GOBLET CELL RESPONSE TO VITAMIN A TREATMENT FOR CORNEAL XEROPHTHALMIA

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In 11 patients with active corneal xerophthalmia, conjunctival biopsies were obtained at various intervals after massive-dose systemic vitamin A therapy. Goblet cells began to repopulate the inferonasal quadrant of the conjunctivas after two weeks, and they reached normal concentrations after one month. Corneal healing proceeded much more rapidly than that, suggesting that a full complement of mucus-secreting conjunctival goblet cells is not essential for restoration and maintenance of normal corneal appearance.

SUBJECTS AND METHODS

Children with corneal xerophthalmia and conjunctival xerosis of similar severity in both eyes were randomly selected for conjunctival biopsy. After receiving informed consents from a parent or guardian, we obtained 3 x 4 mm biopsy specimens of temporal (and usually inferonasal) bulbar conjunctiva before therapy or at a predetermined interval after therapy began, or both. Posttreatment conjunctival specimens were always obtained from a previously unbiopsied eye. Specimens were fixed and processed in routine fashion and stained with Dane's stain and with PAS to identify goblet cells.

RESULTS

We obtained pretreatment conjunctival specimens from 17 patients. The most severe clinical lesion was corneal xerosis in six patients and corneal ulceration in 11. Posttreatment specimens were obtained from nine of these same patients and from two additional patients.

We found no goblet cells in any of the 17 temporal or 15 inferonasal conjunctival specimens obtained before vitamin A therapy. Goblet cells were not observed in the nasal conjunctival specimens obtained one week after treatment, but were present (in reduced numbers) in one of three nasal specimens obtained at two weeks and (in normal numbers) in all nasal spec-
TABLE

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<th>Presence of Goblet Cells in Conjunctival Biopsy Specimens from Patients Who Had Xerophthalmia After Vitamin A Therapy</th>
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<td><strong>Weeks After Treatment</strong></td>
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*Present series combined with those of Sommer, Green, and Kenyon and Sullivan, McCulley, and Dohlman.

imems obtained after the fourth week (Table). The pattern of goblet cell return was similar, but more erratic, in the temporal conjunctival specimens.

Of the 11 cases biopsied after treatment, corneal healing was apparent by day 2 in six cases and by day 4 in all cases. In five cases, healing was completed within one week; in another four cases it was completed within two weeks. In the remaining two cases, with large areas of necrosis that scarred slowly, the duration required for complete healing was not ascertained.

**DISCUSSION**

Biochemical studies and treatment trials indicate that corneal xerophthalmia is a direct consequence of impaired vitamin A metabolism. The exact mechanisms by which corneal xerosis and xerophthalmic ulceration or necrosis occur, however, remain obscure. It is reasonable to suspect that loss of mucus-producing goblet cells early in the disease may play an important role by promoting tear-film break-up that causes localized drying and epithelial loss. Indeed, some of the preulcerative and early ulcerative corneal changes observed in xerophthalmia resemble localized exposure and dellen formation.

Unfortunately, the central role that has been assigned to goblet cells in this process is inconsistent with the time-course of corneal healing and goblet cell return. As with the subjects in this study, mild to moderate manifestations of corneal xerophthalmia (superficial punctate keratopathy, xerosis, and punched-out ulceration) respond rapidly to vitamin A therapy. Healing is generally evident within one to four days and is complete within one to two weeks.

Goblet cells, however, return more slowly. Their rate of reappearance in our patients was consistent with previous reports of corneal and noncorneal xerophthalmia. As the numbers of cases were small, we pooled these results for more precise analysis (Table). Goblet cells begin to reappear in the inferonasal quadrant between one and two weeks after start of vitamin A therapy, and they do not reach their normal complement for an additional two to three weeks, long after corneal healing is apparently complete. Restoration and maintenance of normal corneal appearance seemingly does not require large numbers of conjunctival goblet cells.

This does not mean that mucus production and tear film stability are unimportant. Possibly small numbers of poorly
staining goblet cells, missed on routine microscopy, return early and participate in the healing process; other sources of mucus, such as the lacrimal gland and nongoblet or nonbulbar-conjunctival cells may provide mucus after goblet cells disappear or before they return; the shortened tear film break-up time observed in corneal xerosis may be a result rather than a cause of corneal keratinization. Nor does this rule out the potential importance of another local factor, aqueous tear production, which is reduced early in xerophthalmia and is affected by both vitamin A and protein status.

 Conjunctival specimens from the inferonasal quadrant provided a more reliable index of goblet cell dynamics than those from the temporal quadrant, probably because of the greater density of goblet cells normally present in the inferonasal quadrant and the tendency for xerophthalmic metaplasia to persist in the temporal quadrant. We are now evaluating goblet cell density in the inferonasal quadrant as a physiologic index of vitamin A status.

REFERENCES

FACTORS THAT INFLUENCE THE EFFICACY OF TOPICAL GENTAMICIN PROPHYLAXIS FOR EXPERIMENTAL PSEUDOMONAS KERATITIS

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We evaluated the efficacy of topical gentamicin prophylaxis for experimental Pseudomonas keratitis in rabbits by applying gentamicin in concentrations of 0.3 and 4 mg/100 ml, in both solution and ointment vehicles, one or four hours after a superficial stromal scratch was infected topically with Pseudomonas organisms. Under these conditions the most effective prophylaxis was that given early, in solution, and in high concentration.

Antibiotic prophylaxis is important in recently acquired corneal abrasions and lacerations. Although much experimental work has been done on the treatment of keratitis, we are not aware of any study that evaluated the factors that influence the efficacy of antibiotic prophylaxis. We studied the efficacy of a single application of antibiotic in two concentrations and in two vehicles using a Pseudomonas keratitis model in rabbits that closely resembled the clinical situation.

MATERIAL AND METHODS

Pseudomonas aeruginosa strain 107 was found to be susceptible to gentamicin in vitro by agar dilution, with a minimal inhibitory concentration of 2.5 µg/ml.3

We anesthetized New Zealand white male rabbits weighing 2 to 3 kg each and made a 3-mm linear scratch through the corneal epithelium into the superficial stroma with a sharp needle. We then infected the corneas topically with three drops of undiluted, overnight broth of P. aeruginosa strain 107 grown in Mueller-Hinton broth with Mg++ and Ca++ (1.34 × 10^10 organisms/ml).12

Treatment consisted of a single topical application of placebo or antibiotic. We applied two drops of solution or a strip of ointment, and we treated the rabbits either one or four hours after infection. Gentamicin was supplied by the manufacturer in a 3-mg/ml solution, a 40-mg/ml solution, a 3-mg/g ointment, and a 40-mg/g ointment. The dropper used in the study dispensed 26.7 drops/ml; thus, two drops of the 40-mg/ml solution contained 3 mg of gentamicin, whereas two drops of the 3-mg/ml solution contained 0.22 mg. Twenty strips of ointment, similar to strips used in therapy, had an average weight of 40 mg. Therefore, each 40-mg/g ointment strip contained about