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POTENTIATION OF MYCOTIC OCULAR INFECTIONS BY DRUGS*

A REVIEW

BY

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IN recent years medical practitioners have become increasingly concerned about eye infections which are fungal in aetiology. While medical science has developed a large and generally effective armamentarium of antibiotics to combat ocular infections of bacterial aetiology, and chemotherapeutic agents have recently been developed which may prove to be extremely beneficial in the treatment of certain eye diseases of viral origin, methods of combatting oculomycoses have been described as being "weak and clumsy" (McLean, 1963). Oculomycoses have also become statistically prominent among the various types of eye diseases because of a rise in the numbers of reported cases of fungal eye infections. Haggerty and Zimmerman (1958) have noted a fifteen-fold increase in the incidence of one specific type of oculomycosis during recent years, and others have agreed that these infections are a seriously increasing problem (Anderson, Roberts, Gonzalez, and Chick, 1959; McLean, 1963).

This increase has been variously attributed to the development of better diagnostic procedures, general recognition of the fact that saprophytic fungi are capable of invading and infecting various parts of the ocular apparatus, and to possible potentiation of fungal eye infections by certain drugs which have been routinely used in the treatment of ocular infections (Haggerty and Zimmerman, 1958; Suie and Havener, 1963).

The two types of therapeutic agent most frequently suspected of potentiating mycotic ocular infection are the corticosteroids and certain antibiotics. While potentiation by corticosteroids has been generally accepted, the case against antibiotics is still in debate (McLean, 1963).

Clinical data have indicated that fungal presence and/or infection (systemic as well as ocular) is more frequent after treatment with antibiotics than before such therapy (McLean, 1963; Haggerty and Zimmerman, 1958; Anderson and others, 1959; Smith and Conant, 1960; Cannon, 1955; Newton and Tulevech, 1962; Huppert, MacPherson, and Cazin, 1953; Seligmann, 1952, 1953). *In vitro* experiments have shown growth enhancement of certain fungi by antibiotics, and *in vivo* studies have indicated that certain antibiotics enhance the virulence of fungi for mice (Leber, 1879; Seligmann, 1952, 1953; Huppert and others, 1953; Ley and Sanders, 1956; Gray, 1959). Experimentation concerning fungus potentiation in the eye has not been too

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extensive, although Ley (1956) has shown that one of the more popular tetracyclines enhances the virulence of *Candida albicans* for the rabbit cornea.

The first indentification of a micro-organism as an aetiological agent of human disease occurred in 1839 when Schoenlein isolated a fungus from the disease favus (Gray, 1959; Smith and Conant, 1960). In the same year, Langenbeck identified a yeast-like fungus from a case of thrush (Smith and Conant, 1960), and by 1856 Virchow had coined the word "mycosis" to describe diseases which were of fungal origin (Anderson and others, 1959).

Although most of the fungi pathogenic to man had been isolated and identified by 1900 (Smith and Conant, 1960), these early investigations were overshadowed by contemporary discoveries in the field of bacteriology. Since then, advances in medical mycology have not been as remarkable as in medical bacteriology (McLean, 1963; Smith and Conant, 1960; Gray, 1959).

Perhaps the primary reason for this relative neglect has been that fungi are rarely associated with the widespread dramatic types of epidemics of human disease which are so often associated with bacterial pathogens. Of the thousands of known species of fungi, fewer than fifty are known pathogens of man, and fewer than twelve of these have been identified as aetiological agents of fatal disease (Smith and Conant, 1960). In spite of this the inclination to underestimate fungi as human pathogens must be resisted. According to Gray (1959), a survey by Henrici in 1942 of 1,385,187 deaths in the United States from all causes disclosed that 395 of these deaths were attributable to fungal diseases. Although this was but a small percentage of total deaths, it was nearly twice the total number of deaths from rabies, leprosy, and paratyphoid, and undulant, relapsing, and yellow fevers; more than one-half of the deaths from poliomyelitis, tetanus, or typhoid fever; and more than the total number of deaths from Rocky Mountain spotted fever and other typhus-like diseases.

Fungal infections have become increasingly prominent during recent years, and an increase in the numbers of reported cases of systemic and local mycoses has been correlated chronologically with the increased use of corticosteroids and antibiotics as therapeutic agents (Leber, 1879; Haggerty and Zimmerman, 1958; Cannon, 1955).

Among the localized mycoses that are receiving more attention are oculomycoses, or fungal infections of the eye or ocular apparatus. The first instance of oculomycosis was recorded by Leber (1879), who isolated a species of *Aspergillus* from a corneal infection. Fungi may reach the eye in one or more of four general ways. They may enter from the outer environment, from infected neighbouring structures or parts of the anatomy likely to contact the eye, from penetrating wounds (accidents, surgery), and from blood infections. Oculomycoses contracted from external sources appear to be the most common, although certain fungi which are considered to be endogenous to the eye may also infect (McLean, 1963).

Anderson and others (1959) feel that oculomycoses are more frequent than is generally believed, and McLean (1963) has concurred with Kronfeld's opinion that "oculomycoses are a serious and seriously increasing problem". Haggerty and Zimmerman (1958) have reported a fifteen-fold increase in the rate of occurrence of cases of keratomycoses (fungal infection of the cornea) during the years 1952–6 over and above the period from 1933 to 1952; this last year is the year that first saw steroids used topically (Haggerty and Zimmerman, 1958).

Anderson and others (1959) give a typical description of the development and appearance of lesions of keratomycosis: "There is usually a history of an abrasion, laceration, or foreign body. An ulcer develops. This may temporarily improve under combined antibiotic–steroid therapy. As the bacterial infection is controlled the appearance of the lesion changes . . . The healing process becomes torpid or static. At the site of the original injury . . . a fluffy, white, slightly elevated protuberance appears. The superficial layers of the immediately surrounding cornea seem to liquefy, forming a shallow crater". According to McLean (1963), hypopyon is frequently present. When treated properly the infection is slow to heal, but when not properly attended to the cornea seems to melt, and sloughing and perforation follow with subsequent loss of the eye. The same species of fungus (for example, *Candida albicans*) may produce disease varying from a benign course with slow recovery to progressive necrosis, perforation, and endophthalmitis (spread of the infection to the interior structures of the eye) (Ley, 1956).

It has been generally accepted that steroids enhance ocular fungal infection (McLean, 1963) and much evidence exists to support this. Mitsui and Hanabusa (1955) reported four cases wherein fungal keratitis occurred *de novo* in patients who had been treated with cortisone topically for a variety of other ocular conditions, and experimentation disclosed that fungi appeared more frequently in the conjunctival sacs of patients who had been treated with cortisone topically (67 per cent.) than in those not similarly treated (18 per cent.). Furthermore, 50 per cent. of the people who exhibited no evidence of fungi in the conjunctival sac before cortisone administration gave positive cultures after three weeks of treatment with the steroid. Ley and Sanders (1956) have also reported cases of fungal superinfection subsequent to cortisone therapy.

Ley (1956), and Montana and Sery (1958) have shown that corticosteroids definitely enhance the infectivity of *Candida albicans* for the rabbit cornea, and the latter authors report that prednisolone may enhance the infectivity of the organism for two weeks after injection of the steroid. Studies by Agarwal, Malik, Mohan, and Khosla (1963) have resulted in similar findings.

Enhancement by corticosteroids may be due to direct modification of fungus growth, or to alteration of host resistance (Mitsui and Hanabusa, 1955; Ley and Sanders, 1956; Anderson and others, 1959). Some theories pertaining to the mechanism of host resistance alteration, each one of which has supporting evidence, are impaired killing within phagocytes, especially polymorphonuclear neutrophils (Anderson and others, 1959; Louria and Browne, 1960), depression of inflammatory response (Rebuck and Mellinger, 1953), decreased vascular permeability (Wyman, Fulton, and Shulman, 1953), and diminished phagocytosis (Crepea, Magnin, and Seastone, 1951). Considered in the context of keratomycosis potentiation, the result of these actions is a cornea seriously deprived of its defence mechanisms, and therefore much less resistant to infection than it normally would be (Anderson and others, 1959).

In addition, evidence is accumulating that certain antibiotics may potentiate fungal infection (Newton and Tulevech, 1962), and this is the question which will now be considered.

It has been noted clinically that fungi may be isolated more frequently from patients who are having prolonged antibiotic therapy than from those who are not, and several workers have noted an increase in the occurrence of systemic and ocular mycoses subsequent to antibiotic therapy (Seligmann, 1952, 1953; Huppert, MacPherson, and Cazin, 1953; Cannon, 1955; Haggerty and Zimmerman, 1958; Anderson and others, 1959; Smith and Conant, 1960; Newton and Tulevech, 1962; McLean, 1963).

In addition to the above evidence results of several experiments have indicated that at least two antibiotics—Aureomycin (chlortetracycline) and Terramycin (oxytetracycline)—may either enhance the growth of *C. albicans in vitro*, increase its virulence *in vivo*, or produce both effects. Moore (1951), Huppert and others (1953), and Pappenfort and Schnall (1951), have demonstrated increased growth of *C. albicans* in the presence of Aureomycin *in vitro*. Huppert and others (1953) were successful in quantifying these results with micro-Kjeldahl nitrogen determinations. *In vivo* virulence enhancement of *Candida* by both Aureomycin and Terramycin has also been reported. Seligmann (1952, 1953) showed that intraperitoneal injections of *C. albicans* suspensions simultaneously with either Aureomycin or Terramycin were more highly fatal to white mice than those where the antibiotics were not present in the inoculum, and Dukes and Tettenbaum (1954–55) have reported similar results.

There has not been a great deal of investigation on antibiotic potentiation of oculomycoses, one notable exception being the study of Ley (1956) with experimentally-induced *Candida* ulcers of rabbit corneae. His results indicated that simultaneous intrastromal injections of *Candida* suspensions and Terramycin caused much more severe ulceration in the test eyes than in the control eyes, in which Terramycin was not used, and his conclusion was that the antibiotic had strongly potentiated the infection.

Fungi which have been isolated and identified from oculomycoses include several from genera normally considered as pathogens (*Cryptococcus*, *Blastomyces*, *Coccidioides*, *Histoplasma*, and *Sporotrichum*), as well as others which are generally regarded as saprophytic or of low virulence, such as *Aspergillus*, *Nocardia*, and *Actinomyces* (McLean, 1963; Suie and Havener, 1963). The yeast-like fungus, *C. albicans*, causative agent of thrush, has also been isolated from cases of oculomycoses (Anderson and others, 1959; Hammeke and Ellis, 1960; Louria and Browne, 1960; Birge, 1962; McLean, 1963; Suie and Havener, 1963).

While it is well established that corticosteroids enhance the virulence of several fungi (including *C. albicans*) in ocular infections, the possibility of other chemotherapeutic agents having similar effects is not as generally accepted (McLean, 1963).

Evidence is accumulating, both circumstantial (clinical observations) (Haggerty and Zimmerman, 1958; Anderson and others 1959; McLean, 1963; Seligmann 1952, 1953; Huppert and others 1953; Cannon, 1955; Smith and Conant, 1960; Newton and Tulevech, 1962); and direct (experimental results) (Seligmann, 1952, 1953; Huppert and others, 1953; Ley, 1956), that certain antibiotics are capable of enhancing fungal growth or potentiating fungal virulence.

The work of Ley (1956) is especially pertinent. Using rabbits as experimental

animals, he infected their corneae with *C. albicans* after subconjunctival injections of cortisone. Test eyes were subjected to the antibiotic Terramycin, while control eyes received only organisms. Ley noted that in the majority of animals test eyes were markedly more involved than were controls, and concluded that the antibiotic had strongly potentiated the virulence of the *Candida*.

Solution of this problem has also been complicated by controversy over possible mechanisms of potentiation. Several theories have been advanced to explain enhancement mechanisms of antibiotics, many of which concern effects upon normal flora. Halbert and Swick (1952) and Halbert, Swick, Sonn, and Locatcher-Khorazo (1954) have reported that organisms which produce antibiotic substances may exist as normal ocular flora. The removal of these substances by elimination of normal flora after antibiotic administration may enable opportunists to invade and infect; or it has been suggested that normal flora may provide certain growth factors to host tissue, as in the case of certain intestinal organisms producing vitamin B, which when eliminated from the environment cause a pernicious alteration of cell permeability, thereby allowing opportunists to become more easily established as pathogens. It has also been postulated that removal of competitors (normal flora) permits potential pathogens to multiply less restrictedly because of the subsequently increased availability of nutrients.

In addition to the above considerations involving normal flora, the mechanism of antibiotic potentiation has been attributed to direct action of these agents either on the host tissue, or upon the infecting organism. Certain antibiotics have an irritative or necrotic action upon host tissue when used in local applications, such as Aureomycin and Terramycin when injected subconjunctivally (Leopold, 1954). This action would seemingly impair cellular defence mechanisms. According to Jawetz (1956), neomycin, bacitracin, and polymyxin B are considered to be virtually non-irritative to host tissues when used topically. Bellow and Farmer (1948) have reported, however, that solutions of bacitracin in high concentrations delay regeneration of corneal epithelium in human eyes, although they have been unable to demonstrate the same effect in rabbits. Huppert and others (1953) and Newton and Tulevech (1962) feel that antibiotics may in some way directly alter the virulence of opportunistic micro-organisms, making them capable in many instances of producing infection.

Although evidence is accumulating that antibiotics possibly enhance oculomycoses, more extensive research is necessary to define the problem adequately and determine the mechanisms responsible for the apparent potentiation suggested by various investigators.

Therapy

The two effective fungistatic drugs which may be useful in treatment of ocular fungus infection are amphotericin B and Nystatin. Neither drug penetrates the eye satisfactorily by any route other than direct intra-ocular injection. Both are highly toxic. Corneal fungus infections have been cured, both clinically and experimentally, by amphotericin and/or Nystatin (Mangiaracine and Liebman, 1957; Anderson and others, 1959; Theodore, Littman, and Almeda, 1961). Some weeks are required for

final healing of fungus corneal ulcers. This delay is due to toxic substances which are quite damaging to the cornea even when applied as an extract of killed fungi. Therapy of intra-ocular fungus infections is quite unsatisfactory. Even though the fungus may be destroyed by heroic injections of Nystatin and amphotericin, intra-ocular scarring usually precludes useful vision (Theodore and others, 1961).

Amphotericin is poorly absorbed from the gastro-intestinal tract, so it is given intravenously in concentrations of 0·1 mg./ml. Renal excretion is slow, and demonstrable blood levels persist for 18 hours or more after a single intravenous dose. Unpleasant and potentially dangerous side-effects are almost inevitable at therapeutic dosage levels. Amphotericin B should be used only in hospitals, under close clinical supervision, for treatment of mycotic infections diagnosed by culture. The drug is too toxic for use in vague and undiagnosed conditions merely because a skin test for one of the fungi may be positive. Weeks or months of treatment may be necessary. (Amphotericin is not fungicidal.) Dosage should be adjusted to minimize toxic effects rather than be increased to high levels in the vain hope of obtaining more prompt remission. Therapy is initiated with a daily dose of 0·25 g./kg., and gradually increased as tolerated. For topical ocular use 0·3 per cent. solution of amphotericin B may be prepared in 5 per cent. glucose or distilled water (Theodore and others, 1961). Subconjunctival injection of 125 μg. amphotericin B is reasonably well tolerated, but does not result in appreciable intra-ocular penetration. Intra-ocular injection is extremely toxic; however, 35 μg. in 0·05 ml. volume can be tolerated by the eye.

Nystatin is reasonably well tolerated by the eye as a topical ointment containing 100,000 units/g. or by subconjunctival injection of 5,000 units suspended in 0·5 ml. saline. Neither method produces measurable intra-ocular concentrations of Nystatin; 200 units Nystatin may be injected into the vitreous or aqueous chambers, but cause hyperaemia and leucocytic infiltration lasting from several days to a week (Fine and Zimmerman, 1960). Vitreous assays show that Nystatin levels sufficient to inhibit *Aspergillus* (6–12 units/ml.) persist for only 24 hours after injection. Unfortunately, a second intravitreal injection of 200 units Nystatin 36 hours after the first causes vitreous degeneration.

It is not clear that any benefits accrue from the use of corticosteroids in the treatment of corneal abrasions, purulent corneal ulcers, perforating wounds of the eye, or purulent endophthalmitis. We believe that corticosteroid therapy is strongly contraindicated in the management of such ocular conditions.

Summary

The diagnosis of fungus infection should be strongly suspected in any case of purulent corneal ulcer from which pathogenic bacteria are not readily isolated, and appropriate microbiological studies should be performed.

Amphotericin B and Nystatin therapy have been shown clinically and experimentally to be of value in the management of fungus-induced ulcers of the cornea.

The known value of antibiotics against bacterial infection should not be discounted in the case of a corneal ulcer of uncertain cause, on account of the not-clearly-established concept of antibiotic potentiation of fungus growth.

Corticosteroids unquestionably enhance fungus growth *in vivo* and are of no benefit to injured or infected eyes anyway. Hence, corticosteroid therapy of injured or infected eyes is definitely contraindicated.

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