Cryosurgery and immunotherapy in herpes keratitis

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As early as 1930 herpes simplex keratitis was considered to be the most important specific keratitis in the United States (Gundersen, 1936; Thygeson, 1953). This statement is true today, not only for the United States but for all other countries outside the tropical and subtropical zones having a high standard of hygiene and medical care. With the advent of local steroid medication in the treatment of eye disease, herpes keratitis seems to have become more severe and the once rare bilateral cases are no longer uncommon (Howard and Kaufman, 1962).

Andrews and Carmichael (1930) found antibodies to Herpes simplex in the sera of a large number of normal adults, and noticed that recurrent herpes, that is herpes labialis and herpes of the eye, did not occur in subjects without such antibodies. In other words, patients with herpes keratitis have circulating antibodies and a significant titre of neutralizing and complement-fixation antibodies can be found in their serum.

Krwawicz (1965) introduced the use of low temperature application to the cornea in cases of herpes keratitis and reported good results.

This work was duplicated by the present authors who found inconsistent and poor results in cases of recurrent and deep stromal herpes. For this reason a new method was evolved which is based upon the use of corneal cryosurgery combined with topical application of human immune serum.

Material and methods

From July, 1969, until July, 1972, this method has been used in 43 cases of active herpes keratitis which include eleven dendritic ulcers, eleven superficial stromal cases, thirteen cases of disciform keratitis, and eight of metaherpes keratitis. Local steroids had been used in four, three, and six cases of the second, third, and fourth groups respectively. The age of the patients varied between 14 and 65 years.

Using multiple applications, the entire lesion is frozen and thawed at least three to five times under direct slit-lamp control with a cryoprobe having a very rapid defrosting rate. A 2 mm. retinal cryoprobe is applied warm, exerting a little pressure on the cornea. The application time is 2 to 3 secs. after actuation of the gas flow. The ice-rim formed on the corneal surface around the probe helps in the assessment of the freezing depth (Fig. 1). It is essential to freeze the entire depth of the lesion stopping short of the endothelium in cases of deep stromal herpes. Nitrous oxide gas operating a Joule Thomson cryoprobe is used to give a probe tip temperature of —80°C. (Amoils and Kaufmann, 1972).

The patient arrives for the freezing treatment with a sterile bottle containing fresh serum obtained from 15 ml. of his own blood. Drops of serum are instilled into the treated eye for 1 hr after cryotherapy at intervals of 1 min. (Amoils and Maier, 1971). In the last twenty cases this serum has been mixed with 5 ml. gamma globulin to increase the concentration of herpes antibodies (Howard...
and Allen, 1958). As pain is experienced a drop of local anaesthetic and homatropine is instilled three times during the hour and strong analgesics are used after treatment.

When the surface fluorescein has disappeared (3 to 4 days in deep cases), steroids can be added for the original iritis. Sub-conjunctival depo-steroids have been used in all severe cases with iritis.

In cases of metaherpes keratitis, the cryotherapy is focused on the ulcerated staining areas and surrounding tissue (adjacent and deep). These eyes are kept patched for 2 to 4 weeks as healing is slow in these devitalized corneae. In vascularized corneae (Plate VII) the freezing is concentrated on the central avascular areas.

All drugs especially 5-iodo-deoxyuridine (IDU) are stopped for at least 7 days before therapy is commenced. In two cases of metaherpes, new ulcerative areas appeared when this was done (Fig. 10) and these ulcers were then treated together with the adjacent cornea.

Results

In all cases a cure was obtained with no recurrences to date. The follow-up period varies from 3 years to 3 months. One of the cases of metaherpes keratitis required re-treatment 2 weeks after preliminary therapy as the gas supply ran out and a probe temperature of only —20°C was obtained.

All the epithelial cases (Figs 2, 3, 4, 5, 6) had lost the fluorescein staining by the 3rd or 4th day and the superficial stromal cases (Figs 7, 8, 9) by the 4th or 5th day. The metaherpes cases (Plate I to IV; Figs 10 to 13) healed in 4 to 8 weeks depending on the extent of the lesion and concomitant iritis. The disciform cases (Plate V to VIII; Figs 14 to 17) take from 3 to 4 weeks to settle and seven had postoperative iritis after the therapy which lasted 10 to 12 days.

Local steroids were begun when the fluorescein staining disappeared, and four cases of metaherpes keratitis and four of disciform keratitis were given subconjunctival depo-steroids.

Cases of disciform and metaherpes keratitis were treated vigorously with topical steroids after cryosurgery and serum therapy, and no reactivation of the lesion was seen.

The uveitis responded very well to steroid medication and only one case took 12 weeks to clear. No serious problems arose because of a rise in intraocular pressure but oral Diamox was used in three cases for 10 to 14 days.

No other complications have so far been encountered.

Comment

The rationale of this new treatment is to break open all the infected cells with the multiple freeze/thaw cycles and to release the intracellular virus particles. Significant titres of serum-neutralizing or complement-fixing antibodies have been found in the cases treated. The treated area is then flooded with serum antibodies before the free virus particles can enter another healthy cell. An hour is considered sufficient to fix all the free virus to the serum-antibodies, thus neutralizing them and preventing them from infecting healthy cells. The gamma globulin was added to allow more intensive treatment and higher concentration of antibodies, but no failures were experienced before its usage.

In superficial herpes the infected cells are mechanically ruptured by cryosurgery. The released virus particles can be washed away by the tears or neutralized by antibodies in the tears themselves. However, serum therapy increases the cure rate to 100 per cent.

The method of cryotherapy used in this trial ensures a very rapid freezing rate with the formation of intracellular ice and a maximum kill rate of parenchymatous cells such as epithelium and stromal cells with release of virus particles.
Case 8. Metaherpes keratitis of 18 mths' duration. Calcareous degeneration of inferior third of cornea


Case 10. Recurrent disciform keratitis with corneal oedema

Case 11. Vascularized disciform keratitis

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Herpes keratitis

**FIG. 1** Ice-ball formed in cornea around tip of 2.5 mm. Joule Thomson cryoprobe at -85°C. Slit beam in pupil

**FIG. 2** Case 1. Typical dendritic epithelial ulcers before treatment

**FIG. 3** Case 1. 3 days after cryosurgery and serum therapy

**FIG. 4** Case 2. Y-shaped epithelial dendritic ulcer with terminal arborization

**FIG. 5** Case 2. 1 day after cryosurgery and serum therapy, showing destruction of epithelial cells

**FIG. 6** Case 2. 10 days later (remnants of an old traumatic cataract are seen in pupil)

The repeated freeze/thaw cycles also kill a certain percentage of the virus *per se*. Fluorescein photographs on the first postoperative day show staining of the treated area indicating destruction of the epithelial cells (Fig. 5).
It should be noted that freezing has no effect on the inert collagen fibre framework of the cornea. After cryosurgery, however, mydriatic drops have a very rapid effect suggestive of increased corneal permeability. Histology of rabbit cornea after freezing clearly shows lamellar separation and alteration and oedema of the intracellular matrix (data to be published).
Animal experiments (unpublished data) have given conclusive proof of the importance of antibodies in modifying the pathogenesis of ocular herpes in immune rabbits. These antibodies protect the conjunctiva from infection but do not prevent lesions in the avascular cornea.

The success of this method of therapy strongly indicates that the presence of complete or incomplete virus particles, which can be re-activated by various stimuli, causes the stromal component of herpes keratitis. By inactivating all the virus, the disease process can be cured.

It has frequently been shown that, in tissue removed at keratoplasty from an apparently
Table  Results in four groups of cases

<table>
<thead>
<tr>
<th>Diagnosis before therapy</th>
<th>No. of patients</th>
<th>No. cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Epithelial (dendritic ulcer) Primary</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>6</td>
</tr>
<tr>
<td>II. Superficial stromal</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>8</td>
</tr>
<tr>
<td>III. Deep stromal</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Disciform</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Metaherpes with ulceration</td>
<td>8</td>
</tr>
<tr>
<td>IV. Corneal perforation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
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well healed but opaque cornea which has remained quiet for years, foci of inflammatory cells are found in the scar (Duke-Elder, 1965). This may explain the recurrent habit in most of the cases treated in this series, which includes a large percentage of referred, recurrent cases. The absence of corneal perforation is almost certainly due to the inactivation of all virus particles before intensive steroid therapy was begun.

The reappearance of ulcerative areas in the cases in which preoperative IDU was stopped illustrates the fact that this drug merely inhibits the multiplication of the virus and is not virucidal.

It is interesting to speculate on the value of this method of therapy in conjunction with IDU, fluorothymidine, or other anti-virus drugs. These drugs were never used after cryosurgery in this series of cases.

In conclusion, it is felt that the avascularity of the cornea is the reason for the chronicity and recurrences of many cases of herpes keratitis. It was often noted that, if blood vessels grew into the cornea in chronic lesions, they stopped short of the margin of ulcerated areas as if the herpes virus had a vascular inhibitory effect (Plate I, III; Figs 10, 12). Even in heavily vascularized lesions the vessels do not cross the centre of the lesion (Plate VII).

Summary

Cryosurgery, using repeated freeze/thaw cycles combined with repeated topical application of immune human serum for 1 hour has produced excellent results in 43 cases of herpes keratitis (Table). The most dramatic cures have been seen in cases of intractable metaherpes, and in disciform and recurrent stromal herpes ulceration. No complications have occurred and the early postoperative use of steroids does not reactivate the lesions. No failures have been experienced with this method of therapy and no recurrences have so far been observed.

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References

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HOWARD, J. E., and ALLEN, H. F. (1958) Ibid., 59, 68
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