Clinical Cure of Herpes Simplex Keratitis by 5-Iodo-2′-Deoxyuridine. (27169)

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To date specific chemotherapy has not been successfully employed for the treatment of disease caused by viruses other than the Chlamydozoaceae and Eaton agent. Vigorous research by Tamm, Horsfall, and others has yielded some agents which appear to inhibit virus growth(1) when applied at time of infection, but these effects have not been dramatic and have not been found to cure established viral lesions. Even with interferon, the reversal of established disease, to our knowledge, has not been demonstrated in any *in vivo* or *in vitro* situation.

This paper will report the prompt cure of well established lesions of rabbit cornea produced by herpes simplex keratitis even when treatment is delayed for several days after infection.

Methods. Treatment was administered with 5-iodo-2′-deoxyuridine (IDU)† (2). A saturated solution of IDU at pH 7.4 was prepared in distilled water at 56 degrees Centigrade and then refrigerated. The drug was administered as eye drops, one drop in each eye every 2 hours for 48 hours. In some cases treatment was continued every 2 hours from 8 a. m. to 4 p. m. after the first 2 days, but not in most experiments.

Herpes simplex virus of the Virtue strain with a titer of 10^{-9} in rabbit kidney tissue culture was used for the inoculum(3). The virus had been isolated from a patient with herpetic keratitis and passed 6 times in rabbit kidney tissue culture. The inoculum, which was briefly stored at dry ice temperature, was in a medium 50% of which was Hanks' balanced salt solution containing 2% calf serum, and 50% of which was skim milk. Inoculation of the rabbit eyes was as previously described(3).

The infection rate was 100% and the initial selection of animals for treatment was made on a random basis at the time of infection. In all studies both treated and untreated animals were randomly presented for evaluation, and the investigator was not aware which eyes were treated.

Evaluation was carried out with the aid of fluorescein staining and study by slit-lamp biomicroscope. Although photographs of all the eyes were taken, they are not included.

Results. Control and treated groups were simultaneously infected in all experiments. All control eyes developed a severe dendritic keratitis and iritis which was well established after 24 hours and became progressively worse for at least 10 days after infection when the animals were sacrificed.

Animals in which treatment was begun before infection or in which treatment was delayed until 12 hours after infection did not develop definite herpetic infection. In animals treated with IDU 24 hours after infection, dendritic lesions were present at the time treatment began, but cleared after one to 2 days of therapy. When IDU was delayed 48 hours or longer after infection, a very severe keratitis was present in all animals and iritis was present in most. Despite this, the corneas were much improved over the controls within one day of therapy and by 48 hours of therapy, no residua of the previous keratitis or iritis were apparent. Similar results were obtained when treatment was delayed for 72 hours or even for 5 days after infection.

The IDU did not inhibit the healing of these lesions and did not inhibit reepithelialization of intentionally scarified corneas. Repair and restoration of a crystal-clear cornea appeared to take place unaffected by the IDU. Therapy with the drug for 2 weeks produced no apparent abnormality of the

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TABLE I. Herpes Simplex Keratitis Treated with IDU.

Treatment with IDU begun	Total No. of eyes	48 hr after therapy: Corneal lesions	48 hr after therapy: No corneal lesions
24 hr before infection	7	0	7
2 " post "	12	0	12
12 " " "	10	0	10
24 " " "	12	0	12
48 " " "	6	0	6
72 " " "	4	0	4
5 days " "	3	0	3
Total treated	54	0	54
Saline control	22	22	0

cornea or lens, and the eyes showed no sign of inflammation. When therapy was stopped after 48 hours, there was no recurrence of the lesions.

Preliminary experiments suggest that similar improvement occurs in humans with herpetic keratitis treated with IDU, and that the drug is also effective against ocular vaccinia. These studies will be reported later. Experiments with 5-bromo-2'-deoxyuridine suggest that its effect may be similar to that of IDU, but 5-fluoro-2'-deoxyuridine has only a slight effect on prevention of infection by vaccinia and herpes simplex, and does not alter the course of established lesions.

Discussion. The eye presents a unique site for the trial of anti-viral agents since they can be applied topically in high concentration without systemic toxicity. Ocular and cutaneous infection thus appears ideal for screening of anti-viral agents.

Herpes simplex keratitis has been characterized as the most important specific keratitis in this country. If present impressions of the therapeutic efficacy in man of treatment with IDU are borne out, this may well provide a cure for this blinding and disabling disease.

As important, however, appears the clear-cut demonstration that it is possible to eliminate viral lesions by antimetabolite drugs that cause no apparent harm to the surrounding tissue. This indicates that, in fact, effective anti-viral agents can be found. Even established infection by viruses appears to be specifically treatable with agents that selectively inhibit the synthesis of virus.

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In vitro Alteration of Blood Group Phenotypes of Human Epithelial Cells Exposed to Heterologous Blood Group Substances.* (27170)

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A number of authors(1,2,3,4,5,6) have demonstrated mixed agglutination reactions between human erythrocytes and a variety of other human cells. Such reactions occurred only when the erythrocytes and the cells came from donors possessing a common blood group antigen A or B, indicating that the reactions involved in the agglutinations were specific and useful for identification of blood group antigens in human cells. Accordingly, mixed agglutination tests were applied by us to human amniotic cells cultured *in vitro*, and it was confirmed that these cells contain blood group substances corresponding to the donor's blood group. Identification of A and B

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