how often these leaks can be found at the various stages of gestation, but an idea of their frequency in later pregnancy is given by our finding positive films in 19 out of 240 pregnant women, all examined at the 34th week. Kleihauer and Betke (1960) found a still higher proportion of spills, but they surveyed a far greater number of erythrocytes, and were recording foetal cells when their presence corresponded with a spill of only 0.001 ml.

The accidents of pregnancy increase the likelihood of spill, especially those in the later stages of gestation. Amongst 196 women examined after an abortion between the 12th and 16th weeks of pregnancy, we detected three cases of transplacental leak. But out of four women who had miscarriages between the 20th and 24th weeks, two were found to have foetal cells in the circulation. In all these cases the leak amounted to only 0.1 to 0.2 ml. of foetal blood. Among eight women who suffered an accidental haemorrhage at the 33rd to 34th week of gestation, four instances of foeto-maternal leak were found.

When the frequency and size of these microtransfusions have been fully defined, it will be possible to determine their role in Rh sensitization. This work is now in progress.

SUMMARY

Foetal red cells were searched for in blood taken on the first and second days after childbirth from 635 women. In terms of the ABO system, 535 women bore a compatible child, and a foeto-maternal microtransfusion was found in 166 (31%) of these; 100 bore an incompatible child, and 16 of these women showed a foeto-maternal "spill." The magnitude of the spill was not apparently affected by the ABO compatibility status, but disappearance of the transfused cells on the second day of observation was significantly more common when they were incompatible with the mother's serum. The likelihood of foeto-maternal spill is increased when the accidents of pregnancy occur, especially those in the later stages of gestation.

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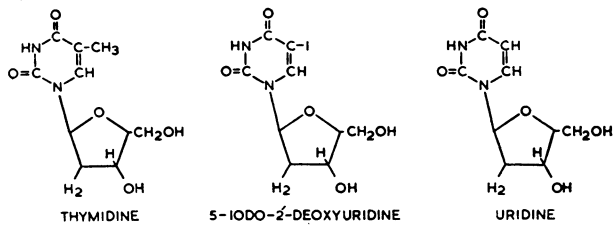
Treatment of Dendritic Corneal Ulceration

Dendritic corneal ulceration presents a serious problem owing to its relative refractoriness to any form of treatment and the marked tendency to recurrences. Untreated cases only very occasionally heal spontaneously (Duke-Elder, 1938). As this is a potentially blinding disease a control series using inert substances was not felt to be justified. Up to the present time no drug has been effective and the only commonly accepted form of treatment has been that of debridement and disinfection of the infected corneal epithelium by the methods of carbolization or iodization.

Jones (1959) has stated that "ocular herpes is an infectious disease caused by a virus against which we have no effective drug," and the visual defect caused by corneal opacities consequent on recurrent herpes simplex infection may be severe, even necessitating eventual keratoplasty. This tendency has been enhanced in recent years by the undesirable effects of the unguarded use of local steroids in this condition.

Recent reports of the work of Kaufman *et al.* (1962), using the compound 5-iodo-2′-deoxyuridine (I.D.U.) as a topical application in the treatment of herpetic corneal ulceration, prompted the present series of cases. The herpes simplex virus is composed mainly of deoxyribonucleic acid in association with protein; and I.D.U., which closely resembles thymidine in molecular configuration (see Formulae), is believed to achieve an antiviral effect by competitively inhibiting the uptake of thymidine into the deoxyribonucleic acid molecule. A consistently high concentration is therefore necessary. Furthermore, the drug is suitable only for topical application.



PRESENT INVESTIGATION

Methods.—Fifteen cases of initial or secondary dendritic corneal ulceration, clinically of the type arising out of corneal epithelial infection with herpes simplex virus and presenting consecutively in the casualty department, were admitted as in-patients. A 0.1% solution of I.D.U. was dropped in the affected eye hourly during the day and night. The affected eye was padded, but no other treatment was given. A daily record of the corneal changes as demonstrated by fluorescein staining, using the slit-lamp and cobalt filter, was made. The medication continued for a period varying from 3 to 11 days. No untoward effects were noted by the patients, and those who had had a similar condition treated by other means at an earlier date were unanimous in their reports of the rapid relief of symptoms.

Table of Results

Case No.	Sex and Age	No. of Previous Dendritic Ulcers	Duration of Symptoms Prior to Treatment (Days)	Duration of Treatment with I.D.U. (Days)	Resolution of Dendritic Staining Areas (Days)	Occurrence of Superficial Erosions (Days)	Resolution of Superficial Erosions (Days)	Stromal Involvement	Follow-up Period (Days)
1	M 50	1	3	4	4	5	12	++	60
2	M 58	1	6	8	5	6	9	++	60
3	F 5	None	42	4	4	—	—	—	53
4	F 51	1	2	9	5	5	12	++	53
5	F 66	None	44	11	5	5	—	++	50
6	M 51	3	22	9	5	6	11	++	46
7	F 11	None	28	4	4	—	—	—	36
8	M 38	,,	10	4	4	4	7	—	30
9	M 34	,,	11	4	4	—	—	—	26
10	M 58	,,	21	5	4	5	6	+	18
11	M 29	,,	30	4	4	—	—	—	16
12	M 32	,,	7	4	4	—	—	—	16
13	M 61	,,	24	5	4	—	—	+	12
14	M 41	,,	7	4	4	—	—	—	10
15	M 76	,,	14	5	4	—	—	+	10

Results.—Resolution of the dendritic ulceration was obtained in all cases. Cases of primary dendritic ulceration without stromal involvement healed in three to four days. Where there was stromal involvement healing was completed in four to six days. The results are presented in the Table.

DISCUSSION

The satisfactory results obtained suggest that this form of treatment is much more effective than those commonly in use, and that I.D.U. has a specific antiviral effect in corneal epithelial infection due to the virus of herpes simplex. No cases of the early recurrence of ulceration which is so common were noted, but only the passage of time will demonstrate whether the virus is completely eliminated from the site of infection.

Three other cases of simple recurrent punctate keratitis, presumptively of viral origin, were also treated with I.D.U. There was no improvement in one, and in the other two an increase in the size and number of the erosions was noted. These latter cases improved on discontinuance of the drug.

An important finding was that in Cases 5 and 6 the initial viral ulceration rapidly disappeared, but owing to the persistence and increase of corneal punctate staining the administration of I.D.U. was continued for up to 11 and 9 days respectively. In both these cases a secondary non-dendritic ulceration and epithelial degeneration appeared at the site of the original ulceration. In Cases 1, 2, 4, and 8 considerable punctate staining was noted after five or six days' administration. In all these except Case 5, the secondary degenerative change was rapidly reversed after the discontinuation of the I.D.U. and without any other treatment. In Case 5 the large erosion persisted for 20 days, but the presence of corneal vascularization suggests that there may have been a secondary factor. It would seem a reasonable hypothesis that, as well as the action of I.D.U. on viral metabolism, there is an effect on the nucleic acid metabolism of the corneal epithelial cells, producing degenerative changes similar in appearance to those which may be observed after exposure to excess doses of ultra-violet light.

Despite the extremely favourable results obtained, it would therefore seem desirable that further attention be paid to the question of duration and frequency of treatment and concentration of the drug when used in cases of recurrent ulceration or where there is a tendency to corneal stromal reaction.

SUMMARY

The results of the treatment of 15 consecutive cases of dendritic corneal ulceration clinically associated with herpes simplex virus epithelial infection with a topical solution of 0.1% 5-iodo-2′-deoxyuridine are reported. Resolution of the dendritic ulceration without early recurrence was obtained in all cases. I.D.U. would seem to be at present the indicated treatment for this condition.

Some apparent secondary effects of the substance on the corneal epithelium are discussed and it is suggested that its prolonged administration should be undertaken only with caution.

Our thanks are due to Smith, Kline and French, and particularly to Dr. Johnston, for kindly supplying the I.D.U. used in this investigation.

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Medical Memoranda

Recurrent Phlyctenular Keratoconjunctivitis Treated by Desensitization to Tuberculoprotein

Keratoconjunctivitis is an uncommon complication of the primary tuberculous complex. In most cases it is mild and local treatment suffices. On rare occasions the condition is most persistent and recurs at frequent intervals over a period of years. Antituberculous drugs have no effect on the phlyctenules, and indeed the condition often develops when the patient is already on such drugs. Pines (1959) described the case of an 11-year-old boy who had recurrent attacks of phlyctenular keratoconjunctivitis for a number of years. Treatment with antituberculous drugs had had no effect. After the discovery that he had a marked sensitivity to tuberculin he was desensitized, and this resulted in his recurrent attacks clearing up completely.

The following is a report of a further case treated along similar lines.

CASE REPORT

A boy aged 6 was seen in February, 1954. At that time he had an erythema nodosum. A chest radiograph showed a left hilar adenitis. The tuberculin test was positive to 1 unit old tuberculin (15 mm. induration and erythema). He was treated with isoniazid and P.A.S. at home. In August he had an acute left otitis media and his first attack of phlyctenular keratoconjunctivitis in the left eye. In October both eyes were involved in a further attack. The first course of antituberculous drugs was given for a period of four months. He was admitted to Crawfordsburn Children's Hospital in May, 1955, partly for social reasons but also because his general condition was rather poor. Gastric washings at this time were negative. He remained in hospital for eight months, and during this time his chest radiograph showed calcification developing in his left hilar shadows but no antituberculous drugs were given. He had recurrent trouble with his eyes, and local treatment was given for this. He also tended to have a low-grade pyrexia most of this time although his erythrocyte sedimentation rate remained within normal limits.

After discharge from hospital in January, 1956, his attacks continued. In November he had a left pleural effusion. In January, 1957, he had a left basal pneumonia, which cleared rapidly with penicillin treatment. In April it was decided to give him a further course of isoniazid and P.A.S. This second course of antituberculous drugs was continued for nine months with no effect on his eye symptoms.

He was admitted to St. Columb's Hospital, Londonderry, in June, 1959, and one month prior to this he had had a further attack of phlyctenular conjunctivitis in both eyes. It was found that he was very strongly sensitive to old tuberculin. He was given 0.1 ml. of a 1 in a million dilution and he had a reaction 6 mm. in diameter.

It was then thought that as his recurrent phlyctenular keratoconjunctivitis was in actual fact due to a very marked sensitivity to tuberculoprotein and that this would explain the lack of response, particularly to the second course of antituberculous drugs, desensitization should be attempted. This was begun with 0.1 ml. of a 1 in a million dilution of old tuberculin and at the same time a further course of P.A.S. and isoniazid was started. The dose of