THE UNFAVORABLE EFFECT OF TOPICAL STEROID THERAPY ON HERPETIC KERATITIS*

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THERE SEEMS TO BE general agreement throughout the country that herpetic keratitis has become more frequent, more severe, and subject to more complications, such as secondary fungal infection, in the postwar years. No similar increase has been observed in the frequency or character of the other manifestations of herpes simplex virus infection, such as herpetic stomatitis, herpetic encephalitis, herpetic hepatitis, or Kaposi's varicelliform eruption. During this period, topical steroid therapy, introduced some ten years ago, has been used extensively in the treatment of herpetic keratitis but not in the treatment of cutaneous or visceral herpes. Since laboratory studies have shown repeatedly that steroid therapy increases the ocular damage in experimental herpetic keratitis of the rabbit, the present study was undertaken in an attempt to determine whether or not the steroids are responsible for the unfavorable change that has taken place in the character of the human corneal disease in the last decade.

THE PRECORTISONE HISTORY OF HERPETIC KERATITIS

In the United States, as in most parts of the world, herpetic keratitis has always been a corneal disease of major importance. In 1936 Gundersen[1] defined it as the most common specific keratitis seen at the Massachusetts Eye and Ear Infirmary. In his extensive series he mentioned no case of corneal perforation, loss of a globe from secondary infection, or intractable uveitis. Herpetic keratitis has long been of great interest to the present authors, and in particular to the senior author who had 18 years' experience with it in Colorado, Iowa, and New

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TR. AM. OPHTH. SOC., vol. 58, 1960

York, and during military service in Florida, Pennsylvania, and California. In this period before, during, and immediately after World War II, the disease as seen by us occurred most commonly in the form of the dendritic ulcer, less commonly as a disciform lesion. The dendritic form was usually responsive to iodine, the thermophore, ether, or other means of destroying the virus in the affected epithelium. Rarely cases were followed by disciform keratitis, and even more rarely by a self-limited type of iridocyclitis of short duration.

In this period, one of us (M. J. H.) saw a single case of corneal perforation following a dendritic keratitis, which healed without impairment of the globe. Such cases of disciform keratitis as we saw were self-limited, healing spontaneously, often without major scarring, in from two to three months. It was not unusual to have a return of vision to 20/20 after what was regarded as a severe disciform keratitis. In a small proportion of cases, late trophic changes with recurrent ulceration were seen after an initial dendritic keratitis, but this was a rare phenomenon. Herpetic keratitis, while a major cause of temporary disability, was a self-limited disease, not leading to blindness or significant permanent visual loss. Bilateral cases were extremely rare, only one example having been seen by the three authors during the 20-year period prior to 1950. We did not see a single case of hypopyon keratitis following dendritic ulcer, or of ulceration extreme enough to menace the integrity of the globe.

In this precortisone period, no one of us found it necessary to use a conjunctival flap in any case under his care, or to refer a case for keratoplasty. Examination of the records at the University of California has revealed that the first case of herpes corneae was referred for keratoplasty in 1953. This was a bilateral dendritic keratitis, seen by one of us (P. T.) in consultation, which had undergone extensive cortisone therapy and in which the disease had progressed to perforation from secondary monilial infection in the right eye, and to a blinding keratouveitis with cataract and secondary glaucoma in the left eye. This patient failed to regain vision in either eye and was the first to be seen by any of us in whom there was bilateral loss of vision attributable to herpes simplex virus.

THE CLINICAL COURSE OF STEROID-TREATED HERPETIC KERATITIS

Before we first received a supply of cortisone acetate for topical application, we were impressed by the favorable reports of its use, particularly in disciform keratitis, that were emanating from eastern

clinics. We expected it to be a valuable supplement to the standard treatment of herpetic keratitis, and in our early trials we were favorably impressed by the patient relief obtained and by the fact that a few cases of dendritic keratitis healed without corneal curettage or iodinization.

Soon, however, we[2, 3] began to encounter dendritic cases which on cortisone therapy progressed to disciform keratitis of a severe nature (Figure 1), often complicated by iridocyclitis and secondary glaucoma. Some of these cases were accompanied by such severe pain that in two

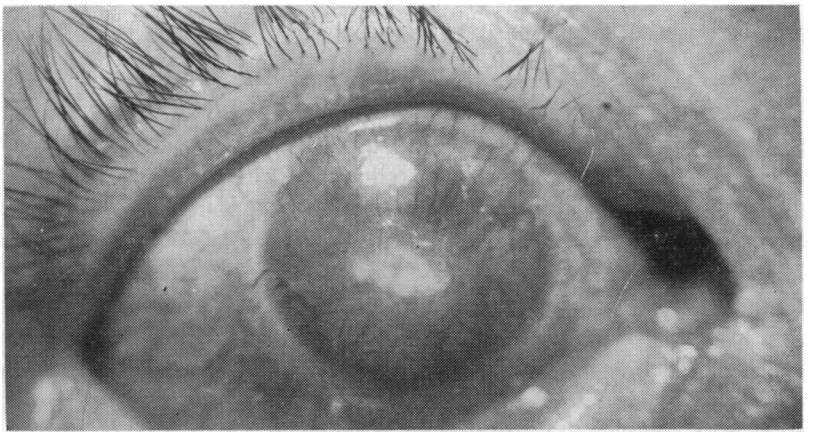

FIGURE 1. SEVERE KERATITIS LEADING TO TOTAL LOSS OF VISION FOLLOWING TREATMENT OF DENDRITIC KERATITIS WITH TOPICAL CORTISONE

instances the patients demanded enucleation, which was of course refused. We did see, however, the loss of the globe in two steroid-treated cases referred to us in consultation. In most of these severe cases, the corneas ultimately became completely vascularized; the eyes no longer had useful vision and were poor subjects for keratoplasty. It was of interest that in these severe cases the patient often displayed an addiction to his steroid drops, which almost always provided appreciable symptomatic relief unless there was also severe uveitis and secondary glaucoma.

In addition to these severe cases with central necrosis of the cornea, often complicated by uveitis, we encountered (i) an increased incidence of disciform keratitis following dendritic ulceration; (ii) a prolongation of the normal course of disciform keratitis; (iii) a number of deep ulcers with hypopyon; and (iv) a number of cases of

chronic herpetic keratitis confined to the epithelium in which the patient was symptom-free under cortisone but developed a red, irritable eye whenever the steroid was discontinued; some of these smoldered for many months in a strictly epithelial stage.

As soon as the deleterious effect of steroids was demonstrated in animal eyes infected with herpes virus by our own[4, 5] and other studies,[6, 7, 8, 9] we abandoned their use. We have been able to follow many steroid-treated cases referred for consultation, however, and these have continued to show the steroid effects outlined above.

THE RELATION OF KERATOPLASTY IN HERPETIC DISEASE TO THE USE OF STEROIDS

Keratoplasty has been in general use for more than a quarter of a century for the relief of corneal scarring. Therapeutic keratoplasty for impending perforation, or for the relief of extensive corneal necrosis, has come into use more recently. Since both therapeutic keratoplasty in active herpetic keratitis, and the classical application of the procedure for the removal of scars in healed cases, have become increasingly popular,[10] the keratoplastic operations performed for the relief of symptoms or sequelae of herpetic disease at the University of California have been analyzed for information bearing on the role of the steroids in herpetic disease. Table I presents the findings in the 55 cases on record.

So far as could be determined, all cases had had steroid therapy, usually topical, prior to keratoplasty. The records of referred cases did not state the type of duration of such therapy but it is certain at

TABLE 1. KERATOPLASTY IN HERPETIC KERATITIS, 1952–1960

	Incidence and type of keratoplasty		*Total no. of cases*
For removal of scars			
Disciform keratitis	Lamellar	3	22
	Penetrating	19	
For treatment of active disease			
Perforated ulcer	Lamellar	8	13
	Penetrating	5	
Chronic ulceration	Lamellar	15	17
	Penetrating	2	
For prophylaxis			
Recurrent dendritic keratitis	Lamellar	3	3
		Total	55

least that the use of steroid therapy did not prevent the complications which led to surgery.

It is of interest that two of the 13 cases of perforated ulcers had fungal infections, one with monilia and the other with Cephalosporium sp., which were certainly related to prolonged steroid and antibiotic therapy. The remaining 11 cases perforated in the absence of bacterial or fungal infection and were presumably a result of virus-induced necrosis of the corneal lamellae. Since only one such perforation is reported in the records of the University of California prior to the use of steroids, and since no one of us had observed such a perforation in our private practices prior to the use of steroids, the connection would seem inescapable. A feature of steroid-treated perforations in our series has been their occurrence in white, painless eyes; only the few cases with severe uveitis were accompanied by pain and inflammation.

In the keratoplasty series, four had postoperative complications that were believed to be related to steroid therapy, and possibly also to antibiotics used simultaneously. In one case of penetrating keratoplasty a monilial infection followed postoperative treatment with topical steroids and neosporin ointment. In a case of lamellar keratoplasty for a perforated ulcer of pure herpetic origin, a second monilial infection followed postoperative topical antibiotic and steroid therapy. A third case developed a dendritic ulcer in the central portion of a penetrating graft four weeks after surgery while receiving hydeltrasol topically. While the fourth case was on topical cortisone therapy, a dendritic ulcer developed in the cornea adjacent to the graft edge, with subsequent extension into the graft. No complications of this type have been seen since steroids were abandoned in the postoperative management of keratoplasty.

THE CLINICAL COURSE OF RECENT CASES OF HERPETIC KERATITIS WHICH HAVE NOT RECEIVED STEROIDS

Four years ago we discontinued all use of steroids in herpetic keratitis seen in private practice and in the University eye clinic. Cases referred to us for special study because of complications have almost without exception been on steroid therapy when referred, in spite of the well-publicized warnings of the manufacturers of steroid preparations that herpetic keratitis should be regarded as a contraindication to their use. In our own non-steroid-treated cases, now totalling well over 100, the clinical course has been that of prewar cases. We have not had a perforation, a case of secondary infection, or a case which

required a conjunctival flap or keratoplasty. On the other hand, the cases referred to us have exhibited all the complications that in our experience have characterized the steroid-treated disease.

Since we must assume that only complicated cases were referred to us for consultation, the two series can of course not be compared. The referring ophthalmologists may well have had many other steroid-treated cases which healed normally. Nevertheless, the contrast between the two series is too marked to be accounted for on the basis of selection alone.

THE MECHANISM OF THE STEROID EFFECT IN HERPETIC KERATITIS

Topically applied steroids have for the most part shown a marked anti-inflammatory effect in herpetic keratitis, and the patient's relief has usually been striking. An inflammed, irritable eye usually becomes white and comfortable under steroids. It is this effect that must account for the still widespread use of the steroids in herpetic keratitis. Only in the presence of a severe iridocyclitis, with or without secondary glaucoma, is this anti-inflammatory effect absent or minimal. We have seen steroid-treated patients with necrotic corneas (Figure 2), and with perforation or impending perforation, in the absence of pain or gross inflammation.

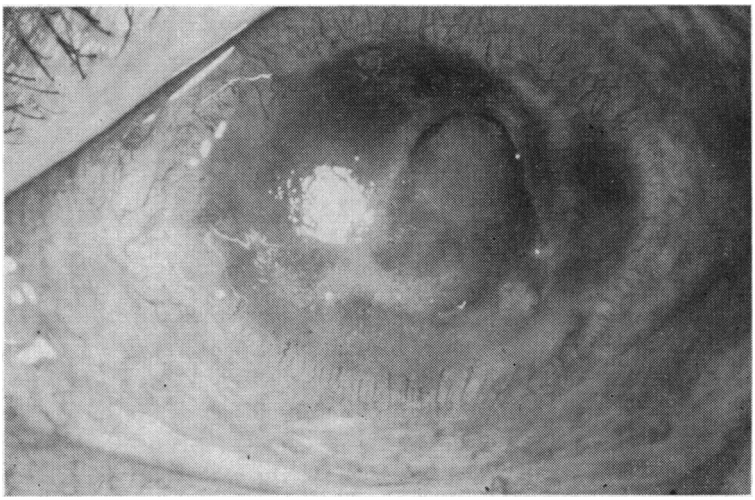

FIGURE 2. DESCEMETOCELE AND IMPENDING PERFORATION IN A WHITE PAINLESS EYE FOLLOWING PROLONGED STEROID THERAPY FOR DENDRITIC KERATITIS

In recent reviews by Leopold,[11] Kass,[12] Kass and Finland,[13] Thomas,[14] Martin and Wellman,[15] and Jasmin and Bois,[16] the essential mechanisms of topical steroid action have been detailed as follows: (i) Increase in capillary resistance; (ii) modification of the permeability of the ground substance and of the cell membrane; (iii) interference with the liberation of histamine and other metabolites; (iv) inhibition of phagocytosis and antibody-formation; (v) reduction in the enzymatic activity of the fibroblasts, with inhibition of cellular growth and division; (vi) inhibition of neovascularization; (vii) promotion, under certain conditions, of necrosis of inflamed tissues; (viii) atrophy of the skin when administered subcutaneously; and (ix) general lowering of resistance to bacterial and fungal invasion.

All available evidence indicates that the steroids have a direct inhibitory effect on cellular activity at the cellular level. If the various features of steroid action are examined in the light of the results of steroid therapy on herpetic keratitis, the necrosis of inflamed tissues would seem to be of first interest since this is apparently the precise complication that leads to perforation and severe scar formation. The exact mechanism of the production of this necrosis does not seem to have been established, but it could be related to such factors as the inhibition of the enzymatic activity of the fibroblasts, the inhibition of antibody formation and of phagocytosis, and the modification of the permeability of the ground substance and cell membranes. This necrotic effect has been encountered in fields other than ophthalmology; the development of arthropathies simulating Charcot's joints in certain patients treated by intra-articular steroid injection is an outstanding example.[17]

Next in order of importance would seem to be the increased incidence of secondary bacterial and fungal infections following topical steroid therapy. The lowered resistance of the tissues to secondary invaders is probably related chiefly to the inhibition of local defense mechanisms and of phagocytosis in particular. Lowered resistance to fungal infection has been exceptionally striking, and the combining of a broad-spectrum antibiotic with the steroid seems to potentiate the mechanism. This unfavorable result of steroid therapy has been particularly well documented by clinical observation and laboratory study.[18, 19]

Prolongation of the clinical course of herpetic keratitis as a result of topical steroids is apparently related to interference with normal defense mechanisms. It is not known whether local antibody-formation plays a role in spontaneous healing, but the steroid effect is in all

probability a local effect. The role of antibody in herpes simplex virus infections needs further study, but there is no doubt that antibody has a protective effect on vascularized tissues in the human subject. This is apparent in the difference between the primary acute herpetic keratoconjunctivitis that develops in the antibody-free subject, and the dendritic keratitis without conjunctival involvement that characterizes the recurrent attack when the antibody level is high. There is evidence to indicate that the phagocytic activity of leukocytes may be important in herpetic disease.[20]

STEROID-INDUCED HERPETIC KERATITIS

Neither topically nor systemically administered steroids seem to have played any major role in stimulating relapses of herpes labialis or cutaneous herpes. None of the dermatologists or internists to whom we have put the question has observed an undue incidence of herpetic relapse among his patients being treated with steroids, however intensively. Many ophthalmologists, on the other hand, have reported attacks of herpetic keratitis following the use of topical steroids for allergic conjunctivitis or other disorders.

In our own experience we have noted 15 cases in which herpetic keratitis developed during topical steroid therapy for other conditions. Nine of these were patients with no history of previous keratitis of any kind; the other six were patients known to have had previous attacks of keratitis which could have been herpetic. Two of our patients were receiving topical steroid therapy for allergic conjunctivitis and developed bilateral dendritic keratitis. Two were receiving topical steroid therapy for zoster keratouveitis, and both developed dendritic ulcers. This was the first time any of us had seen herpes simplex as a complication of ophthalmic zoster. One was a case of Sjögren's syndrome with severe keratitis sicca and rheumatoid arthritis. The patient developed a dendritic ulcer shortly after treatment with topical and systemic steroids was instituted; the ulcer left a dense scar when it healed.

We have seen in consultation an additional 11 patients in whom dendritic keratitis developed during topical steroid therapy. The majority were being treated for allergic conjunctivitis or blepharoconjunctivitis at the time the herpetic keratitis occurred. Only three of these patients had a history suggestive of previous herpetic disease.

The exact mechanism by which the attack of herpetic keratitis is precipitated can only be conjectured since none of the laboratory

animals are subject to either natural infection or recurrences. Presumably the virus is latent in the corneal tissues as a result of an inapparent primary infection, and becomes active as a result of lowered tissue resistance.

It is noteworthy that all but five of the 26 cases cited above had been treated with topical hydrocortisone; only one had received topical cortisone.

DISCUSSION

In view of the experimental and clinical evidence of the deleterious effect of steroids in herpetic keratitis that has been reported in the literature in recent years, their continued use in this infection by ophthalmologists is difficult to understand. It can only be accounted for by the failure to distinguish anti-inflammatory effects from curative effects in a disease for which no specific therapy is yet available. Even many of those who no longer use steroids in dendritic keratitis continue to use them in the disciform type of the disease in the belief that this condition is an allergic manifestation and not due to direct action of the virus. They also use steroids quite regularly when uveitis develops. So prevalent has become the use of steroids in uveitis of all types that for the most part no distinction is made between herpetic uveitis and acute nongranulomatous uveitis for which the steroids are definitely indicated. The pharmaceutical houses continue to cite herpetic keratitis as a contraindication to steroid therapy, and a number of medicolegal actions are pending throughout the country in connection with steroid-treated herpetic keratitis whose outcome has been unfavorable. It is to be hoped that the data presented in this paper will contribute to the campaign against this unwise therapeutic practice.

In view of the striking anti-inflammatory action of topically administered steroids in herpetic keratitis, and the important symptomatic relief they give, it is natural to ask if they may safely be used selectively; that is, are there ever any indications for steroid therapy in herpetic keratitis or its complications. Since steroids are never used in cutaneous or systemic herpes, it is well to examine the relation of the steroids to other viral infections for possible examples of beneficial action.

The old suggestion advanced by Hench[21] that cortisone provided an "asbestos suit" against the fire of infection has long been in the discard. Animal studies have almost uniformly shown that steroids have increased host susceptibility to viral infections. There is no general agreement as to the exact mechanism, or mechanisms, of this suscepti-

bility-increase, but it seems certain that it is at the cellular level. Reports of clinical studies, on the other hand, include a number claiming favorable action in various viral diseases, including herpes zoster,[22] pneumonia,[23] varicella,[24] encephalopathy following rabies and smallpox vaccinations, mumps orchitis,[25] and viral hepatitis.[26] In the absence of double-blind studies of these diseases, however, isolated clinical case reports must be viewed with skepticism. Only in postvaccination encephalopathy, which is generally believed to be an allergic manifestation after disappearance of the virus, would there seem to be a logical reason for the reported favorable results. Moreover, unfavorable results have also been reported by a large number of observers studying clinical material. Of these reports perhaps the most important have been those dealing with fatalities in children with varicella who were placed on steroid therapy.

So far as ocular viral diseases are concerned, steroids have apparently been used with relative impunity, both topically and systemically, in herpes zoster ophthalmicus. Only three accidents have come to our attention; the first was an eye lost because of corneal infection with cephalosporium, and the other two were eyes in which dendritic ulcers developed in corneas already affected by zoster. In acute follicular conjunctivitis due to the adenoviruses, the steroids have been used topically with impunity and symptomatic relief has been claimed. No accidents or prolongation of the disease have come to our attention. In epidemic keratoconjunctivitis due to type 8 adenovirus, steroids have been used topically and some symptomatic relief has been claimed. A single case so treated developed a severe secondary iridocyclitis—an unusual complication in this self-limited infection. Our own opinion is that the steroids do not influence the course of this disease. In trachoma, topical steroids have been used as a provocative test of activity[27, 28] since smoldering, subclinical cases can be activated by this means. The same effect has been noted in inclusion conjunctivitis.[29] In the suspected viral disease known as superficial punctate keratitis, the steroids have been widely used to suppress the epithelial opacities and diminish the irritation, without apparently influencing the ultimate course of the infection. In no other ocular viral disease have the steroids been used sufficiently to warrant comment on their effect.

The experimental work on animals in connection with other viral diseases would suggest that the anti-inflammatory effect of the steroids has no curative effect. An analysis of clinical reports alone would suggest that certain viral diseases have actually benefited by having

their courses shortened and the overdevelopment of fibrous tissue prevented, but clinical studies of this relationship must be interpreted with great caution. It is difficult, in fact, to avoid the conclusion that steroids cause more harm than good in viral disease, and that indications for their use are limited to a relatively few special conditions such as the encephalopathy following smallpox and rabies vaccinations, and to such special situations as the need for a provocative test of activity in trachoma. In herpetic keratitis the authors have found steroid-induced complications in all stages of the disease and can only conclude that the over-all picture of the disease would change for the better if steroids were avoided completely.

SUMMARY AND CONCLUSIONS

1. Herpes simplex virus infections of the cornea have become more frequent, more severe, longer lasting, and more likely to be complicated by secondary infection, perforation, uveitis, and secondary glaucoma in the postwar years. In addition there has been an increased incidence of bilateral disease, a rare finding in prewar years. There appears to have been no similar increase in the frequency or severity of cutaneous herpes or of the primary types of herpetic infection in infants and young children.

2. In our series of cases derived from both private practice and the University eye clinic, analysis shows that without exception steroids have been employed topically, and sometimes systemically, in all cases complicated by secondary infection, perforation, and intractable uveitis with secondary glaucoma. Since we abandoned the use of steroids in our own practice and in the eye clinic, the only complicated cases we have seen have been those referred from outside sources. With only an occasional exception, these cases have been referred after treatment with steroids, usually prolonged.

3. Analysis of University records of clinic and private cases shows that the first corneal transplant for herpetic keratitis was performed in 1953, and that this first case (a bilateral herpetic keratitis with perforation of the globe of the right eye) had received extensive topical steroid therapy before being referred to us. Prior to the introduction of the steroids, only one case of perforation, and no case of secondarily infected herpetic keratitis, had been observed by the authors.

4. In view of the now extensive studies in animals, which clearly demonstrate the deleterious effect of steroids in experimental herpetic keratitis, supported by this and other clinical studies, the conclusion

seems inescapable that the change in the character of human herpetic keratitis in 1952 and 1953, at a time when steroids were being widely used in almost all external ocular disease, was more than coincidental. The conclusion that the increase in secondary infection of herpetic ulcers, particularly by fungi, is in large part a steroid effect is substantiated by experimental evidence as well as by clinical observation.

5. Until a specific chemotherapeutic agent becomes available for the treatment of herpetic keratitis, it must be concluded that the symptomatic relief produced by topical steroid administration does not offset the increased incidence of severe complications which must be expected. Herpetic keratitis should therefore be considered a contraindication to the use of steroid therapy.

6. Since steroids topically applied have been shown occasionally to trigger attacks of herpetic keratitis, the common practice of employing these preparations indiscriminately for every type of external inflammation of the eye must be decried.

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DISCUSSION

DR. TRYGVE GUNDERSEN. As usual, Dr. Thygeson has given us a searching analysis of a subject which ranks foremost in the minds of all who treat corneal disease. He has recalled his large experience over 18 years with this disease, analyzed his cases well, done additional research on animals, and reached firm conclusions. This important paper should be read in its entirety by everyone.

He reaffirms his conclusions of four years ago when all steroid therapy for herpes corneae was discontinued by him and his co-workers. Since then he has noted that in over 100 cases the disease has reverted to its prewar nature.

I would like to point out that herpes corneae was not always a mild disease even before cortisone. The authors were kind enough to cite my paper on this subject (*Arch. Ophth.*, Feb. 1936) 24 years ago. I reported that 13 of my 221 patients had an accompanying hypopyon. (To be sure,

none of these perforated. They were treated vigorously with chemical or thermal cauterization and some with cautery combined with conjunctival flaps). In addition 34 other patients developed what was then called keratitis metaherpetica, a serious complication which frequently lasted from three to six months. Herpes corneae may still be a serious and devastating disease, even though cortisone is not used. This may be illustrated by the following two cases; neither one had a single drop of cortisone.

The first case, a young woman 35 years old, was seen by Dr. Taylor Smith. She had two attacks of epithelial herpes in 1952 and 1954. She had the disease for two weeks when I first saw her in consultation. We gave her a "vigorous expectant treatment" for a month and nothing happened. Dr. Smith then applied iodine vapor (according to the technique described by M. T. Grant). Examination 10 days after treatment revealed a fairly characteristic early stromal herpes, and about a month later further progression of this severe disease was evident. Two months later, without steroids of any kind, and on the usual conservative treatment, she developed a large hypopyon, and the day following this it was cauterized with the actual cautery; a flap was placed on the cornea, but in spite of this, the cornea perforated, and six months later the eye was enucleated.

The second case was a young woman whom Dr. A. Scott and Dr. M. Hogan saw when the latter was our Professor of Ophthalmology protemp. a short time ago. She had a child born at the beginning of this year and developed a severe staphylococcic cellulitis of the face. Dr. Scott saw her with an accompanying bilateral dendritic keratitis. He applied iodine, and in March of this year her right eye showed severe stromal herpes with marked vascularization; the left eye showed the same to a milder degree. Two weeks later, keratitis of the right eye showed marked advance. At this time a lamellar graft was done by Dr. Dohlmann of our laboratory. Unfortunately, all the disease could not be removed, and when Dr. Hogan saw it, there was obvious infection in the graft. This went from bad to worse, and a second graft was put on two weeks ago. The eye does not look well, and I do not believe the graft is going to survive.

The term keratitis metaherpetica, meaning with or after herpes, in my opinion should be abandoned. The complications of epithelial herpes or stromal herpes can be more accurately defined and divided into two categories. The first result from vascularization of the cornea—fascicular keratitis—the second from the accompanying loss of sensation. In the latter case the disease becomes more and more similar to neuroparalytic keratitis. These two complications may co-exist, as they do in a young boy of 14 who has had his disease for four months. This boy has been out of school for seven months, has no actual pain, but the eye has been irritable during the entire period. No virus has been demonstrated.

An elderly gentleman who has had the disease for five or six months, and suffers from an ulcer on the right hand side, was successfully treated with

a flap with return of fairly good vision. Also a woman of 56 has a combination of both diseases, the fascicular and the neuro-paralytic aspects.

I can but agree with practically all Dr. Thygeson's conclusions. Whether or not there is an increase in the incidence of herpes corneae since the war must remain unproved. My impression is that the incidence is about the same. Certainly no one can deny that there are more perforations and it is practically certain that the excessive use of steroids must be responsible. The natural inflammatory process which accompanies herpetic infection of the cornea seems to be a necessity for the cornea's defense, and it must not be blocked, at least not completely.

Whether or not one can condemn the use of local steroid therapy in all forms of ocular herpetic infection, particularly of the cornea, still may be subject to some question. Although I have never seen any benefit derived from its use in epithelial herpes, still when used in weak concentration (e.g., .5 per cent hydrocortisone) and by infrequent instillations (every six to eight hours) I have seen dramatic benefit in stromal herpes with uveitis. The question may be not whether or not it is used, but how much of it is used. This point requires further study and clarification.

The occasional dramatic improvement in stromal herpes after treatment with small doses of cortisone may be illustrated by the following case: This is a young woman I saw through the courtesy of Dr. Jacob Rice. She had had epithelial herpes that went on to stromal herpes. From March to April the eye had worsened and showed severe stromal herpes with marked uveitis and beginning glaucoma. Dr. Rice started steroid therapy at this point. On May 3 she had had no treatment for a week, and her vision had practically returned to normal; there are a few old keratitic precipitates, and there is at present no evidence of active disease.

No one will deny the usefulness of steroid therapy following keratoplasty. Most surgeons use it routinely to prevent the dreaded immune reaction. Even after therapeutic lamellar keratoplasty for herpes, cortisone has a beneficial rather than an evil effect.

In summary, Dr. Thygeson has given us a splendid review of a timely subject. It behooves us all to decry its indiscriminate use for all ocular inflammations, but I believe that cortisone still has an important place following therapeutic lamellar keratoplasty for herpes, and may be used sparingly in certain cases of stromal herpes.

DR. MICHAEL J. HOGAN. I really did not want to discuss our own paper, but Dr. Thygeson felt I should bring some keratoplasty pictures. I would like to show a few results of keratoplasty following the use of corticosteroids and antibiotics.

We have had two recurrences of epithelial herpes following keratoplasty, both of them subsequent to topical corticosteroid therapy. The first was a man who developed a recurrence in the cornea adjacent to a penetrating

graft. The ulcer migrated into the graft itself and finally formed a very large lesion over the entire graft. The second, a woman, had a rather marked iritis following a penetrating keratoplasty for a disciform keratitis. Finally it was decided to give topical prednisolone therapy. A dendritic ulcer developed in the center of the graft.

A third case developed an infiltrate at the margin of the graft about a month after surgery, after topical administration of corticosteroid preparation and an antibiotic. Unfortunately it spread to involve the entire cornea and the eye was lost. It proved to be a Monilia infection following corticosteroid and antibiotic therapy.

A fourth patient had a cloudy cornea about six weeks after surgery. Corticosteroid therapy was given at that time with the idea of preventing a host reaction. A herpetic ulcer developed in the cornea adjacent to the graft and spread onto the graft. With the entire graft with necrosis of the stroma, complete scarring and vascularization resulted. Cultures and scrapings of the cornea failed to show a mycotic agent in this case.

DR. A. D. RUEDEMANN. Dr. Thygeson has brought out some very important points in regard to the treatment of this corneal condition. I believe we are just beginning to collect our own publicity, because I think the use of steroids has been pushed further and more often by the medical people than probably that of any other drug that has come out. The trouble with this is that the men who listen to this publicity are not always well trained. The cases we are seeing are coming from medical people who are not oculists, and from some oculists who do not attend our meetings. This is a very serious business, because I have had several cases from the same so-called oculists treating patients exactly the same way, for once they start steroid therapy the entire character of the lesion changes. It is my opinion that this paper by Dr. Thygeson and his co-authors should get into the Journal of the A.M.A. and be substantiated by some of the other men in order to stop it in the places where it flourishes. Even today there are still too many men in ophthalmology pushing steroid therapy; it has taken the place of any other therapy in medicine. The reason I would like it discussed is that when we see these cases they are so far advanced the best we can get out of them is a case for corneal transplant.

DR. ALSON BRALEY. Dr. Thygeson did not mention some of the serious complications that we got into BC (Before Cortisone) or BS (Before Steroids), as Dr. Ascher said yesterday, but I remember a case Dr. Pfeiffer sent me that developed a herpetic ulcer, had a very difficult time, and finally lost both eyes.

It has been said that the use of steroids by mouth or by injection has no effect on herpes corneae, but I would like to illustrate its effect by telling you about a patient with ulcerative colitis who was an cortical steroids by

mouth. Steroids would control the ulcerative colitis, but every once in a while the patient would come down with a perfectly quiet dendritic ulcer of the cornea. We could control this dendritic ulcer by decreasing the amount of steroids taken by mouth.

I think now, and I would like to ask Dr. Thygeson whether he agrees, that the incidence of secondary infection in herpes is much more widespread at present, and whether these secondary infections appear to be more of fungus origin than of some other origin.

In the treatment of dendritic keratitis I have gone back to the old Shahan thermaphore. I am not sure it is the best treatment, but it is better than some of the others. I would like to point out that we will, in the near future, have a fairly reliable laboratory test to determine some of the cases of herpes. The use of fluoresceine antibody technique in scrapings from the cornea may help us in diagnosing some of these puzzling cases of superficial keratitis on which practitioners use cortisone because it makes the eye quiet.

I would like to ask Dr. Thygeson if he feels the combination of antibiotics and steroids may be even more serious than the use of local steroids.

DR. JAMES H. ALLEN. Dendritic keratitis and its complications are not peculiar to California or Boston, as the following cases illustrate: firstly, that of an individual who was treated with steroids for a simple dendritic keratitis and very comfortably but progressively developed a typical disciform keratitis without the usual signs of inflammation.

Secondly, a patient with three descemetoceles in the cornea was treated with steroids for nine months for a lesion which in the beginning was a simple dendritic ulcer. There was a little more inflammation than in the preceding patient but there was relatively little circumcorneal injection compared to the extent of corneal ulceration.

These two patients are typical examples of 12 with descemetoceles and three with disciform keratitis which I have seen in the past eight years who have had steroid therapy for dendritic keratitis. In the 20 years before that I saw only three or four examples of disciform keratitis and no descemetoceles following dendritic keratitis. Therefore, I believe there is an actual increase in the incidences of these complications.

I would like to remind you that four or five years ago I reported the development of dendritic lesions in keratoplasties in two cases in which steroid therapy had been used because I was unaware of the fact that the patients had had dendritic keratitis preceding corneal trauma. I have done eight transplants in cases of herpetic keratitis without steroid therapy and have had satisfactory results in these patients.

The argument is always brought up by someone, "I had a case in which I treated the patient with steroid, and he got along beautifully." The answer to that has been demonstrated well in the laboratory. Some strains of herpes simplex virus apparently show increased virulence in experimental animals

treated with steroids but other strains do not. At present there is no way to predict the effect. This is also unpredictable in clinical cases of the disease. For that reason one might use steroids without inducing severe complications. However, exacerbations and complications are so frequent and so severe that I feel it is dangerous to take this risk.

I would like to emphasize the point that general steroid therapy is just as deleterious to herpes simplex infection as local steroid therapy. However, this is not peculiar to herpes infections, but is the rule of all virus infections. I have previously gone on record as saying that the combination of antibiotics and steroids is contraindicated in true virus infections for they do not respond to antibiotics, nor are they favorably influenced by steroids.

In closing I would like to say that local irritants, in some cases, may have just as serious an effect as steroids or the antibiotics. I have seen a severe disciform keratitis develop from a herpes lesion treated by iodine because the individual was sensitive to iodine. However, the number of patients who are sensitive to iodine is quite small.

DR. THYGESON. I thank those who have discussed my paper for their interesting contributions. Time does not permit me to take up all the questions raised, but I think one of the most important is that of the herpes-stimulating effect of steroids. We have a series of our own, and we have a second series, accumulated by mail and verbal reports from confreres, indicating that steroids used topically can act as a trigger to unleash an attack. We have had bilateral herpetic keratitis develop in allergic cases treated for allergic conjunctivitis. This herpes-stimulating effect is an argument for the cautious use of steroids, even in diseases in which their action is quite useful.

In considering Dr. Braley's comment about antibiotics, we certainly agree that the broad spectrum antibiotics, like the steroids, predispose to fungus infections, particularly with Candida albicans. Certainly the combination of a steroid with a broad spectrum antibiotic is dangerous in a corneal lesion in which the stroma is exposed from ulceration and loss of epithelium.

Dr. Gundersen had a precortisone experience with herpetic keratitis which was much more severe than mine. In his original paper he described 11 cases of herpetic hypopyon ulcer—but without loss of the globe in any case. My personal experience was different; I never had seen an herpetic hypopyon ulcer prior to the cortisone era. It is possible I may be exaggerating the benign course of precortisone herpetic keratitis. Certainly it was a most serious disease, but in my personal experience there was no perforation, no total loss of vision, and no instance of bilateral disease. It should be mentioned that bilateral cases have become quite common in steroit-treated cases. I believe it is significant that since I abandoned the use of steroids in herpetic keratitis, my cases have followed the relatively benign course that I encountered before the steroids were introduced.