Volume five

Current concepts in OPHTHALMOLOGY

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with 157 illustrations and 1 color plate

The C. V. Mosby Company
Saint Louis 1976

Volume five

Printed in the United States of America

International Standard Book Number 0-8016-2627-7
Library of Congress Catalog Card Number 67-14718

Distributed in Great Britain by Henry Kimpton, London

GW/CB/B 9 8 7 6 5 4 3 2 1

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Preface

The faculty of the Department of Ophthalmology of the University of Florida have written this book to convey what they believe is most interesting and important in terms of new developments in the practice of ophthalmology. Whereas research papers and journal publications tend to accentuate one small fact or limited development, the creation of a book such as this permits the synthesis of a number of findings and their adequate explanation in a way that can be more comprehensive and useful. We as a group have conscientiously attempted, through the broad range of areas that have been of particular interest to us, to convey what we think is most important in terms of newer developments. and, because of this, the scope and the style of different chapters are bound to vary. Some chapters are more concerned with a synthesis and summary of the most useful developments in a given area, whereas others emphasize newer developments and theories that we think are likely to be of considerable clinical importance. We hope that by so doing, we will not only convey more recent thoughts and information but also stimulate questions in the mind of the reader that will point out areas where new information is needed.

This book is a departmental effort both of the authors and of other members of the department who have helped generate the knowledge involved, as well as modifying and criticizing the chapters. It is not intended as a smooth-flowing book with a central theme or as a reference book, but rather it is intended to stimulate the reader by emphasizing newer knowledge and concepts in important areas of ophthalmology and pointing out the questions that remain to be answered in these areas.

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Chapter 1

Herpetic keratitis

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Herpes simplex virus infection is endemic in man. Although the majority of infections are subclinical, the keratitis caused by this virus has become the leading corneal cause of visual loss in the United States (Thygeson et al., 1956). In most developed countries in the temperate zones it has replaced trachoma as the leading infectious cause of blindness. Since a previous review of herpetic keratitis in this series (Pettit, 1969), there have been further advances in the understanding and therapy of this potentially devastating condition. An accurate concept is essential so that herpetic keratitis can be effectively managed by all ophthalmologists.

THE VIRUS

Herpes simplex virus is a member of the herpes family, which includes also the varicella-zoster, cytomegalovirus, and E-B viruses of man. It is a double-stranded DNA virus about 1800 nm in diameter (Davis et al., 1973). The DNA core is surrounded by an icosahedral protein capsid and an outer envelope.

The virus enters cells after adsorption to the cell membrane. In the cytoplasm the DNA is stripped of its protein coats and enters the nucleus, where virus multiplication takes place. The new DNA cores then become enveloped by a nucleoprotein capsid. These naked virus particles formed in the nucleus gain a final lipid envelope during passage through the nuclear membrane (Juel-Jensen and Maccallum, 1972). The period from viral adsorption to detectability of new mature particles, the eclipse phase, lasts at least 6 hours. Virus particles are released shortly thereafter.

The process within the host cell after virus adsorption and penetration begins with removal of the viral protein coat, probably by cellular enzymes. The viral DNA is released into the nucleus, where it is transcribed into messenger RNA. This translated nucleoprotein is for the synthesis of virus specific proteins such as thymidine kinase and DNA polymerase, and causes the cell nucleus to shift to manufacturing viral DNA; some of the messenger RNA is released into the cytoplasm, where capsid

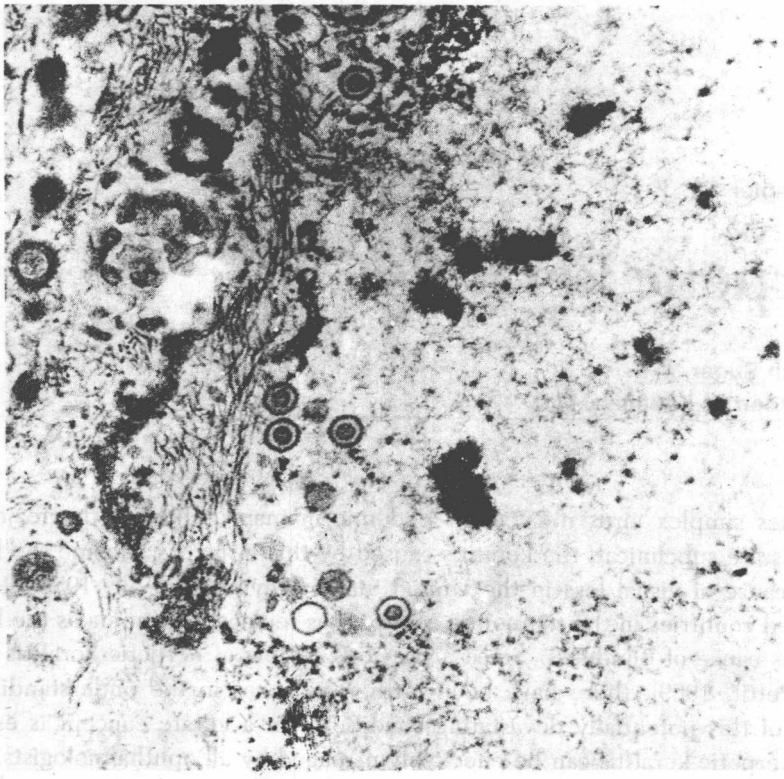

Fig. 1-1. Electron-microscopic picture of herpesvirus particles in human corneal epithelium.

proteins are synthesized. These are transported to the nucleus and incorporated into the virion. Assembled subunits then gain further coats on passage through nuclear or cell membranes (Fig. 1-1).

While the nuclear virus factory is active, the nucleus and its chromatin increase in volume, and chromatin spreads to the periphery. During this early stage, basophilic inclusions containing virus are present. Later, however, the more frequently seen eosinophilic inclusion with a surrounding clear halo develops (McKee, 1963). This lesion no longer contains virus particles. Mitosis of the host cell is inhibited by herpes infection, and such nondividing cells may fuse to form characteristic multinucleated giant cells.

Two antigenically distinct subtypes of herpes simplex virus can be distinguished in man and are named type 1 and type 2. Clinically type 2 is associated with genital disease, whereas type 1 usually causes facial, oral, and ocular lesions.

DIAGNOSIS

The diagnosis of herpetic keratitis must be generally based primarily on clinical history and examination, since laboratory methods are not readily available except in

major centers. The typical clinical features will be described in the next section below.

In epithelial disease the diagnosis can occasionally be confirmed on cytologic examination of corneal scrapings. Eosinophilic intranuclear inclusions and multinucleated giant epithelial cells may be seen on Giemsa stain. Thygeson (1958) found 74% positive scrapings in dentritic keratitis and 22% in deep keratitis, whereas Zaitseva et al. (1973) found multinuclear giant cells in only 7% to 10% of superficial and in 30% of deep herpetic keratitis. We have also found inclusions difficult to detect in our patients. A more reliable laboratory method depends on isolation of the virus. This is done on tissue culture, where a typical cytopathogenic effect is seen within 2 or 3 days, or by inoculation of rabbit cornea. Isolation in tissue culture is positive in 78% of cases with typical dendrites (Coleman et al., 1969) but of little or no value in purely stromal disease.

Fluorescent antibody staining of corneal tissue or scrapings can be helpful when the more routine techniques are negative and clinical diagnosis is equivocal, since it may detect viral antigen when other techniques cannot (Kaufman, 1960; Pettit et al., 1964). In a recent large series, 62% of superficial and 44% of deep keratitis scrapings were positive (Zaitseva et al., 1973).

Serologic techniques are limited by the high incidence of subclinical infection in the general population and by the stability of serum antibody levels during and between recurrent episodes. A significant rise in titer from acute to convalescent sera is therefore usually indicative of primary disease (Rake, 1957) but is not helpful for the vast majority of patients.

CLINICAL INFECTION

Primary herpes simplex

The initial infection with herpesvirus occurs in childhood after the first 6 months of life and involves up to 90% of the population. Clinical manifestations occur, though, in less than 10% of those infected (Howard and Kaufman, 1962). The most frequent lesions involve the oral cavity, lips, and skin. More severe infection can cause a generalized disease with fatal hepatitis or encephalitis. Generalized vesicular skin disease in children with eczema is known as Kaposi's varicelliform eruption.

The initial infection is generally asymptomatic, although a small proportion of people develop the syndrome called *primary herpes*. Primary ocular herpes presents with vesicles on the lids followed by a follicular, often pseudomembranous, conjunctivitis with regional lymphadenopathy. Punctate corneal epithelial disease develops in about two thirds of cases (Patterson and Jones, 1967) and can lead to dendritic or stromal lesions. Primary herpes in the neonatal period, especially with type 2 virus, has been associated with keratitis, iritis, and chorioretinitis, and the virus has been cultured from a congenital cataract (Hagler et al., 1969; Cibis and Burde, 1971). Neonatal infection limited to the cornea is a rarity (Bobo et al., 1970), but congenital keratitis with type 1 herpes has been reported (Hutchinson et al., 1975). Corneal infection with type 2 virus in adults occurs rarely (Oh et al., 1975).

Primary herpetic keratoconjunctivitis is generally a self-limited disease, but treatment with antiviral agents may be helpful in minimizing corneal scarring (Patterson and Jones, 1967) and shortening the course of disease.

Recurrent herpes

Although the clinical manifestations of a primary herpetic infection may disappear or be inapparent in the first place, the virus persists in tissues in a dormant state. It can be reactivated to cause secondary, recurrent disease by a number of triggers. These include fever, which commonly activates labial fever blisters, ultraviolet light, trauma, emotional upset, menstruation, and importantly, corticosteroid therapy. The ease with which experimental keratitis can be reactivated with epinephrine injection suggests persistent virus (Laibson and Kibrick, 1967), and chronic virus shedding in the tears suggests slow multiplication or true latency or both (Kaufman et al., 1967). The recent discovery of herpes simplex virus in the trigeminal ganglion of rabbits with past keratitis and in humans demonstrates a possible locus for long-term viral dormancy (Stevens et al., 1972). It is also possible that viral particles may reside in corneal stromal cells in an inactive state in some necrotic recurrent stromal forms of disease (Dawson et al., 1968), but this has not been supported in a study by Darrell (1972). It is difficult to explain the unilateral nature of herpetic keratitis if virus persists in tissues unless circulating antibodies are extremely efficient in preventing dissemination from a local site. It is estimated that less than 10% of patients have bilateral involvement (Thygeson et al., 1956), although the incidence in our patients has been much lower.

Recurrent herpes simplex conjunctivitis without corneal involvement can occur. It may be mild or severe and destructive. Follicular response and adenopathy are absent, and culture may be necessary to confirm the diagnosis (Brown et al., 1968).

Epithelial keratitis

Dendritic keratitis is the most typical and most easily diagnosed form of herpetic keratitis. It results from virus replication in epithelial cells. The lesions begin as fine epithelial opacities, which become vesicular and coalesce in a branching linear pattern (Fig. 1-2). The infected epithelial cells degenerate leaving the typical dendritic ulcer (Spencer and Hayes, 1970). Such lesions may be single or multiple, large or small, and have a tendency to involve the pupillary area (Thygeson et al., 1956). Although this lesion has been considered to be pathognomonic, it should be noted that small stellate medusalike figures can occur in herpes zoster ophthalmicus, and the zoster virus has been cultured from these lesions (Pavan-Langston and McCulley, 1973; Piebenga and Laibson, 1973). Punctate epithelial lesions can also occur in herpes simplex keratitis but are usually associated with dendritic lesions. Symptoms are usually limited to mild irritation, photophobia, tearing, and blurred vision in adults. The usual pain of epithelial defects is absent because of a marked and characteristic decrease in corneal sensation. Corneal hypesthesia is helpful in diagnosis but not an absolutely reliable sign. It should be noted, how-

Fig. 1-2. Fluorescein staining of large dendritic figure.

ever, that children with herpetic epithelial lesions usually have marked photophobia, pain, and redness in contrast to the mild symptoms of adults.

Dendritic lesions may be self-limited, responsive to therapy, or may progress to more extensive keratitis. The various modes of therapy will be discussed. Resolved dendritic lesions often leave a fine subepithelial scar, which tends to fade with time. Such ghost figures can be helpful in confirming the diagnosis of herpes in atypical recurrent disease. Patients with dendritic keratitis can be warned that after their first lesion about 25% will suffer a recurrence within 2 years. After a second attack the recurrence rate rises to about 50% (Carroll et al., 1967).

If the process of virus multiplication in epithelial cells continues, the dendritic pattern may widen into what is described as a geographic, maplike, or ameboid ulcer. These lesions can usually be distinguished by their irregular margins, which have areas of branching suggestive of dendrites (Fig. 1-3). These ulcers can progress to stromal ulceration, leaving more extensive residual scarring, and may heal with great difficulty, especially if chronic, even though virus has been eradicated.

After damage to the corneal epithelium by herpetic infection, there may be damage to its basement membrane, which prevents firm adhesion of healing epithelial cells. This can lead to a delay in healing of defects despite a drug-induced halt in virus multiplication and may contribute to the formation of geographic lesions. More commonly an ovoid irregular epithelial defect will develop weeks or months after healing of a herpes lesion. These lesions are not dendritic, do not contain virus, and are often associated with mild stromal edema. Corneal sensation may be

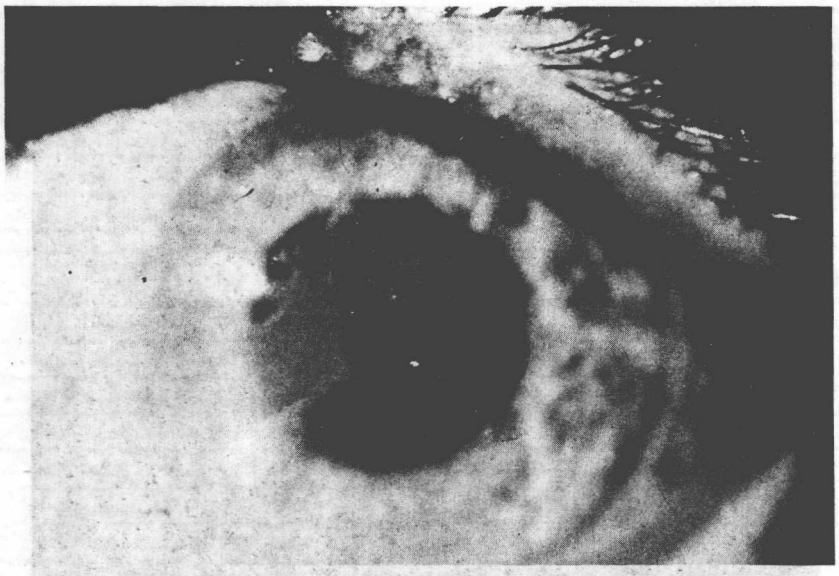

Fig. 1-3. Geographic epithelial herpetic lesion. Note dendritelike extension from margin.

normal or decreased. The patient often gives a history of pain on opening the eyes in the morning, probably due to stripping of the epithelium from its bed by the lids. This lesion has been called *metaherpetic keratitis* in the past, but, since this term has been used for other forms of herpetic disease and since the lesion is identical to recurrent epithelial erosions from other causes, it is best avoided (Kaufman, 1964). Such erosions can be treated by patching and lubricating ointments. Occasionally debridement of the epithelium may be helpful, but often it exaggerates the problem. We have found the use of soft contact lenses to be of considerable value in recalcitrant cases.

Stromal keratitis

Although the cause of stromal forms of herpetic keratitis is not well understood, it is convenient to separate stromal involvement into fairly distinct categories with probable differing pathogenesis. We have found it helpful to differentiate disciform keratitis, stromal necrosis, and diffuse bullous keratopathy. In addition, ulceration may or may not be present.

The most common corneal stromal lesion of herpes is disciform keratitis, which may follow typical dendritic lesions or which may arise without a history of previous epithelial disease. Although herpes is by far the most common cause, vaccinia, zoster, and mumps viruses can rarely cause similar lesions (Duke-Elder and Leigh, 1965). Unilateral localized bullous keratopathy caused by trauma, Fuchs' dystrophy, or hydrops in keratoconus may also be confused with disciform herpes. Disciform keratitis is typically a central round lesion with stromal edema, epithelial edema, and folds in Descemet's membrane (Fig. 1-4). Keratic precipitates are probably

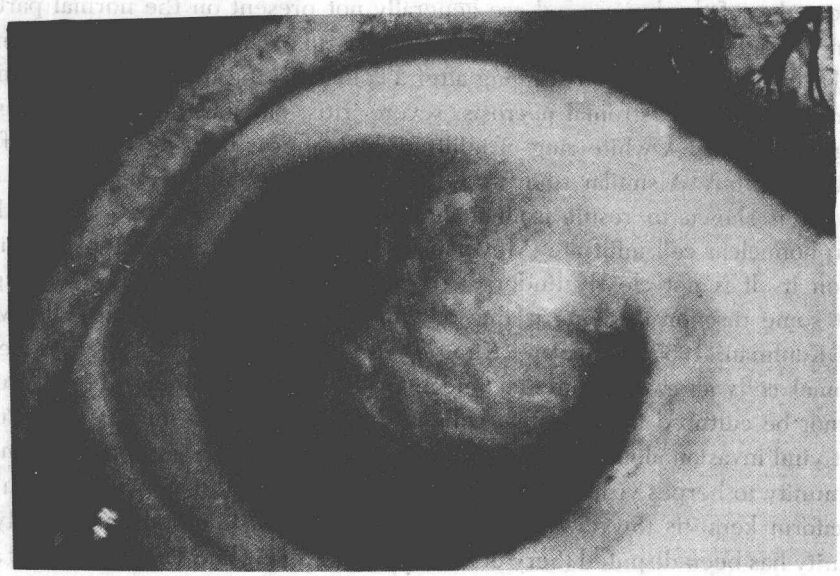

Fig. 1-4. Extensive herpetic disciform keratitis.

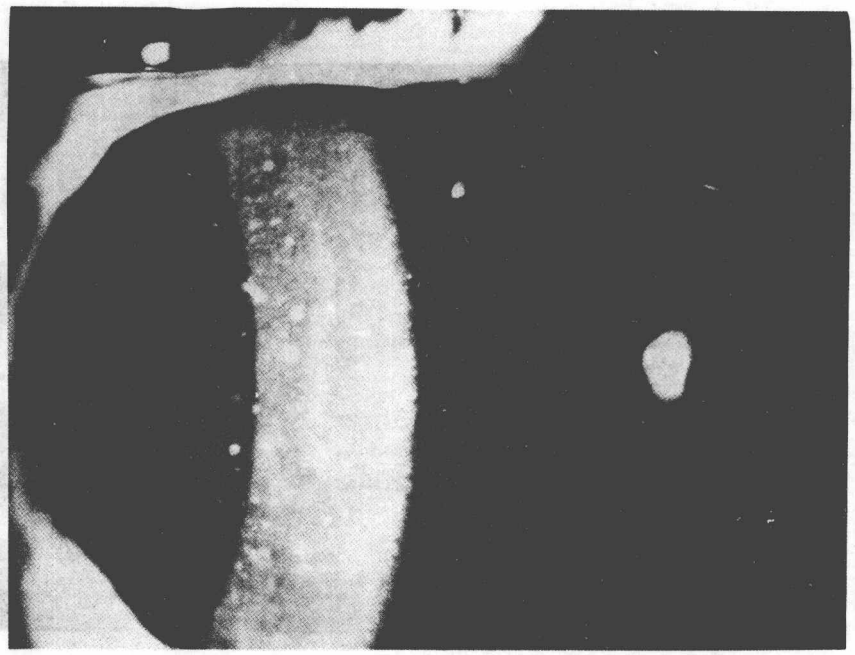

Fig. 1-5. Keratic precipitates on endothelium in areas of disciform keratitis.

always present in the area of edema (Kaufman, 1967), are usually best seen at the lower edge of the lesion, and are generally not present on the normal part of the cornea (Fig. 1-5). There is initially no neovascularization. The milder forms may heal with minimal stromal scarring after a course lasting from weeks to months. In more severe forms stromal necrosis, severe iritis, vascularization, and dense scarring may ensue. A white ring of infiltrate may appear between the area of edema and the limbus. A similar ring produced by experimental injection of viral antigen has been shown to result from a viral antigen–antibody interaction with polymorphonuclear cell infiltrate (Meyers and Pettit, 1973). The cause of the disciform lesion itself is not clearly understood, however. Although it has been suggested that some disciform edema is due to viral damage to endothelial cells (Maloney and Kaufman, 1965; Irvine and Kimura, 1967), viral antigen has been detected in stromal cells after experimental infection (Tanaka and Kimura, 1967). But virus cannot be cultured from stromal cells in disciform keratitis, and it seems unlikely that viral invasion alone would cause the various pathologic findings. Cell-mediated immunity to herpes virus has been shown in animals and may play a role in human disciform keratitis (Swyers et al., 1967). The role of humoral antibody–type immunity has been disputed (Sery et al., 1973a,b; Meyers and Pettit, 1973). It appears most likely that direct virus invasion does occur but is followed by a more complex immunologic process (Kaufman, 1967).

Stromal keratitis with cheesy white infiltration and necrosis may develop, and, since it often responds slowly to systemic antiviral therapy (Kaufman et al., 1967),

Fig. 1-6. Cheesy white stromal infiltration. Small hypopyon is present.

it may result from direct viral invasion. These lesions are often not disc shaped and not central but run a chronic course with intense vascularization and scarring (Fig. 1-6). When they are round, they should be distinguished clinically from the exquisitely steroid-sensitive, primarily hypersensitivity lesion of disciform edema. Severe uveitis is usually present.

Diffuse bullous keratopathy can develop as a result of stromal herpes or as a result of herpetic uveitis. This keratopathy has a chronic course and may not resolve without corneal scarring and vascularization.

Stromal ulcers

Deep corneal ulceration may follow progression from dendritic keratitis through disciform keratitis. Stromal ulcers often have a pattern similar to geographic epithelial lesions and can extend down to Descemet's membrane or lead to perforation. Eyes with deep herpetic ulceration may be surprisingly quiet, but they more often are severely inflamed. The presence of a hypopyon is not unusual, but, although it indicates severe disease, it is not necessarily an ominous sign. Virus cannot be cultured from aqueous humor samples in such patients. In such ulcers it is also necessary to rule out and treat secondary bacterial or fungal infection, although this has been exceptionally rare in our cases.

Corticosteroid therapy has long been implicated in the development of severe ulcerative disease after dendritic keratitis (Thygeson et al., 1953). Although many of the cases are unquestionably the result of inappropriate steroid treatment, stromal ulcers can occur as part of the natural history of the disease.

Keratouveitis

Anterior segment inflammation may accompany any of the stages of herpetic keratitis. In dendritic keratitis some anterior chamber cells and flare may be present as part of the vascular response seen with any epithelial defect. With stromal keratitis, however, the uveitis may be severe and destructive. It is possible for uveitis to appear without active corneal disease and be followed by later dendritic or stromal lesions (Sugar, 1971). Virus particles have been detected by fluorescent antibody stains in cells from aqueous humor aspirates in some cases (Patterson et al., 1968), but they cannot be cultured (Kaufman et al., 1971). Cell-free virus has also been seen in culture-negative samples. This may represent virus antibody complexes, and such complexes may have a direct toxic effect on the endothelium. Clinically moderate-sized widely distributed keratic precipitates are present, and posterior synechiae and glaucoma often develop. The glaucoma may be due to infiltration of the trabecular meshwork by inflammatory cells (Townsend and Kaufman, 1971) or to secondary encroachment on the angle by an edematous iris and cornea. The role of other mechanisms such as the prostaglandin system has not been studied. The glaucoma is usually self limited and resolves when the uveitis is treated. During the expectant severe stages, carbonic anhydrase inhibitors, possibly epinephrine, and occasionally hyperosmotic agents are of some value.