Ocular fungus

Report of two cases

I. A. ABBOUD AND L. S. HANNA

From the Department of Ophthalmology, Cairo University, and the Department of Ophthalmology, Tanta Faculty of Medicine, Egypt

Fungi are a large group of plant-like micro-organisms, which grow in filaments or "hyphae", and intertwine in a mat-like growth called a mycelium. Reproductive bodies or spores are produced from the colony or mycelium.

Ocular fungus was described by the early mycologists, including Leber (1879), who first reported the invasion of the cornea by *Aspergillus* causing hypopyon ulcer, and Gilchrist (1896), who described ocular involvement in blastomycosis. Ophthalmological research in fungus diseases began in the early 20th century, and interest has recently been renewed by discoveries in the field of antibiotic medicine and the development of cortisone and allied hormonal derivatives.

Hammeke and Ellis (1960) surveyed the fungi of the conjunctival sac, and in cultures from 520 eyes found fungi in 10.3 per cent. of adults, 5.0 per cent. of children, and 0.1 per cent. of infants. Williamson, Gordon, Wood, Dyer, and Yahya (1968) isolated fungi from 2.9 per cent. of healthy conjunctival sacs, and from 13.3 per cent. of patients with Sjögren's syndrome (the isolates included *Candida albicans* and *C. parapsilosis*).

The majority of fungus infections arise on the skin, which constantly receives debris from the air. Ringworm infections (tinea capitis, tinea barbae, tinea glabrosa, tinea cruris, and dermatophytosis) may involve the eyelids. Bedell (1946) reported a corneal ulcer due to cephalosporium (related to *Trichophyton gypseum*) successfully treated with potassium iodide.

Ocular blastomycosis frequently involves the lids, leading to scarring and distortion, with a liability to corneal ulceration. Theodorides and Koutrolikos (1953) reported four cases of blastomycosis of the conjunctiva. Schwartz (1931) described the only known case of metastatic infection reaching the eye from a generalized blastomycosis.

Streptothricosis conjunctivae (actinomycosis) commonly causes concretions in the canaliculi, and nodular granulations in the conjunctiva as well as corneal ulcers have been described. Actinomycosis is known to invade the orbit and eye from the sinuses and also from the jaw after dental extraction. Verhoeff (1924) reported the presence of actinomycosis after cataract extraction in both eyes, as well as by metastasis from an infection in which the fungus was isolated from the heart valves. Fuchs (1919) also found the fungus in enucleated eyes after cataract extraction.

Nocardia asteroides experimentally implanted in the eye by McCarthy, Kennedy, and Hazard (1959) caused granulomata and microabscesses similar to the conglomerate tubercle.

Mycetoma (maduromycosis) begins with a subcutaneous swelling and forms a typical granulomatous lesion, which in India usually involves the foot, but two cases have been recorded in which the eyelids were affected (Aldridge and Kirk, 1940).

Sporotrichotic conjunctivitis was reported by Hamburger (1912) in 58 cases in which typical nodules broke down to form indurated ulcers. Toulant (1913) reported 23 ocular cases. McGrath and Singer (1952) found that salt-meadow hay harboured *S. schenckii*, which infected the palpebral conjunctiva.

Keratomycosis (moniliasis) usually follows trauma to the eye by an earthy substance, the mycotic corneal ulcer being covered by a dry membrane. Sykes (1946) reported a case of mycotic keratitis which appeared identical to dendritic keratitis and was treated by large doses of iodides, and by mycostatin locally and parenterally. Obstruction of the nasolacrimal duct is frequently due to *Candida albicans* (Birge, 1963).

Ocular involvement in coccidioidomycosis may occur in the form of conjunctivitis or proliferative retinitis in the initial stage of *C. immitis* infection (Levitt, 1948). Granulomatous uveitis was described at a later stage by Brown, Kellenberger, and Hudson (1958), who demonstrated endospores in the ciliary body and iris histologically, and observed others ophthalmoscopically in areas of choroïdo-retinitis.

Woods and Wahlen (1960) pointed out that benign histoplasmosis might cause granulomatous uveitis. In a survey of 293 patients with both granulomatous and non-granulomatous uveitis, they suggested that in the initial phase of benign infection, small granulomata appear at the periphery of the choroid. Haemorrhagic-oedematous lesions later appear at the fovea. These may be explained as hypersensitive reactions or atypical granulomata. Singer and Smith (1964) noticed lesions resembling phlyctenular keratitis and interstitial keratitis in the course of experimental histoplasmosis in rabbit eyes, after stromal injections of *Histoplasma capsulatum*; lesions resembling dendritic and disciform keratitis followed intra-epithelial inoculations.

Fleckner and Goldstein (1969) reported two cases of cerebral mucormycosis in diabetic patients, which were manifested by ptosis, proptosis, total ophthalmoplegia, loss of vision, and rhinitis.

Intraocular fungus infection may arise from a mycotic infection of the outer eye and adjacent tissues, or from a blood-borne infection from systemic disease (Duke-Elder and Perkins, 1966). Hammeke and Ellis (1960) reported cases of endophthalmitis in which fungi were isolated after surgery or trauma; of ten cases, five were saprophytes and five pathogens. Intraocular endogenous fungus infection has been recorded by Harley and Mishler (1959).

Case reports

Case 1, a girl aged 12 years, came to the out-patients clinic of the Ophthalmic Hospital at Tanta, complaining of sand particles in the left eye. The condition had started a month previously after she got sand in her left eye, and after 3 days the sand-like discharge increased in spite of washing out the conjunctival sac every half hour. The 'sand' increased during the night when the washings were stopped, and spilled out on to the left cheek. Terramycin eye ointment was given besides the frequent washings with cold water, but the condition still progressed.

Examination

The right eye was normal and the visual acuity 6/6.

The left eye showed a greyish-brown granular discharge like sand particles which filled the whole lower fornix and was spilling on to the lower lid (Figs 1 and 2). The eye was normal except for a mild conjunctival hyperaemia at the lower fornix. The fundus was normal and the visual acuity 6/12.

FIG. 1 Case 1, showing fungus infection in the left conjunctival sac and on the lower lid

FIG. 2 Case 1, showing fungus infection in the left lower fornix, and on the lower lid

Bacteriological examination

Wet smears from the conjunctival discharge showed numerous broad septate branching hyphae (Fig. 3). A few dark spherical spores were also seen.

Cultures on Sabouraud's glucose agar medium incubated at room temperature showed growth starting on the third day in the form of a coal-black colony with solid dark spore heads (Fig. 4).

FIG. 3 Wet smear with Gram stain from the conjunctival discharge, showing the hyphae, and a spore of *Aspergillus niger* $\times 1,000$. Oil immersion

FIG. 4 Cultures on Sabouraud glucose agar medium, showing *Aspergillus niger* colonies

The spores were arranged in chains attached to sterigmata arising from the central vesicle (Fig. 5, overleaf). The cultures were typical of *Aspergillus niger*.

The right eye was also examined bacteriologically for fungus infection, but both wet preparations and cultures gave negative results.

FIG. 5 Culture on Sabouraud glucose agar medium, showing spores of *Aspergillus niger* $\times 1,300$. Oil immersion

Treatment

Mycostatin tablets (Nystatin), were prescribed in a dose of one tablet (500,000 units) orally three times daily for 2 weeks. The discharge was washed out thoroughly every hour and all local antibiotics were stopped. The condition continued to progress, however, and the discharge increased. Griseofulvin in a dose of one tablet (125 mg.) orally three times a day for 2 weeks was also ineffective, as were intramuscular injections of Sulpha-iode B (sulpha with iodine in organic form, with vitamin B₁) given every other day for ten injections.

Lastly, local mycostatin ointment (100,000 units Nystatin per g. in plastibase) was applied three times daily, and the condition responded completely after 5 days.

Case 2, a girl aged 13 years, came to the out-patients clinic of the Ophthalmic Hospital at Tanta, complaining of "mud growing" in the right eye. The condition had started gradually 2 months before, with a muddy discharge which progressively increased to fill the conjunctival sac, in spite of frequent washing with cold water. A vague history was given of dust particles entering the eye a week before the start of the discharge. The patient was using decadron eyedrops, and terramycin eye ointment, as well as the washing, but with no result.

Examination

The right eye showed a brownish-black discharge like mud at the lower fornix (Fig. 6). The lower lid was slightly oedematous, but the globe and fundus were normal, and the visual acuity was 6/12.

The left eye was normal with a normal fundus and the visual acuity was 6/18.

FIG. 6 Case 2, showing fungus infection in the right lower fornix

Bacteriological examination

Aspergillus niger was identified in the right conjunctival sac by wet smears and cultures on Sabouraud's medium. The appearances were similar to those in Case 1.

Treatment

The condition resolved after the application of local mycostatin ointment.

Discussion

The *Aspergillus* forms a very large group of easily isolated fungi. It is a rare cause of conjunctival infection, but corneal infections are more common, and the lacrimal passages and orbit may also be involved (Duke-Elder, 1965).

Aspergillus fumigatus has been identified as a cause of blepharitis (Rosenfold, 1942) and dacryocystitis; it has also been found to invade the cornea after 5 days' treatment of dendritic keratitis (Mitsui and Hanabusa, 1955).

An intractable and necrotic corneal ulcer is not uncommonly produced by the *Aspergillus*, particularly *A. fumigatus*, and a severe toxic iridocyclitis may result from the developing keratitis (Duke-Elder and Perkins, 1966). Perforating corneal ulcers have also been reported (Castroviejo and Muñoz Urrea, 1921). The fungus may penetrate into the inner eye causing a vitreous abscess and panophthalmitis (Schirmer, 1896; Nobbe, 1898). Similar infections, which may be milder, have been reported after perforating injuries (Römer, 1902; Kampherstein, 1903; Purtscher, 1910; Rychener, 1933; Watelet, 1950).

Aspergillus niger was reported by Donahue (1949) in a 12-year-old girl: a brownish-black swelling containing a treacle-like fluid was found in the conjunctiva and inferior canaliculi.

Aspergillus can easily be identified by the examination of wet smears for broad, septate, branching hyphae. Small dark spherical spores, 2 to 3 μ in diameter, may sometimes be seen. Cultures on Sabouraud's glucose agar or Littman's ox-gall agar incubated at room temperature show a rapid growth (within 2 to 3 days), beginning as a fine filamentous surface growth and producing conidiophores. The *Aspergillus* is characterized by the swollen ends of the conidiophore called sterigmata, from the tips of which the spores arise in long chains. The colour of the colony depends on the species. *Aspergillus niger* produces a coal-black spore head (Moss and McQuown, 1960).

Fungi can be diagnosed macroscopically by the characteristic colony formation and the fusion of their mycelia, and microscopically by the type of spore. The recognition of the arrangement of the spores is essential for identification of the species. Conjunctival smears and biopsy material, together with mucous plugs from the tear ducts, may be examined directly under the microscope (Birge, 1963). The pathogenic fungi all form hyphae, or irregularly segmented filaments, in the human body; whereas spores are rarely present except in artificial culture.

Most fungi are demonstrated with ordinary histological stains such as haematoxylin and eosin; but Gram, periodic acid-Schiff, and silver stains are usually more effective. If tissue is available, the PAS staining technique readily reveals the morphological characteristics of many fungi (McManus, 1948). For photo-micrographic work, Gomori's methenamine silver nitrate technique has been recommended.

Fungus culture media, like Sabouraud's glucose agar medium, make the growth and identification of fungi more specific. It is important to inhibit bacterial growth in routine cultures, and Sabouraud's media do this by their acid pH (5.5) and also by their high sugar content (Hynes, 1964). Filtered ultraviolet irradiation may be used to assist the study of fungus colonies (Birge, 1963).

Immunological procedures are also available for certain fungi, but the complex antigenic structure of most of them makes the interpretation of such tests difficult (Conant, Smith, Baker, Callaway, and Martin, 1954). Skin hypersensitivity tests performed by the intracutaneous injection of the antigen are available for *Mucor*, *Aspergillus*, *Candida*, and *Histoplasma*, but the positive results tend to appear late in the course of the infection (Duke-Elder and Perkins, 1966). Animal inoculation may be used, especially with deep mycotic infections, to establish the pathogenicity or to obtain a pure strain. Agglutination and precipitation tests are also available for histoplasmosis (Saslaw and Campbell, 1948; Salvin and Hottle, 1948).

The treatment of oculomycosis is unsatisfactory. Most cases are not precisely diagnosed to begin with, so that intensive broad-spectrum antibiotics and steroids are usually administered as a routine measure. Most fungi thrive in the presence of antibiotics, particularly streptomycin and the tetracyclines (Duke-Elder and Perkins, 1966). Torack (1957) reported thirteen cases of fungus infection associated with antibiotic and steroid therapy, and Mitsui and Hanabusa (1955) found that patients treated with corticosteroids for 3 weeks had a 49 per cent. greater chance of fungus invasion than those not so treated. Ley (1956) has also shown the enhancing effect of corticosteroids in fungal infections of the cornea in experimental animals.

The most effective fungistatic agents are mycostatin, amphotericin B, and griseofulvin. Experimental intraocular infection with *Aspergillus fumigatus* in rabbits (Fine and Zimmerman, 1960), proved that mycostatin, derived from *Streptomyces noursei* (200 units in 0.1 ml. saline solution), controlled the intraocular infection completely after 7 weeks; the best results were obtained when treatment was started 24 to 48 hours after the infection. Hammeke and Ellis (1960) advised the use of prophylactic pre-operative local antifungoidal drugs, such as amphotericin or nystatin.

Summary

Two cases of conjunctival *Aspergillus niger* infection are reported. A dramatic response was obtained by the local use of mycostatin ointment.

References

- ALDRIDGE, J. S., and KIRK, R. (1940) *Brit. J. Ophthalm.*, **24**, 211
 BEDELL, A. J. (1946) *Trans. Amer. ophthalm. Soc.*, **44**, 80
 BIRGE, H. L. (1963) In "Modern Ophthalmology", ed. A. Sorsby, vol. 2, pp. 253-272. Butterworths, London
 BROWN, W. C., KELLENBERGER, R. E., and HUDSON, K. E. (1958) *Amer. J. Ophthalm.*, **45**, 102
 CASTROVIEJO, R., and MUÑOZ URRÁ, F. (1921) *Arch. Soc. oftal. hisp.-amer.*, **21**, 453
 CONANT, N. F., SMITH, D. T., BAKER, R. D., CALLAWAY, J. L., and MARTIN, D. S. (1954) "Manual of Clinical Mycology", 2nd ed. Saunders, Philadelphia
 DONAHUE, H. C. (1949) *Amer. J. Ophthalm.*, **32**, 207
 DUKE-ELDER, S. (1965) "System of Ophthalmology", vol. 8, part 1, p. 390. Kimpton, London
 ——— and PERKINS, E. S. (1966) "System of Ophthalmology", vol. 9, pp. 383-411. Kimpton, London
 FLECKNER, R. A., and GOLDSTEIN, J. H. (1969) *Brit. J. Ophthalm.*, **53**, 542
 FINE, B. S., and ZIMMERMAN, L. E. (1960) *Arch. Ophthalm. (Chicago)*, **64**, 849
 FUCHS, E. (1919) *v. Graefes Arch. Ophthalm.*, **101**, 24
 GILCHRIST, T. C. (1896) *Johns Hopk. Hosp. Rep.*, **1**, 269
 HAMBURGER, W. W. (1912) *J. Amer. med. Ass.*, **59**, 1590

- HAMMEKE, J. C., and ELLIS, P. P. (1960) *Amer. J. Ophthalm.*, **49**, 1174
- HARLEY, R. D., and MISHLER, J. E. (1959) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **63**, 264
- HYNES, M. (1964) "Whitby and Hynes Medical Bacteriology", 8th ed., pp. 411-413. Churchill, London
- KAMPHERSTEIN (1903) *Klin. Mbl. Augenheilk.*, **41**, pt. 1, 151
- LEBER, T. (1879) *v. Graefes Arch. Ophthalm.*, **25**, abteil 2, p. 285
- LEVITT, J. M. (1948) *Amer. J. Ophthalm.*, **31**, 1926
- LEY, A. P. (1956) *Ibid.*, **42**, 59
- MCCARTHY, J. L., KENNEDY, R. J., and HAZARD, J. B. (1959) *Arch. Ophthalm. (Chicago)*, **62**, 425
- MCCRATH, H., and SINGER, J. I. (1952) *Amer. J. Ophthalm.*, **35**, 102
- MCMANUS, J. F. A. (1948) *Stain Technol.*, **23**, 99
- MITSUMI, Y., and HANABUSA, J. (1955) *Brit. J. Ophthalm.*, **39**, 244
- MOSS, E. S., and McQUOWN, A. L. (1960) "Atlas of Medical Mycology", 2nd ed., pp. 141-148. Williams and Wilkins, Baltimore
- NOBBE, W. (1898) *v. Graefes Arch. Ophthalm.*, **45**, 700
- PURTSCHER, A. (1910) *Ibid.*, **77**, 131
- RÖMER, P. (1902) *Klin. Mbl. Augenheilk.*, **40**, pt. 1, 331
- ROSENVOLD, L. K. (1942) *Amer. J. Ophthalm.*, **25**, 588
- RYCHENER, R. O. (1933) *Trans. Amer. ophthalm. Soc.*, **31**, 477
- SALVIN, S. B., and HOTTLE, G. A. (1948) *J. Immunol.*, **60**, 57
- SASLAW, S., and CAMPBELL, C. C. (1948) *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 559
- SCHIRMER, O. (1896) *v. Graefes Arch. Ophthalm.*, **42**, pt. 1, p. 131
- SCHWARTZ, V. J. (1931) *Arch. Ophthalm. (Chicago)*, **5**, 581
- SINGER, J. A., and SMITH, J. I. (1964) *Brit. J. Ophthalm.*, **48**, 293
- SYKES, E. M. (1946) *Tex. St. J. Med.*, **42**, 330
- THEODORIDES, E., and KOUTROLIKOS, D. (1953) *Amer. J. Ophthalm.*, **36**, 978
- TORACK, R. M. (1957) *Amer. J. Med.*, **22**, 872
- TOULANT, P. (1913) "Essai sur la sporotrichose oculaire". Thèse. Vigot, Paris
- VERHOEFF, F. H. (1924) *Arch. Ophthalm. (Chicago)*, **53**, 517
- WATELET, A. (1950) *Bull. Soc. belge Ophtal.*, no. 95, p. 465
- WILLIAMSON, J., GORDON, A. M., WOOD, R., DYER, A. MCK., and YAHYA, O. A. (1968) *Brit. J. Ophthalm.*, **52**, 127
- WOODS, A. C., and WAHLEN, H. E. (1960) *Amer. J. Ophthalm.*, **49**, 204