I. INTRODUCTION

Epidemiology treatises are notoriously dull as they recite statistics on the incidence and prevalence of infection as well as the implications of these infections on the salubrity of the community. In these commentaries, the data presented and their evaluation, which is often subject to multiple interpretations, invariably reflect the bias of the author. In studies of herpes simplex viruses (HSV), these biases are particularly apparent. The field has been influenced by many investigators who have performed excellent research aimed toward the understanding of the physiology of these viruses and their interactions with the host. Every attempt will be made to distinguish sound and precise clinical observations from those that warrant further clarification. Controversial issues range from the very simplistic, such as the incidence of symptomatic versus asymptomatic primary infections, to the more complex and unique propensities of these viruses, namely their apparent ability to cause recurrent disease and incrimination as oncogenic agents.

This chapter will review the epidemiology of HSV infections of man and will provide a background of historical developments, including the clinical and social significance of these infections, in order to assess the scientific advances of our understanding of these infections. A distinction between primary, nonprimary initial, recurrent, and exogenous (re)infections from both a clinical and a laboratory standpoint becomes essential to the epidemiology of these viruses. Clinical, virologic, and

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serologic assessments that directly or indirectly incriminate HSV as the causes of disease will be discussed. Major controversies requiring pursuit will be explored relative to the application of methods developed in the laboratories of our colleagues in molecular virology. Through knowledge gained from application of these tools in future studies, it will be possible to understand more rationally the epidemiology of these viruses and, consequently, to develop regimens for prevention and/or specific therapeutic intervention in human disease, the ultimate goal of biomedical investigators.

II. HISTORICAL BACKGROUND

The impact of HSV infections on man has been well documented historically. Record of human HSV infections, particularly of spreading cutaneous lesions thought to be of herpetic etiology, dates to ancient Greek times (Nahmias and Dowdle, 1968) and particularly to the writing of Hippocrates (Wildy, 1973). The association between fever and mouth lesions was attributed to Herodotus (Mettler, 1947). Many of these original observations were predicated on Gallen's premise that the lesions themselves were an attempt by the body to rid itself of evil humors and, perhaps, resulted in the name of herpes excretins. However, these descriptions probably bear little resemblance to those of 20th century infections (Beswick, 1962). As noted by Wildy (1973), Shakespeare was no doubt cognizant of recurrent labial lesions as was recounted in *Romeo and Juliet* where Queen Mab, the midwife of the fairies, stated:

O'er ladies lips, who straight on kisses dream which oft the angry Mab with blisters plagues, because their breaths with sweetmeats tainted are.

It was not until the 18th century that Astruc, physician to the King of France, drew the appropriate correlation between herpetic lesions and genital infection (Hutfield, 1966). By the early 19th century, the vesicular nature of lesions associated with herpetic infections was well characterized; however, it was not until 1893 that Vidal specifically recognized human transmission of HSV infections from one individual to another (Wildy, 1973).

Observations at the beginning of the 20th century brought an end to the early imprecise descriptive era of HSV infections. First, histopathologic studies described the multinucleated giant cells associated with all herpesvirus infections (Unna, 1896). Second, the unequivocal infectious nature of HSV was recognized by Lowenstein (1919) who demonstrated that virus from the lesions of human herpes keratitis and the vesicles of herpes labialis produced lesions on the rabbit cornea. Vesicle fluid from patients with herpes zoster failed to produce similar dendritic lesions. In fact, these observations were actually attributed to earlier investigations by Gruter (1920) who performed virtually identical experiments around 1910 but did not report them until later.