Recurrence in ocular herpes simplex infection

Continuing recurrence of disease is one of the most troublesome characteristics of herpes simplex keratitis. If ocular herpes were a one-time infection, the likelihood of deep involvement, with its scarring, decreased vision, and even blindness, would be much smaller. With each recurrence, the chance of encountering these complications increases.

Recent advances in research have led to a better understanding of the state in which the herpes simplex virus (HSV) exists in carriers between manifestations of recurrent disease. The most tenable theory to date is that the virus enters a stage of “latent” infection, during which time it is present within host cells in subviral form or in amounts too small to be detected by conventional means. Periodically, the latent virus undergoes reactivation. Infectious virus can then be found in the tear film with or without clinically recognizable disease. One explanation for this phenomenon is that neuron cell bodies act as the reservoir for latent herpes. Their axons then function as conduits transporting virus to and from peripheral tissues. The foregoing assumptions have been termed the neuronal hypothesis. A great deal of evidence in support of this hypothesis has been amassed through the years.

In 1929, Goodpasture proposed the nervous system, particularly the sensory ganglia, as the site of the latent virus. It was not until 1971, however, that the presence of latent HSV infection was clearly demonstrated. At that time, Stevens and Cook worked out a method to detect latent HSV in the spinal ganglia of mice. They used animals which had recovered from posterior paralysis caused by foot-pad infection with the virus. By explanting the appropriate ganglia and maintaining whole cells in organ culture, they were able to isolate infectious virus. Only after organ culture cultivation was typical HSV detected in ganglionic cells by electron and fluorescence microscopy and by viral isolation. They found that various ganglionic cell types were susceptible to HSV infection, but latent HSV was detected only in the neuron cell body itself. In a recent elegant study, Cook, Bastone, and Stevens have actually demonstrated the presence of herpes virus DNA within neuron cell bodies of latently infected mice by autoradiography following DNA-RNA hybridization during reactivation.

The most logical approach to eradication of recurrent HSV involves interrupting the sequence by which latent infection of the nervous systems is translated into active disease in the peripheral tissues. For this reason, a reliable and reproducible means of achieving in vivo HSV reactivation and peripheral virus shedding has long sought as a means for investigation of the latency-reactivation process. Scriba has observed spontaneous recurrence of HSV in the foot pads of latently infected guinea pigs. Although this system may hold some promise, it is not directly applicable to ocular disease. Walz and associates demonstrated in vivo reactivation of latent HSV in mouse sacrosciatic spinal ganglia. Ganglionic reactivation was stimulated by cutting the

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nerve trunk. Since the nerve was severed, the animals showed no propagation of infection into the peripheral tissues, thus no actual recurrence of disease. Underwood and Weed\textsuperscript{4} and Hough and Robinson\textsuperscript{7} have reported low cutaneous recurrence rates of herpes virus-infected mice after treatment with prednisone and cyclophosphamide, respectively.

Unfortunately, murine disease is not typical of the human herpes syndrome, due to a lack of natural recurrences. Ocular herpes infection in the rabbit, on the other hand, is characterized by these spontaneous recurrences. Between recurrences, latent virus can be isolated solely from trigeminal ganglia and only in organ culture, as in the murine system.\textsuperscript{5}

Additional indirect substantiation for the neuronal hypothesis in the rabbit recurrence model is as follows. Nesburn\textsuperscript{9} showed that disruption of preganglionic trigeminal nerve function, both prior to and following ocular infection with HSV, significantly altered spontaneous recurrence rates. Prior to ocular infection, the preganglionic trigeminal nerve on one side of the rabbit was stereotaxically disrupted. The remaining side was sham operated. Following acute infection, the recurrence rate of HSV shedding, as measured by virus isolated from the tear film, was negligible on the side of the temporarily disrupted nerve, yet remained normal (6 to 10 per cent) on the sham-operated side. Thus, when the trigeminal nerve was damaged before the animal was infected, the usual recurrence pattern was prevented, even after the nerve regenerated and sensation returned. The same procedure carried out on "latently" infected animals (animals with spontaneous ocular recurrences following acute ocular infection) resulted in a statistically significant decrease in the number of instances of HSV shedding on the operated side, as compared to the shammed side. This decrease, however, was temporary. When the nerve regenerated (based on return of sensation to the eye and lids), the shedding of HSV returned to normal.

In vivo peripheral recurrences have been induced both pharmacologically and by stimulation of trigeminal ganglia. Reactivation, as a result of application of epinephrine ointment to the eye, was variable and took up to 7 days.\textsuperscript{10} In contrast, trigeminal ganglia stimulation by stereotaxis caused a prompt shedding of virus (within 48 hours) in the tear film of 33 per cent of the animals, some of which manifested typical dendritic keratitis.\textsuperscript{11} When latently infected rabbit trigeminal ganglia were subjected to direct mechanical stimulation, over 80 per cent of the eyes shed virus within 48 hours.\textsuperscript{12} This model, in which virus reactivation occurs in a high percentage of animals in a reliable and reproducible time frame, adds a new dimension to herpes research, opening the whole field of latent HSV reactivation to investigation.

Attempting to assess the relevance of the work with animals to the human herpes syndrome, Baringer and Swoveland\textsuperscript{13} and Bastian et al.,\textsuperscript{14} working independently, identified latent HSV in human trigeminal ganglia obtained at autopsy. In addition, Baringer\textsuperscript{15} has reported isolating HSV from autopsy-obtained human sacral ganglia which supply the genital area. In each case, the virus was obtained only in organ culture, indicating that it was present in latent form. Similar treatment of ganglia from dermatomes, not normally expected to be sites of HSV infection, were negative.

An extensive neurosurgical literature further indicates the nervous system as the most likely place for latent HSV infection. Operating on the fifth nerve to relieve facial neuralgia, Carton and others developed substantiating data. They found that if the nerve was severed between the face and the ganglion, herpes did not appear on that side of the face postoperatively, but if surgery was executed through the middle of the ganglion, a high percentage of patients developed facial herpes.\textsuperscript{10}

Additional support for the neuronal theory comes from transplant studies. When skin is taken from an area where a
Table I. Proposed scheme for the ocular HSV recurrence cycle

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<tr>
<th>Step 1: (Primary) Clinical or subclinical ocular infection</th>
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<tr>
<td>During infection, virus in the tear film spreads to cornea, conjunctiva, deep ocular structures, and adnexal tissues.</td>
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<th>Step 2: Latent infection of neurons</th>
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<td>The virus passes via nerve endings to the axons of the trigeminal nerve. It establishes a latent infection in the neurons of the trigeminal ganglion and nucleus. Virus disappears from the peripheral tissues.</td>
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<th>Step 3: Viral reactivation in the neurons</th>
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<td>A spontaneous or triggered reactivation of viral synthesis occurs in the neuron. This virus passes via the axon to peripheral tissues.</td>
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<th>Step 4: Peripheral viral synthesis and shedding</th>
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<td>HSV replicates in peripheral ocular tissues and is shed into the tear film.</td>
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<th>Step 5: Possible recurrent clinical disease</th>
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<td>Clinical disease becomes manifest if virus is present in high titer or if host defenses are compromised.</td>
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<th>Step 6: Re-establishment of latent infection of neurons</th>
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<tr>
<td>Whether or not clinical infection occurs, HSV replicating in the tissues passes again via the nerve supply to the neurons, re-establishing latent infection. The cycle is thus completed.</td>
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The patient has had many recurrent bouts of herpes, then transplanted elsewhere on the same person, the skin in the new area does not develop herpetic lesions. But in many cases, the previously uninfected skin transplanted to the site of recurrent infections soon evidences lesions.16

Taken collectively, these animal and human studies constitute strong evidence that HSV travels along the sensory nerves to the neuron cell bodies, where it persists either in the dynamic or static state, perhaps throughout the life span of the individual. A schematic representation of the ocular latency-reactivation cycle for HSV, as currently perceived, is presented in Table I. While the trigeminal ganglion appears to be the most important reservoir, the role of the fifth nerve nucleus, ciliary ganglion, superior cervical ganglion, or other ocular tissues has yet to be elucidated.

Fascinating advances in herpes biochemistry may elucidate the molecular basis of latency and reactivation. Currently available genetically mapped mutants of HSV may make it possible to identify the genes responsible for latency. Recent careful work has shown that previously undiscernable differences in substrains of HSV can be delineated by analysis of polypeptides produced by virus-infected cells. This polypeptide “fingerprinting” of viral substrains may facilitate the association of biochemical peculiarities of substrains with specific clinical syndromes.18

Intensive investigation of the foregoing laboratory systems should further clarify the recurrence mechanism leading to ultimate modification or interruption of this cyclic clinical disease.

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REFERENCES


