

Changing Epidemiology of Herpes Simplex Virus Infections

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(See the Major Article by Bernstein et al on pages 344–51.)

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The rapid spread of genital herpes simplex virus (HSV) type 2 in the population was recognized in the late 1970s and early 1980s. Indeed, *Time* magazine featured an article on the subject and recognized HSV as a social plague because of its propensity to cause recurrent genital ulcerative disease and be transmitted either knowingly or unknowingly by sexual contact [1]. The ability of the virus to establish latency in sensory ganglia and reactivate with the proper provocative stimulus is integral to the pathogenesis of infection. Since then HSV-2 infections have attracted global interest because of the medical and psychological morbidity associated with frequent recurrences and the recognition that once someone is infected, there is no cure [2]. Importantly, life-threatening disease caused by HSV-2 in newborns was recognized because of contact with infected maternal genital secretions [3]. Furthermore, the association between genital ulcerative disease caused by

HSV-2 and increased probability of acquisition of human immunodeficiency virus (HIV) infection, particularly in the developing world, sparked numerous efforts to develop interventions that prevented recurrences and thereby decreased the probability of HIV acquisition [4].

Although antiviral therapies improved the quality of life, none prevented person-to-person transmission or the establishment of latency. The National Institutes of Health and private foundations provided significant funding to elucidate the molecular pathogenesis of the disease, develop new therapeutic and diagnostic strategies, and, more recently, develop a vaccine to prevent HSV-2 infections. As these latter vaccine studies were designed and implemented, the primary goal was to reduce the probability of acquisition of HSV-2. Herein lies the fundamental problem: *the disease has changed*.

Bernstein and colleagues have redefined the epidemiology of primary genital and, to a lesser extent, oral HSV infections [5]. Women who participated in the HERPEVAC clinical trial of an HSV vaccine but were randomized to the control arm (hepatitis A vaccine recipients), provided the cohort for analysis. The primary results of the HERPEVAC trial were reported by Belshe and colleagues earlier this year [6] and demonstrated no effect on the acquisition of HSV-2 but a modest benefit in preventing

the acquisition of HSV-1. Importantly, the women who participated in the control arm provided an outstanding opportunity to better understand the presentation and manifestations of primary HSV infection in young women, because all volunteers were HSV seronegative at the time of enrollment. With >3400 women followed up prospectively for 20 months, Bernstein and colleagues report that HSV-1 infections were more than twice as common as HSV-2 infections and appeared 3 times more frequently in the genital tract. Specifically, 84% of primary infections were genital. This study represents the largest prospective study of HSV infection in young adults ever performed to date, albeit including only women, and confirms without doubt that HSV-1 is now the most common cause of infection in this age group [5].

The additional lessons that were learned from the study have reinforced our knowledge of genital HSV infection. First, the study reiterates that most infections occurred without recognized signs or symptoms of disease. Second, for those individuals evaluated for primary infection, there were absolutely no differences in clinical presentation. Third, no patient developed HSV-2 infection of the oropharynx. Fourth, younger participants were more likely to acquire HSV-1 infection than older ones. Finally, differential acquisition of HSV-1 and 2 was noted by race.

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The implications of the study are obvious. Although the study included only women between the ages of 18 and 30 years, it documents a significant change in the epidemiology of genital HSV infections as HSV-1 replaces HSV-2 as the most common cause of infection. Such findings have been suggested from other studies on a smaller scale [2]. That HSV-2 genital infections are less common has been suggested by the most recent National Health and Nutrition Examination Survey data indicating a decreasing seroprevalence of infection caused by that serotype [2]. Importantly, it is well recognized that HSV-1 is likely to recur in the genital tract and, therefore, may alleviate significant medical and psychological morbidity. However, while less likely to recur, HSV-1 remains a significant cause of neonatal HSV infections; thus, preventive efforts should not be abandoned [7]. No genital infection should be trivialized and every effort should be made to prevent them.

The authors should be congratulated on wisely using a control population to teach the reader new insights on the

natural history of disease. All studies should be presented to the medical public in such a fashion.

Indeed, we have now come full circle. For so many of us, HSV-1 was thought to be only a trivial infection of the mouth or lips, although it could cause life-threatening disease. In the 1980s few would have considered it a cause of genital herpes. Now that sexual practices have changed with increased oral-genital sex, it is likely that we can account for the displacement of HSV-2 as the most common cause of initial infection. Because of this changing epidemiology of genital HSV infections, future vaccine trials will need to be rethought. Instead of using antigens directed solely against HSV-2, as in the HERPVAC trial, broader antigenic exposure will need to be considered. Similarly, end points for such vaccine studies will need to be carefully reassessed.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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