

CORNEAL INFECTIONS AFTER CORTISONE THERAPY*

BY

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CORTISONE and hydrocortisone are now widely used in the treatment of ocular inflammations, particularly in allergic conditions such as phlyctenular keratoconjunctivitis, vernal conjunctivitis, scleritis, uveitis, and some kinds of keratitis. In the treatment of diseases in the anterior segment of the eye, an inexpensive topical application in the form of a suspension or ointment may be used with benefit. Such applications seem to have few side-effects, but Thygeson (1953) calls attention to the fact that cortisone is a double-edged weapon, since, though it may control the inflammation, it may also increase the susceptibility of the individual to micro-organisms. He encountered cases of fungus infection of the cornea after treatment with cortisone.

(1) Fungus Keratitis after Cortisone Therapy

In our clinic during the past 2 years, we have experienced two cases of corneal infection with fungi among 698 cases in which cortisone or hydrocortisone was used topically for over one week. We also observed two other cases of fungus keratitis in which cortisone had been given by other physicians.

Case Reports

Case 1, a 64-year-old male, suffered from a serous iritis in the left eye and was given 0.5 per cent. cortisone ointment six times a day. After 6 days there was a considerable improvement in the iritis and the visual acuity improved from 20/200 to 20/30. The instillation of the cortisone was continued, and on the 11th day the patient suddenly complained of a visual disturbance, ocular pain, and headache. The visual acuity was reduced to 20/200. An infiltration 2 mm. in diameter was observed at the centre of the cornea and there was a slight circumcorneal injection. An instillation of oxytetracyclin ointment was added, but the corneal infiltration increased and, 2 days later, ulceration with hypopyon became evident (Fig. 1, opposite). No bacteria were found in the discharge but a fungus spore was demonstrated in scrapings from the cornea (Fig. 2, opposite). The cortisone application was stopped immediately. The ulcer was scarified and cauterized and high concentrations of various antibiotics and gentian violet were applied. The inflammation subsided gradually in the course of 2 months, but a total leucoma of the cornea resulted.

Identification of the Fungus:—Bacterial culture was negative but fungus culture on Sabouraud media resulted in a positive growth, more profuse at 25°C. than at 37°C. The colony looked white and cream-like, round in shape, soft, and wet. In the hanging drop culture, isolated blastospores appeared. No membrane formation occurred in Sabouraud peptone water. Greyish-white colonies round in shape developed on blood agar. The pseudohyphae were formed on corn meal agar with chlamydospore formation at 37°C. (Fig. 3, opposite). Fermentation of glucose and sac-

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FIG. 1.—Case 1, hypopyon ulcer.

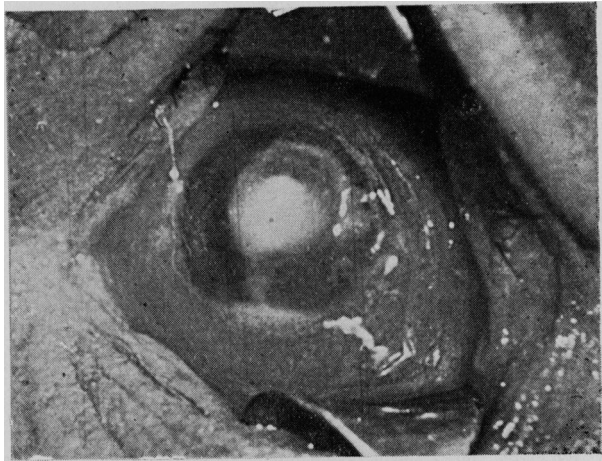


FIG. 2.—Case 1, fungus spore in corneal scraping.

FIG. 3.—Case 1, pseudohyphae with chlamyospore formation.



charose was positive, but that of maltose and lactose was negative. When enough of the colony to be suspended from a platinum-loop was injected in saline solution intravenously into rats, it proved lethal within 6 days. Necropsy revealed multiple abscesses and nodules in the liver and kidney; the organism isolated from these lesions was identified as *Candida albicans*.

When the cultivated organism was injected into the stroma of the cornea, either at the centre or at the periphery, ulceration with hypopyon resulted, which spread steadily for the first 2 weeks and was followed by corneal vascularization. The keratitis resolved spontaneously in the course of 1 to 2 months, leaving a corneal leucoma.

Case 2, a 41-year-old female, was being treated with cortisone and antibiotics by the family doctor for herpetic dendritic keratitis of the left eye at the margin of the cornea. Cortisone ointment was applied every hour during the day and an improvement was apparent after 5 days. On the sixth day, however, ulceration and infiltration with hypopyon appeared at the centre of the cornea. When the patient entered our clinic 10 days after the onset of the hypopyon keratitis, 90 per cent. of the cornea was densely infiltrated. The hypopyon was apparent (Fig. 4, opposite) while the conjunctiva was intensely inflamed. No bacteria were found in the smear, but a fungus was demonstrated in corneal scrapings. Scarification of the cornea with cauterization and application of sodium propionate and gentian violet were tried with little benefit. After about 50 days the inflammation subsided, leaving a total leucoma of the cornea.

Identification of the Fungus.—In scrapings from the ulcer, hyphae, conidiospores, and vesicles of a fungus were demonstrated in great number (Fig. 5, opposite). Bacterial culture on blood agar was negative, but a rapid growth of fungus was obtained on Sabouraud agar at 37°C. A rapid growth was also obtained at 40°C. but at 25°C. the growth was slow. The early colony was round, and consisted of semi-translucent, radiating, silk-like hyphae. In the course of several days, the colony occupied the entire surface of the media; the colour changed to greyish-white and a bluish-green spore zone appeared. In old culture of 3 week's duration, the entire surface of the media was covered by a blackish-brown colony. In the hanging drop culture, hyphae with septa, conidiospores, vesicles, and sterigmata were formed, and conidia formed at the end of the sterigmata (Fig. 6, opposite). A thick white colony developed on peptone agar. The organism was thus identified as *Aspergillus fumigatus*.

When the cultivated organism was injected initially into rabbit cornea, a hypopyon keratitis developed in 3 days. The entire cornea became infiltrated in the course of one week with an appearance of pannus crassus, and the infiltration reached a climax by the end of the second week. In 2 months the inflammation subsided to result in a corneal leucoma. When the inoculation was made at the periphery of the cornea, the course of the keratitis was similar but a little milder.

Case 3, a 27-year-old male, was being treated by us for phlyctenular keratitis in his left eye, by the instillation of hydrocortisone ointment with good results, but after 14 days suddenly complained of a severe pain in the eye. There was a disciform ulceration and infiltration about 5 mm. in diameter at the centre of the cornea. No bacteria were found in the smear, but in scrapings of the ulcer hyphae and fungus spore were demonstrated. The application of hydrocortisone was immediately stopped. The ulcer was curetted and cauterized. The treatment was repeated twice after 5 and 11 days and an application of 0.05 per cent. trichomycin* ointment was added, whereupon the corneal inflammation began slowly to subside. After 48 days a leucoma remained at the centre of the cornea, but visual acuity of 20/200 was preserved.

Identification of the Fungus.—In scrapings from the ulcer, hyphae with septa and a chain of spores were demonstrated. A good growth of fungus was obtained on Sabouraud agar at 25°C. The colony was at first white and wool-like, but in time turned pink with a spore zone of a cream-coffee colour. In the hanging-drop culture, hyphae with septa, conidiospores, sterigmata, and conidia were seen, without the formation of a vesicle (Fig. 7, overleaf). The organism was thus identified as *Penicillium sp.*

When the cultivated organism was injected into the rabbit cornea, it caused a hypopyon keratitis; the clinical course of the keratitis was similar to that caused by inoculation of *Aspergillus fumigatus* but a little milder.

* Trichomycin is a new antibiotic found in Japan and is selectively effective against fungus group of microorganisms. It caused irritation when applied to the conjunctival sac at a higher concentration than 0.1 per cent., but the 0.05 per cent. ointment was well tolerated.

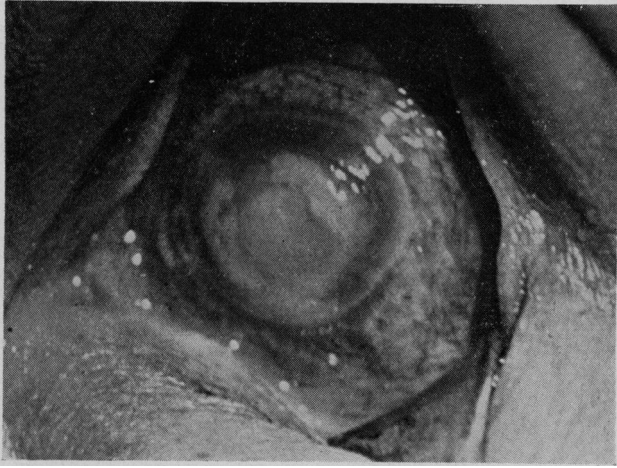


FIG. 4.—Case 2, hypopyon ulcer.

FIG. 5.—Case 2, hyphae, conidiospores, and vesicles of a fungus in corneal scrapings.

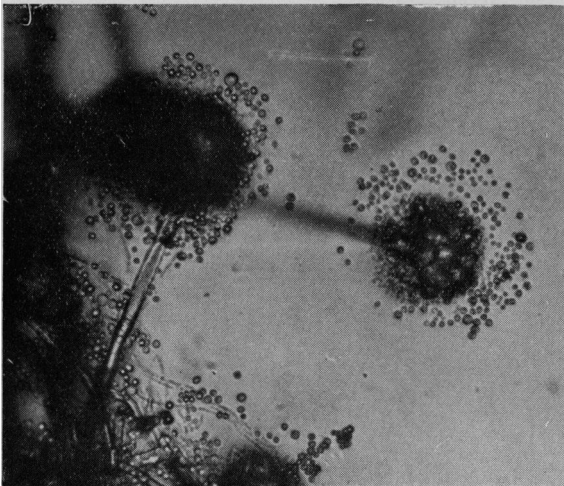
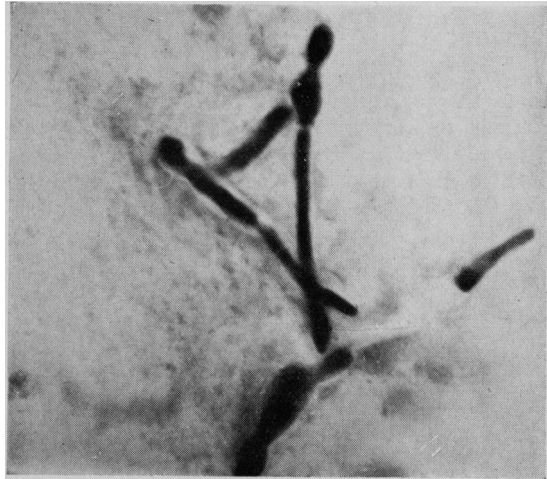
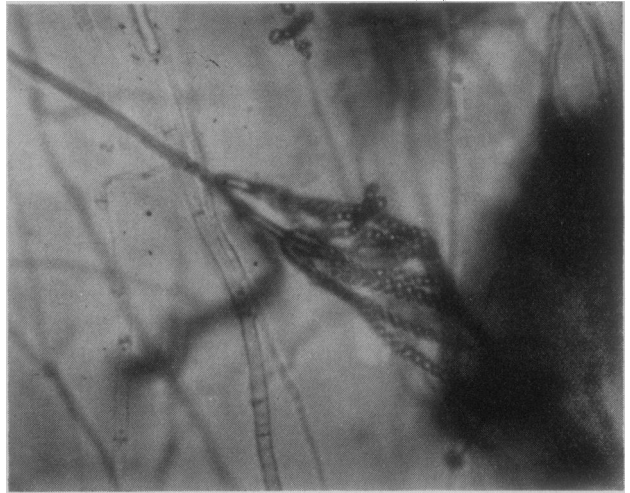


FIG. 6.—Case 2, formation of conidia at end of sterigmata.

FIG. 7.—Case 3, hyphae with septa, conidiospores, sterigmata, and conidia, without vesicle formation.



Case 4, a 26-year-old male, was being treated by his family doctor with cortisone and antibiotics for a peripheral corneal infiltration of the right eye. The condition was cured after 7 days' treatment with cortisone ointment applied every 3 hours. The patient continued to apply cortisone, and 2 days later complained of pain and visual disturbance. When he visited our clinic one week later, there was ulceration and infiltration near the centre of the cornea with ciliary injection but without hypopyon. Visual acuity was counting fingers at 2 m. No bacteria were found in the smear, but fungus hyphae were demonstrated in scrapings of the ulcer. Scarification and cauterization of the ulcer were performed immediately, and 0.05 per cent. trichomycin ointment applied every 4 hours, whereupon the inflammation began slowly to subside. Cultures from the ulcer were negative until after 6 days when one colony of the fungus appeared in the culture. On the next day, therefore, surgery was again applied. The ulcer was cured 10 days thereafter, but it was 8 weeks before all inflammatory signs disappeared. Visual acuity of 20/60 was preserved.

Identification of the Fungus.—Bacteria did not grow on blood-agar culture. A good growth of fungus was obtained on Sabouraud agar at 37° and 40°C., and less at 25°C. The morphology, biology, and pathogenicity of the fungus corresponded to that isolated from Case 2, and the fungus was identified as *Aspergillus fumigatus*.

Incidence of Fungus Appearance after Cortisone Therapy.—The frequent occurrence of fungus keratitis after cortisone therapy suggested the advisability of studying the propagation of fungi in the conjunctival sac after therapy of this type.

We selected 63 cases in which topical treatment with cortisone had been continued for more than 3 weeks. From these cases the conjunctival surface was scraped with a platinum loop and cultures were made on Sabouraud glucose agar, wort agar, malt agar, and corn starch agar, at 25°, 37°, and 40°C., for at least 10 days. If any fungus appeared in the culture, identification experiments (such as hanging-drop culture, inoculation into animals, and fermentation tests) were performed. Fungi were demonstrated in 42 of these 62 cases (67 per cent.). The identification experiments revealed that the following groups were involved:

| | | | | | |
|-----------------------------|---|------------------------------|---|----------------------------|---|
| <i>Penicillium</i> | 9 | <i>Oospora</i> | 2 | <i>Verticillium</i> | 1 |
| <i>Candida</i> | 5 | <i>Cystospora</i> | 2 | <i>Mycelia</i> | 1 |
| <i>Saccharomyces</i> | 4 | <i>Scopulariopsis</i> | 2 | <i>Hyalops</i> | 1 |
| <i>Aspergillus</i> | 4 | <i>Phoma</i> | 2 | <i>Achorion</i> | 1 |
| <i>Rhodotorula</i> | 4 | <i>Torulopsis</i> | 2 | <i>Cladosporium</i> | 1 |
| | | <i>Mucor</i> | 1 | | |

As a control experiment, 65 other cases in which no cortisone had been used were selected at random and examinations for fungi were performed, using the same procedure as above. Fungi were demonstrated in twelve of these 65 cases (18 per cent.). The nature of the fungi was as follows:

| | |
|------------------------------|------------------------------|
| <i>Rodotolura</i> 4 | <i>Torulopsis</i> 1 |
| <i>Saccharomyces</i> ... 3 | <i>Schizosaccharomyces</i> 1 |
| <i>Aspergillus</i> 1 | <i>Mucor</i> 1 |
| <i>Trichophyton</i> 1 | |

In the second experiment we selected eighteen cases in which no fungus of any kind was demonstrated either in smear or in culture. In these cases, a hydro-cortisone ointment was applied topically five to six times a day for about 3 weeks. At the end of the third week, cultures for fungus cultivation were made from these cases as in the first experiment, and in nine of the eighteen cases fungi were found in the conjunctival sac. The following groups were involved:

| | |
|-----------------------------|--------------------------|
| <i>Penicillium</i> 4 | <i>Hyalops</i> 1 |
| <i>Rhodotorula</i> 2 | <i>Dematium</i> 1 |
| <i>Aspergillus</i> 1 | |

(2) *Pseudomonas* Infection after Cortisone Therapy

In addition to fungus keratitis, we observed one case of hypopyon keratitis due to an infection of *Pseudomonas aeruginosa* induced by topical cortisone.

Case Report

Case 5, a 25-year-old female, was being treated with topical cortisone by her family doctor for interstitial keratitis in the left eye; 6 days after the beginning of the treatment she complained of a foreign-body sensation in this eye, and 4 days later she had a severe pain in the eye with headache, nausea, and vomiting. The following day she entered our clinic. There was an intensive circumcorneal injection in the left eye; the cornea was diffusely cloudy and there was a dense central infiltration 6 mm. in diameter with an ulcer about 3 mm. in diameter and a necrotic centre; an hypopyon was apparent in the anterior chamber. The scraping of the ulcer contained Gram-negative bacilli with a few Gram-positive cocci, but no fungus. A combination ointment (tetracyclin, 1.0 per cent.; erythromycin, 1.0 per cent.; colistin,* 0.2 per cent.) was then administered topically every 30 min., carbomycin 1.8 g. daily was given by mouth in six doses, and atropine was instilled. The pain began to subside in the course of 12 hrs, and after 24 hrs a clinical improvement was obvious. After 48 hrs the hypopyon disappeared, the cornea became a little more transparent, and the infiltration as well as the ulceration was reduced. The antibiotic ointment was then administered less frequently during the night. The ulceration was finally cured after 8 days' treatment and bacteriological examination was negative. The treatment was continued, with the exception of the systemic administration of carbomycin. After 2 weeks' treatment, the patient was discharged; 2 months later, there was a leucoma at the centre of the cornea due to the ulcer and a slight but diffuse cloudiness of the cornea due to interstitial keratitis. Visual acuity was hand movements.

Identification of the Bacteria.—Colonies of Gram-negative bacilli with polar flagellates grew abundantly on ordinary agar at 37°C. Bluish-green pigment was produced. Gelatin was liquefied. Litmus milk was softly coagulated, showing an alkaline reaction. The organism was identified as *Pseudomonas aeruginosa*.

* Colistin is a new antibiotic found in Japan. The spectrum is similar to that of polymyxin.

Discussion

It is generally known that the use of antibiotics often results in a fungus infection, particularly with the moniliasis *Candida albicans*. In the field of ophthalmology, however, antibiotics do not seem to favour such infections on topical application. Tanaka (1952) has already studied this subject and reported that the incidence of *Candida* in the conjunctiva after antibiotic treatment (7.5 per cent.) was not much greater than in control cases (5.7 per cent.). She considered that this might be due to the high concentration of antibiotics in topical applications. She demonstrated *in vitro* that antibiotics of the tetracycline group did not accelerate the growth of *Candida* but inhibited it at concentrations of 0.5 to 1.0 per cent. such as are routinely used in ophthalmology in the form of solution or ointment.

Although fungus infection after antibiotic treatment has not proved to be a complication, it would seem that corneal infections of this type may be a sequel of treatment by cortisone. The incidence of fungus infection after cortisone therapy was about 0.3 per cent. (2 : 698) among cases in which cortisone was given topically by us for more than one week. We have also observed other cases in which cortisone had been given by the patient's own physician. In four cases of fungus keratitis and one of *Pseudomonas* keratitis the infection became manifest 1 to 2 weeks after beginning cortisone therapy.

The incidence of the presence of fungi in the conjunctival sac after cortisone therapy was found to be 67 per cent. (42 : 63), while in control cases it was only 18 per cent. (12 : 65). When hydrocortisone was applied in eighteen cases in which no fungus had been demonstrated, this type of organism appeared in nine of them (50 per cent.) after 3 weeks' application.

Corneal infection by fungi and *Pseudomonas* cannot easily be controlled by the antibiotics so far available to us and it presents a serious hazard to the safety of the eye, for the loss of all useful vision is not an unusual termination. It may, therefore, be wise to make periodical bacteriological examinations of the conjunctiva before and during a course of cortisone treatment. If any dangerous signs appear, the application of cortisone should be stopped.

Summary

Four cases of hypopyon keratitis due to a fungus infection and one case due to *Pseudomonas* infection are described. All these infections followed the topical application of cortisone or hydrocortisone.

The cortisone used in this study was partially supplied by Dr. Alpert, Merck Co., New Jersey, U.S.A., the trichomycin by Mr. Kobayashi, Sanyo Co., Nagoya, Japan, and the colistin by Mr. Koyama, Kakenyaku Co., Tokyo, Japan.

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