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Herpes Simplex Virus Ophthalmia

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Herpes simplex virus ophthalmia (HSVO) is caused by herpes simplex virus (HSV). HSV is a common cause of keratoconjunctivitis and it is the major infectious cause of corneal blindness in industrialised countries. HSVO has been intensively studied at the Institute of Ophthalmology, and these studies have led to major advances in the recognition of the range of eye diseases caused by HSV, methods of diagnosis and treatment, and in our understanding of the pathogenesis of HSVO. Professor Barrie Jones initiated these studies and many people have been involved. Their names are not mentioned here, but they appear on the many papers which have been published. I felt that it would be appropriate to mark the fortieth anniversary of the Institute of Ophthalmology by reviewing these papers, and also the papers written by those people who began their studies of HVSO at the Institute of Ophthalmology, and who have continued their studies at other institutions.

Two papers published in the late 1950s serve as reference points.[1,2] They make interesting reading for anyone concerned about infections of the outer eye, and they serve to remind us of the difficulties our predecessors faced in the diagnosis and management of patients with HSVO. The opening paragraph of the first of these papers reads as follows:

"Conjunctivitis is rather an ophthalmic Cinderella for she appeared to be an uninteresting drudge to whom few people paid any real attention. However, if we follow in the Prince's footsteps and really look at her we find that she is actually fascinating and attractive, full of diverse possibilities and eager to reward our interest."[1]

Some ophthalmologists may still consider conjunctivitis and keratoconjunctivitis to be "an uninteresting drudge", but all those who have followed in the Prince's footsteps have helped to create the fascinating but as yet incomplete picture of HSVO which is presented here.

The Pathogen

Herpes simplex virus is an enveloped DNA virus. It can be divided into two types, HSV type 1 (HSV-1) which is associated with infections of the eye, nose and lip, and HSV type 2 (HSV-2) which is associated with genital infections. Recurrent disease is a characteristic of HSV infections. This results from the ability of HSV to infect sensory nerves and remain dormant in the sensory nerve ganglia, protected from the host's defence mechanisms. From time to time, HSV spreads from its ganglion along the nerves to the skin or mucous membranes, causing recurrent disease. HSV can also persist in the cornea in the absence of active HSVO. In a recent study, HSV was isolated from 10 out of 34 (29%) corneal buttons obtained from patients with a definitive history of ulcerative herpetic keratitis who were undergoing penetrating keratoplasty.[3] HSV may also be able to persist elsewhere.

It has often been assumed that there is little or no difference between different strains of HSV-1. However, studies in animal models (which are described later) indicate that a strain of HSV-1 isolated from a particular clinical form of HSVO produces the same form of HSVO in experimentally infected animals. These observations indicate that different strains differ in their pathogenicity in the eye. Although the biological basis for this difference is not yet clear, some preliminary studies indicate that strains of HSV-1 isolated from patients with chronic stromal disease excrete larger amounts of

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'soluble' precursor glycoprotein D than strains isolated from patients with recurrent dendritic ulcers or keratoconjunctivitis.[4]

Epidemiology

Source of infection

There are several ways in which HSV-1 can reach the eye. It can be transferred mechanically from herpetic lesions elsewhere on the same individual or from herpetic lesions on another individual. Barrie Jones considered that herpetic lesions on other individuals were the source of infection, and he divided his patients into two groups: "the first consisting of children who have been kissed by their blistered parents, and the second consisting of young adults who have been kissed by their blistered lovers. To the eye, the menace of the virus-laden kiss is heightened by the tendency of the labial herpetic to avoid lip contact and prefer instead cheek or brow."[2] Laboratory animals develop HSVO following inoculation of HSV-1 into the eye, and these findings support the hypothesis that HSVO can result from direct infection of the eye. How many patients acquire HSVO by direct infection? In a study in London of patients experiencing their first attack of HSVO, nine patients (8%) had been in contact with individuals who had active herpetic skin lesions, and 17 patients (16%) had herpetic lesions on their own lips, nose or face.[5] However, 82 patients (76%) had no history of contact with herpetic lesions.

How do the majority of patients acquire their infections? There are several possibilities. They could acquire it through the transfer of HSV to the eye from the discharges of individuals who shed HSV-1 in their discharges but who are asymptomatic. This hypothesis is supported by the observation that HSV was isolated from tears and saliva of four out of 11 individuals (36%), none of whom had a history of herpes infection.[6] Thus apparently normal individuals can be sources of infection. Infection of the eye could be followed immediately by the development of HSVO. Alternatively, it could remain asymptomatic and therefore undiagnosed, but later recur, producing typical HSVO. Another possibility is that HSV infection may occur first at another site (eg skin or mouth), and later spread to the eye through the nerves producing HSVO. This hypothesis is supported by studies in mice. HSV-1 was inoculated into the snout skin. It could be isolated from eye-washings on day four, and corneal disease was first seen on day six. Spread of HSV to eye-washings and the development of corneal disease could be prevented by removing a section of the sensory nerves which supply the snout. This indicates that spread to the eye from the snout requires an intact nervous supply.[7]

At present we do not know how HSV-1 reaches the eye in the majority of patients. We need to know in order to develop effective methods of preventing HSVO.

Prevalence

In 1957, there were 23 cases of HSVO in a series of 124 patients (19%) with acute conjunctivitis attending Moorfields Eye Hospital and the London Hospital. HSV was the most common cause of acute conjunctivitis in these patients.[1]

It could be predicted that there should have been an apparent rise in the prevalence of HSVO in the past 30 years. Recognition of the range of eye diseases caused by HSV-1 and improved methods of laboratory investigations should have increased the frequency with which an accurate diagnosis of HSVO is made, but this does not appear to have happened.

Some recent studies give widely differing estimates of the prevalence of HSVO. In a study of patients with acute conjunctivitis attending an ophthalmic casualty clinic at Moorfields Eye Hospital, nine out of 140 patients (6%) had clinical features typical of HSVO.[8] HSV was isolated from four of these patients and from a further four patients who lacked typical lid and/or corneal lesions. This gives a prevalence rate of 9%. In addition, serological results indicated that a further 16 had recent or current HSV-1 infection. If it is assumed that all of these 16 patients had HSVO rather than cold sores or genital infection, then this gives a prevalence rate of 21%. This figure is similar to that reported earlier.[1] In a survey of 4,132 unselected specimens from patients with conjunctivitis or keratoconjunctivitis, HSV was isolated from 94, which gives an isolation rate of 2.3%.[9] This figure is much lower than that reported earlier,[1] but is an underestimate of prevalence. Specimens for viral isolation are often not taken from patients who have typical clinical features of HSVO, while other patients have serological findings which suggest current or recent

exposure to HSV-1, but HSV cannot be isolated from them. In a study of patients with acute or chronic conjunctivitis attending an eye casualty clinic at St. Thomas' Hospital, 14 out of 248 patients (6%) had dendritic ulcer, but HSV could not be isolated from any of them. Serological studies indicated that four of these 14 had current or recent exposure to HSV-1 as did a further 24 patients. If it is assumed that these 24 patients all had HSVO, then the prevalence rate is 14%.[10] This figure is also lower than that reported earlier.[1]

These three studies have produced widely varying estimates of the prevalence of HSVO, one of which is a little higher than the figure obtained in 1957, and the other two are substantially lower. During this time, it has been recognized that HSV-1 causes a range of eye diseases and several new and improved laboratory tests have been developed for the diagnosis of HSVO, but there has not been any substantial increase in the prevalence of HSVO. This suggests that the current prevalence of HSVO is probably lower than the prevalence in 1957.

There are very few studies of HSVO in developing countries. A survey of corneal ulceration in Tanzanian children showed that HSV was the commonest cause of corneal ulceration. It was associated with corneal ulceration in 47 out of 130 children (36%). A total of 16 children (12%) in the study became blind, but only one of these was a child with HSVO, indicating that it is not a common cause of childhood blindness in Tanzania.[11] These findings are in marked contrast to those obtained in a study of children in northern Nigeria, where corneal ulceration following measles is the commonest cause of childhood blindness. HSV was detected in ocular specimens from 16 out of 34 children (47%) and it was concluded that HSVO secondary to measles keratitis was a major cause of blindness.[12]

Seasonal Variations

In 1957, HSVO was most common in the Autumn.[1] In more recent studies of patients with a first attack or recurrent attacks of HSVO, the highest number of cases occurred in June, but there was no clear seasonal pattern.[5,13] Other studies have not included data on seasonal variation.

Age

Barrie Jones divided his first group of 17 patients with what he described as "primary" HSVO into two groups.[2] The first group consisted of eight patients (47%) who were 10 years old or less. The second group of nine patients (53%) were between 15 and 30 years old. However, this bimodal age distribution has not been observed subsequently. It is not known whether this is a phenomenon which has since disappeared, or whether it occurred by chance.

A continuous age distribution has been observed in all subsequent studies. In a study of patients with herpetic corneal ulceration, the mean age was 49 years and the age range was eight to 80 years. The mean age was rather high because these patients took part in a treatment trial from which women of child-bearing age were excluded.[14] Patients with bilateral herpetic ulceration had a mean age of 28 years and a range of five to 60 years.[15] Patients experiencing their first attack of HSVO also had a continuous age distribution, ranging from nine months to 66 years, with a mean age of 25 years. Thirty-nine patients (36%) were less than 15 years old and 69 patients (64%) were aged 15 years or more.[5] The ages of the patients who experienced recurrent attacks of HSVO ranged from 18 months to 56 years and the mean age was 18 years. Recurrent attacks of HSVO were significantly more common in patients under 20 years than in older patients.[13]

In the study of corneal ulceration in Tanzanian children, 51% of children were less than two years old, 21% were aged two to four years old and 28% were aged five to 10 years old.[11]

Sex

There has been a long-running debate as to whether sex has an effect on susceptibility to HSVO. Studies carried out at the Institute of Ophthalmology have produced a crop of conflicting observations, which are listed in Table I. It appears that men and women are equally susceptible to acute follicular conjunctivitis,[16] a first attack of HSVO,[5] and recurrent HSVO.[13] Men appear to be at greater risk of developing ulcerative herpetic keratitis,[14] and are even more likely to develop recurrent ulcerative herpetic disease. Men are also more likely to develop bilateral ulcerative herpetic disease.[15] However, there was no preponderance of men among the

Table I *Sexual distribution of forms of HSVO*

Form of HSVO	*Number*	*Males (%)*	*Females (%)*	*Reference*
Acute follicular conjunctivitis	25	12 (48)	13 (52)	16
First episode of HSVO	108	58 (54)	50 (46)	5
Recurrent episode of HSVO	35	16 (46)	19 (54)	13
Ulcerative herpetic keratitis	152	98 (65)	54 (36)	14
Recurrent ulcerative herpetic keratitis	61	49 (80)	12 (20)	14
Bilateral ulcerative herpetic keratitis	30	21 (70)	9 (30)	15
Keratouveitis	50	21 (42)	29 (58)	17
Severe disease requiring keratoplasty	20	7 (35)	13 (65)	18
Severe disease requiring keratoplasty	34	17 (50)	17 (50)	3

patients who developed complicated HSVO. In a group of 50 patients with HSV kerato-uveitis and raised intra-ocular pressure (IOP), there were fewer males than females.[17] In one study of patients with severe HSVO who required keratoplasty, seven out of 20 patients (35%) were men and 13 (65%) were women.[18] In another study, there were equal numbers of men and women who required keratoplasty following severe HSVO.[3]

The situation therefore remains confused and further studies are needed. It would be interesting and helpful to determine if one sex is at greater risk of developing complicated HSVO than the other, since it would indicate that host factors related to sex are important in the development of complicated and potentially blinding HSVO.

Clinical features

HSV causes a spectrum of ocular diseases, including follicular conjunctivitis with or without lid lesions, corneal disease, uveitis, glaucoma and retinitis. HSVO is commonly divided into primary and recurrent disease. Primary HSVO is described as an acute, moderate to severe follicular conjunctivitis or keratoconjunctivitis, commonly associated with typical periocular vesicles and/or ulcers. It was reported in 1957 that HSV caused nearly one-third of all cases of follicular conjunctivitis.[1] In 1959, the majority of patients (61%) had many typical HSV lesions on their eye lids, 26% had a few lesions, and 13% had no lesions. The cornea was involved in two-thirds of cases.[2]

The absence of lid and corneal lesions in some cases of HSVO presents problems in the differential diagnosis of HSVO, adenovirus ophthalmia and adult chlamydial ophthalmia. At Moorfields Eye Hospital, 25 such patients were seen in an 18-month period. They were diagnosed by the isolation of HSV (88%) or a four-fold or greater increase in complement-fixing (CF) antibodies against HSV (12%). Although there were no herpetic lesions on the lids, face or cornea at presentation, five (20%) subsequently developed herpetic lesions. All the cases had unilateral disease at presentation and eight patients (32%) subsequently developed bilateral disease.[16]

In a study of 108 patients with a first episode of HSVO in London,[5] the infection was unilateral in 88 patients (81%), and bilateral in 20 patients (19%). Twelve out of these 20 patients presented with bilateral HSVO, while eight had unilateral HSVO at presentation and developed bilateral disease within a week. Common symptoms were redness, lacrimation, discharge, itching, irritation and swelling of lids. All patients had conjunctivitis which was accompanied by lid vesicles and/or ulcers in 100 patients (93%), while eight patients (7%) had follicular conjunctivitis without typical lid or corneal lesions. Almost all patients had moderate to severe papillary responses, particularly in the upper palpebral conjunctiva. Most patients had follicles which were small and discrete and were found mainly in the lower palperbral conjunctiva. Epithelial and subepithelial punctate keratitis were found in 36 patients (33%). Sixteen patients (15%) had dendritic ulcers, while two patients had disciform keratitis.[5] Dendritic ulcers and disciform keratitis are generally considered to be forms of recurrent HSVO but these patients were experiencing their first attack of HSVO.

It is generally accepted that recurrent HSVO affects the cornea and uvea, causing dendritic, geographic or amoeboid ulcers, stromal disease including diffuse stromal keratitis, interstitial keratitis and limbal vasculitis, and anterior uveitis. In 1959, Barrie Jones stated "recurrent episodes in which the latent virus-host relation is upset by some non-specific trigger mechanism factor, tend to produce circumscribed lesions within the area initially infected. Typical vesicles and ulcers appear on the lids but the acute follicular conjunctivitis of the primary infection is not repeated".[2] However this no longer appears to be true of patients seen in London.[13] Patients who had a first attack of HSVO were followed for two to 15 years. Recurrent HSVO occurred in 35 out of 108 patients (32%), and the clinical features were similar to those of the first attack. All patients with recurrent HSVO had conjunctivitis with or without lid lesions. Only three (9%) had dendritic ulcer, which was associated with a disciform keratitis in only one case. Patients who had severe conjunctivitis and lid lesions in their first attack were more likely to develop recurrent HSVO than patients who had mild conjunctivitis and lid lesions. However there was no relationship between corneal disease and recurrent HSVO. The recurrence rate was higher in patients who were less than 20 years old than in older patients, and tended to be higher in patients whose first attack was bilateral compared with those whose first attack was unilateral. The duration and severity of HSVO was reduced in successive attacks.[13]

The prognosis for patients with HSVO is generally considered to be poor. "The disease is especially serious in children because of the likelihood of multiple recurrences and progressive ocular damage throughout life".[19] However, studies at the Institute of Ophthalmology show that the prognosis for the vision of a patient presenting with a first attack of HSVO appears to be much better than predicted. Only one-third of patients who had a first attack of HSVO had a repeated attack. These repeated attacks resembled the first attack but were less severe, while recurrent corneal disease affected only a very small proportion of patients. Further studies of patients with HSVO are needed to see if these findings can be confirmed elsewhere or whether they are unique to London. These findings also indicate that the present terminology of primary and recurrent HSVO is confusing and potentially misleading since there appears to be no clear-cut distinction between the clinical features of primary and recurrent HSVO. It has therefore been proposed that the present terminology of primary HSVO and recurrent HSVO should be abandoned, and HSVO should be described by its clinical features, regardless of whether it is a first attack or recurrent attack.[20] For example, HSVO can be described as HSV conjunctivitis or blepharoconjunctivitis (with lid vesicles or ulcers), HSV blepharokeratoconjunctivitis, or HSV keratitis (dendritic ulcer, geographic ulcer or diffuse keratitis) or HSV keratouveitis. The adoption of this nomenclature would help to provide a clearer clinical picture of HSVO, and it would not affect management and treatment. The terms primary HSVO and recurrent HSVO should be reserved for those patients whose immunological status has been determined. Only those experiencing a first attack of HSVO who seroconvert during infection should be described as having primary HSVO.

Bilateral herpetic corneal ulcers are unusual, and a survey of patients at Moorfields Eye Hospital showed that it occurred in approximately 3% of all patients with HSV corneal disease.[15] Thirty patients were studied and bilateral corneal ulcers occurred simultaneously in the first episode of HSVO in 17 of these 30 patients (57%). Twenty patients (67%) were under 30 years old, and 12 (40%) were atopic. Recurrent ulcers were common, and were followed by the development of stromal keratitis. These patients also had a high likelihood of developing progressive corneal inflammation and opacification.[15] HSV keratouveitis can lead to raised intraocular pressure (IOP) and glaucoma. Raised IOP was observed in 50 out of 183 patients (28%) with HSV keratouveitis, and five (3%) developed a glaucomatous visual field defect. Patients with raised IOP had all developed corneal ulcers or stromal keratitis during their first attack of HSVO. They had suffered from recurrent HSVO for a few weeks to 30 years before the development of raised IOP. However, none of these patients had active corneal ulcers when they presented with raised IOP.[17]

Diagnosis

(1) Clinical diagnosis

Careful history-taking and clinical examination are needed to establish a correct aetiological diagnosis. The presence of moderate to severe papillae and follicles with lid vesicles or ulcers, dendritic or geographic corneal ulcers, disciform or diffuse stromal keratitis can all indicate HSVO. However, HSVO can present as conjunctivitis without lid lesions or corneal ulcers, and in such cases, a correct aetiological diagnosis can only be made from the results of laboratory tests. In a study of patients with acute conjunctivitis at Moorfields Eye Hospital, four out of 140 patients (3%) had HSVO without typical lesions.[8] A correct aetiological diagnosis is essential for the provision of effective treatment of HSVO; an incorrect diagnosis may be followed by treatment which is ineffective or which exacerbates the disease and leads to sight-threatening complications.

(2) Laboratory diagnosis

"The specific viral nature of the cutaneous vesicles or ulcers is readily proved by the examination of scrapings, in which multinucleate viral giant cells and others with acidophil intranuclear inclusions are found".[2]

The modern laboratory does not rely solely on material from vesicles or ulcers, and nowadays, conjunctival scrapings and swabbings, tears and blood are all used. Current laboratory methods for the diagnosis of HSVO can be divided into three types: direct detection tests, culture tests and serological tests. Modern tests are highly specific and sensitive, but they all depend on the ability of the clinician to take adequate specimens at the appropriate stage of the disease.

Direct detection tests

Tests for the direct detection of HSV have been developed using immunofluorescent staining methods to detect infected cells. The use of these tests to diagnose HSVO using conjunctival and corneal specimens has begun, and they appear to compare well with conventional culture tests.[21]

Culture tests

HSV can infect many cell types, and a conventional method of growing HSV is to inoculate cells and look for the development of typical cytopathic effect. At the Institute of Ophthalmology, human embryonic kidney cells or HEp2 cells were used. The test took 21 days, which was much too long, and more rapid methods of growing HSV and identifying infected cells have been developed. It was found that high speed centrifugation (15,000xg at 35°C for one hour) significantly increased the rate of HSV isolation from clinical ocular and genital specimens and also from laboratory isolates. Centrifugation did not affect the time taken for the appearance of cytopathic effect. This suggests that centrifugation does not affect growth of HSV agent in cells, but it increases the efficiency with which cells are infected.[22] Centrifugation can be combined with an immunofluorescent method of staining infected cells after 48 hours of incubation. This rapid method detected 21% more infected specimens than the conventional method.[23]

Serological diagnosis

A presumptive diagnosis of HSVO can be made by detecting specific antibodies in blood or tears. The universally accepted criteria for serological diagnosis are seroconversion or a four-fold or greater rise in serum titre. However, two samples of serum, collected during acute and convalescent stages at least two weeks apart, are required. This limits the usefulness of serological tests in diagnosing HSVO. Tests on a single specimen can be useful. It is generally accepted that IgM is the first antibody produced during an immune response, and hence its presence is an indicator of active or very recent infection. High levels of IgG antibodies in blood and the presence of antibodies in tears may suggest current or recent infection. Serological tests for HSVO must also distinguish between antibodies to HSV-1 which is associated with HSVO and skin infections, and HSV-2 which is associated with genital infections.

Serological diagnosis of HSVO presents problems because many people have antibodies against HSV-1 in their blood but no history of infection with HSV. The prevalence of antibodies to HSV varies widely and reflects standards of living. In the mid 1960s, it was observed that 33% of British-born clinical students at Oxford had antibodies compared with 62% of students born in third-world countries.[24] The prevalence of HSV antibodies is lower in people born after 1945 than in older people,

which indicates that HSV infection is becoming less common. Serological diagnosis of HSVO based on seroconversion, four-fold rise in titre or the presence of IgM or high levels of IgG is therefore becoming far more useful.

The CF test is the conventional test for the serological diagnosis of HSV infection. However, this test has several limitations. Blood must be collected by venepuncture and serum collected from the clotted blood, so the CF test is not rapid or convenient to perform. The volume of tears which can be collected is too small for this test. A micro-IF test, using small volumes of blood or tears collected on cellulose sponges and naked viral particles as antigen was therefore developed.[25] This test was used to study antibodies in sera from 68 patients with HSVO from whom HSV had been isolated. IgM antibodies against HSV-1 were found in sera from 27 patients (40%), and IgG antibodies were found in sera from 63 patients (93%). In contrast, no patients had IgM antibodies against HSV-2, and only 10 patients (15%) had IgG antibodies against HSV-2, which were present at much lower levels than IgG antibodies against HSV-1. Serological studies of patients with typical dendritic corneal ulceration showed that six out of 28 patients (21%) seroconverted.[26] These patients were therefore presumably experiencing their first exposure to HSV-1, and these findings support the observation that corneal ulcers can develop during a first attack of HSVO.

HSV may cause acute retinal necrosis, and serological studies support this hypothesis. Three patients with acute retinal necrosis had IgG antibodies to HSV-1 in their intraocular fluids, and two had IgG antibodies to HSV-1 in their sera. In contrast, antibodies were detected in the intraocular fluids of only two out of 120 (2%) control patients undergoing routine intraocular surgery, although 25 had antibodies in sera.[27] While these observations do not prove that HSV-1 causes acute retinal necrosis, they suggest that it may be involved. The presence of antibodies in intraocular fluids may be due to local antibody production, sequestration of antibodies in the eye, or leakage from the blood. Similarly, antibodies against HSV-1 in the tears may be locally produced, or they may leak into the tears from the blood. IgA acquires secretory pieces during its passage through epithelial cells and is then known as secretory IgA. It is found in discharges, but is not present in blood. Secretory IgA antibodies against HSV in tears may be a better indicator of HSVO than other antibodies in tears because they are locally produced. Studies carried out in other laboratories have indicated that the presence in tears of secretory IgA antibodies against HSV may be helpful in diagnosing HSVO. A comparison of antibodies in tears from patients with HSVO, patients with inflamed eyes due to other causes and controls with normal eyes was carried out using radioimmunoassay. Significant amounts of secretory IgA antibodies against HSV were found in tears from patients with HSVO but not from other patients and controls and were therefore good indicators of HSVO. In contrast, IgG antibodies were found in tears from patients with HSVO and from other patients with inflamed eyes. IgG antibodies in tears indicate ocular inflammation and are therefore poor indicators of HSVO.[28] A recent study of HSVO using an enzyme immunoassay to measure HSV antibody levels produced similar results. The presence of secretory IgA was found to be a good indicator of HSVO since it was present in 20 of 53 HSV patients (38%), but it was not found in control patients with inflamed eyes due to other causes. IgA and IgG were present in tears from both groups of patients. They were present at lower levels in tears than in sera. It was therefore concluded that IgA and IgG antibodies against HSV in tears came from the blood and were transudated into tears in inflamed eyes. They were therefore not reliable indicators of HSVO.[29] Clearly, our present serological methods of diagnosing HSVO have their limitations and there is a need for tests which are more specific.

Treatment

"Herpes is an infectious disease caused by a virus against which we have no effective drug".[2] Thirty years ago, there were no antiviral drugs. So what could the ophthalmologist do? According to Barrie Jones, there were six "potent weapons" for treating HSVO, viz:

1. debridement and disinfection of epithelial lesions;
2. masterly inactivity;
3. antibiotic therapy to reduce the danger of intercurrent bacterial or fungal infection;

Table II *Comparative clinical trials of antiviral agents and methods of tissue removal for the treatment of HSVO*

Treatment	*Form of HSVO*	*Reference*
Iodoxuridine vs placebo	Dendritic ulcer	30
Iodoxuridine vs cauterisation	Dendritic ulcer, dendritic ulcer with stromal keratitis, steroid-enhanced dendritic ulceration	38
Cryotherapy vs carbolisation with iodoxuridine vs placebo	Dendritic ulcer, steroid-enhanced ulcer	39
Trifluorothymidine vs iodoxuridine	Dendritic ulcer, geographic ulcer	31
Trifluorothymidine with or without hydroxy propyl methyl cellulose	Dendritic ulcer, geographic ulcer	32
Debridement with interferon vs placebo	Dendritic ulcer	37
Trifluorothymidine vs adenine arabinoside	Geographic ulcer	33
Acyclovir vs iodoxuridine	Dendritic ulcer, geographic ulcer	34
Acyclovir vs adenine arabinoside	Dendritic ulcer	36
Acyclovir and debridement vs acyclovir	Dendritic ulcer	35

4. lamellar grafting to limit the extent and duration of stromal disease;
5. steroid therapy to minimise or abolish the stromal reaction;
6. tarsorraphy to help indolent nonviral ulcers to heal.

Atropine, heat, dark glasses, bandages, tonics and general supportive measures were also considered to be important. In addition "the problem of preventing recurrences is by no means hopeless. To a recurrent herpetic patient it is worth the time and trouble it takes to track down the individual trigger factor; to use aspirin in full doses for any febrile upset; to avoid excessive sun and use dark glasses; to have sedation for emotional upsets; or in troublesome cases to have a preventive lamellar keratoplasty. Above all it is important to explain the disease as a whole to the sufferer and to his family, who, together with the surgeon, become a team whose aim it is to prevent stromal and other complications".[2]

Current methods of treatment of HSVO have two aims: firstly to reduce viral replication and shedding of viral particles, and secondly to reduce tissue damage. Antiviral agents and mechanical removal of infective tissue reduce viral replication and shedding of viral particles, and they are used to treat follicular conjunctivitis, keratoconjunctivitis and corneal ulcers. Anti-inflammatory drugs prevent tissue damage, and are used to treat stromal keratitis and uveitis.

The first antiviral drug used to treat HSVO was idoxuridine (IDU). The results of the first clinical trial of IDU conducted at the Institute of Ophthalmology were published in 1963.[30] In the past 25 years, comparative clinical trials of several other antiviral drugs and mechanical methods for removing infected tissue have been carried out (Table II). There are two questions which these comparative clinical trials have sought to answer; first, is the treatment effective against various forms of HSVO and secondly, does the treatment affect the rate of recurrence of HSVO?

In the first trial of IDU, several groups of patients with dendritic ulceration and, at most, minimal stromal keratitis, were treated in a double-blind fashion. It was concluded that "IDU was a highly effective therapeutic agent in the treatment of simple dendritic ulceration . . . maximal benefit was attained with five days' intensive treatment in conjunction with pad and heat. With these measures a beneficial therapeutic response was noted in 86% of ulcers whilst complete resolution was attained in 76% of the cases".[30] Other antiviral drugs which have been used in clinical trials are trifluorothymidine (F_3T),[31,32] adenine arabinoside (AA),[33] and acyclovir.[34,35,36] The antiviral agent interferon has also been tested.[37] The first antiviral drugs had very limited solubility in water, making it unlikely that therapeutic levels could be attained in the deeper corneal tissues. In addition, they evoked toxic or hypersensitivity responses in some patients, while other patients had ulcers which appeared to be resistant to treatment. At present, topical acyclovir is the treatment of choice.

Methods of removing infected tissue include cauterisation,[38] cryotherapy and carbolisation,[39] proflavine photoinactivation,[40] and mechanical debridement.[41,35,37] It has been found that all these methods of treatment are useful and they are usually followed by treatment with antiviral agents. In a review of the advantages and disadvantages of various methods for removing infected tissue, it was concluded that mechanical debridement with a cotton-tipped applicator was the most effective and safest, since diseased epithelial cells brushed off very easily, leaving the normal cells behind.[41]

The second aim of treatment is to prevent recurrent HSVO. However, it soon became apparent that antiviral measures had little effect on the rate of recurrent disease. Recurrent disease was observed within the first year in patients who were treated with IDU or placebo drops in the first trial.[30] It was reported that five years after this trial, the mean interval between attacks of HSVO in the group of patients whose dendritic ulcers were cured with IDU was 3.6 years. The mean interval was 3.1 years in the group whose dendritic ulcers failed to respond to placebo drops and who required cauterisation. There was no significant difference in the mean interval between the two groups.[38] More detailed analysis of these patients was later carried out.[42] There was no difference in the rates of recurrent corneal ulceration and subsequent stromal disease in the two groups. They were 56% and 26% respectively in the group treated with IDU, and 66% and 24% respectively in the group treated with placebo. However, the rate of recurrence was much higher in patients who had a previous episode of HSVO before the trial compared with those who had not experienced a previous episode (83% and 43% respectively). Patients with a previous episode were also more likely to develop stromal disease compared with those without a previous episode (35% and 17% respectively). Comparison of the patients who took part in the trial of IDU and cauterisation showed that the rate of recurrence of HSVO was the same in both groups.[42]

A review of the patients who took part in the comparative clinical trial of F_3T and IDU[32] showed that there was no significant difference in the rate of recurrence or the development of stromal keratitis in the two groups of patients. All the patients who had a previous history of herpetic corneal ulcer before entering the trial suffered from recurrence regardless of which treatment they received. There were early indications that the rate of recurrence was lower in patients experiencing their first herpetic corneal ulcer who were treated with F_3T compared with those treated with IDU. However, when the patients were at a later stage, it was found that the rate of recurrence within 12 months was 23% in the group treated with IDU and 24% in the group treated with F_3T.[43]

A five-year follow-up of patients with dendritic or geographical corneal ulcers who had been treated with AA, F_3T or mechanical wiping debridement[14] revealed that 32 out of 152 patients (21%) developed recurrent ulcers within six months and that 61 (40%) had recurrent ulcers within five years. Recurrences were more common in patients whose ulcers healed slowly than in those whose ulcers had healed quickly, and were more common in men than in women. Recurrent ulcers developed in 39 out of 73 patients (53%) who had a previous episode of herpetic ulceration before the trial compared with 22 out of 79 patients (28%) who did not have a previous episode.[14] In a comparative clinical trial of acyclovir and AA for the treatment of dendritic ulcers, patients in both groups developed recurrent ulcers and disciform keratitis. In the group treated with acyclovir, eight out of 28 patients (29%) and in the group treated with AA, nine out of 29 patients (31%) were affected.[36]

These results are disappointing to the clinician treating patients with HSVO, because they show that at present there is no way of preventing recurrent HSVO. However, the observation that the rate of recurrence of corneal ulceration is higher in people with a previous episode than in those without a previous episode is interesting. It suggests that the rate of recurrence depends on the strain of virus and/or on host responses which can control recurrence. These are interesting avenues which require further exploration.

Anti-inflammatory drugs are used in the treatment of HSVO, and the effects depend on the form of HSVO. Steroids are beneficial in treating stromal keratitis and uveitis, but have a deleterious effect on those forms of HSVO which respond well to antiviral measures. Barrie Jones reported the beneficial effects of cortisone on

stromal disease.[44] However, it was later observed that concomitant treatment with antiviral drugs was needed to prevent recurrence of corneal ulceration.[38] When patients with stromal disease were entered in a double-blind trial of steroid drops with IDU or placebo, it was observed that 10 out of 24 patients (42%) treated with steroid and placebo developed dendritic ulceration, compared with four out of 26 patients (15%) treated with steroid and IDU.[38] The deleterious effects of steroid treatment on the forms of HSVO which respond well to antiviral treatment have been reported in several clinical trials. In one trial, the size of the dendritic lesions were measured before treatment commenced. They were significantly larger in patients who had been treated with topical steroids by the referring practitioner compared with patients who had not received topical steroids. Extensive geographic ulcers were found in 22 out of 24 patients (92%) who had been treated with topical steroids compared with three out of 77 patients (4%) who had not been treated with topical steroids. It was observed that treatment with IDU ointment was significantly better than cauterisation in patients who had previously been treated with steroids and that these patients also had a high incidence of severe complications.[38]

In the comparative clinical trial of F_3T and IDU, all eight patients who had received steroids before antiviral treatment suffered from recurrent corneal ulcers. Four out of eight patients (50%) developed significant stromal disease compared with five out of 27 patients (19%) who had not initially received steroids.[32]

Problems resulting from the use of steroid drops to treat HSVO continue. A total of 130 patients with HSV corneal ulcers who had received topical steroids before referral were seen at Moorfields Eye Hospital in the 10-year period between 1967 and 1976. These patients tended to present later, have larger dendritic ulcers, and were more likely to have geographic ulcers. Their ulcers took longer to heal, and recurrent disease and visual impairment were more common.[45] More recently, it was reported that 54 out of 1800 patients (3%) presenting in one month at the Casualty Department at Moorfields Eye Hospital had received steroid eye drops from their general practitioners. Two of these had HSVO; one had a geographic ulcer with thinning and threatened perforation while the other had a geographic ulcer and uveitis.[46]

There are indications that acyclovir treatment may reduce the need for steroid therapy. In a comparative clinical trial of acyclovir and AA,[36] steroids were not required to treat any of the 15 patients with stromal infiltration who were treated with acyclovir, whereas four out of the 20 patients with stromal infiltration who were treated with AA required steroids. These observations may reflect the ability of acyclovir to reach the deeper layers of the cornea and prevent HSV replication. The rate of HSV isolation from corneal buttons of patients with quiescent HSVO undergoing keratoplasty was much lower in patients treated with acyclovir than in patients treated with other antiviral drugs.[3] IDU, F_3T and AA.

Corneal grafting can restore sight to the patient who has major visual impairment due to corneal opacification resulting from HSVO. In a review of corneal grafting in patients with severe HSVO[43], 132 grafts were performed on 91 patients. The two-year survival rate was 64% and the five-year survival rate was 62%. Graft rejection was related to the degree of vascularization in the recipient's own cornea. The rejection rate was 54% in recipients whose own corneas were fully vascularized, and 16% in recipients whose own corneas were avascular. HSVO recurred in 32% of patients who had received high doses of steroids for graft rejection, but only in 6% of patients who had not rejected their grafts and had not received high doses of steroids.

Although there have been major advances in the treatment of HSVO in the past 30 years, it is clear that there is still a need for substantial improvements in treatment to prevent recurrent disease and to limit the damage which can follow the development of HSVO. These improvements may come from a better understanding of the immunopathogenesis of HSVO, including, for example, the roles of glycoproteins in different forms of HSVO.

Host responses

The observation that steroid treatment has a deleterious effect on some forms of HSVO and a beneficial effect on others indicates that host responses have two major roles in HSVO. Steroids have a deleterious effect on forms of

Table III *Experimental HSVO in the rabbit eye*

Treatment	*Reference*
Amphotericin B methyl ester with iodoxuridine	50
Interferon	51
Adenine arabinoside and analogues	52
Acyclovir vs trifluorothymidine, adenine arabinoside and analogues	53
Acyclovir vs idoxuridine	54
Idoxuridine and adenine arabinoside in non-immune and previously infected animals	55
Previous skin or eye infection	57
Previous skin infection and/or topical steroids	58
Hyperimmune gammaglobulin	60
Vaccination	59

HSVO which respond to antiviral treatment, and this suggests that they are important in controlling replication of HSV. On the other hand, steroids have a beneficial effect on herpetic stromal disease and uveitis, suggesting that host responses are involved in tissue damage. Systemic host responses have been studied because this is easier than looking at responses in the infected eye. Studies of systemic immune responses in HSVO have shown that there are no major differences between patients with different forms of HSVO.[48] Levels of CF antibodies were similar in patients with dendritic ulcers or active stromal disease, atopic patients with HSVO and controls. Cell-mediated immune responses to HSV were assessed using lymphocyte transformation and macrophage migration inhibition. There were no major differences in lymphocyte transformation between serologically-positive controls and the three groups of patients with HSVO when purified lymphocytes were used, although responses were markedly lower in patients with stromal disease when a whole-blood technique was used. Significant amounts of macrophage migration inhibiting factor were produced by peripheral blood lymphocytes from all nine patients with stromal disease, six out of nine patients with dendritic ulcers and five out of 12 controls. The amounts produced were highly variable.[48] However, nothing is known about the function of lymphocytes in the eyes of patients with HSVO, and it could be misleading to extrapolate results of systemic responses *in vitro* to local responses *in vivo*.

Animal Models

HSV is not highly host specific. It infects the eyes of several species of laboratory animals and the rabbit has commonly been used because it has large eyes. The rabbit cornea can be trephined and infected in a reproducible manner at several sites using capillary tubes which have been dipped into preparations containing HSV, so that a small number of rabbit eyes can be used to assay the effects of antiviral measures or immunisation on the infectivity of HSV. This technique was first used to study the effects of topically-applied anti-vaccinia virus serum on vaccinia virus infection of the rabbit eye.[49] It has since been used to study the effects of antiviral and anti-inflammatory drugs on, and immune responses to HSV infection of the rabbit eye (Table III). It was found that all the antiviral drugs tested were active against HSV in the rabbit cornea. Amphotericin B methyl ester (AME) inhibited the development of HSV ulcers, and when AME and IDU were used together, their effects were additive, showing that they inhibited HSV replication in different ways. However, AME had no effect on established corneal ulcers.[50] Human interferon also inhibited the development of corneal lesions, and the degree of inhibition depended on the concentration of interferon in the first treatment given one hour after inoculation.[51] The effects of AA and various analogues were also investigated.[52] Acyclovir was also tested and found to be more effective than F_3T, AA or its analogues,[53] and as effective as IDU.[54]

It was observed that antiviral drugs were less effective in previously infected animals than in non-immune animals.[55,56] The effects of previous HSV infection were analysed in more detail, and it was found that animals with previous infection of the skin or contralateral eye were equally resistant to ocular infection, and that previously infected eyes were more resistant.[57] Steroid treatment produced a far larger exacerbation of corneal ulceration in previously infected animals, compared with animals infected for the first time,[58] supporting the hypothesis that host responses play an important role in limiting the development of HSVO. Topical treatment with human hyper-immune gamma globulin was very effective in the early stages of infection, but had little effect on established disease, or on disease in pre-

viously infected animals with or without steroid treatment.[59] It was found that vaccination with an inactivated subunit vaccine induced resistance to corneal infection and reduced the extent of corneal ulceration.[60]

It has generally been assumed that there is very little difference in the pathogenicity of different strains of HSV-1 for the eye. However, recent studies using guinea-pigs and rabbits have shown that strains isolated from patients with conjunctivitis produced conjunctivitis, while strains isolated from patients with corneal ulcers produced corneal ulcers.[61] Clearly, this is an area which requires further research, which can only be carried out in animals.

The Future?

In most people, the relationship between HSV and its human host is amicable and, as in all the best fairy-tales, "they lived happily ever after". The problem is how to make this come true for everyone infected with HSV-1. As this review has demonstrated, we understand far more about HSVO and methods of treatment have changed almost beyond recognition in the past 30 years. However, HSV-1 can still cause damage to the eye. Antiviral treatment limits infection, but it does not prevent recurrent disease, and we do not know how HSV-1 infection is transmitted. A sub-unit vaccine has produced promising results in experimental infection HSVO in the rabbit.[58] Could this vaccine be used to prevent HSVO in humans? A prospective trial would involve the vaccination of a large number of people, very few of whom would be at risk of developing HSVO and might therefore be considered impractical. Alternatively a live vaccine could be developed using a non-disease-producing strain, provided it is possible to distinguish between disease-producing and non-disease-producing strains, and if there is cross-protection between the two. But here again, the number of people required for a prospective trial would be very large and such a vaccine would not help patients who already have HSVO. The story therefore remains incomplete, the happy ending remains elusive and there is still plenty of scope for the ophthalmologist, virologist, immunologist and biochemist to collaborate in finding the solution.

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