</sup> or at least 0.5% to 1% of days.<sup>2</sup> Another report indicates that at least 1 in every 100 adults excretes oral HSV-1 at any given time.<sup>13</sup>

The age-specific prevalence of antibodies to HSV-1 has been

decreasing during the past 40 years in Western industrialized countries.<sup>9</sup> In lower socioeconomic populations, 70 to 80% are infected by adolescence, whereas in the middle class or developed countries, many patients now have antibodies detected for the first time much later in life.<sup>11</sup> Although primary HSV-1 infections are largely confined to early childhood in developing countries and in poor urban populations in the United States, the majority of middle and upper income children in Western societies now escape HSV-1 infections during childhood and experience a second peak of infections in adolescence and early adult life. This has resulted in a previously unrecognized disease of acute herpetic pharyngotonsillitis. Moreover, the increasing population now reaching puberty without having HSV-1, which induces a partial immunity to subsequent HSV-2 infection, may be an important factor in the current epidemic of genital HSV-2 infection.

### SEROLOGIC EPIDEMIOLOGY OF HSV

Because clinical history is not accurate in determining the prevalence of prior herpes infection in the population or the individual, serologic studies are used in defining the prevalence of prior infection and also reflects those with latent infection. Several serologic studies have reported the prevalence of HSV-1 and -2 antibody in various populations; wide variations exist from country to country (Table 2).<sup>11</sup> Current data suggests that 50% of United States' citizens are presently infected with HSV-1; this is less than in prior decades. In lower socioeconomic populations, approximately one third of children have serologic evidence of HSV infection by 5 years of age; this frequency increases to 70 to 80% by early adolescence. Middle-class individuals acquire antibodies later in life, such that seroconversion over the first 5 years occurs in 20% of children, followed by no significant increase until the second or third decades of life, at which time the prevalence of antibodies increases to 40 to 60%.<sup>11</sup> The annualized rate of infection among university students averages 5 to 10%. The National Health and Nutritional Examination survey showed more than 35% of African-Americans by age 5 years have HSV-1 but only 18% of Caucasians are infected; by age 40 years, however, the prevalence is similar.<sup>11</sup>

In an inner city community with a high prevalence of acquired immune deficiency syndrome (AIDS) in San Francisco, CA, U.S.A.,<sup>14</sup> the prevalence of HSV-1 infection correlated with older age, less education, and with being Hispanic or African-American. There was a low sensitivity correlation with facial herpes. HSV-2 serology correlated with female gender, number of sexual partners, low education, and with being African-American or Hispanic. In this series, only 19% with serology for HSV-2 had a history of genital herpes; therefore, self-reporting of infection was very in-

**TABLE 2.** *HSV serology*


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Clinical history of infection unreliable so serology best to study epidemiology
HSV-1 serology is declining in the United States and developed countries
HSV-1 being acquired at adolescence rather than childhood
Higher prevalence of HSV-1 in certain racial groups, crowded populations
HSV prevalent by age 1 y in Hong Kong; uncommon in United Kingdom at age 1 y
HSV seroprevalence increases markedly during college years
HSV-1 in 23% at age 15 y; 50% by age 30 y (Swedish school girls)
HSV-2 in 0.4% at age 15 y; 22% by age 30 y (Swedish school girls)

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sensitive and only moderately specific. The herpesvirus seroprevalence in England and Hong Kong was contrasted.<sup>15</sup> Although HSV infection is common in Hong Kong by the age of 1 year, it is uncommon in the United Kingdom at that age. Also, in comparison with the other herpesviruses, HSV and cytomegalovirus are less efficiently transmitted during childhood.<sup>15</sup>

HSV infection was prospectively chronicled in a day-care center in North Carolina<sup>16</sup> among 115 children followed for 12 years. Thirty-seven percent were infected by age 5 years. Four clusters of infection occurred over the 12-year period but none involved more than six children (representing 55% of the infections). Forty-five percent of the infections occurred sporadically. Gingivostomatitis was identified in 26% but was not associated with increased transmission of HSV.

The HSV serology in U.S. college students was reported in 1990.<sup>17</sup> Thirty-seven percent of freshman had serologic evidence of infection with HSV-1 in the first year and 46% by the fourth year. Only 0.4% had HSV-2 serology in the first year, but 4.3% had it by the fourth year. Predictors of HSV-1 serology were female gender, African-American race, first intercourse before age 15 years, total years of sexual activity, and partners with oral sores. Predictors for HSV-2 serology were African-American race, years of sexual activity, and a history of other sexually transmitted disease. Swedish schoolgirls (*n* = 839) aged 14 to 15 years were followed prospectively for 15 years and reported in 1992.<sup>18</sup> At age 15 years, 23% were seropositive for HSV-1, but 50% were seropositive by age 30 years. At age 15 years, 0.4% were seropositive for HSV-2, but 22% were seropositive by age 30 years.

In a study from Africa, HSV-1 serology was present in greater than 80% in almost all age groups except young children.<sup>19</sup> HSV-2 serology was very high in certain groups, especially prostitutes (80%). In a Japanese study of 536 adults,<sup>20</sup> HSV-1 serology was common and correlated with age. HSV-2 serology varied widely from 7% among pregnant women to 23% among patients with sexually transmitted disease and 80% among homosexuals. Over the past several decades in Japan, they documented a decreasing prevalence of HSV-1 infection during childhood and an increasing incidence of the primary HSV infection being caused by a genital infection with HSV-2; they speculated that the clinical manifestations and health burden to Japan will increase because of this phenomenon.

**THE EPIDEMIC OF GENITAL HERPES**

HSV-2 is transmitted sexually by contact with infected genital secretions or mucocutaneous surfaces; acquisition is directly related to sexual activity. Most HSV-1 and -2 transmission, however, occurs during periods of asymptomatic shedding in the absence of recognized signs or symptoms of disease. Only a minority of persons who are HSV-2-seropositive have a history of symptomatic disease. Most patients (70%) are not aware of infection with genital HSV; with education, however, 50% can be taught to identify the clinical infection.<sup>21</sup> Virtually all persons who have symptomatic primary genital HSV-2 will experience both symptomatic recurrence and asymptomatic shedding. All of the seropositive patients have latent infection and probably experience reactivation at least occasionally. Shedding occurs about 1 to 2% of any given days, but is higher in the few months after primary infection.<sup>9</sup> A

recent study reported subclinical shedding of HSV in about 3% of patients who were seropositive for HSV-2, with an almost identical incidence in patients with a history of genital herpes and those with no history of genital herpes; 98% of 53 patients with no prior symptoms of genital herpes demonstrated clinical or virologic signs of recurrence during the study period (mean, 94 days).<sup>22</sup> We conclude that, among patients with HSV-2 seropositivity, asymptomatic patients shed just as often as symptomatic patients. Symptomatic genital HSV is estimated to be 500,000 annually in the United States with 40 to 60 million Americans (16–22% of the population) with latent HSV-2 infection.<sup>9,23</sup>

HSV-2 infections have risen dramatically in the middle class of Western industrialized countries in the past two decades,<sup>24,25</sup> such that at least one in six persons in the United States have a positive HSV-2 serology (Table 3).<sup>26</sup> A sobering study in the *New England Journal of Medicine* in 1997<sup>27</sup> reported a 31% increase in HSV-2 serology in the previous 13 years in the United States. This marked increase in HSV-2 seropositivity in the United States with the marked shift toward younger age<sup>27</sup> has also been reported in other countries.<sup>25,28</sup> The *New England Journal of Medicine* study reported that 21.9% of adults over the age of 12 years have HSV-2 serology; yet less than 10% of these (2.6% of the total) reported a history of genital infection. The seroprevalence was higher among women (25.6%) than men (17.8%) and higher among African-Americans (45.9%) than whites (17.6%). Patients who practice unprotected sex with multiple sexual partners are guaranteed to risk exposure. Positive predictive factors of HSV-2 serology in that study included female gender, African-American or Hispanic race, older age, less education, poverty, cocaine use, and multiple sexual partners. The rate had quadrupled among white teenagers and doubled among whites in their twenties in the past decade. There was a mild increase in African-Americans and older whites. The authors also concluded that a genital ulcer in a patient with HSV-2 serology is more likely to represent the reactivation of a previously unrecognized HSV-2 infection and is not traceable to a recent sex partner; silent spread is the rule and not the exception.

Various previous series have evaluated the prevalence of HSV-2

**TABLE 3. The epidemic of genital HSV**

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HSV-2 infections have risen dramatically in developed countries in past 2 decades
21.9% of adults in United States are HSV-2-seropositive (1994 data)
Women (25.6%), men (17.8%), blacks (45.9%), whites (17.6%)
Quadrupled among white teenagers and doubled among white adults
Lower rate of HSV-2 in Japan (7% among pregnant women in 1998 study)
Low rate of HSV-2 in Italy (0.1% among healthy young men in 1988 study)
Low rate of HSV-2 in Spain (3.6% among men and women in 1999 study)
Most seropositive for HSV-2 have no history or symptoms
Spread of infection occurs by both symptomatic and asymptomatic patients
Genital shedding occurs about 5% of days
Factors correlated with the increase in HSV-2
Sexual activity among adolescents, increased number of sex partners, high frequency of asymptomatic infections, decreased use of barrier contraception, reduced proportion of adolescents with partial immunity to HSV-1
In the absence of modulating HSV-1 antibody, HSV-2 genital infection more severe
HSV genital infection increases risk of acquisition of HIV infection
An increasing proportion of genital HSV is caused by HSV-1
10% in United States (increasing) but up to 50% in Europe
Makes interpretation of serologic data more problematic
The clinical appearance of these infections may differ from HSV-2 infections

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serology in the United States population. It ranged from 0% in children and celibate adults and increased to 35% by age 60 years, but may be present in 80% of prostitutes.<sup>29</sup> It correlated with the following: African-Americans, women, divorced, city residents, patients with multiple sex partners, early age of first intercourse, years of sexual activity, female prostitutes (75%), male homosexuals (83%), and history of other sexual transmitted disease.<sup>11</sup> HSV-2 serology was found in 30 to 50% of persons in a sexually transmitted disease clinic, but only a minority of patients reported the clinical manifestations.<sup>24</sup> HSV-2 serology has been reported in 7.6% of random blood donors and 22.7% of patients in a genitourinary clinic, with only 30% of the latter having diagnosed genital herpes.<sup>28</sup> Other studies correlate the increasing prevalence of HSV-2 in the past decade with the increasing sexual activity of adolescents, increased number of sexual partners, high frequency of asymptomatic infections, decreased use of barrier contraceptive, and reduced proportion of white middle class adolescents who had partial immunity to HSV induced by childhood HSV-1 infection.<sup>30</sup> Although there is a higher prevalence of HSV-2 seropositivity among women, men are more effective vectors of transmission.<sup>2</sup> In one study correlating racial features in the United States reported in 1989,<sup>23</sup> HSV-2 serology was positive in 20% of white men, 25% of white women, 40% of African-American men, and 60% of African-American women.

The serology of HSV-2 was considerably different in one study from Italy reported in 1988.<sup>31</sup> HSV-2 serology was reported in 0.1% of healthy young men ( $n = 1,169$ ), in 4.8% of health workers ( $n = 411$ ), and in 55% of homosexuals ( $n = 397$ ). In a 1999 report from Spain,<sup>32</sup> the overall prevalence of antibodies to HSV-2 was 3.6% and was about equal in men and women; HSV-2 serology was not associated with increasing age. In a study contrasting Greenland and Denmark reported in 1988,<sup>33</sup> HSV-2 serology was found in 68.2% of Greenland women but in only 30.9% of Danish women. They correlated the positive serology to HSV-2 with cervical cancer rates. The seroprevalence of HSV-2 is also very high (70%) among patients with cervical cancer in India<sup>34</sup> although the association of HSV-2 with cervical cancer remains unclear.

A substantial number of women entering their childbearing years are infected with HSV-2 or are at risk of contracting infection because their partners are more likely to be infected; their infants will be exposed to HSV-2 at delivery. The risk of a susceptible woman contracting HSV from an infected man is 80% after a single contact.<sup>11</sup> Transmission of HSV-2 between monogamous sexual partners with discordant infection status is 10 to 15% yearly.<sup>11</sup>

There may be other implications of this earlier acquisition of HSV-2. First episodes of HSV-2 in the presence of preformed HSV-1 antibody results in milder episodes of HSV-2 infection with a lower frequency of signs and symptoms and a shorter duration, probably because of a partial protection.<sup>35,36</sup> One study reported that previous HSV-1 infection did not reduce the rate of HSV-2 infection but it did increase the likelihood of asymptomatic seroconversion, as compared with symptomatic seroconversion, by a factor of 2.6.<sup>37</sup> In the absence of HSV-1 antibody, HSV-2 genital infection can be severe. This HSV-2 infection, because it is an ulcerative disease, may further increase the risks of acquisition of HIV, as indicated by increased relative risks of 1.5 to 2.0.<sup>11</sup> When HSV-2 causes genital ulcers, the mucocutaneous barriers are disrupted and CD4<sup>+</sup> T cells move to the site, thus making the transfer of HIV from an infected person more likely.<sup>38</sup> The presence of

genital ulcers increases the transmission of HIV, and the presence of HIV adversely affects the natural history of HSV infection.<sup>39</sup> The rates of HSV seropositivity are very high in HIV-infected persons; a study in Baltimore revealed HSV-2 seroprevalence of 81% among homosexual or bisexual men who were HIV-positive.<sup>40</sup>

The frequency of recurrences of genital HSV varies among individuals. One third of patients are estimated to have recurrences in excess of eight or nine per year and one third will have between four and seven recurrences per year.<sup>11</sup> Recent studies have suggested a high frequency of HSV DNA in genital secretions, as detected by PCR, between clinical recurrences,<sup>35</sup> confirming the continued asymptomatic shedding of this virus. The frequency of clinical recurrences of HSV-2 genital disease varies somewhat between men and women, with calculations of 2.7 and 1.9 recurrences per 100 days, respectively.<sup>11</sup> Overall, several studies have calculated that the frequency of clinical recurrences is as high as 60%<sup>11</sup> for women with established genital HSV-2 infections and asymptomatic shedding is detected on at least 1 to 5% of days when cultures are performed.<sup>11</sup> In one study, women shed HSV-2 on 28% of days but only 40% of these had clinical signs.<sup>36</sup> When PCR is used to evaluate serial genital swabs from women with genital infection, a significant increase in the frequency of HSV DNA shedding is observed, suggesting chronic infection rather than intermittent infection.<sup>11</sup> The asymptomatic and perhaps chronic shedding from genital HSV probably explains the recent explosion in HSV-2 serology prevalence. In a review paper on genital herpes the authors concluded "Herpes infection cannot accurately be described as a recurrent disease, but as a chronic infection of the sensory ganglia with variable levels of epithelial expression".<sup>41</sup> Although precise data on genital shedding is lacking, emerging data suggests that reactivation and viral shedding persist for at least 8 to 10 years.<sup>35</sup>

This increase in genital HSV occurred at a time when the practices recommended for reducing HIV transmission were being promoted and were effective, suggesting that this same approach may not be effective for prevention of transmission of genital HSV or, alternatively, that people at risk of HSV-2 are not sufficiently motivated to adopt safer practices. Although antiviral therapy suppresses clinical and subclinical shedding, shedding still occurs at a low frequency and titer during antiviral therapy.

An increasing proportion of genital infections, moreover, is attributable to HSV-1 rather than to HSV-2.<sup>11,42-44</sup> The decreasing prevalence of HSV-1 before puberty in the affluent or developed countries and the increase in orogenital sexual practice have lead to a change in the epidemiology of HSV-1 and -2. HSV-1 is now causing disease in a territory formerly inhabited exclusively by HSV-2 and vice versa. Among sexually active adults, new genital HSV-1 infections are as common as new oropharyngeal HSV-1 infections, probably with a correlating association.<sup>37</sup> The frequency of HSV-2 in the orofacial and ocular area has not been recently chronicled. Because HSV-1 seropositivity may provide partial protection against HSV-2 infection,<sup>35</sup> the clinical manifestations of HSV-2 infection are probably more pronounced in the absence of HSV-1 serology.<sup>45</sup>

Genital infections by HSV-1 are usually both less severe clinically and are less prone to recur than HSV-2 genital infections.<sup>11</sup> In the United States, approximately 10% of genital HSV is caused by HSV-1, but this percentage is increasing;<sup>9</sup> it is estimated that 2 to 15% of all patients who are HSV-1-seropositive have genital

involvement by HSV-1.<sup>46</sup> About one third of new cases of genital HSV are possibly caused by HSV-1, worldwide.<sup>47</sup> In Edinburgh, Scotland, genital infection caused by HSV-1 has increased from 20 to 40%.<sup>48</sup> In one study from England reported in 1990,<sup>49</sup> genital HSV was caused by HSV-1 in 48% of women and 29% of men. In some areas of the United Kingdom, 50% of cases of primary genital HSV are now caused by HSV-1.<sup>48,50,51</sup> These studies implicating HSV-1 in genital infections make interpretation of serologic data in the literature more problematic because most genital infections are silent—an increasing number may be caused by HSV-1—and, therefore, HSV-2 serology alone cannot estimate the prevalence of genital herpes. In a prospective study of new infections, nearly 40% of newly acquired HSV-2 infections and nearly two thirds of new HSV-1 infections were symptomatic (experienced physicians conducted the study).<sup>37</sup> Among sexually active adults, the new genital HSV-1 infections were as common as new oropharyngeal HSV-1 infections.

The recurrence patterns of HSV-1 and -2 are different. HSV-1 tends to recur in the orofacial area but not in the genital area after primary infection at one of these sites; conversely, HSV-2 tends to recur in the genital area but not in the orofacial area after primary infection at one of these sites. Subclinical shedding of HSV-1 after genital infections occurs at less than one third of the frequency of the shedding of HSV-2 after genital infections.<sup>36</sup> Ninety-five percent of recurrent genital symptoms result from HSV-2.<sup>52</sup> Although 90% of symptomatic primary genital infections with HSV-2 will have a recurrence of symptoms, only 60% of those with HSV-1 genital infection will have recurrent symptoms. Among 664 persons with genital HSV followed for more than 14 months,<sup>21</sup> the recurrence rate was about one per year if HSV-1 caused the primary genital herpes; the recurrences were about five per year if HSV-2 caused the primary genital herpes. Over time, the HSV-2 recurrences become less frequent, but there is considerable variability among patients.

**OCULAR HSV EPIDEMIOLOGY**

There have been several epidemiology studies of HSV ocular disease, although all remain limited in scope and confirmation. HSV, nonetheless, appears to be the most common infective cause of blindness in many developed countries,<sup>53</sup> primarily because of its recurrent nature. The primary reports to be summarized include the studies from Moorfields Eye Hospital in London, the epidemiology studies from Rochester, Minnesota, and the Herpetic Eye Disease Study (HEDS) funded by the National Eye Institute (Table 4). Ocular disease may be classified as primary or recurrent and may also be classified as blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, iridocyclitis, or retinitis based on the inflamed tissue. Recurrences are typically with the same strain and may be triggered by fever, hormonal changes, ultraviolet exposure, psychological stress, ocular trauma, and trigeminal nerve manipulation.<sup>10</sup> The excimer laser has been shown to be an efficient trigger for reactivation of latent HSV-1,<sup>54</sup> but there has not been a recognized epidemic of HSV keratitis after the recent boom in refractive surgical procedures.

**Moorfields Studies**

Investigators from Moorfields Hospital in London have looked at the epidemiology of ocular HSV disease with several different

**TABLE 4. Ocular HSV epidemiology**

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Recurrences caused by same strain of virus as initial infection
Known triggers to reactivation; no recognized epidemic despite refractive surgery
Ocular HSV is at least six times more prevalent after corneal transplant surgery
Up to 21% of acute conjunctivitis may be caused by HSV
Recurrent HSV can present with isolated lid, conjunctival, epithelial, stromal or intraocular inflammation (most recurrences do not affect the cornea)
Recurrences in 20% by 2 y, 40% by 5 y, and 67% by 7 y
About 20–25% develop stromal keratitis
Over 90% of patients maintain good visual acuity despite prolonged disease
Epidemiology of ocular HSV (reported in 1988)
New episodes of HSV: 8.4/100,00/y
All episodes of HSV: 20.7/100,000/y
Prevalence of HSV: 149/100,000 people
Bilateral disease in about 10–12%: more common in atopes, immunosuppressed
Oral acyclovir effective in decreasing incidence of recurrent HSV ocular disease
Oral acyclovir not effective in preventing subsequent stromal keratitis or iritis
Oral acyclovir not effective in stromal keratitis
Topical steroids reduce persistence/progression of stromal inflammation
Topical steroids do not significantly increase risk of recurrent epithelial disease
HSV keratitis tends to be more severe in children
Despite multiple laboratory techniques, ocular HSV is difficult to confirm
HSV in patients with HIV has same clinical course, except for increased recurrence rate

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studies over decades. In a series of patients with acute follicular conjunctivitis and keratoconjunctivitis reported in 1978,<sup>55</sup> there were 25 cases of herpes simplex. Most of these were in the age range of 20 to 35 years and five of these developed typical herpetic lesions on the lids or cornea. They emphasized for the first time the presentation of primary HSV as conjunctivitis in adults.<sup>55</sup> In a further series of all patients with acute conjunctivitis reported in 1984, 21% were determined to have HSV as the etiology.<sup>56</sup>

Primary ocular HSV infections between 1973 and 1980 were detailed in 108 patients.<sup>57</sup> All ages were represented with the mean age for this first episode of ocular HSV being 25 years. Sixty-four percent were over the age of 15 years and 7% were under the age of 5 years. An upper respiratory infection was present in 35% and generalized symptoms, in 31%. Moderate or severe conjunctivitis was present in 84%; moderate or severe blepharitis was present in 38%. During this first episode of ocular HSV, dendritic ulcers occurred in 15% and disciform keratitis in 2%. Seven percent had acute follicular conjunctivitis only and in 15%, a chronic blepharoconjunctivitis lasted for months. Overall, moderate disease occurred in 38% and severe disease, in 15%. The disease was unilateral in 81% and bilateral in 19%. The observed ocular HSV infections were probably modulated by previous systemic infection with HSV-1, which was prevalent at the time of the study.

These same 108 patients with primary ocular HSV were then followed for 2 to 15 years to determine the pattern of recurrent disease.<sup>58</sup> Thirty-two percent had a recurrence, which was more frequent in patients under the age of 20 years. Of those with a recurrence, 49% had 1 recurrence, 40% had 2 to 5 recurrences, and 11% had 6 to 15 recurrences. The interval between attacks shortened with time. Patients with more severe conjunctival signs during primary ocular HSV infection had a higher incidence of recurrent infection; severity of corneal signs had no influence on the incidence of recurrent infection. Recurrences usually occurred ei-

ther as conjunctivitis or lid lesions; corneal disease was uncommon. Of those with a corneal infection during the primary episode, only 31% developed a recurrent infection. Only 9% had a dendritic ulcer during a recurrence and only one patient had disciform keratitis. Therefore, most recurrences did not involve the cornea.

The prognostic factors for recurrence of HSV were identified in a different series of 152 patients followed for 5 years after epithelial keratitis.<sup>59</sup> The average age was 49 years with 64.5% being male. At entry into the study, 119 had a history of a prior dendritic ulcer (78%) and 22% had a history of a prior geographic ulcer. Fifty-five percent of the latter were taking steroids. Forty percent had a recurrence of epithelial disease within 5 years; 21% had more than one recurrence. Twenty-five percent developed stromal keratitis, of which 63% had a disciform keratitis and 37% had an irregular stromal keratitis. Five percent developed ocular hypertension. On final evaluation, vision was 20/20 to 20/40 in 73%, 20/60 to 20/200 in 24%, and less than 20/200 in 3%. Only 6% of the total 152 eyes had poor vision related to stromal keratitis, despite 22% of eyes having stromal scarring. There was no correlation of treatment with topical antiviral on the recurrence rate. Ocular surgery was performed on three patients (one penetrating keratoplasty).

A random selection was made of a 1-week period in July 1994, during which all patients with ocular HSV were categorized.<sup>60</sup> Of 229 patients seen that week, 39 patients were identified. In comparison with prior studies, the authors felt that the prevalence of ocular HSV disease had decreased but that the resultant visual impairment had worsened. The predominant disease being treated was stromal keratitis (at this referral institute) and patients had significant morbidity and visual handicap. It was their impression that age of onset, gender, and the incidence of bilateral disease had not changed in 20 years.

### Rochester, Minnesota Series

In the study by Liesegang et al.,<sup>53</sup> 122 patients with their first recognized clinical episode of ocular HSV were followed for up to 33 years. In this study, ocular HSV was defined as any lid, conjunctival, and corneal disease between 1950 and 1982. The incidence (age-adjusted) was calculated to be 8.4 new cases per 100,000 people per year. The initial episodes involved the lids or conjunctiva in 54%, the superficial cornea in 63%, the deep cornea in 6%, and the uvea in 4%.

The incidence of all episodes was calculated at 20.7 cases per 100,000 people per year. The prevalence of ocular HSV disease in the community was calculated at 149 per 100,000 population. There was no evident seasonal trend. The mean age of onset was 37.4 years, which increased slightly each decade of the 33-year study. There was a shorter time interval between recurrences with each recurrence. The recurrence rates for any form of ocular disease was 9.6% at 1 year, 22.9% at 2 years, 36% at 5 years, and 63.2% at 20 years; the rates increased with subsequent repeated episodes. Other recurrence rates reported in the ophthalmic literature ranged from 22.9 to 33% at 2 years, 40% at 5 years, and 67% at 7 years.<sup>53,61-63</sup>

The disease was bilateral in 11.9%; other studies in the literature vary because most prior studies limited the definition to bilateral corneal involvement. The predominant form of recurrent disease was dendritic corneal involvement, although 20% had only recurrent lid involvement. Of 151 patients with recurrent disease, 28 (20%) developed stromal disease. Patients tended to get a recur-

rence of the same type of ocular disease they had previously, that is, patients with epithelial disease tended to get recurrent epithelial disease; this was similar for conjunctival disease and stromal disease. The average length of debility during the first episode was 17 days (average 4 visits to the ophthalmologist) but increased to 28 days with recurrent episodes (average 5.9 visits to the ophthalmologist). Of 131 eyes, 91 maintained 20/20 vision; only 3 of 131 eyes had final vision that was worse than 20/100. In this series, no cases of retinal or neonatal herpetic disease were recognized. The epidemiology of ocular herpes simplex was contrasted with other herpetic disease in the Rochester community in the 1970s and early 1980s; it was demonstrated that ocular HSV is less common than other herpetic diseases (Table 5).

### HEDS Study

The HEDS study evaluated patients from different therapeutic perspectives but yielded valuable epidemiologic data. Patients were selected for the study so they do not represent the entire spectrum of patients with ocular HSV disease. Patients were limited to over 12 years of age; pregnant or nursing women or patients on systemic corticosteroids or previous penetrating keratoplasty were excluded. After a prior episode of ocular HSV, 703 immunocompetent patients were treated with 400-mg acyclovir or placebo twice daily with 12 months of treatment and 6 months of observation.<sup>64</sup> In this somewhat selective group, 54% were men. The average age was 49 years with 79% Caucasians, 9% African-American, 8% Hispanic, and 3% Asians. All had ocular HSV within the previous 12 months. Before entry into the study, 29% of the patients had one episode of ocular HSV, 33% had two or three episodes, and 39% had more than four previous episodes. Disease within the previous 12 months included blepharitis or conjunctivitis only (4%), epithelial disease with no stromal disease (47%), stromal and epithelial disease (32%), stromal with no epithelial disease (16%), and iritis only (1%). There was a history of orofacial HSV disease in 49% and a history of genital disease in 1%. A recurrence of some form of ocular HSV occurred in 19% of acyclovir-treated and 32% of the placebo-treated ( $p < 0.001$ ) during the 18 months of the study. There was a recurrence of stromal disease in 14% of the treated group and 28% of the placebo group ( $p = 0.005$ ). There was a recurrence of non-ocular HSV in 19% of the acyclovir-treated and in 36% of the placebo-treated ( $p = 0.001$ ). The beneficial effect of acyclovir was established and there was no rebound after acyclovir was withdrawn. Earlier studies, before oral acyclovir, reported that patients with HSV stromal keratitis had recurrent HSV stromal keratitis in 27 to 64% of eyes within 2 years.<sup>65,66</sup>

A 3-week course of oral acyclovir was used as prophylaxis to prevent HSV stromal keratitis or iritis in patients being treated for active epithelial keratitis with topical trifluridine.<sup>67</sup> There were

**TABLE 5.** Comparative frequency of herpetic diseases in Rochester, Minnesota

Disease	Incidence/100,000/y	Reference
Ocular HSV	8.4	53
Genital HSV	50 (in 1965)	147
Genital HSV	128 (in 1979)	147
Herpes zoster	125	148
Herpes zoster ophthalmicus	11.7	148
Neonatal HSV	(0 in 12,500 births)	147

289 patients who were studied: 153 in the acyclovir group and 134 in the placebo group. This was the first episode of ocular HSV for 46% (133) of the patients. There was a history of epithelial keratitis in 145 patients, prior epithelial keratitis but no history of stromal keratitis or iritis in 105, and prior epithelial keratitis plus a history of either stromal keratitis or iritis in 40. Thirty-nine patients had previous HSV stromal keratitis and 11 had previous HSV iritis. Two patients had stromal keratitis without epithelial keratitis and one patient had iritis without a history of epithelial keratitis. HSV stromal keratitis or iritis developed in 11% of 153 patients in the acyclovir group and 10% of 134 patients in the placebo group; the development of stromal keratitis, however, was more frequent in patients with a prior history of HSV stromal keratitis (23 vs. 9%). This was different than an analysis of several series in the literature, which suggested that 25% develop stromal keratitis or iritis after epithelial keratitis, with 75% developing it in the first year.<sup>67</sup> The authors concluded that there was no apparent benefit from oral acyclovir in preventing subsequent stromal keratitis or iritis. Patients in the acyclovir group tended to have fewer recurrences of epithelial keratitis during the 3-week treatment period but more during the remainder of the 12 months of follow-up than the patients in the placebo group.

The HEDS study evaluated the effect of topical steroids on HSV stromal keratitis.<sup>68</sup> Among 106 patients, the type of stromal keratitis was nonnecrotizing in 91%, necrotizing in 6%, and mixed in 3%. Iridocyclitis was present concomitantly in 36% and a high intraocular pressure (trabeculitis) in 16%. Despite all patients having stromal keratitis, the final vision in this series was 20/40 or better in 67%, 20/50 to 20/190 in 22%, and 20/200 or worse in only 10%. The topical corticosteroid regimen used in the study was significantly better than placebo in reducing persistence or progression of stromal inflammation and in shortening the duration of HSV stromal keratitis. Postponing steroids during careful observation for a few weeks delayed resolution of stromal keratitis but had no detrimental effect as assessed by visual outcome at 6 months.

The HEDS study evaluated patients for the effect of oral acyclovir on HSV stromal keratitis.<sup>69</sup> Among the 104 patients randomized, the type of stromal keratitis was nonnecrotizing in 88%, necrotizing in 7%, and mixed in 5%. Iridocyclitis was present concomitantly in 30% and a high intraocular pressure (trabeculitis) was present in 14%. Despite all patients having stromal keratitis, the final vision in this series was 20/40 or better in 65%, 20/50 to 20/190 in 27%, and 20/200 or worse in 8%. There was no statistical or clinically significant beneficial effect of oral acyclovir in patients already being treated with topical steroids and trifluridine with regard to time-to-treatment failure, proportion of patients who failed treatment, proportion of patients whose keratitis resolved, time-to-resolution, or 6-month best corrected visual acuity.

The HEDS study evaluated the risk factors for HSV epithelial keratitis recurring during treatment of stromal keratitis or iridocyclitis.<sup>70</sup> Epithelial HSV recurred in 4.6% of 260 patients during the follow-up period of 16 weeks. It recurred in 2% of the topical placebo-treated patients ( $n = 49$ ), in 6.5% of the topical steroid-treated with no acyclovir ( $n = 138$ ), and in 2.7% of the topical steroid-treated with acyclovir ( $n = 73$ ) (no significant differences). This study differs markedly from the literature in that Patterson and Jones<sup>71</sup> showed 42% recurrence in a placebo group compared to 15% in an idoxuridine-treated group. Sundmacher<sup>65</sup> reported 21% recurrence in the placebo and 0% in a trifluridine

treated group. A prior study suggested an equal protective effect of either topical antiviral or oral acyclovir.<sup>72</sup> In the HEDS study, there was a suggestion that oral acyclovir may have additive suppressive effects in patients on topical steroids; however, HSV occasionally recurred despite combined treatment with oral and topical antiviral agents. These studies also confirmed that patients with multiple prior episodes of HSV tended to have future recurrences.<sup>73</sup> Patients who are more likely to have recurrence of HSV epithelial keratitis include patients with prior HSV epithelial keratitis and nonwhite patients. Adverse effects of trifluridine prophylaxis included acute allergic blepharoconjunctivitis in 3.8% and corneal epithelial erosions in 4.2%.

### Other Ocular HSV Studies

The recurrence rate of epithelial keratitis in the United States was reviewed in 1981 among patients with at least two prior episodes of epithelial herpetic disease.<sup>63</sup> The estimate of recurrence of epithelial herpes was 24.5% within 12 months and 32.9% within 24 months. Short intervals between attacks tended to be associated with short intervals between future attacks. These recurrence rates were higher than other studies because they already selected patients who had two prior epithelial episodes.

HSV keratitis in children tends to be more severe, with a higher incidence of geographic ulcers as compared to adults.<sup>74</sup> In a series of 31 eyes with HSV keratitis in children reported from Dublin,<sup>74</sup> there was more astigmatism, reduction of vision, and recurrences as compared to studies in adults. In children with geographic or disciform keratitis, 89% had reduced visual acuity, 78% had induced astigmatism, and 87% had recurrences. A prior study of HSV keratitis in 21 children also emphasized the frequent recurrences and visual loss in children.<sup>75</sup>

Ocular HSV was studied over a 30-year period in Japan in 370 eyes of 356 patients. The patients were divided into a 1963–1979 group and a 1980–1992 group, primarily to determine whether there has been a change in the natural history since the introduction of acyclovir ointment in 1980.<sup>76</sup> The earlier group had its highest incidence in the age range of 30 to 39 years (mean, 36.0 years); the later group had its highest incidence in the age range of 40 to 49 years (mean, 40.0 years). The mean age of patients with primary HSV keratitis was 7.06 years in the earlier group but was 24.2 years in the later group ( $p < 0.005$ ); the authors concluded that this correlated with the entire Japanese population contracting herpes simplex disease at a later age. Other studies have confirmed a decrease in HSV serology among adults in Japan.<sup>77</sup> Men predominated both series. The predominant ocular disease was epithelial, present in 50 to 57%; stromal disease was present in 39 to 49% and endotheliitis in 0 to 4%. Severe stromal keratitis was seen in less than 10%. In evaluating their data, the authors found no change in the clinical types of ocular HSV seen over the previous 30 years. Bilateral keratitis (usually epithelial only) was seen in 9.4%; it was more frequent in men, younger patients, and atopic patients (36%). The authors found a significant decrease in recurrence rates in the acyclovir-treated (17.5%) versus idoxuridine-treated patients (52.9%;  $p < 0.05$ ).

Ocular HSV was evaluated in South India between 1995 and 1997.<sup>78</sup> There were 234 patients (2.1:1, male:female ratio) among 3,000 patients attending a corneal clinic. The mean age of the patients with ocular HSV was 29 years (range, 9 months to 65 years) with no seasonal variability identified. There were 137 primary ocular HSV episodes and 97 recurrent ocular episodes. Re-

currences were more frequent in men, consistent with other studies.<sup>53,73,79</sup> Among the primary episodes, 50% occurred among adolescents and young adults, with only 10% under the age of 5 years. The authors felt this was a higher age than was previously reported, but provided no supporting data.<sup>80</sup> One hundred fifty-three patients had epithelial disease and 81 had stromal keratitis. Among the patients with epithelial disease, 68% had dendritic keratitis, 11.1% had geographic keratitis, and 9.8% had punctate epithelial keratitis. Among the patients with stromal keratitis, disciform keratitis was present in 28.2% and necrotizing keratitis in, 6.4%. The major focus of the study was to evaluate laboratory tests in aiding the diagnosis; using multiple diagnostic tests (viral culture, HSV-specific antigen detection by indirect immunofluorescence, serum immunoglobulin G [IgG] or IgM, or tear secretory IgA), only 34.2% of clinically suspected HSV cases could be confirmed.

The incidence of ocular HSV per 100,000 people per year has been estimated at 4.1 in Croatia<sup>62</sup> and 5.9 to 12 in Denmark,<sup>61,81</sup> compared to 20.7 in Rochester, Minnesota.<sup>53</sup> The incidence of HSV epithelial keratitis is six times (120 per 100,000 people per year) higher in patients who have undergone corneal transplantation (for non-herpetic corneal disease).<sup>82</sup>

There is only one study on the incidence of adult ocular disease caused by HSV-1 as compared to HSV-2; this was reported in 1978 from Germany.<sup>83</sup> In a continuous series of 457 patients, virus isolation and typing revealed 154 patients with HSV-1 and three patients with HSV-2. There is no recent large study to determine whether that frequency has changed. There is at least one report of simultaneous HSV-1 and -2 infecting a cornea in a patient with AIDS.<sup>84</sup> Approximately 10% of corneal transplants in the United Kingdom between 1987 and 1991 were performed because of HSV keratitis.<sup>85</sup>

The frequency of bilateral ocular HSV varies in the literature, partially because the definition of bilateral disease varies; some report any form of lid, conjunctival, or corneal disease and others report only keratitis. Atopy, HIV infection, and other forms of immunosuppression predispose to prolonged or bilateral disease.<sup>10,86,87</sup> In a series of 1,000 patients with ocular HSV keratitis, 30 patients (60 eyes) or 3% had a history of bilateral corneal dendrites.<sup>88</sup> Seventy percent were men and atopic disease was present in 40%. There was a recurrence in 41 of the 60 eyes (68%) and stromal disease occurred in 24 of the 60 eyes (40%). Patients with bilateral disease tended to be younger and had a higher proportion of ocular complications. In a series of 356 patients followed over 30 years in Japan, bilateral keratitis was found in 9.4%.<sup>76</sup> It was more frequent in men and younger patients, although 36% were atopic. In this series, HSV usually affected the epithelium only. In the community-based series from Rochester, Minnesota, that was followed over 33 years,<sup>53,73</sup> ocular HSV was defined as any form of herpes simplex, including lid, conjunctival, or corneal. Using this definition, 11.9% (18 patients) had bilateral ocular HSV; 5 of these 18 patients (28%) were atopic. Most bilateral episodes represented lid and conjunctival disease at their first episode of ocular HSV. Simultaneous corneal involvement was seen in only one patient.

Several studies reviewed the circannual rhythm of ocular HSV with most studies reporting a more frequent occurrence during the winter months. One specific study evaluated the circannual rhythms of ocular HSV among 541 patients over a 14-year period in Israel.<sup>89</sup> A peak was found in January, but only for epithelial

keratitis and only in men; atopic patients, however, had a higher incidence in September. There was no association of rhythms and triggers for upper respiratory infection. In a study in the United States, November through February was found to have the highest frequency of ocular HSV recurrences<sup>90</sup>; another study found the peak frequency in November.<sup>53,73</sup> In a study from Japan, the highest number of episodes occurred in the December to February months (winter and spring in Japan).<sup>76</sup>

The role and frequency of ocular shedding (either spontaneous or induced) in recurrent ocular disease is far from clear. There are useful animal models with predictable induced ocular shedding. Animal models have also been shown to demonstrate spontaneous asymptomatic HSV ocular shedding, but there are significant species differences.<sup>91,92</sup> In humans, the data are conflicting and confusing; asymptomatic shedding has been found in up to 30% of humans,<sup>93</sup> whereas a more recent study failed to detect any ocular shedding.<sup>94</sup>

The incidence and clinical profile of ocular HSV was compared in patients who were positive and negative for HIV.<sup>95</sup> Seven cases in the HIV-positive group were identified and contrasted with 27 cases in the HIV-negative group. There was no statistically significant difference between the groups for any of the outcome measures, except for recurrence rates. The recurrence rate was 2.48 times more frequent among patients positive for HIV. Except for recurrence rate, the incidence and clinical course of HSV keratitis in this study was no different among patients positive and negative for HIV. Unlike cytomegalovirus and varicella-zoster virus infections, ocular HSV does not seem to be a major problem among patients who are HIV-positive. They did not confirm a lower incidence of stromal keratitis, as was suggested in a prior study.<sup>96</sup> There is at least one report of simultaneous HSV-1 and -2 infecting a cornea in a patient with AIDS.<sup>84</sup>

## CONGENITAL AND NEONATAL HSV

HSV-1 and -2 can be acquired in utero, by transplacental or ascending infection, by exposure to genital lesions during delivery, or postnatally from relatives or attendants.<sup>97</sup> There is a spectrum of clinical manifestations of HSV infection depending on the stage or trimester when HSV is contracted.<sup>98</sup> The route of viral transmission may play a role in clinical manifestations. Intrauterine acquisition of the virus is thought to comprise just 4% of neonatal HSV, whereas 86% of infections are thought to occur at the time of birth, with the remaining 10% presenting as postnatal infections.<sup>99</sup> Congenital infection is characterized by the triad of skin vesicles or scarring, eye disease, and microencephaly or hydranencephaly. Typical findings of congenital ocular HSV infection include microphthalmos, retrolental masses, retinal dysplasia, cloudy lenses, optic atrophy, and retinal scarring. Congenital HSV retinitis is associated with other clinical evidence of intrauterine infection with HSV-1 or -2. Congenital HSV occurs in mothers who have a new onset HSV-2 genital disease during pregnancy. The history can sometimes be elicited, but there are usually no active genital infections in mothers at delivery.

Neonatal HSV infection is characterized by an equal male to female ratio, lower socioeconomic class, and usually first full term pregnancy.<sup>100</sup> It is a bilateral disease in infants occurring at 2 days

to 2 weeks of age.<sup>101</sup> Thirty percent of mothers have signs or symptoms of HSV genital infection around the time of delivery. Up to 50% infants are born prematurely. Skin involvement is observed in 80% (whereas 20% have no skin involvement to aid in making the diagnosis).<sup>100,101</sup> Active ocular infection occurs in 20 to 25% of neonates who are HSV-infected, with 5% developing HSV retinitis. Typical ocular findings in neonatal-acquired herpetic disease include corneal ulceration, anterior uveitis, cataract formation, vitreal inflammation, chorioretinitis, and optic atrophy.<sup>98</sup> The retina may be infected by direct viral invasion.<sup>102</sup> Retinal findings are usually not apparent until 1 month or later.<sup>101</sup> Most cases of neonatal HSV retinitis are associated with HSV infection of the central nervous system, but 20% are associated with conjunctivitis, keratitis, or dermatitis.<sup>103</sup> There is a higher prevalence of ocular infection (60%) when HSV encephalitis is present, and 20 to 25% of these may develop retinitis.<sup>103</sup> Although 35% of neonatal HSV disease is caused by HSV-1,<sup>104</sup> almost all neonatal HSV retinitis is caused by HSV-2; one exception has been reported.<sup>105</sup>

The epidemiology of neonatal HSV infection is better known than that of congenital HSV-related diseases. An increase in neonatal and congenital HSV was anticipated and is occurring because of the recent marked increase in genital herpes. Neonatal HSV has been reported in Denmark<sup>106</sup> at a rate of 2.36/100,000 live births from 1977 to 1984 and of 4.56/100,000 live births from 1984 to 1991. During this time, there were 30 infants with serious neonatal herpes. In California between 1985 and 1995, the rate of neonatal HSV was approximately 11.4/100,000 live births.<sup>107</sup> Neonatal HSV in Britain<sup>108</sup> was reported at a rate of 1.65/100,000 live births (76 infants). Among these 76 infants, the HSV infection was caused by HSV-1 in 25, by HSV-2 in 24, and unknown in 27. Disseminated infection occurred in 27 infants, encephalitis in 23, and localized infection in 26. Of all, 19 neonates died and 25 later died of sequelae. Most had symptoms only after discharge from the maternity ward and only two had the diagnosis antenatally. Most mothers had no symptoms or history, so antenatal screening is not effective.

In a Center for Disease Control study of neonatal herpes among 184 hospital-based cases reported in 1989,<sup>109</sup> only 22% of mothers had a history of genital infection and 9% of mothers had genital lesions at the time of delivery. Cesarean delivery failed to prevent infection. This study confirmed prior studies in that mothers of infected neonates usually have no history of genital HSV and are usually asymptomatic at delivery.<sup>110</sup> These findings put limitations on current preventive strategies.

In a study from Sweden in 1995 reporting 39 children with neonatal HSV,<sup>111</sup> 13 mothers had primary infection (6 with HSV-1 and 7 with HSV-2). Most neonates with HSV-1 infection recovered completely, whereas all but one with infection associated with HSV-2 died. The mean age of onset of disease was at day 7, most commonly as disseminated disease. Of the 20 mothers with recurrent herpes disease (2 with HSV-1 and 18 with HSV-2), most of the children had localized disease with onset at 14 days but with high neurologic sequelae. Two mothers had no serologic signs of HSV infection. Changes in the presentation of neonatal HSV infection over the past two decades include an increase in the frequency of skin, eye, and mouth disease with a relatively unchanged rate of central nervous system disease and a relative decline in disseminated infection.<sup>112</sup>

## EPIDEMICS OF HSV

Epidemics of HSV infections have been reported when nonimmune individuals are intimately exposed to another infected person. Herpetic whitlows are an occupational hazard for health care workers exposed to oropharyngeal secretions; it has an estimated incidence of 2.4 cases per 100,000 people per year.<sup>11</sup> Nosocomial outbreaks have occurred in neonatal nurseries, in intensive care units, and in dental practices. HSV-1 may spread through closed, susceptible populations of young children, such as nurseries and daycare centers.<sup>113</sup> HSV-1 skin infections have been transmitted in wrestlers (herpes gladiatorum) and rugby players.<sup>114</sup> Burn patients<sup>115</sup> are at risk, as well as other immunocompromised individuals. Prostitutes with HSV-2 can easily spread the disease with the appearance of an epidemic; anal and perianal HSV-2 infection can spread among homosexual men.

Most epidemics of HSV do not involve the eye but have been reported in wrestlers (herpes gladiatorum).<sup>116</sup> Of 175 wrestlers attending a 4-week intensive training camp, 60 (34%) developed HSV disease; 5 (8%) developed ocular involvement, mainly with follicular conjunctivitis, blepharitis, and phlyctenular disease. Epidemiologic studies confirmed the same strain of herpes simplex.

## OTHER OCULAR DISEASE CAUSED BY HSV

Acute retinal necrosis (ARN) is a severe form of necrotizing retinitis usually caused by HSV-1 in younger patients and varicella-zoster virus in older patients; HSV-2 is less commonly a cause.<sup>117</sup> A recent review of 28 patients with the ARN syndrome, however, detected varicella-zoster virus in aqueous or vitreous samples in 13 patients, HSV-1 in 7 patients (6 of these patients had HSV encephalitis), HSV-2 in 6 patients, and cytomegalovirus in 1 patient.<sup>118</sup> The authors conclude that varicella-zoster virus or HSV-1 causes ARN in patients older than 25 years, whereas HSV-2 causes ARN in patients younger than 25 years. A history of central nervous system infection in a patient with ARN syndrome suggests that HSV is likely to be the viral cause.

In a recent study of 16 cases of ARN from Japan, 7 were associated with HSV-2, 9 were associated with varicella-zoster virus, and none were associated with HSV-1.<sup>119</sup> The authors note that in Japan, HSV genital infection is caused by HSV-2 in only 34.5% of women and that the seroprevalence of HSV-2 in women is markedly lower in Japan (7%) compared to the United States (27.8%); these statistics may support their belief that HSV-2 is the cause for ARN in Japan. There may be genetic, biologic, or host sensitivity differences to explain the differences between reports in the United States and Japan.

Typical cases of ARN begin with retinal vasculitis and a diffuse uveitis. In the original definition of ARN syndrome, immunocompetency was a requisite.<sup>120,121</sup> The definition is now expanded to include immunosuppressed patients. In both healthy and immunosuppressed adults, HSV-1 has been shown to cause other types of ocular inflammatory syndromes that differ from classic ARN syndrome.<sup>120</sup>

HSV has been detected in the aqueous humor of patients with the Posner-Schlossman syndrome.<sup>122</sup> HSV has been implicated as a possible cause of Fuchs' uveitis syndrome<sup>123</sup> and the iridocorneal endothelial syndrome.<sup>124</sup> Linear endotheliitis is a form of HSV infection of the endothelium and has been reported with a variety of names in the literature, including keratitis linearis mi-

grans, presumed autoimmune corneal endotheliopathy, progressive herpetic corneal endotheliopathy, and idiopathic corneal endotheliopathy.<sup>125-131</sup> Several of these latter patients have had an anterior chamber paracentesis that disclosed a positive antibody to HSV antigen or detected HSV by PCR.<sup>127,128</sup> HSV has also been implicated in early corneal graft failure.<sup>132-134</sup>

The concept of corneal latency for HSV has been discussed in recent years, although no firm conclusion has been established.<sup>135,136</sup> If confirmed, the cornea would be the first human tissue other than nervous tissue to harbor latent virus and may place ocular tissue at a higher risk for recurrence and may also help distinguish the ocular epidemiology compared to the epidemiology of orofacial or genital recurrences.

### IMPLICATIONS FOR THE FUTURE OF OCULAR HSV

HSV disease is a significant health problem (Table 6).<sup>38,137-139</sup> The virus is latent in almost all older patients. Antiviral drugs do not eliminate latent virus. Asymptomatic shedding is common; these patients are contagious and the primary source of spread of the disease. Recent evidence suggests that chronic genital shedding may occur, at least in some clinical situations. Naturally infected persons can also still be reinfected, superinfected, or autoinoculated. Although most HSV infections are spread by close personal contact, some are contracted by fomites and medical-dental procedures. High at-risk groups includes patients with atopic disease, HIV, and immune-suppressed patients.

Assays of HSV-specific antibodies have been used in seroepidemiologic surveys in the past to confirm the presence of preexisting HSV-1; preexisting HSV-1 antibody reduces the severity of genital HSV-2 infection.<sup>139</sup> Because HSV-1 infection during childhood is decreasing, primary genital HSV-2 infection, with its higher frequency of clinical manifestations, is becoming a greater burden to the public health in the United States and the world.<sup>20</sup> The serologic prevalence of HSV-2 infections is rising at an alarming rate. At the same time, the epidemiology of genital HSV is changing with an increasing incidence of genital HSV caused by HSV-1. It is not clear how many patients may have both HSV-1 and -2 as a cause of genital HSV infection. The increasing acquisition rate of genital HSV among women of childbearing age has been associated with more neonatal herpes than in past decades.<sup>11</sup> Less than 10% of orofacial infections are caused by HSV-2, except in selected sexually active populations where oral-genital contact is frequent.<sup>12</sup> There are no recent studies concerning the incidence of ocular infection by HSV-1 versus HSV-2, except for the in-

creasing association of HSV-2 with ARN noted both in the United States and Japan.<sup>118,119</sup>

Previous HSV-1 or -2 infection of the eye or other sites is partially protective of subsequent ocular HSV reinfection, although the degree of protection or amelioration is unknown. The change in type (from HSV-1 to HSV-2) or a later age of acquisition may alter future patterns of ocular HSV. Viral reactivation and clinical recurrences occur despite humoral and cellular immunity. The local regional response may have more of an influence on recurrence than previously credited.<sup>5</sup>

Genital HSV-2 (and probably genital HSV-1) infection is a risk factor for HIV infection.<sup>140</sup> Breaks in the genital mucosal barrier and the recruitment of CD4<sup>+</sup> lymphocytes into areas of HSV replication increases the risk of acquisition of HIV.<sup>40,140,141</sup> Transmission of HIV to sexual partners may also be aided by the presence of genital ulcers. High levels of HIV have been documented in HSV lesions.<sup>142</sup> An acute HSV episode can result in increased HIV transcription and plasma virus load.<sup>143</sup> Thus, HSV may be a cofactor in the acquisition of HIV infection, or may contribute to in vivo activation of HIV or may cause severe infections. HSV keratitis in patients with HIV has more recurrences, but the incidence and clinical course does not appear to be different from patients who are HIV-negative.<sup>95</sup> With a growing population of iatrogenically immunocompromised patients from organ and autologous bone marrow transplantation and the increased number with HIV infection, there will be more manifest herpetic infections in the future; more frequent use of day care facilities may also lead to a different age of acquisition of herpesviruses.<sup>144</sup> Although genital HSV may be a chronic infection, the frequency of symptomatic genital reactivation decreases over time in the majority of patients; however, the magnitude of the annual decrease is small and highly variable.<sup>21</sup>

Because of the increased incidence of genital HSV, the association of genital HSV with increased risk of acquiring HIV, and the increased rate of neonatal HSV, every effort should be made to prevent genital HSV infections. Studies reported in 1988 estimate that there are approximately 20,000 new cases of ocular HSV each year and 48,000 total episodes with a prevalence in the population about 400,000 affected people in the United States.<sup>145</sup> It is not known whether this rate has increased to correspond with the increase in HSV-2 serology and whether the ocular cases are more frequently associated with HSV-2 now.

Physicians and the public need to be aware of this epidemic and need to increase safe practices. The use of vaccination to prevent HSV infections introduces unique problems because recurrences are known to occur in the presence of humoral- and cell-mediated immunity. Vaccines have been ineffective to date but continue to be studied.<sup>11,146</sup>

**TABLE 6.** Summary of HSV epidemiology

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HSV is increasing as a health problem
Most infections acquired by asymptomatic shedding
Patients may shed HSV chronically
HSV-1 infections are acquired at a later age now
HSV genital infections are increasing
HSV-1 is an increasing cause of genital infections
HSV serology is becoming problematic in determining site of clinical infection
An increase in neonatal HSV infections is anticipated and observed
Unknown whether the epidemiology of ocular HSV is affected
Acute retinal necrosis is increasingly associated with HSV-2
Genital HSV is an increased risk factor for acquisition of HIV
Vaccine initiatives have not yet been fruitful

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### REFERENCES

1. Miyagawa H, Yamanishi K. The epidemiology and pathogenesis of infections caused by the high numbered human herpesviruses in children: HHV-6, HHV-7 and HHV-8. *Curr Opin Infect Dis* 1999;12: 251-5.
2. Umene K, Sakaoka H. Evolution of herpes simplex virus type 1 under herpesviral evolutionary processes. *Arch Virol* 1999;144:637-56.
3. Liedtke W, Opalka B, Zimmermann CW, et al. Age distribution of latent herpes simplex virus 1 and varicella-zoster virus genome in human nervous tissue. *J Neurol Sci* 1993;116:6-11.
4. Obara Y, Furuta Y, Takasu T, et al. Distribution of herpes simplex

- virus types 1 and 2 genomes in human spinal ganglia studied by PCR and in situ hybridization. *J Med Virol* 1997;52:136–42.
5. Posavad CM, Koelle DM, Corey L. Tipping the scales of herpes simplex virus reactivation: the important responses are local. *Nat Med* 1998;4:381–2.
  6. Johnson LS, Polsky B. Herpes simplex virus infection in the cancer patient. *Infect Med* 1993;10:18–52.
  7. Safrin S. Treatment of acyclovir-resistant herpes simplex virus infections in patients with AIDS. *J Acquir Immune Defic Syndr* 1992; 5:S29–32.
  8. Stewart JA, Reef SE, Pellett PE, et al. Herpesvirus infections in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21(suppl 1):S114–20.
  9. Gorbach SL, Bartlett JG, Blacklow NR. *Infectious Diseases*, 2nd ed. Philadelphia: Saunders, 1998.
  10. Wilhelmus KR. Epidemiology of ocular infections. In: Baum J, Lie-segang TJ, eds. *Duane's Foundations of Clinical Ophthalmology*, vol. 2. Philadelphia: Lippincott Williams & Wilkins, 1998:1–46.
  11. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. *Clin Infect Dis* 1998;26:541–553; quiz 554–545
  12. Goodman JL. Infections caused by herpes simplex viruses. In: Ho-eprich PD, Jordan MC, Ronald AR, eds. *Infectious diseases: a treatise of infectious processes*, 5th ed. Philadelphia: Lippincott, 1994:930–43.
  13. Douglas RG Jr, Couch RB. A prospective study of chronic herpes simplex virus infection and recurrent herpes labialis in humans. *J Immunol* 1970;104:289–95.
  14. Siegel D, Golden E, Washington AE, et al. Prevalence and correlates of herpes simplex infections. The population-based AIDS in Multi-ethnic Neighborhoods Study. *JAMA* 1992;268:1702–8.
  15. Kangro HO, Osman HK, Lau YL, et al. Seroprevalence of antibodies to human herpesviruses in England and Hong Kong. *J Med Virol* 1994;43:91–6.
  16. Schmitt DL, Johnson DW, Henderson FW. Herpes simplex type 1 infections in group day care. *Pediatr Infect Dis J* 1991;10:729–34.
  17. Gibson JJ, Hornung CA, Alexander GR, et al. A cross-sectional study of herpes simplex virus types 1 and 2 in college students: occurrence and determinants of infection. *J Infect Dis* 1990;162:306–12.
  18. Christenson B, Bottiger M, Svensson A, et al. A 15-year surveillance study of antibodies to herpes simplex virus types 1 and 2 in a cohort of young girls. *J Infect* 1992;25:147–54.
  19. Ghebrekidan H, Ruden U, Cox S, et al. Prevalence of herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus infections in Eritrea. *J Clin Virol* 1999;12:53–64.
  20. Hashido M, Lee FK, Nahmias AJ, et al. An epidemiologic study of herpes simplex virus type 1 and 2 infection in Japan based on type-specific serological assays. *Epidemiol Infect* 1998;120:179–86.
  21. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 1999;131:14–20.
  22. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000;342:844–50.
  23. Johnson RE, Nahmias AJ, Magder LS, et al. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989;321:7–12.
  24. Kinghorn GR. Epidemiology of genital herpes. *J Int Med Res* 1994; 22:14A–23A.
  25. Forsgren M, Skoog E, Jeansson S, et al. Prevalence of antibodies to herpes simplex virus in pregnant women in Stockholm in 1969, 1983 and 1989: implications for STD epidemiology. *Int J STD AIDS* 1994; 5:113–6.
  26. Cates W Jr, Hinman AR. Sexually transmitted diseases in the 1990s. *N Engl J Med* 1991;325:1368–70.
  27. Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;337:1105–11.
  28. Cowan FM, Johnson AM, Ashley R, Corey L, Mindel A. Antibody to herpes simplex virus type 2 as serological marker of sexual lifestyle in populations. *BMJ* 1994;309:1325–9.
  29. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;69:19–36.
  30. Stanberry L, Cunningham A, Mertz G, et al. New developments in the epidemiology, natural history and management of genital herpes. *Antiviral Res* 1999;42:1–14.
  31. Pasquini P, Mele A, Franco E, et al. Prevalence of herpes simplex virus type 2 antibodies in selected population groups in Italy. *Eur J Clin Microbiol Infect Dis* 1988;7:54–6.
  32. Garcia-Corbeira P, Dal-Re R, Aguilar L, et al. Is sexual transmission an important pattern for herpes simplex type 2 virus seroconversion in the Spanish general population? *J Med Virol* 1999;59:194–7.
  33. Kjaer SK, de Villiers EM, Haugaard BJ, et al. Human papillomavirus, herpes simplex virus and cervical cancer incidence in Greenland and Denmark. A population-based cross-sectional study. *Int J Cancer* 1988;41:518–24.
  34. Lakshmi N, Kumar AG, Anand T, et al. Sero-prevalence of herpes simplex virus type-2 among cancer cervix patients. *Ind J Cancer* 1993;30:189–91.
  35. Mertz GJ, Benedetti J, Ashley R, et al. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992;116:197–202.
  36. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev* 1999;12: 1–8.
  37. Langenberg AG, Corey L, Ashley RL, et al. A prospective study of new infections with Herpes Simplex Virus Type 1 and Type 2. *N Engl J Med* 1999;341:1432–8.
  38. Arvin AM, Prober CG. Herpes simplex virus type 2—a persistent problem. *N Engl J Med* 1997;337:1158–9.
  39. Severson JL, Tyring SK. Relation between herpes simplex viruses and human immunodeficiency virus infections. *Arch Dermatol* 1999; 135:1393–7.
  40. Hook EWd, Cannon RO, Nahmias AJ, et al. Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals. *J Infect Dis* 1992;165:251–5.
  41. Brown TJ, Yen-Moore A, Tyring SK. An overview of sexually transmitted diseases. Part I. *J Am Acad Dermatol* 1999;41:511–32.
  42. Corey L, Wald A. Genital herpes. In: Holmes KK, Mardh PA, Sparling PF, et al., eds. In: *Sexually Transmitted Diseases*. New York: McGraw-Hill, 1999:285–311.
  43. Wald A, Benedetti J, Davis G, et al. A randomized, double-blind, comparative trial comparing high- and standard-dose oral acyclovir for first-episode genital herpes infections. *Antimicrob Agents Chemother* 1994;38:174–6.
  44. Christie SN, McCaughey C, McBride M, et al. Herpes simplex type 1 and genital herpes in Northern Ireland. *Int J STD AIDS* 1997;8: 68–9.
  45. Kinghorn GR. Limiting the spread of genital herpes. *Scand J Infect Dis Suppl* 1996;100:20–5.
  46. Schomogyi M, Wald A, Corey L. Herpes simplex virus-2 infection. An emerging disease? *Infect Dis Clin North Am* 1998;12:47–61.
  47. Lavery HA, Connolly JH, Russell JD. Incidence of herpes genitalis in Northern Ireland in 1973–83 and herpes simplex types 1 and 2 isolated in 1982–4. *Genitourin Med* 1986;62:24–7.
  48. Ross JD, Smith IW, Elton RA. The epidemiology of herpes simplex types 1 and 2 infection of the genital tract in Edinburgh 1978–1991. *Genitourin Med* 1993;69:381–3.
  49. Woolley PD, Kudesia G. Incidence of herpes simplex virus type-1 and type-2 from patients with primary (first-attack) genital herpes in Sheffield. *Int J STD AIDS* 1990;1:184–6.
  50. Tayal SC, Pattman RS. High prevalence of herpes simplex virus type 1 in female anogenital herpes simplex in Newcastle upon Tyne 1983–92. *Int J STD AIDS* 1994;5:359–61.
  51. Rodgers CA, O'Mahony C. High prevalence of herpes simplex virus type 1 in female anogenital herpes simplex [letter]. *Int J STD AIDS* 1995;6:144.
  52. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994;121: 847–54.
  53. Liesegang TJ, Melton LJD, Daly PJ, et al. Epidemiology of ocular herpes simplex. Incidence in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol* 1989;107:1155–9.
  54. Dhaliwal DK, Barnhorst DA Jr, Romanowski E, et al. Efficient re-activation of latent herpes simplex virus type 1 infection by excimer laser keratectomy in the experimental rabbit ocular model. *Am J Ophthalmol* 1998;125:488–92.

55. Darougar S, Hunter PA, Viswalingam M, et al. Acute follicular conjunctivitis and keratoconjunctivitis due to herpes simplex virus in London. *Br J Ophthalmol* 1978;62:843-9.
56. Wishart PK, James C, Wishart MS, et al. Prevalence of acute conjunctivitis caused by chlamydia, adenovirus, and herpes simplex virus in an ophthalmic casualty department. *Br J Ophthalmol* 1984;68:653-5.
57. Darougar S, Wishart MS, Viswalingam ND. Epidemiological and clinical features of primary herpes simplex virus ocular infection. *Br J Ophthalmol* 1985;69:2-6.
58. Wishart MS, Darougar S, Viswalingam ND. Recurrent herpes simplex virus ocular infection: epidemiological and clinical features. *Br J Ophthalmol* 1987;71:669-72.
59. Wilhelmus KR, Falcon MG, Jones BR. Bilateral herpetic keratitis. *Br J Ophthalmol* 1981;65:385-7.
60. Claoue C, De Cock R. The spectrum of herpes simplex virus disease of the anterior segment in the 1990s. *Acta Ophthalmol Scand* 1996;74:407-10.
61. Norm MS. Dendritic (herpetic) keratitis. I. Incidence-seasonal variations-recurrence rate-visual impairment-therapy. *Acta Ophthalmol* 1970;48:91-107.
62. Ribaric V. The incidence of herpetic keratitis among population. *Ophthalmologica* 1976;173:19-22.
63. Shuster JJ, Kaufman HE, Nesburn AB. Statistical analysis of the rate of recurrence of herpesvirus ocular epithelial disease. *Am J Ophthalmol* 1981;91:328-31.
64. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med* 1998;339:300-6.
65. Sundmacher R. Trifluorothymidin-prophylaxis of dendritic keratitis in steroid-treated herpetic keratouveitis [author translation]. *Klin Monatsbl Augenheilkd* 1978;173:516-9.
66. Shimomura Y, Ohashi Y, Maeda N, et al. Herpetic keratitis therapy to reduce recurrence. *Curr Eye Res* 1987;6:105-10.
67. The Herpetic Eye Disease Study Group. A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. *Arch Ophthalmol* 1997;115:703-12.
68. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology* 1994;101:1883-96.
69. Barron BA, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994;101:1871-82.
70. Wilhelmus KR, Dawson CR, Barron BA, et al. Risk factors for herpes simplex virus epithelial keratitis recurring during treatment of stromal keratitis or iridocyclitis. Herpetic Eye Disease Study Group. *Br J Ophthalmol* 1996;80:969-72.
71. Patterson A, Jones BR. The management of ocular herpes. *Trans Ophthalmol Soc U K* 1967;87:59-84.
72. Porter SM, Patterson A, Kho P. A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis. *Br J Ophthalmol* 1990;74:283-5.
73. Liesegang TJ. Epidemiology of ocular herpes simplex. Natural history in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol* 1989;107:1160-5.
74. Beigi B, Algawi K, Foley-Nolan A, et al. Herpes simplex keratitis in children. *Br J Ophthalmol* 1994;78:458-60.
75. Poirier RH. Herpetic ocular infections of childhood. *Arch Ophthalmol* 1980;98:704-6.
76. Uchio E, Hatano H, Mitsui K, et al. A retrospective study of herpes simplex keratitis over the last 30 years. *Jpn J Ophthalmol* 1994;38:196-201.
77. Ukkonen P, Hovi T, von Bonsdorff CH, et al. Age-specific prevalence of complement-fixing antibodies to sixteen viral antigens: a computer analysis of 58,500 patients covering a period of eight years. *J Med Virol* 1984;13:131-48.
78. Pramod NP, Rajendran P, Kannan KA, et al. Herpes simplex keratitis in South India: clinico-virological correlation. *Jpn J Ophthalmol* 1999;43:303-7.
79. Laibson PR, Leopold IH. An evaluation of double blind IDU therapy in 100 cases of herpetic keratitis. *Ophthalmology* 1964;68:22-34.
80. Herpes simplex-changing patterns. *Lancet* 1981;2:1025-6.
81. Mortensen KK, Sjolie AK. Keratitis dendritica. An epidemiological investigation. *Acta Ophthalmol (Copenh)* 1979;57:750-4.
82. Remeijer L, Doornbal P, Geerards AJ, et al. Newly acquired herpes simplex virus keratitis after penetrating keratoplasty. *Ophthalmology* 1997;104:648-52.
83. Neumann-Haefelin D, Sundmacher R, Wochnik G, et al. Herpes simplex virus types 1 and 2 in ocular disease. *Arch Ophthalmol* 1978;96:64-9.
84. Rosenwasser GO, Greene WH. Simultaneous herpes simplex types 1 and 2 keratitis in acquired immunodeficiency syndrome. *Am J Ophthalmol* 1992;113:102-3.
85. Ficker LA, Kirkness CM, Rice NS, et al. The changing management and improved prognosis for corneal grafting in herpes simplex keratitis. *Ophthalmology* 1989;96:1587-96.
86. Robinson MJ, Newton C. Bilateral herpes simplex keratitis in a patient with graft-vs-host disease. *Am J Ophthalmol* 1991;112:468-9.
87. Margolis TP, Ostler HB. Treatment of ocular disease in eczema herpeticum. *Am J Ophthalmol* 1990;110:274-9.
88. Wilhelmus KR, Coster DJ, Donovan HC, et al. Prognosis indicators of herpetic keratitis. Analysis of a five-year observation period after corneal ulceration. *Arch Ophthalmol* 1981;99:1578-82.
89. Gamus D, Romano A, Sucher E, et al. Herpetic eye attacks: variability of circannual rhythms. *Br J Ophthalmol* 1995;79:50-3.
90. Bell DM, Holman RC, Pavan-Langston D. Herpes Simplex keratitis: epidemiologic aspects. *Ann Ophthalmol* 1982;14:421-2.
91. Gordon YJ. Pathogenesis and latency of herpes simplex virus type 1 (HSV-1): an ophthalmologist's view of the eye as a model for the study of the virus-host relationship. *Adv Exp Med Biol* 1990;278:205-9.
92. Gordon YJ, McKnight JL, Ostrove JM, et al. Host species and strain differences affect the ability of an HSV-1 ICP0 deletion mutant to establish latency and spontaneously reactivate in vivo. *Virology* 1990;178:469-77.
93. Kaufman HE, Brown DC, Ellison EM. Recurrent herpes in the rabbit and man. *Science* 1967;156:1628-9.
94. Kaye SB, Madan N, Dowd TC, et al. Ocular shedding of herpes simplex virus. *Br J Ophthalmol* 1990;74:114-6.
95. Hodge WG, Margolis TP. Herpes simplex virus keratitis among patients who are positive or negative for human immunodeficiency virus: an epidemiologic study. *Ophthalmology* 1997;104:120-4.
96. Young TL, Robin JB, Holland GN, et al. Herpes simplex keratitis in patients with acquired immune deficiency syndrome. *Ophthalmology* 1989;96:1476-9.
97. Jeffries DJ. Intra-uterine and neonatal herpes simplex virus infection. *Scand J Infect Dis Suppl* 1991;80:21-6.
98. Reynolds JD, Griebel M, Mallory S, et al. Congenital herpes simplex retinitis. *Am J Ophthalmol* 1986;102:33-6.
99. Whitley RJ. Herpes simplex virus. In: Remington JS, ed. *Infectious Diseases of the Fetus and Newborn*. Philadelphia: W.B. Saunders, 1990:282-305.
100. Margolis TP, Atherton SS. Herpes simplex virus diseases: posterior segment of the eye. In: Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular Infection and Immunity*. St. Louis: Mosby, 1996:1155-67.
101. Whitley RJ, Nahmias AJ, Visintine AM, et al. The natural history of herpes simplex virus infection of mother and newborn. *Pediatrics* 1980;66:489-94.
102. Cibis GW, Flynn JT, Davis EB. Herpes simplex retinitis. *Arch Ophthalmol* 1978;96:299-302.
103. Nahmias AJ, Visintine AM, Caldwell DR, et al. Eye infections with herpes simplex viruses in neonates. *Surv Ophthalmol* 1976;21:100-5.
104. Corey L, Whitley RJ, Stone EF, et al. Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. *Lancet* 1988;1:1-4.
105. Reersted P, Hansen B. Chorioretinitis of the newborn with herpes simplex virus type 1. Report of a case. *Acta Ophthalmol* 1979;57:1096-100.
106. Fonnest G, de la Fuente Fonnest I, Weber T. Neonatal herpes in Denmark 1977-1991. *Acta Obstet Gynecol Scand* 1997;76:355-8.
107. Gutierrez KM, Falkovitz Halpern MS, Maldonado Y, et al. The epidemiology of neonatal herpes simplex virus infections in California from 1985 to 1995. *J Infect Dis* 1999;180:199-202.
108. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. *Paediatr Perinat Epidemiol* 1996;10:432-42.

109. Stone KM, Brooks CA, Guinan ME, et al. National surveillance for neonatal herpes simplex virus infections. *Sex Transm Dis* 1989;16:152-156
110. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med* 1991;324:1247-52.
111. Malm G, Berg U, Forsgren M. Neonatal herpes simplex: clinical findings and outcome in relation to type of maternal infection. *Acta Paediatrica* 1995;84:256-60.
112. Jacobs RF. Neonatal herpes simplex virus infections. *Semin Perinatol* 1998;22:64-71.
113. Callen JP. Epidemic herpes simplex virus infection. *Am J Dis Child* 1983;137:182-4.
114. Skinner GR, Davies J, Ahmad A, et al. An outbreak of herpes rubrum managed by vaccination of players and sociosexual contacts. *J Infect* 1996;33:163-7.
115. Bourdarias B, Perro G, Cutillas M, et al. Herpes simplex virus infection in burned patients: epidemiology of 11 cases. *Burns* 1996;22:287-90.
116. Holland EJ, Mahanti RL, Belongia EA, et al. Ocular involvement in an outbreak of herpes gladiatorum. *American Journal of Ophthalmology* 1992;114:680-4.
117. Thompson WS, Culbertson WW, Smiddy WE, et al. Acute retinal necrosis caused by reactivation of herpes simplex virus type 2. *Am J Ophthalmol* 1994;118:205-11.
118. Ganatra JB, Chandler D, Santos C, et al. Viral causes of the acute retinal necrosis syndrome. *Am J Ophthalmol* 2000;129:166-72.
119. Itoh N, Matsumura N, Ogi A, et al. High prevalence of herpes simplex virus type 2 in acute retinal necrosis syndrome associated with herpes simplex virus in Japan. *Am J Ophthalmol* 2000;129:404-5.
120. Duker JS, Nielsen JC, Eagle RC Jr, et al. Rapidly progressive acute retinal necrosis secondary to herpes simplex virus, type 1. *Ophthalmology* 1990;97:1638-43.
121. Sidikaro Y, Silver L, Holland GN, et al. Rhegmatogenous retinal detachments in patients with AIDS and necrotizing retinal infections. *Ophthalmology* 1991;98:129-35.
122. Yamamoto S, Pavan-Langston D, Tada R, et al. Possible role of herpes simplex virus in the origin of Posner-Schlossman syndrome. *Am J Ophthalmol* 1995;119:796-8.
123. Mitchell SM, Phylactou L, Fox JD, et al. The detection of herpesviral DNA in aqueous fluid samples from patients with Fuchs' heterochromic cyclitis. *Ocular Immunol Inflamm* 1996;4:33-8.
124. Alvarado JA, Underwood JL, Green WR, et al. Detection of herpes simplex viral DNA in the iridocorneal endothelial syndrome. *Arch Ophthalmol* 1994;112:1601-9.
125. Sutcliffe E, Baum J. Acute idiopathic corneal endotheliitis. *Ophthalmology* 1984;91:1161-5.
126. Olsen TW, Hardten DR, Meiusi RS, et al. Linear endotheliitis. *Am J Ophthalmol* 1994;117:468-74.
127. Robin JB, Steigner JB, Kaufman HE. Progressive herpetic corneal endotheliitis. *Am J Ophthalmol* 1985;100:336-7.
128. Ohashi Y, Yamamoto S, Nishida K, et al. Demonstration of herpes simplex virus DNA in idiopathic corneal endotheliopathy. *Am J Ophthalmol* 1991;112:419-23.
129. Ohashi Y, Kinoshita S, Mano T, et al. Idiopathic corneal endotheliopathy. A report of two cases. *Arch Ophthalmol* 1985;103:1666-8.
130. Hakin KN, Dart JK, Sherrard E. Sporadic diffuse corneal endotheliitis. *Am J Ophthalmol* 1989;108:509-15.
131. Sugar A, Smith T. Presumed autoimmune corneal endotheliopathy. *Am J Ophthalmol* 1982;94:689-91.
132. Cleator GM, Klapper PE, Dennett C, et al. Corneal donor infection by herpes simplex virus: herpes simplex virus DNA in donor corneas. *Cornea* 1994;13:294-304.
133. Cockerham GC, Krafft AE, McLean IW. Herpes simplex virus in primary graft failure. *Arch Ophthalmol* 1997;115:586-9.
134. Holbach LM, Asano N, Naumann GO. Infection of the corneal endothelium in herpes simplex keratitis. *Am J Ophthalmol* 1998;126:592-4.
135. Cook SD, Hill JH. Herpes simplex virus: molecular biology and the possibility of corneal latency. *Surv Ophthalmol* 1991;36:140-8.
136. Liesegang TJ. Biology and molecular aspects of herpes simplex and varicella-zoster virus infections. *Ophthalmology* 1992;99:781-99.
137. Wheeler CE, Jr. The herpes simplex problem. *J Am Acad Dermatol* 1988;18:163-8.
138. Corey L, Handsfield HH. Genital herpes and public health: addressing a global problem. *JAMA* 2000;283:791-4.
139. Slomka MJ. Seroepidemiology and control of genital herpes: the value of type specific antibodies to herpes simplex virus. *Communicable Disease Report. CDR Review* 1996;6:R41-5.
140. Holmberg SD, Stewart JA, Gerber AR, et al. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA* 1988;259:1048-50.
141. Stamm WE, Handsfield HH, Rompalo AM, et al. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988;260:1429-33.
142. Schacker T, Ryncarz AJ, Goddard J, et al. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA* 1998;280:61-6.
143. Mole L, Ripich S, Margolis D, et al. The impact of active herpes simplex virus infection on human immunodeficiency virus load. *J Infect Dis* 1997;176:766-70.
144. Levin MJ. Impact of herpesvirus infections in the future. *J Med Virol* 1993;1(suppl):158-64.
145. Liesegang TJ. Ocular herpes simplex infection: pathogenesis and current therapy. *Mayo Clin Proc* 1988;63:1092-105.
146. Mascola JR. Herpes simplex virus vaccines—why don't antibodies protect? [editorial]. *JAMA* 1999;282:379-80.
147. Chuang TY, Su WP, Perry HO, et al. Incidence and trend of herpes progenitalis. A 15-year population study. *Mayo Clin Proc* 1983;58:436-41.
148. Ragozzino MW, Melton LJ, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)* 1982;61:310-6.