five layers of stratified squamous epithelial cells, in the duct of an experimental animal seven to 10 cell layers were observed by 1 month of experimental treatment. In the basal layer of the epithelium, there were many mitotic cells, and in the superficial layer irregular shaped keratohyaline granules were evident in the cytoplasm (Fig. 3). The lumen of the duct was enlarged and was filled with keratinized cells. The orifice of the duct was also enlarged. Because of the variety of the pigment granules in the conjunctiva of the control monkeys, it was difficult to determine whether abnormal pigmentation had been induced. The retina and choroid of the experimental animals were morphologically similar to those of the control animals.

Discussion. Since the outbreak of PCB poisoning in humans, numerous experiments in small animals have been reported. However, none of the small animals has had findings similar to those observed in humans. In the monkey, Allen et al.[7] have reported a decrease in body weight, hair loss, swollen eyelids, purulent discharge from the eyes, acne, and hyperplasia of the gastric mucosa. Our study shows that the cause of the discharge from the eyes of PCB-intoxicated monkey is not hypersecretion of the Meibomian glands but rather hyperkeratinization of the epithelial cells of the duct. This explains the "sticky" nature of the discharge of the Yusho patients prior to visual loss. Ocular symptoms in Yusho patients appeared first; 2 or 3 months later, acneform eruptions and the pigmentation of the skin became evident.[4] Accordingly, the secretion of white, cheeselike material from the ducts of Meibomian glands when the eyelid is squeezed by fingers is the first clinical sign. A primary loss of Meibomian substance might result in a secondary keratinization.

It is generally held that a cyst of the human Meibomian gland follows obstruction of the duct and that the cystic contents differ from the keratin material filling an epidermal inclusion cyst.[8, 9] Therefore the keratic cyst of this gland may be considered one of the characteristic findings of PCB-intoxicated mammals. On the basis of our experiments, the photograph of the eyelid reported by McNulty and Griffin as "Possible polychlorinated biphenyl poisoning in rhesus monkey" does indeed identify the cause as PCB.[10]

We are grateful to members of a Study Group of Yusho.

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Key words: polychlorinated biphenyls, polychlorinated dibenzofuran, Meibomian gland, hyperkeratosis, squamous metaplasia

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Effect of iontophoretic and topical application of antiviral agents in treatment of experimental HSV-1 keratitis in rabbits.*

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Cathodal (−) iontophoresis of 9-β-D-arabinofuranosyladenine 5'-monophosphate (vidarabine monophosphate; Ara-AMP) was performed once daily for 3 days for the treatment of experimental herpes simplex virus type 1 (HSV-1) keratitis in rabbit eyes, and the therapeutic efficacy was compared with that of topical treatment of Ara-AMP and idoxuridine (IDU) administered five times daily for 4 days. With the treatment initiated 24 hr after viral inoculation, Ara-AMP cathodal iontophoresis resulted in significant suppression of epithelial and an-

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terior segment disease processes. Topical IDU (0.5%) or Ara-AMP (10%) also significantly improved the disease process when compared to the placebo-treated group; however, iontophoresis of Ara-AMP resulted in a more marked improvement. Slit-lamp examination indicated that iontophoresis did not cause any observable pathologic changes in corneal epithelium, stroma, conjunctiva, or iris of rabbit eyes. This experiment suggests that iontophoresis of Ara-AMP is a safe and effective approach for preventing the development of herpes simplex keratitis in rabbits.

Vidarabine monophosphate (9-β-D-arabinofuranosyladenine 5'-monophosphate; Ara-AMP) is an antiviral agent known to be useful in the treatment of herpes simplex keratitis,[1, 2] encephalitis,[3] and herpes genitalis[4] and cutaneous infections.[5] Ara-AMP has been shown to be metabolically stable[6] and more soluble than its related nucleoside, vidarabine (Ara-A).[2] However, topical Ara-AMP has been reported to cause toxic changes in regenerating corneal epithelium, ocular irritation, and a retardation of epithelial healing.[7] It was the purpose of this investigation to determine whether the iontophoresis of Ara-AMP once daily for 3 consecutive days would be efficacious in the treatment of herpes simplex keratitis in rabbit eyes while potentially reducing its untoward side effects.

Materials and methods. The unscarified corneas of New Zealand albino rabbits were inoculated with 2 drops of herpes simplex virus, type 1 (HSV-1), McKrae strain (10^7 pfu/ml), and the closed eyes were gently massaged for 1 min; both eyes were infected. All animals developed gross clinical disease by the third day following inoculation in a preliminary experiment.

Rabbits were randomly assigned to five treatment groups: (1) topical application of placebo gel; (2) topical application of 0.5% idoxuridine (IDU); (3) topical application of 10% Ara-AMP gel; (4) cathodal iontophoresis of 3.4% (0.1M) Ara-AMP solution; and (5) cathodal iontophoresis of 0.9% NaCl. Both eyes of each rabbit were given the same treatment. Topical applications were carried out five times daily for 4 consecutive days. All treatments were initiated 24 hr after virus inoculation. Iontophoresis was performed once daily for 3 consecutive days, with the Medtherm Electro-Medicator, Model AE1 (Medtherm Corp., Huntsville, Ala.) used as a direct current iontophoressor. Under anesthesia with xylazine (4 mg/kg, i.m.) and ketamine (20 mg/kg, i.m.), an eyecup was inserted with its periphery within the limits of the corneal limbus of the rabbit eye. A 1 ml quantity of 3.4% (0.1M) Ara-AMP solution was then added into the eyecup. The anode (+) was attached to a shaved forelimb, and the cathode (−) made a wet contact with the antiviral solution through a cotton wick. Current was applied at 0.5 mamp (electromotive force ≃ 5 volts) for 4 min.

Table I. Rate of complete suppression of keratitis establishment

*Treatment**	*Eyes inoculated*	*Eyes with keratitis*	*Rate of complete suppression (%)*
Placebo, topical	20	20	0
IDU, topical	20	20	0
Ara-AMP, topical	20	20	0
NaCl, iontophoresis	10	10	0
Ara-AMP, iontophoresis	20	9	55

*Treatments were initiated 24 hr after virus inoculation.

The rabbit eyes were observed once daily with a slit lamp using fluorescein stain and scored as follows.[8] Corneal epithelial scoring utilized 0 = no stain, 1+ = 25% surface ulceration, up to 4+ = 100% staining. Stromal scoring of 1+ represented mild edema, whereas 4+ represented severe edema. Iris scoring of 1+ represented mild hyperemia, and 4+ a fibrinous anterior chamber reaction. Conjunctival scoring of 1+ represented mild hyperemia, and 4+ severe hyperemia and edema. The clinical scoring was not done in a masked fashion.

Results. Table I shows the rate of complete inhibition of viral keratitis following the various treatments. In the IDU and Ara-AMP topical application groups after 4 days of treatment, the lesion worsened rapidly, eventually developing into severe keratitis. However, in the Ara-AMP iontophoresis group (in which treatment was stopped after 3 days), 55% showed no lesion development throughout the experimental period.

Fig. 1. shows the effect of different treatment regimens on the course of epithelial keratitis. The herpetic epithelial keratitis of the placebo-treated infection group reached its maximum about 1 week after infection and then showed a gradual resolution of ulceration. IDU had a suppressive effect on the development of epithelial keratitis which was superior as compared to the placebo control group. However, after cessation of treatment, a rebound phenomenon was observed. Topical application of Ara-AMP also resulted in the suppression of keratitis development but severely

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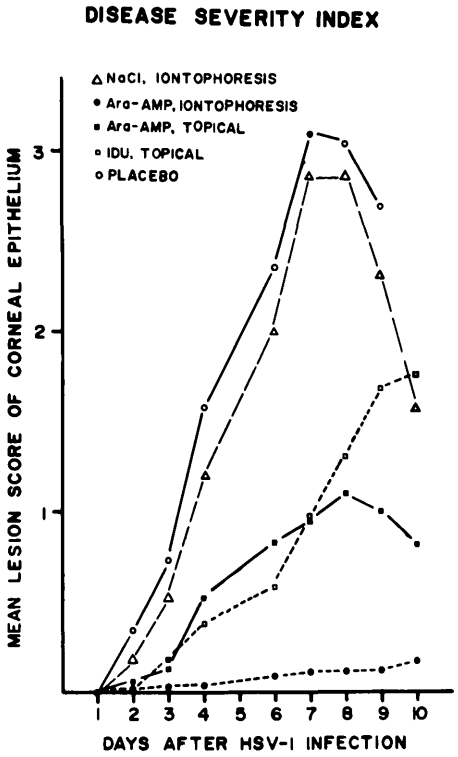

Fig. 1. Effects of Ara-AMP iontophoresis and topical application of Ara-AMP and IDU on the course of corneal epithelial disease development. Each point represents the *mean* lesion score of epithelial keratitis in each treatment group on the day indicated.

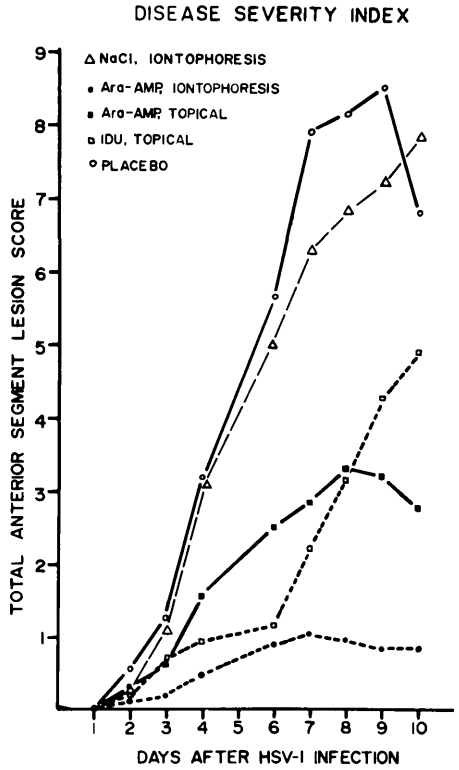

Fig. 2. Effects of Ara-AMP iontophoresis and topical application of Ara-AMP and IDU on the severity of anterior segment disease in rabbit eyes. Each point represents the sum of the averages of lesion scores for epithelial keratitis, stromal keratitis, conjunctivitis, and iritis on the day indicated.

irritated the rabbit eyes. Ara-AMP iontophoresis resulted in a marked suppression of lesion development, showing this treatment to be superior in comparison to IDU or Ara-AMP topical application ($p < 0.05$).

Fig. 2 summarizes the total anterior segment scores, i.e., the sum of the average lesion scores of corneal epithelium, stroma, conjunctiva, and iris. The total lesion score of the eyes treated by Ara-AMP iontophoresis did not go over 1.0. Table II shows a statistical analysis of the total anterior segment scores. Iontophoresis of Ara-AMP was significantly more effective than topical application of Ara-AMP or IDU in suppressing lesion development.

Iontophoresis of NaCl into infected eyes as a control (Figs. 1 and 2) did not show any difference in disease course from the placebo-treated infection group. This indicated that the amount of electrical current used had no observable effect on the infectious-inflammatory process in eye tissues.

Discussion. Iontophoresis is a simple, safe, well-documented method of assuring penetration of charged chemicals through surface tissues, which has been used to increase drug penetration.[5, 9–15] IDU and Ara-AMP were effective at similar inhibitory concentrations in vitro against HSV-1 McKrae strain (data not shown). The high rate of complete suppression of keratitis establishment (Table I) and low lesion score (Fig. 1) in the cathodal iontophoresis Ara-AMP group compared to IDU and Ara-AMP topical groups suggest that a therapeutic amount of drug was delivered and reduced the severity of the disease in the acute stages. These data are consistent with the expected results from the pharmacokinetic study of Ara-AMP iontophoresis[12]; that is at 60 min after application, the ratio of Ara-AMP concentration for cathodal iontophoresis compared to topical application was cornea 12.2, aqueous humor 17.5, and iris 2.5. Extremely low total anterior segment lesion scores (less than 1.0) in the iontophoresis

Table II. Comparison of different treatments for herpetic eye infections

	Total anterior segment score					*Significance*		
Day after infection	*Placebo* topical*	*Ara-AMP* iontophoresis*	*Ara-AMP* topical*	*IDU* topical*	*NaCl† iontophoresis*	*Ara-AMP (I) vs. IDU (T)*	*Ara-AMP (I) vs. Ara-AMP (T)*	*Placebo vs. IDU (T)*
1 (24 hr)	0	0	0	0	0			
2	0.55	0.11	0.31	0.16	0.20	$p < 0.01$	$p < 0.1$	$p < 0.1$
3	1.24	0.18	0.63	0.68	1.10	$p < 0.05$	$p < 0.01$	$p < 0.1$
4	3.18	0.44	1.60	0.93	3.10	$p < 0.05$	$p < 0.001$	$p < 0.01$
6	5.66	0.89	2.48	1.29	5.00	N.S.	$p < 0.01$	$p < 0.001$
7	7.90	1.01	2.85	2.21	6.30	$p < 0.05$	$p < 0.001$	$p < 0.001$
8	8.15	0.96	3.30	3.16	6.80	$p < 0.001$	$p < 0.001$	$p < 0.001$
9	8.50	0.82	3.20	4.29	7.24	$p < 0.001$	$p < 0.01$	N.S.
10	6.68	0.84	2.77	4.92	7.83	$p < 0.001$	$p < 0.01$	N.S.

I = iontophoresis; T = topical.
* Each group consists of 20 eyes.
† Group consists of 10 eyes.
Student t test was performed for the statistical analysis; NS = not significant.

group seem to indicate that iontophoretic application can restrain, to a certain extent, the spread of virus into deeper eye tissues and reduce the severity of ocular inflammation.

In a supplementary study, three groups of uninfected rabbit eyes (group I, topical application of Ara-AMP; group II, iontophoresis of Ara-AMP; group III, iontophoresis of NaCl) were observed by slit-lamp examination following fluorescein staining immediately and 24 hr after application under the same conditions as the experimental groups for 3 consecutive days. All eyes had varying numbers of punctate corneal erosions immediately after the topical or iontophoretic application of Ara-AMP and NaCl, but within 24 hr there were no observable differences from untreated rabbits. Scanning electron micrographs of corneal epithelium immediately after topical and iontophoretic application of Ara-AMP showed a very small amount of epithelial pitting with limited exposure to cells underlying the superficial epithelium.[12] These were equal to or less than those seen with the topical application of widely used preservatives in ophthalmic preparations.

Ara-AMP gel (10% aqueous base), Ara-AMP powder, and placebo (aqueous base) were obtained through the courtesy of Drs. T. Petrick and R. Buchanan, Warner-Lambert/Parke-Davis Pharmaceutical Research Laboratories, Ann Arbor, Mich. HSV-1, McKrae strain, was obtained through the courtesy of Dr. D. Pavan-Langston, Harvard Medical School, Boston, Mass.

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Supported in part by grant from NIDR-DE-04917 (J.M.H. and L.P.G.). Submitted for publication March 26, 1979. Reprint requests: Dr. James M. Hill, Department of Cell and Molecular Biology, Medical College of Georgia, Augusta, Ga. 30901. *Contribution No. 0523.

Key words: iontophoresis, herpes, cornea, keratitis, Ara-AMP, vidarabine monophosphate

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Improved electrode for electroretinography.

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Corneal electrodes useful for clinical electroretinography require topical anesthesia, interfere with vision, can abrade, and are not well accepted by most children and many adults. A low mass conductive thread, corneal (DTL) electrode is described and comparatively tested against the Burian-Allen electrode. The DTL electrode was found to have few of the limitations of the hard contact lens electrode. Furthermore, the DTL electrode signal quality was comparable to that of the Burian-Allen electrode and provided less between-patient variability.

The clinical value of electroretinography has been described by Krill[1] and Fishman.[2] Both writers report the use of the Burian-Allen corneal electrode, which is widely accepted in the United States and is discussed, along with several other electrode types, in a recent review by Riggs.[3] Numerous other methods have been described in the literature. Signal variation with recording site of the noncorneal electrode, described first by Armington and Tepas,[4] has been analyzed by Giltrow-Tyler et al.[5] A particularly interesting and stable electrode which is usable with DC potentials was first described by Knave et al.[6] and has figured in several publications on the low-frequency components of eye potential changes since that time. Patient comfort is improved where lid "hook" electrodes are used, but electroretinogram (ERG) amplitudes were consistently reduced relative to a corneal electrode.[7]

Many of the problems associated with the Burian-Allen electrode have been solved in our clinic since we began using soft contact lens cushions between the cornea and the standard Burian-Allen lens.[8] However, even this modification requires corneal anesthesia and results in an occasional corneal or conjunctival abrasion in agitated patients with exaggerated eye movements. We also find that corneal electrodes like the Burian-Allen are poorly accepted by children. This paper describes our experience with a new electrode which measures electrical potentials from the cornea and which appears to have few of the difficulties commonly associated with clinical use of contact lens electrodes.

Materials and methods. Our electrode (the DTL electrode) is based upon an extremely low mass conductive thread which makes contact between the tear film of the eye and an adjacent stranded, insulated electrical wire. The thread consists of a 2 cm length of spun nylon fibers impregnated with metallic silver by a proprietary method. The individual fibers are 12 μm in diameter, and the spun thread consists of three to six fibers. The fibers are manufactured under the trade name X-Static by Rohm & Haas Co. of Philadelphia, Pa. A practical DTL corneal electrode is pictured in Fig. 1. The loosely spun conductive fibers were woven between the spread strands of the tip of a piece of 24-gauge copper electronic "hook-up" wire with vinyl insulation. After the conductive thread was woven into the strands, the joint was covered with a conductive epoxy and subsequently insulated with a fast drying epoxy. DC resistance of the DTL electrode thread is approximately 100 ohms/cm. At 1 to 2 cm from the thread-wire junction, a plastic support button was attached with epoxy to the vinyl insulation of the hookup wire. The remaining hookup wire was terminated in a connector which allowed the electrode to be attached to our usual ERG junction box, in place of a Burian-Allen electrode. We find that the DTL electrode may be autoclaved or gas-sterilized without resistance change. Marked resistance changes do occur if the electrode is cleaned in alcohol.

For recording potentials, the DTL electrode support button is attached with adhesive to the skin near the outer canthus. The dry conductive thread is of such low mass that it floats in the air currents and must be "captured" before it can be placed upon the cornea. (We use a small plastic or

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