MYCOTIC CORNEAL ULCERS*

BY

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CORNEAL ulcers present one of the major ophthalmic problems of India. Mitsui and Hanabusa (1955), Ley (1956), and Ley and Sanders (1956) considered that antibiotic and/or corticosteroid therapy might convert non-pathogenic into pathogenic fungi. Seligmann (1953), Mankowski and Littleton (1954), and Vogel, Michael, and Timpe (1955) have reported the systemic dissemination of fungus infection after systemic cortisone therapy. Conant, Smith, Baker, Callaway, and Martin (1954) stated that mycotic keratitis was mainly due to potentially pathogenic fungi. Leber (1879), Berliner (1882), Schirmer (1896), Uthoff (1897), Stern and Kulvin (1950), Thygeson, Hogan, and Kimura (1953), Pautler, Roberts, and Beamer (1955), Anderson, Roberts, Gonzalez, and Chick (1959), and Barsky (1959) have reported clinical cases of mycotic infection of the cornea, and Fazakas (1953), Ley (1956), Hirose, Yoshioka, Abe, Kanemitsu, and Kiya (1957), and Montana and Sery (1958) have produced mycotic keratitis experimentally.

Some of our recent cases of corneal ulcer, in spite of suitable antibiotic and other therapy, progressed relentlessly and ended in blindness. We assumed that, besides bacteria, other pathogens were complicating these ulcers and we were able in a few to isolate fungi. We therefore attempted to produce experimental fungal keratitis in rabbits and to study the corneal ulcers thus obtained.

Material and Methods

White albino rabbits of about 3 lb. in weight were used and *Aspergillus fumigatus* and *Candida albicans* were injected intra-corneally.

Aspergillus fumigatus and *Candida albicans* isolated from normal conjunctival sacs were grown on Sabaraud's medium. When there was profuse growth a gross suspension in normal saline was made. The suspensions of *Candida albicans* contained 10^4 yeast forms per cu. mm. *Aspergillus terreus* was obtained from a case of proptosis secondary to mycotic granuloma of the maxillary antrum. (Agarwal, Malik, Mohan, and Mahopatra, 1962).

Penicillin-sensitive coagulase-positive *Staphylococcus aureus* grown on blood agar was also used. A suspension of the organisms was made in normal saline, conforming to Nephelometer tube 3, i.e. 900 million organisms per cu. mm.

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The rabbits were divided into four main groups, and intra-corneal injections of fungi and/or staphylococci were given into the left eye of each by the technique of Ley (1956) and Montana and Sery (1958); the right eye, used as a control, was injected with 0.1 ml. sterile normal saline into the superficial corneal lamellae.

The production of ulcers, presence of hypopyon, presence of slough, ciliary congestion, vascularization, iritis, and recovery of pathogens were observed.

No control eye showed any ulceration. A mild keratitis was noticed in a few cases but this cleared up without treatment and with no complications.

Results

GROUP I: INTRA-CORNEAL INJECTION OF FUNGI. No treatment.

- (a) *Aspergillus terreus*: 5 rabbits
- (b) *Aspergillus fumigatus*: 5 rabbits
- (c) *Candida albicans*: 5 rabbits

After the intra-lamellar injection the weal remained raised for about 2 days during which time the black line of injected fungi was seen. In the case of *Candida* there was a white speck. There was conjunctival discharge and mild congestion. In a few cases the epithelium broke down over the injected area where an ulcer was produced (Fig. 1). The ciliary congestion was mild and there was no vascularization. Hypopyon was produced in two instances. The ulcers gradually increased in extent and depth, the clinical course of those produced by *Candida albicans* and *Aspergillus fumigatus* being identical.

FIG. 1.—Ulcer produced by *Aspergillus fumigatus* (Group 1b)

FIG. 2.—Vegetative forms of *Aspergillus terreus* in corneal ulcer (Group 1a) P.A.S. $\times 280$.

Aspergillus terreus, isolated from a case of granuloma of the maxillary antrum, produced a typical severe mycotic ulcer when injected intra-corneally (Fig. 2), and was always associated with slough, iritis, and hypopyon.

GROUP II: INTRA-CORNEAL INJECTION OF FUNGI AND PENICILLIN-SENSITIVE COAGULASE-POSITIVE *Staphylococcus aureus*. No treatment.

(a) *Aspergillus fumigatus*: 5 rabbits

(b) *Candida albicans*: 5 rabbits

All developed corneal ulceration, with marked conjunctival congestion and chemosis, ciliary congestion, and discharge. The epithelium broke down and produced sloughing corneal ulcers (Figs 3 and 4), hypopyon (2 rabbits), and iritis (4 rabbits). There was early vascularization of the cornea. The lesion was progressive and ultimately all these untreated eyes were lost. *Staphylococcus aureus* was recovered from all of them, but fungus from only seven eyes on re-culture. Culture from the hypopyon was sterile.

FIG. 3.—Ulcer and corneal vascularization after intra-corneal injection of *Candida albicans* and coagulase-positive *Staph. aureus* (Group II).

FIG. 4.—Vegetative forms of *Aspergillus fumigatus* in corneal layers (Group IIa) P.A.S. $\times 280$

GROUP III: INTRA-CORNEAL INJECTION OF FUNGI AND PENICILLIN-SENSITIVE COAGULASE-POSITIVE *Staphylococcus aureus*. Treatment with penicillin.

(a) *Aspergillus fumigatus*: 5 rabbits

(b) *Candida albicans*: 5 rabbits

1 mega unit penicillin dissolved in 0.5 ml. normal saline was given sub-conjunctivally daily for a week, and 1 per cent. sterile atropine eye ointment was applied once daily for the same period.

The corneal ulcers, conjunctival congestion, and chemosis were more severe than in Group I and less severe than Group II (Figs 5 and 6). There was some corneal vascularization, evidenced by dilatation of the limbal capillaries; the ulcer area was not invaded. Hypopyon and iritis developed in all cases. In those with *Aspergillus* infection, iritis developed earlier than in those with *Candida* infection. The fungus was recovered from all ulcers but no *Staphylococcus* could be re-cultured from most of them. The hypopyon was sterile in most eyes but fungus was recovered in two.

FIG. 5.—Extent of corneal ulcer in Group III. Note slough. P.A.S. $\times 35$.

FIG. 6.—Vegetative forms of *Candida albicans* in corneal ulcer (Group III) P.A.S. $\times 280$

GROUP IV. INTRA-CORNEAL INJECTION OF FUNGI AND PENICILLIN-SENSITIVE COAGULASE-POSITIVE *Staphylococcus aureus*. Treated with Penicillin and Corticosteroids.

(a) *Aspergillus fumigatus*: 5 rabbits

(b) *Candida albicans*: 5 rabbits

The rabbits were given a sub-conjunctival injection of 0.5 ml. suspension containing 12.5 mg. hydrocortisone sub-conjunctivally on alternate days and 100,000 units penicillin dissolved in 0.5 normal saline daily for a week.

The clinical picture in this group was deceptive. Within 3 to 5 days of the intra-lamellar corneal injection of the infecting organisms the epithelium broke down. There was only mild conjunctival and ciliary congestion, but there were conjunctival chemosis and profuse discharge, so that the eyelashes were matted together. There was no vascularization of the ulcer, but it progressed rapidly (Figs 7 and 8, opposite), and the slough increased considerably, with fairly severe iritis and hypopyon. Three rabbits had marked posterior corneal abscess. The ulcers perforated rapidly and the eyes were

lost. Fungus was recultured from all the eyes and *Staphylococcus aureus* from one, which ultimately developed panophthalmitis.

FIG. 7.—Corneal ulcer in Group IV.

FIG. 8.—Vegetative forms of *Candida albicans* in corneal ulcer and slough (Group IV). P.A.S. $\times 280$

Discussion

Group I.—Non-pathogenic fungi injected intra-corneally by the technique of Ley (1956) were usually capable of producing corneal ulcers (Group I, *b* and *c*), but pathogenic fungi always produced a corneal ulcer (Group I *a*), and these showed no vascularization. Our findings differ slightly from those of Ley (1956) and Montana and Sery (1958), who produced corneal ulcers in every rabbit even with non-pathogenic fungi, and from those of Conant and others (1954) who found that only pathogenic fungi produced corneal lesions. The absence of hypopyon in most of our experiments differs from the findings of Barsky (1959) and Byers, Holland, and Allen (1960) that fungi produced a dense purulent keratitis with hypopyon.

Group II.—Pathogenic bacteria and fungi injected intra-corneally caused a violent reaction and a severe sloughing corneal ulcer with hypopyon. The ulcers were vascularized and might perforate, culminating in panophthalmitis. Fazakas (1950) suggested that in some cases antibiosis may take place, as a result of which there is no keratitic reaction, but this we have not been able to confirm.

Stern and Kulvin (1950) suggested that in some instances the plaque, consisting of mycelial threads mixed with necrotic corneal fibres, is cast off quite easily, after which the ulcer heals rapidly and perforation rarely occurs.

In our series, although the lesion produced by the fungi alone was mild, the fungus could be re-cultured from the ulcer margin, which shows that all the fungal mass is not cast off. The lesion in Stern and Kulvin's series may have been superficial because the injection was not deep enough. We found no perforated corneal ulcers in eyes infected with fungi alone.

Group III.—Intra-corneal injection as in Group II, but treated with penicillin, resulted in an ulcer milder than in Group II and more severe than in Group I. The penicillin probably destroyed the *Staphylococcus*, but the growth of the fungus led to hypopyon and iritis. Since the ulcers were more violent than those produced by fungus alone and since both fungus and *Staphylococcus* could be re-cultured from the ulcer margins, it seems, as suggested by Fazakas (1950) and Pautler and others (1955), that a symbiotic activity exists and that the pathogenicity of one is increased by the other.

Group IV.—Mitsui and Hanabusa (1955) reported four cases of mycotic keratitis after topical cortisone. Whether cortisone increases the virulence of the fungi is uncertain. The clinical course of the corneal ulcers was very violent in Group IV, whereas in Group III it was comparatively mild. In both groups pathogenic staphylococci served to activate the fungi and were then removed by intensive penicillin therapy. In Group IV corticosteroids were also given and the violent course of the ulcers in this group suggests that this addition enhanced the virulence of the fungi, so that cortisone should not be used in treating corneal ulcers unless fungal infection can be ruled out.

Corneal ulcers produced by fungi resemble other types of ulcer. Corticosteroids appear to activate non-pathogenic fungi and increase the virulence of pathogenic fungi. In ulcers due to fungi alone the inflammatory reaction is mild and the lesion may become static though it is usually slowly progressive. The margins swell and the infected area shows at first a fluffy elevation. Then the surrounding area shows oedema and infiltration, necrosis occurs, and a sharply-defined greyish ulcer forms with an overhanging oedematous margin. Slough formation is minimal and hypopyon is uncommon with non-pathogenic fungi. The central area becomes laminated and there is a mild conjunctival reaction with mild ciliary congestion. The eye looks surprisingly quiet and there is no vascularization. This last finding is in agreement with that of Anderson and others (1959) but differs from that of Mitsui and Hanabusa (1955). If, however, these fungal (mycotic) ulcers are secondarily infected, vascularization is the rule. Mycotic ulcers seldom perforate but secondary infection may lead to perforation with panophthalmitis.

Summary

(1) Data on the experimental production of mycotic corneal lesions are presented.

(2) These lesions may be produced by non-pathogenic fungi, but those due to pathogenic fungi are more severe.

(3) A mixed infection by fungi and pathogenic bacteria produces a severe corneal reaction and leads to vascularization of the cornea, the presence of bacteria apparently increasing the pathogenicity of the fungus.

(4) Corticosteroids further increase the virulence of the fungus.

(5) The clinical appearance of typical mycotic corneal ulcers is described.

(6) Antibiotics and corticosteroids should not be used indiscriminately in the treatment of corneal ulcers.

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