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Antiviral activity of nucleoside derivatives against thymidine kinase-deficient acyclovir resistant mutants of Herpes simplex virus type I.

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Characterized were two acyclovir (ACV)-resistant, thymidine kinase-deficient mutants of HSV-1 strain F isolated after challenging viruses with the increased concentration of ACV in Vero cell culture. Both showed about 100-fold increased EC_{50} value of ACV than that of the parental type virus. They showed broad resistance- spectrum against several nucleoside derivatives tested and their spectrum patterns were not identical each other. There were no significant differences found in one step growth curves and in temperature sensitivity. By analyzing mutation sites on their TK gene, we would like to list the series of compounds whose antiviral activity might be changed by mutation of certain site on TK gene.

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In Vitro Acyclovir Susceptibility Monitoring of HSV Clinical Isolates. E. L. Hill, J. T. Rogers, M. N. Ellis. Division of Virology, Wellcome Research Laboratories, Research Triangle Park, NC 27709, U.S.A.

Since the introduction of effective antiviral chemotherapies, there has been widespread concern over the emergence of viruses resistant to these drugs. There is general agreement that acyclovir (ACV) resistant HSV is of little clinical significance in patients with normal immunity. This being the ten-year anniversary of the introduction of ACV in the clinic it seems an appropriate time to reevaluate these concerns. The _in vitro_ 50% effective dose (ED_{50}) values were determined for a pre-ACV population of HSV clinical isolates (recovered before 1980 and kindly provided by Dr. Larry Corey, University of Washington, Seattle, Washington). These values were compared to the values determined for isolates recovered at the first off-therapy episode of recurrent disease from patients that received seven years of suppressive oral ACV therapy. Sixteen of 304 (5.3%) patients of the pre-ACV population and 8 of 127 (6.3%) patients in the suppression group shed ACV-resistant viruses. These compare favorably with our previously reported _in vitro_ sensitivity data which indicated that 6.4% of all patients with normal immunity shed ACV-resistant viruses. The _in vitro_ ED_{50} values were determined by the dye uptake assay where ACV-resistance is defined as an ED_{50} of $\geq$ 3.0 ug/ml. The possible mechanism of ACV drug resistance in these viruses were elucidated by plaque autoradiography with I^{125} Iododeoxycytidine and C^{14} thymidine and their _in vitro_ susceptibilities to a variety of other anti-HSV drugs were determined.