Control of herpes virus infections by drugs or vaccines?

Herpes viruses cause a wide spectrum of clinical illness including the relatively common oral lesion, herpetic keratitis, venereal infections and, more unpleasantly, herpes encephalitis. Two types of herpes virus (I and II) exist and although formerly it was considered that type II virus was restricted to the genital regions and that oral infections for example were caused by type I virus, there is now evidence that, in young persons at any rate, up to a third of genital isolates are type I (Chang, 1977).

A small upsurge in papers relevant to the control of herpes virus infections both by chemoprophylaxis and by vaccination has recently appeared and many describe encouraging results. The American antiviral substances programme has now published the results of its 5-year-long multicentre placebo controlled study of the purine nucleoside analogue vidarabine or Ara-A (Whiteley, Soong, Dolin, Galasso, Ch'ien & Alford, 1977), which had been shown previously to be effective for systemic therapy of herpes zoster infections in immuno-compromised persons (Whitley, Ch'ien & Dolin, 1976). The trial studied 28 virologically proven cases of encephalities caused by herpes type I. Brain biopsy of the focal area of involvement was obligatory for admission to the series. Placebo or drug were administered intravenously at a dosage of 15 mg/kg/day for a 12-h period for 10 days. In summary, treatment reduced mortality from 70 to 28%, a significant decrease, indicating the compound to be considerably more active than idoxuridine or Ara-C (which have been used in previous trials Longson & Bailey, 1976). Of great interest was the observation that over half the survivors had only moderate or no neurological after effects. In fact the reduction in mortality was significant enough for the controlled trial to be stopped for ethical reasons. There are some reservations at this stage however. Clinically, once the comatose stage was reached, therapy was shown to be futile and 57% of comatose patients died in spite of therapy and all the survivors were severely debilitated. Ara-A is an insoluble compound and its administration in large volumes of fluid was a problem of some importance. Clearly there is a lot of work to be done yet investigating such parameters as optimal drug dosage, usefulness of more soluble molecular forms of Ara-A and, of great importance, the development of more rapid and reliable diagnostic methods for herpes virus infections. The year 1976 saw two large gatherings of virologists in New York and London and both discussed hopefully the possible future demise of the virus in the face of more potent antivirals. The New York meeting, recently published (Third Conference on Antiviral substances, 1977) spent the first morning discussing the potential of Ara-A. Data concerning the usefulness of the more soluble Ara-AMP, at least in the treatment of experimental keratitis (Falcon & Jones, 1977) as well as studies of Ara-A in tissue culture and in laboratory animals was discussed at the Society's 2nd meeting on antivirals in London. Also, other compounds are on the horizon including phosphonoacetic acid (Shipkowitz et al., 1973) which appears to have a specific inhibitory effect on the virus induced DNA polymerase. It has already excited the interest of molecular virologists but clinical application may be a long way off.

Both antiviral drugs and vaccines need to be considered in attempting to deal with the important uncontrolled virus diseases like herpes, influenza and hepatitis. Herpes-vaccine-virologists have tended to centre their interest around the potential oncogenic effects of herpes viruses. Herpes type 2 has been linked with cervical cancer (Rapp, 1973) while more certainly Epstein-Barr virus has been implicated in the aetiology of African Burkitt's lymphoma (Epstein, 1976) and nasopharyngeal carcinoma. Certainly Marek's disease lymphoma in chickens is prevented very
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In humans one would be reluctant to use a live DNA virus, even attenuated for virulence, which might still have viral genes possibly coding for cell transformation. Interest at present is concentrated around the potential, as inactivated vaccine, of membrane antigens induced in herpes virus infected cells. A new method for isolating cell plasma membrane vesicles may be important in this approach (Pearson & Scott, 1977). Addition of formaldehyde and dithio threitol to virus infected cells induced cell surface 'blebs' which were then released into the culture medium as free vesicles. By electron microscopy the vesicles were free of virus particles and yet the vesicles contained herpes virus membrane antigens as detected by immunofluorescence. Primates immunized with the vesicles produced antibodies to the membrane antigens and also virus neutralizing antibodies. Of great importance was the failure to detect infectious virus in the vesicles and correlated with this, less than 1 ng of DNA was calculated to be present in 1 mg of vesicle protein. There are plenty of problems with this approach, not the least being the paucity of knowledge of the immunological response to a complex virus like herpes with a large DNA genome with coding potential for over 50 polypeptides, each presumably having many antigenic determinants. So discoveries and work in several laboratories has increased optimism about the future control of herpes infectious by chemotherapy or vaccines. Perhaps as virologists we could learn from the old TB bacteriologists and explore a combination of two approaches, immunological and chemical, to solve an otherwise very difficult problem.

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References


