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Regular Review

Recurrent herpes simplex: the outlook for systemic antiviral agents

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Members of the herpesvirus family typically establish intimate and lifelong relationships with their hosts. An acute primary infection generally subsides after several days and immunity may be shown by various methods. Despite this the virus may persist, often subclinically, or remain latent, sometimes giving rise to recurrent disease. For example, herpes labialis and genitalis are common diseases associated with a latent infection with herpes simplex virus in neurones of the peripheral[1] and possibly central nervous system.[2] During the recrudescences the virus multiplies to considerable titres in the lesions, allowing transmission to a new host. In otherwise normal adults these recurrences may be painful, inconvenient, and sometimes debilitating, but are rarely life threatening. In those with impaired immunity, however, particularly when cell-mediated responses are abnormal, the recurrent infections can be prolonged and severe.[3]

Detection of latent infections—Whether the disease is mild or severe, once the clinical signs of herpes subside there is at present no means of predicting whether the infection has been completely eradicated. More refined immunological techniques may be informative in the future, but so far the only methods are retrospective—either observation of a further episode or culture of necropsy tissue from a sensory ganglion related to a previously affected skin site and reactivation of the hidden virus from the explant culture in vitro.[4 5] These circumstances militate against clinical study of antiviral drugs that are active against herpes simplex virus; we are therefore obliged to study latent infections in animals.

Inhibitory compounds active against herpes simplex virus—Idoxuridine and trifluorothymidine are useful in treating herpes in man.[6–8] Both these compounds are "activated" by healthy cells, so their selectivity is poor and they are too toxic for systemic use. They are, however, helpful in topical treatment, particularly of ocular infections. A third compound, adenine arabinoside, is suitable as a systemic drug but is not very effective; this may be due partly to its rapid conversion in man to an inactive form as a result of deamination by the enzyme adenosine deaminase.[9]

Recently several new highly selective nucleoside analogues have been discovered that are extremely active against some herpesviruses in vitro yet appear to have very low toxicity in man. Foremost among these are acyclovir (acycloguanosine)[10] and bromovinyldeoxyuridine.[11] The initial step in the metabolism of both these drugs is conversion to their respective nucleotides. This phosphorylation is accomplished by a virus-specified enzyme, thymidine kinase.[12] Both these nucleoside analogues are poor substrates for cellular enzymes; thus the drugs accumulate only in virus-infected cells. The monophosphate forms of the compounds are rapidly converted to the deoxynucleotide triphosphates, and these molecules interfere with the action of a second virus-induced enzyme, DNA polymerase, and thus inhibit virus replication.[13] Both drugs have proved effective against acute herpes simplex virus infections in animals, and trials in man are under way. While these trials will doubtless soon yield information on the short-term effects of the drugs on the clinical signs of the acute phase, discovering how the drugs affect the establishment and maintenance of latent infection will be much more difficult. Some insight into these aspects, however, may be obtained from the results of work in animals.

The efficacy of nucleoside analogues in vivo—Several workers have shown that acyclovir[14–17] and bromovinyldeoxyuridine[11 18] are remarkably effective against acute primary herpes simplex virus infections in animals. Active virus replication in the skin and nervous system diminishes and clinical manifestations are appreciably reduced. Most published work has been on the effects on primary virus replication, but one report[19] showed that in mice recurrent skin infections were aborted by systemic treatment with acyclovir. The results from several laboratories suggest that treatment of a primary skin infection in mice could prevent the initial establishment of a latent infection.[16 17 20] Prompt treatment, however, was required—when it was delayed for more than 24 hours after inoculation of virus no protective effect was found. The prevention of latency may have been related to the effective inhibition of virus replication in the skin around the inoculation site, so reducing the likelihood that virus would enter sensory nerves and translocate to the ganglionic neurones. In an attempt to separate the effects of treating skin and neural tissue virus was inoculated directly into the sciatic nerve of mice.[16] Virus replication in the sciatic

nerve, lumbrosacral ganglia, and spinal cord were quickly suppressed in the acute phase, but the mice none the less acquired latent infections affecting many cells within related dorsal root ganglia. These results suggested that once latently colonised with a virus neurones would be unaffected by treatment—a view confirmed by several groups using acyclovir[16 19 20] and more recently bromovinyldeoxyuridine.[21] When the drugs were given daily either by intraperitoneal inoculation or in the drinking water there was no effect on established latent infections. There is one contradictory report[22]: in mice given eye infections while receiving systemic acyclovir treatment for 15 days there was a fall in the proportion from which virus could be recovered by reactivation in vitro, suggesting that the latent infection had been eradicated.

The frequent observation that latent infections are refractory to systemic treatment is consistent with the concept of latently infected cells which contain virus in a resting state and which do not express the virus genome for long periods. One report described the detection of herpes thymidine kinase in the dorsal root ganglia of latently infected mice for up to 60 days after inoculation; but even after thymidine kinase activity was no longer detectable the ganglionic tissue was shown to contain latent virus.[23] Other studies using sensitive methods for the detection of thymidine kinase have yielded negative results in guinea-pigs.[24] No virus-specific antigens are detectable in the ganglion cells. Furthermore, while herpes DNA has been detected in the cells of latently infected mice, no virus-specified messenger RNA could be detected by methods of similar sensitivity.[25] These findings strongly imply that while the virus is present in the resting state most of its genome is not expressed. The two enzymes interacting with acyclovir and bromovinyldeoxyuridine arise late in the productive virus replication cycle, and these enzymes are probably not expressed during the latent phases of infection—which explains why such infections are not eradicated by systemic treatment with nucleoside analogues.

Whether herpes simplex virus or the cells that contain the latent infection become susceptible to such drugs during virus reactivation in vivo is not known. Whether the natural reactivation event itself inevitably leads to the lysis of the neurone containing the infection is not yet clear. Blyth *et al*[19] showed that systemic acyclovir treatment of a series of stimulated recurrent infections in mice did not reduce the incidence of latency or further recurrent lesions in the same mice when treatment was withheld.

Conclusions—These two highly selective nucleoside analogue inhibitors of herpes simplex virus appear to have low toxicity for mammalian systems, and we expect such drugs to ameliorate the acute effects of herpes simplex virus infections by suppressing virus multiplication both in the skin and in the nervous system. They may also abort recurrent infections provided that treatment is prompt. In both primary and recurrent infections this should lessen the amount of virus shed from the skin and would reduce the likelihood of infecting other people as a result of close oral or genital contact. When the agents are given early enough in the primary infection we may expect a reduction in the number of neurones that become colonised by the virus —and similarly treatment of recurrences ought to limit the number of neurones that are newly colonised. Thus the drugs may help to prevent the initiation of latency. In contrast, attempts to eradicate the latent infection during the quiescent phase are likely to be fruitless and these drugs should not be used for this purpose.

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