CHRONIC HERPETIC KERATOUVEITIS*

BY Phillips Thygeson, M.D.

Herpes simplex virus (*Herpesvirus hominis*) infects more than 50 per cent of the population of the United States, producing severe visceral lesions occasionally in its primary attack and fever blisters typically in its recurrent attacks. When the first attack is an ocular attack, the lesion may be an acute blepharokeratoconjunctivitis, sometimes with pseudomembrane or membrane formation. Otherwise the typical ocular lesion is a recurrent keratitis (without conjunctival involvement) that varies in severity from attack to attack. The lesion is usually limited to the epithelium (dendritic keratitis), but may involve the stromal layers (disciform keratitis) and in severe cases the iris (herpetic keratouveitis). All forms of herpes simplex infection, including the primary visceral and encephalitic forms, tend to recur, but each individual attack is typically self-limited. Except for the "chronic" herpetic keratouveitis that has been seen in the past 15 years and is the subject of this paper, no chronic form of herpes simplex infection is recognized.

The commonest lesion of herpes simplex—the fever blister—involves the mucocutaneous junction and runs a spontaneous course to healing in ten days or less. During the interval between attacks of the cutaneous disease, no clinical signs of virus activity are recognizable in the previously involved area. It is interesting, however, that recent work has shown that virus may occasionally be "shed" in the intervals between attacks. Except when the eye is affected, all herpetic infection involves epidermis only and is therefore non-cicatrizing. The latent infection can be reactivated by a variety of stimuli, including fever, ultraviolet light, shock, and steroids, but the reactivated disease (unless it affects the eye) always involves ectodermal tissue alone, and chronicity is unknown. Even in the visceral and encephalitic forms that are seen characteristically in young children as primary manifestations,

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death or recovery supervenes without the intervention of a chronic phase.

Until recently, ocular herpetic infections tended to run a predictable course: the lid lesions behaved like herpetic vesicles elsewhere on the skin, the conjunctivitis of the primary disease lasted only two or three weeks, and the dendritic corneal ulcers subsided spontaneously within a two- or three-week period. Only the stromal (disciform) disease ran a longer course, usually of from three to five months, rarely if ever more than six months. Although the term "chronic" was frequently applied to this stromal form of the disease, it was not strictly chronic in the sense of failing to heal spontaneously; healing just took longer—a few months instead of a few weeks.

During the past 15 years, I have followed or seen in consultation more than 50 cases of herpetic infection that have run long clinical courses of a year or more, and a smaller number of cases (26) that can be called truly "chronic" in that they have shown no sign of healing after much longer periods of observation (2 to 13 years). In the clinical study reported here, a number of these greatly prolonged and chronic cases will be analyzed, and possible reasons will be suggested for the change in the clinical course of ocular herpetic disease that began to appear about 15 years ago. This clinical analysis is to be followed in a subsequent communication by a report of experimental studies that have a bearing on this serious problem and are currently under way.

THE NATURAL HISTORY OF HERPETIC KERATITIS

The natural history of untreated herpetic keratitis in the United States has never been adequately studied, but all available evidence indicates that in all its forms it is a self-limited disease. My first interest in herpetic keratitis was kindled almost 40 years ago (1928) when I was an intern at the Colorado General Hospital in Denver and saw attacks of dendritic keratitis that had been triggered by malarial therapy for syphilis. Since then I have studied over a thousand cases of the disease in its various forms. I was early impressed (1) by the inadequacy of treatment measures that served only to reduce or eliminate virus from the corneal epithelial cells without affecting virus located in the corneal nerves, stroma, or conjunctiva, and (2) by the fact that the typical dendritic lesion, particularly in the initial attack, behaved very much like a fever blister, undergoing spontaneous resolution in a matter of days or a week or two. Extensive dendritic figures
were sometimes seen that healed spontaneously before treatment could be undertaken.

For some years my own cases of primary herpetic disease have been allowed to heal spontaneously without removal or cauterization of corneal epithelium. With only one exception, the results in a series of 23 primary cases have been good. In the one exception, the corneal ulcer persisted for four weeks before healing. There was no stromal or uveal involvement in the course of any of these 23 primary attacks, but two of the patients developed disciform keratitis in subsequent attacks.

It is of interest that during my six years in New York at the Columbia-Presbyterian Medical Center where I conducted an external disease unit in the Vanderbilt Clinic, herpetic keratitis was the corneal disease most frequently seen. During these six years, however, not a single herpetic patient developed industrial blindness (20/200 or less) or required keratoplasty. Nor did any patient develop secondary bacterial or fungal infection, or the infiltrative type of uveitis that has recently been so common.

It is realized that this experience of mine with herpetic keratitis, in which only the classical forms of therapy were applied (denudation of the epithelium in the epithelial form and no treatment other than the occasional use of a cycloplegic in the stromal form), was more favorable than Gundersen's experience in Boston. But the same favorable results were again observed during World War II (1942-46)—three years in Florida and one year divided between Pennsylvania and California—when numerous cases of herpetic keratitis were seen in air force personnel. Although there were a few cases of disciform keratitis, no officer or enlisted man under my care failed to return to full-duty status within a reasonably short time.

In my personal experience with the disease prior to 1950 or thereabouts, no eye with herpetic keratitis, either under my personal care or seen by me in consultation, resulted in industrial blindness or in loss of the globe. This is not to say that stubborn cases were not encountered, or that temporary or permanent impairment of visual acuity did not occur, particularly in recurrent disease with trophic changes. But in comparison with the herpetic disease we have encountered in the past 15 years, herpetic keratitis prior to 1950 or so was relatively benign and free from such complications as perforation, secondary infection, and severe infiltrative uveitis. Above all, it can be stated categorically that no case under my care became chronic in the strict sense of showing no tendency to heal spontaneously.
In recent years, and in my experience coincidentally with the introduction of the corticosteroid ophthalmic preparations, the character of herpetic keratitis in the San Francisco Bay area, as seen by me in the University of California Eye Clinic and in private practice, has undergone a marked change.

In 1951 I used cortisone suspension in the treatment of four cases of typical dendritic keratitis. Three of them ran normal courses to spontaneous healing. The fourth case developed stromal disease with uveitis and secondary glaucoma and eventually there was total vascularization and thinning of the cornea that resulted in blindness. Keratoplasty was attempted but failed to restore vision. Shortly after this devastating experience, I saw in consultation a middle-aged woman who had developed bilateral dendritic keratitis, and subsequently bilateral disciform keratitis, after treatment with topical corticosteroids. The ulcer of the right cornea became infected with *Candida albicans* and failed to respond to topical and systemic Terramycin therapy. Perforation occurred in the right eye and the left cornea became completely vascularized. Keratoplasty was later performed on both eyes but without success.

These experiences of a loss of vision which progressed to blindness in three eyes that had been treated with corticosteroids led my associates and me\(^3\) to examine the effect of corticosteroids on experimental herpetic keratitis of the rabbit. The results of our studies, and of studies conducted in other laboratories, showed that these preparations are capable of influencing unfavorably the course of the experimental rabbit disease. As a result of these corroborative findings, I have not used corticosteroids in any subsequent cases of herpetic keratitis that have been my exclusive responsibility. In the small series of 59 such cases that have been under my care since the disastrous episodes described above, none of the complications commonly attributed to steroid therapy, such as perforation, secondary glaucoma with severe uveitis, or secondary infection, has developed, and the clinical course of these cases has not differed from that observed in herpetic keratitis during presteroid days.

**COMPLICATIONS ATTRIBUTABLE TO CORTICOSTEROID THERAPY**

**CORNEAL PERFORATIONS**

In the presteroid period, perforation in herpetic keratitis in the absence of secondary infection was unknown to me. It was presumably
Chronic Herpetic Keratouveitis

a rare phenomenon since a search of the literature failed to uncover a single example of it. Perforation as a result of secondary infection was also unknown to me personally in this period but has been reported in the literature.

Following the introduction of the steroid preparations, corneal perforation in herpetic keratitis became a common phenomenon. Most instances of it have occurred in association with bacterial and fungal superinfection, but 12 perforations in pure herpetic keratitis have been seen by me, all in consultation with referring ophthalmologists. In each instance, these perforations followed high-dosage steroid therapy of disciform keratitis in which the inflammatory phase had been suppressed. This steroid effect on collagen, with perforation, has been induced in a rabbit model. The exact mechanism of the phenomenon is still in doubt but is under study in our laboratories. It is hypothesized that the steroids diminish or prevent collagen replacement.

SECONDARY KERATOMYCOSIS

The remarkable increase in keratomycosis as a complication of herpetic keratitis in the past 15 years is now widely recognized as a steroid effect. Prior to the introduction of the steroids, keratomycosis was a rare disease, limited almost entirely to secondary infection of injured agricultural workers by Candida and Aspergillus species. Recent years have seen a striking increase in keratomycosis due to the so-called “opportunistic” fungi, including such genera as Penicillium, Cephalosporium, and Fusarium, the most prominent fungi to play this role in the San Francisco Bay area. Coincidentally with the recent drop in the use of steroids, there has been a decrease in the amount of keratomycosis as a complication of herpetic keratitis.

It has been suggested that steroids are not the only potentiators of fungal action. It has long been recognized that the use of broad-spectrum antibiotics makes infection with Candida sp. more likely, but I have seen no evidence that they have a significant effect on other fungal diseases.

SECONDARY BACTERIAL INFECTION

The first bacterial superinfection of herpetic keratitis that we observed was with Pseudomonas. We have studied six such cases but were unable to establish with certainty the source of the organism. The contamination of certain steroid preparations on the market had been established but FDA regulations requiring sterilization of ophthalmic solutions had not yet been formulated. Pseudomonas is ubiquitous,
however, and could very well have been introduced by other means, including contaminated fluorescein. All six cases had been referred to us and we did not have access to the solutions that had been used before their referral. No recent cases of Pseudomonas invasion of herpetic keratitis have been encountered.

The most recent bacterial infections have been with pneumococcus, alpha streptococcus, and *Staphylococcus aureus*. We have also had one case of herpetic keratitis contaminated by Moraxella sp., the diplobacillus of Petit. An unusual feature of the *Staphylococcus aureus* and streptococcal cases has been the extraordinarily large number of organisms that were found in corneal scrapings. It is possible that the cytotoxic effect of IDU (iododeoxyuridine) played some role in the severity of these bacterial infections.

**INFLITRATIVE UVEITIS WITH SECONDARY GLAUCOMA AND COMPLICATED CATARACT**

In recent years, severe iridocyclitis with grossly visible K.P. and much cellular infiltration has been seen commonly as a complication of herpetic keratitis in the San Francisco Bay area. Before being referred, these cases had all received extensive corticosteroid therapy, often in large doses, and often by the systemic route as well as topically. Secondary glaucoma with major tension rise has been a frequent and important concomitant of this type of uveitis. A relationship between corticosteroid therapy and the uveitis and tension rise is presumed because of the rarity of these complications in herpetic keratitis prior to the introduction of the drugs. It has been possible to produce the same type of uveal lesion in rabbits with herpetic keratitis by dosing them heavily with steroids.

There is as yet no information available as to a possible direct connection between steroid therapy and the complicated cataract commonly seen as a complication of severe herpetic keratouveitis.

**CHRONIC HERPETIC KERATOUSEITIS**

It now seems clear that a new entity—chronic herpetic keratouveitis—has developed in the past 15 years, presumably as a result of interference with the normal immune mechanisms that function to bring an attack of herpetic keratitis to a close. It is further postulated that this chronic disease is peculiar to the cornea by virtue of the cornea's avascularity and relative acellularity; chronic herpetic lesions of other tissues have not been seen by the author or recorded in the literature.
Chronic Herpetic Keratouveitis

That the chronicity of the corneal disease is definitely steroid-related is attested by the fact that all 26 cases here reported had long histories of continuous steroid medication.

All 26 of these patients, none of whom were children, had secondary herpetic keratitis as judged (1) by their histories of previous mucocutaneous or ocular herpetic lesions, and (2) by the absence of the follicular or pseudomembranous conjunctivitis that characterizes a primary ocular attack. Most cases had had one or more recurrences of classical dendritic keratitis before developing the syndrome of chronic herpetic keratouveitis. The chronic disease was readily differentiated from the late trophic phase of herpetic keratitis (fortunately rare) in which a totally anesthetic, partially vascularized cornea (the result, usually of repeated herpetic attacks) develops a trophic keratopathy with epithelial disturbance and, occasionally, trophic ulceration. The chronic disease was also easily distinguished from the Fuchs' type of epithelial-endothelial dystrophy that occasionally follows a severe attack of stromal herpetic keratitis.

The characteristics of the clinical entity of chronic herpetic keratouveitis in our 26 cases were as follows:

1. All cases in the series were unilateral, and in all cases the vision in the affected eye was severely damaged.
2. All cases involved stromal and uveal tissue. There were no examples of prolonged herpetic disease involving only the epithelium, although dendritic episodes also occurred periodically in some patients.
3. All 26 cases were of long duration; the shortest observation period was two years, the longest 14 years.
4. All cases showed marked suppression of inflammation by steroids, and immediate return of inflammation on discontinuance of steroids.
5. The steroid dosage necessary to suppress gross inflammatory signs was often remarkably small. For example, in the case of a dentist with chronic inflammation, left eye, since 1954, the dosage required has been one drop of prednisolone acetate 0.2% every other day.
6. None of the 26 cases had the complications commonly described as associated with high-dosage steroid therapy: for example, corneal ulceration (with secondary bacterial or fungal infection), corneal perforation, or prolonged elevation of tension. Lenticular opacities were observed in some cases but could not be related with any certainty to the prolonged use of steroids.
7. It was not possible to eliminate steroid therapy in any of the 26 cases, all of which were still active when last seen. Attempts to terminate the attacks by discontinuing the steroids met with resistance,
the patients apparently considering ocular comfort more important than vision. All were willing to settle for a white, comfortable eye.

8. None of the 26 patients exhibited any clinical signs of immunodeficiency disease, such as unusual susceptibility to bacterial, fungal, or viral disease of the skin or mucous membranes.

9. None of the cases was favorably affected by IDU (iododeoxyuridine) therapy.

CASE REPORT

The following case report describes the most prolonged of the 26 cases and is of special interest since the patient was observed by me in consultation early in his attack and has been under my observation for the past five years.

W.B., a dentist 54 years of age, developed dendritic keratitis of the left eye while on military service in the South Pacific in 1945. The lesion was treated by chemical cauterization and healed without significant loss in vision. A recurrence in the same eye took place in 1954 and was treated by cauterization and corticosteroid therapy. When first seen by me, the patient had a severe keratouveitis with pressure rise, but the corneal ulceration had healed.

Several attempts to eliminate steroids failed because of the red, painful eye that resulted as soon as therapy was discontinued, and finally it was decided to maintain the patient on the smallest dosage of steroids that could provide a comfortable, white eye. Under this regime the eye continued to show minimal activity by slit-lamp examination of the cornea, aqueous, and iris. One drop of steroid every second day usually suppressed the inflammation satisfactorily, but occasionally a flare-up, sometimes with dendrite formation, would occur. On these occasions the patient would use, on his own initiative, more frequent instillations of steroid, and in later years of IDU. Most of the time he has continued to use one drop of prednisolone acetate 0.2% every second day and is still on this dosage. His corrected vision, which was 20/20 at the onset of his attack, has dropped to 20/70. On this regime it has not been necessary to use a cycloplegic, and tension has stayed within normal limits.

This is regarded as a case of chronic herpetic keratouveitis that has been continuously active for 13 years, and as an example of the new type of chronic keratouveitis that has recently developed.

DISCUSSION

There is quite general agreement that in the United States the character of herpetic keratitis has changed markedly for the worse in the past 15 years. Judging from experience in the San Francisco area, one would say that it has become more frequent, that more of it is
Chronic Herpetic Keratouveitis

bilateral, that more cases of visual loss necessitating keratoplasty are encountered, and that secondary mycotic and bacterial infection, formerly virtually unknown in my experience, have become commonplace. In a large series of cases, corneal perforations were never encountered by me during the first 20 years of my clinical and experimental work with herpetic keratitis. Uveitis, which was formerly a transient complication of disciform keratitis, is now a very prominent feature of the herpes simplex picture. Secondary glaucoma and cataracta complicata were also rare formerly, but now they occur all too frequently.

There is reason to believe that during the past years, at least in the San Francisco Bay region, the pendulum has begun to swing in the opposite direction so that herpetic keratitis is again becoming a relatively mild disease with fewer complications. The disease’s “gravity” is of considerable interest, both clinically and virologically. Many diseases wax and wane in their clinical and economic importance, and many factors are concerned in this cycle.

Viruses are particularly prone to mutate. There are many examples of mutations toward virulence as, for example, the “asiatic flu” mutation of influenza virus. There are also many examples of changes in disease in the direction of mildness that are apparently the result of microorganismal mutation. Trachoma, for example, has become milder than it was in many parts of the world; in our Indian population of the southwest, it now rarely causes economic blindness even when untreated. Herpes simplex virus was formerly thought to be a single immunologic entity, but many recent studies have shown definite, if minor, strain differences, both immunologically6-8 and in pathogenicity for the rabbit cornea. It is therefore possible that Herpesvirus hominis has undergone mutation, and that this accounts for the change in severity of the disease. The arresting point here, however, is that no similar increase in the severity of herpetic infection in other than ocular tissues has been reported in the literature. Extensive questioning of pediatricians, internists, dermatologists, and oral surgeons in the San Francisco Bay area has yielded no suggestion of a change in the character of the disease at other sites.

Since IV (iododeoxyuridine) has been used widely in the treatment of herpetic keratitis but not in the treatment of herpes simplex elsewhere in the body, it might be that a selection of strains, with elimination of IV-sensitive strains and retention of IV-resistant strains, has occurred. However, there is no clinical or experimental evidence that IV has been able to eradicate any strain of herpes simplex virus; its
action has been suppressive only. Furthermore, the change for the worse in the character of herpetic corneal disease occurred several years before IDU was introduced.

The possibility that the increase in gravity was introduced into the ocular picture of herpes simplex infection iatrogenically has been suggested by many observers, with steroids the supposed offender. A strong case can be made for the unfavorable influence of steroids on the disease. In my experience, its worsening coincided with the introduction of steroid therapy, and its recent improvement has coincided with the very marked decrease in the use of topical steroids resulting from the recognition that they may be glaucomogenic and cataractogenic.

The unfavorable effect of steroids on the course of experimental herpetic keratitis in the rabbit has been well documented by numerous investigators. By varying the steroid dosage of the experimental disease in rabbits at the University of California, we have been able to produce all of the corneal complications of steroid-treated human disease, including extensive vascularization, cicatization, uveitis, perforation, and secondary bacterial and fungal infection. It has not yet been possible to produce an experimental model of the human “chronic” herpetic disease; in spite of its prolonged course and complications, the steroid-treated keratitis in the rabbit is still spontaneously self-limited. Persistence of latent virus may be presumed, of course.

Evidence is mounting that the chronic form of herpetic keratitis is steroid-related. The factors that bring about the spontaneous remission of an attack will be considered in a subsequent communication. Also to be discussed in another paper is the possibility that steroids paralyze the defense mechanisms concerned in spontaneous remission. Impaired cellular resistance to herpes simplex virus occurs in the Wiskott-Aldrich syndrome, with persistence of herpetic gingivostomatitis.

It may be wondered why ophthalmologists have been so slow to recognize these unfavorable effects of steroid therapy. The extraordinary anti-inflammatory or masking effect of steroids on the stromal manifestations of herpetic keratitis has led many ophthalmologists, particularly those who see only a few cases a year, to confuse it with clinical improvement. Many young ophthalmologists, unfamiliar with the relatively benign natural course of herpetic keratitis prior to the steroid era, have not been alarmed by deep ulceration, perforations, uveitis, secondary infections, and other complications, apparently considering them a part of the natural history of the disease. It should be recalled also that more than ten years were required before the
Chronic Herpetic Keratouveitis

It seems evident that the entity of chronic herpetic keratouveitis is corticosteroid-related, probably because the normal mechanisms (still undetermined) which bring an attack of herpetic keratitis to a spontaneous close are depressed by the corticosteroids. It is assumed that circulating antibody protects the vascularized tissues of the body, such as conjunctiva and skin, from deep invasion by the virus, limiting the recurrences of herpetic disease of these structures to ectodermal tissue. It is difficult to understand, however, why the tissue defenses do not promptly regain their activity when the steroids are discontinued, and why vascular tissue such as the iris should participate so vigorously in the chronic disease.

An effort has been made to survey patients with immune deficiencies, such as can occur in leukemia or Hodgkin’s disease, for evidence of chronic herpetic keratouveitis unrelated to steroid therapy. No examples have been found, but the search is continuing. It has not yet been possible to produce in the rabbit an experimental model of the syndrome by the use of steroids, although several observers have reported long persistence of virus in the steroid-treated rabbit eye and periodic epithelial recurrences.

In this study the small amount of steroid required to suppress the disease has been noteworthy. All of the patients required a minimal dosage to maintain a white, comfortable eye, and this small dosage did not seem to promote secondary bacterial and fungal infection or major elevations of tension as large dosages have done. On the other hand, it seems probable that the occasional dendritic relapses that occurred may have been induced by even these small dosages.

SUMMARY AND CONCLUSIONS

1. In the past 15 years, herpetic keratitis in the San Francisco Bay region has undergone a cyclical change in clinical characteristics from mild to severe to less severe. This change has roughly paralleled the use of steroids in the treatment of the disease.

2. Herpetic keratitis, untreated or treated by classical methods, is a self-limited disease, comparable to herpetic infection elsewhere in the body. Disciform (stromal) keratitis lasting longer than six months was never seen by the author over a 20-year observation period.

3. Chronic cases (i.e., cases showing no tendency to heal spontaneously over long periods of time) in which gross inflammatory, but
not biomicroscopic, signs are suppressed by steroid therapy have been encountered. The longest observed case has been active since 1954. Prior to the introduction of steroids, no such chronic case had ever been seen.

4. In a series of 59 patients with herpetic keratitis that have been managed personally by the author and have received no steroids, no case of chronic disease has developed.

5. It is concluded that steroids are contraindicated in the therapy of herpetic keratitis, and that the anti-inflammatory action of steroids may so suppress the natural defenses that chronic disease of indefinite duration results.

6. Chronic herpetic keratitis requiring steroids for the suppression of inflammatory signs is essentially an iatrogenic disease.

REFERENCES


DISCUSSION

Dr. Alson E. Braley. The term "chronic herpetic keratouveitis" indicates that herpes simplex infection becomes a chronic disease in the eye. Nearly every bacteria may cause a chronic infection, but no virus worthy of the name would become chronic. Then again, maybe herpes simplex is the exception, as it is in so many other instances.

Dr. Thygeson has said he did not see a single case develop industrial blindness while he was at Columbia-Presbyterian Medical Center. Perhaps it was after 1942 when Dr. Thygeson went in the army and before I went in the navy, but I remember that Dr. Pfeiffer had a patient with bilateral
herpes simplex infection who lost both eyes. To my knowledge that was the only one I had ever personally seen. During my three years in the navy I saw many recurrent cases of herpes, none of them as severe as those I have seen in the last ten years.

[Slide] My first case of perforation from steroids occurred in 1955. As many of you will remember, I suggested the use of steroids in the Gifford Lecture. That was when I believed that disciform keratitis was produced by a delayed hypersensitivity to the virus in the epithelium and the antibodies that were present in the stroma. There was no doubt that steroids would make the stromal edema disappear. However, the steroids many times produced another problem. [Slide] This is similar to that shown by Dr. Thygeson. Here, as you can see, there is marked thinning of the cornea. This is a steroid-induced keratitis—a very severe case.

During the period of time that steroids are used in herpes, however, the virus can be shed, and sometimes you can find the virus in the epithelium. Recently I have diluted the steroids I give, but for a long time I would have the patient come in daily for the one drop of steroid I would give him. Since the steroid is dispensed in plastic bottles, it is very difficult to dilute the contents. I therefore make my own dilution. I will empty out about half of the contents of the plastic bottle by squeezing it, and then immerse the tip in a medicine glass of sterile saline solution. The saline is drawn up into the plastic bottle to the amount of dilution one desires. While this is not very scientific or very accurate, it is practical. I am always told by the dispensing pharmacist that he cannot dilute the material.

Dr. Thygeson is to be congratulated on bringing this form of herpes simplex infection to our attention. I also want to thank him very much for the opportunity to read his paper, which I recommend to everyone.

DR. S. RODMAN IRVINE. I would like to ask Dr. Thygeson if he will discuss the possibility of increasing interferon by giving typhoid, and if he feels this is of practical value in these cases. In the past we have always felt that fever was contraindicated, but Dr. Rasmussen, our chief virologist, has found that herpes does respond to temperature, and perhaps this is the result of the development of interferon. Is interferon significantly increased by small doses of typhoid, and if so how often should they be given?

DR. MICHAEL J. HOGAN. I hesitate to discuss my former preceptor's paper, but some observations should be made about the assessment of the changes that occur in the cornea in herpes simplex infections.

First, the effect of the virus on the normal corneal stromal cells. It has been demonstrated histologically and by electron microscopy that the keratocytes are seriously affected by the herpes simplex virus. This, in turn, affects the corneal stroma. It has been shown that the corneal cells are responsible for the formation of the keratosulfate in the ground substance of the cornea. They also are responsible for the formation of the reticulin
and collagen of the stroma. Therefore, if the cells are damaged their ability to restore the ground substance and repair the process by the new formation of reticulin and collagen is affected. It is clear from our electron microscopic studies of herpes simplex infections that the corneal collagen is seriously changed and that a type of fibrillary degeneration occurs in the collagen that prevents it from performing as a normal stroma.

Therefore, there are three effects—(1) that on the cell; (2) that on the ground substance and collagen; and (3) that on the new formation of collagen. An important effect is that the collagen undergoes degenerative change and acts as a sequestrum, as it does in bone. These three changes which occur in the cornea can perpetuate the chronic herpetic inflammation. In order to restore the cornea to its former healthy state they must be kept in mind. The need for removal of necrotic collagen must be recognized, a process similar to the debridement of wounds done in the past to restore the tissues to a healthy state.

Dr. Frederick W. Stocker. We sometimes face a dilemma. We need massive steroid therapy, but on the other hand we risk infection by bacteria or, particularly, fungus.

It has happened to me two or three times. A corneal graft had cleared after a homograft reaction, but was kept on a prolonged steroid therapy after the inflammatory signs had subsided. After a while a fungus ulcer developed in the center, a very severe complication in a corneal graft. So, I have recently used a prophylactic fungostatic medication whenever I felt the need for a prolonged topical steroid therapy. Once a day I use either a drop of amphotericin or a milder fungostatic solution called Neo-Propisol. Since I have been using this combination, I have not seen any more fungus ulcers develop in grafts under prolonged steroid treatment.

I imagine one could possibly do something similar in a chronic keratitis of the herpetic type, which in some instances would also benefit from prolonged steroid therapy.

Dr. John Warren Henderson. I will attempt to partially answer Dr. Rodman Irvine's inquiry. About fifteen years ago, at the time Dr. Thygeson was noticing his change in the severity and intensity of herpes simplex and before the use of steroids, I noted the same change among our patients. At that time, we gave a series of patients either typhoid-H antigen or the triple typhoid vaccine of Lederle and observed that none of these therapies seemed to help. Our reason for giving this typhoid vaccine was to induce a greater antigen response and to produce fever, in the hope that an increase in heat would bring about a more rapid healing of the herpes. But, as I say, we were disappointed. However, I still feel that a local, rather than a systemic, increase of heat is very helpful in the healing of herpes. By simple application of hot packs peripheral vascularization of the cornea is encouraged and herpes simplex will heal faster.
Unfortunately there are quite a few of these cases now that seem to be indolent and in them vascularization in the peripheral cornea cannot be induced, even by the use of local heat.

Dr. Guillermo Picó. We are conscious of the seriousness of herpes simplex keratitis in most of the United States but in Puerto Rico we have always noticed that the severity of the infection is milder in most cases, in both the epithelial and the stromal types, and that the incidence is lower.

Some of our eye residents who used to come to the continental United States for their basic science training in ophthalmology came back to Puerto Rico with a very grim outlook for cases of herpes simplex keratitis. At first we had difficulty in convincing them that most of our cases recover completely and that the incidence of complications is usually lower than they had been led to believe in lectures. We do not use alcohol and iodine applications, and we do not scrape the cornea. However, we have found that treatment with IDU brings faster healing and we combine it with an antibiotic to combat any secondary bacterial invader.

I wish to ask Dr. Thygeson whether it is possible that some of the strains of this virus might be of low virulence, and if that might explain the mildness of the clinical picture of herpes simplex keratitis in Puerto Rico.

Dr. Thygeson. I want to thank Dr. Braley and the other discussers for bringing up some very interesting questions and problems.

Starting first with Dr. Picó's discussion, we now know that there are definite strain differences. These can be shown clearly in the rabbit. Some strains have an affinity for the central nervous system while others have very little tendency to involve the brain. We do not know that there has been any selection of severe and mild strains in the United States since we are continually isolating both types from herpetic keratitis. Originally herpes virus was thought to be a single immunologic type; now very fine but definite differences are being shown among strains. Future immunologic work may bring considerable information on strain differentiation.

Interferon is the most exciting phenomenon at the moment in the study of virus diseases, and in some virus diseases such as vaccinia it has been shown very definitely that healing occurs simultaneously with the production of interferon. However, this has not yet been established for herpes. Interferon production seems to be less marked in herpes than in vaccinia and most other virus infections. However, certain things are known about interferon production. It is known that a temperature rise increases the amount of interferon produced; and in the cornea we are dealing with a tissue which is below the body temperature. There is therefore very good rationale for raising the corneal temperature. I remember well Dr. Algernon Reese's teachings at Columbia to the effect that closure of the eye with a couple of Wheeler adhesions was beneficial in disciform keratitis. This would raise the temperature of the cornea and would also protect the doctor and
relatives from having to look at the eye! This has been a very useful procedure for me over the years.

Interferon can also be produced non-specifically. We used to use repeated vaccinations without much rationale. It is now known that repeated smallpox vaccinations do stimulate interferon production, thus providing a minor rationale for an old procedure.

Dr. Oh of our laboratories has been interested in the fact that endotoxins, such as typhoid endotoxin, can stimulate interferon production, and he is presently engaged in testing in an experimental animal the effect of this endotoxin-induced interferon on herpes virus keratitis. Perhaps this may be a very fruitful line of investigation because there are substances that do not induce fever but still produce interferon.

I was interested in Dr. Henderson's comment on the lack of results with typhoid-H antigen. This has been a little different from our experience because we think we have had some favorable effects. That typhoid vaccine has occasionally been an inciter of a herpetic reaction does not necessarily mean that using it while the disease is under way would be unfavorable. Dr. Rasmussen at UCLA has shown that stress can bring on an attack of herpes, but stress after the herpes is under way may be very beneficial. So, there are a lot of facets to this herpes problem that we need to look into.

Dr. Stocker's comment about amphotericin and Neo-Propisol is very important. People used to use antibiotics to prevent secondary infection in herpes. This is not good rationale because, in the case of Candida at least, antibiotics promote infection. It is better to use sulfonamides or mercurials. There is good rationale too for antibacterial and antifungal protection when steroids are being given systemically. In any event any open lesion on the cornea should be protected from secondary infection even under ordinary conditions in a healthy person.