were put on and the lens left in place, the cornea thinned to its original base line measurements, and the vertical striae disappeared. When the hyperbaric oxygen was then removed and the lens left in place, the cornea gradually swelled again and vertical striae reappeared in about three hours. The right eye had no lens on (control) and did not swell or develop striae during the test period. Identical results occurred in the other two gel lens wearers.

Discussion. We have shown that vertical corneal striae can be produced experimentally by causing the cornea to become edematous. These lines have a similar appearance to the corneal striae occurring in pathological corneas and in gel lens wearers. As little as 6 per cent corneal edema can cause the striae and therefore they may serve as a useful indicator of early disturbances in normal corneal physiology.

We have shown that the corneal striae accompanying gel lens wear are caused by corneal edema which is a result of atmospheric oxygen deprivation. The ability to reverse the striae with hyperbaric oxygen suggests that using lenses of higher oxygen permeability may make it possible to eliminate the corneal edema and vertical striae accompanying gel lens wear.

Corneal edema resulting from gel lens wear is often difficult to observe with the biomicroscope. However, vertical striae are easily seen and their appearance probably indicates the presence of 6 per cent or more of corneal edema. This edema may be unacceptable and thus the appearance of striae may prove a useful indicator of when the fit of the lens needs to be changed.

From the University of California School of Optometry, Berkeley, Calif. This study was supported in part by United States Public Health Service Grant EY00906-3 to R.B.M. Submitted for publication Dec. 15, 1975.

Key words: corneal thickness, vertical striae, hyperbaric oxygen, gel lens.

REFERENCES

Teratogenicity of adenine arabinoside (Ara-A). ANTONIO R. GASSET AND TAKASHI AKABOSHI.

The potentially teratogenic effect of antiviral drugs, particularly when given systemically, prompted the evaluation of the teratogenic effect of Ara-A when given systemically in doses significantly higher than those used clinically. Under the conditions of this study, neither teratogenic nor embryocidal effects of Ara-A were observed.

The fact that ophthalmic medication can produce teratogenic effects when given topically to the eye in doses equivalent to those used clinically has been previously demonstrated by us. In this report, nonradioactive IDU (5-iodo-2-deoxyuridine), while not teratogenic to rats, was found to produce fetal malformations in rabbits when administered topically to the eye in clinically equivalent doses, 2 drops of 0.1 per cent solution four times a day for 12 days, to pregnant rabbits. These malformations included exothalmos-like appearance and clubbing of the forelimbs.

In contrast, F 3 TDR (trifluorothymidine), another antiherpetic agent currently under investigation but not available for general use, was found not to be teratogenic to rabbits.

The purpose of this study is to evaluate the potential teratogenic effect of adenine arabinoside (Ara-A) when given systemically in doses equivalent to those used clinically. In addition to the evaluation of gross external malformations, serial histologic sectioning and bone-staining studies were done.

Materials and Methods. Ten female adult albino rabbits were each mated twice with the same male. Day of conception was determined by the presence of sperm on vaginal smear. Each pregnant rabbit received a total amount of 20 mg. per kilogram, or 6.15 mg. per rabbit per day, from day 6 to day 18 of gestation. All rabbits were killed on day 29 of gestation; the fetuses were removed by cesarean section and examined for external malformations, then killed by immersion in formaldehyde and alcohol solution. In addition, serial histologic sectioning and skeletal examination with alizarin red S were done in all cases, whether or not malformations were suspected.

Results. The effects of the intraperitoneal injection of 20 mg. per kilogram per rabbit, divided into 6.15 mg. per rabbit per day, from day 6 to 18 of pregnancy in 10 rabbits are summarized in Table I. As can be seen in this table, neither teratogenic nor embryocidal effects of Ara-A were observed. Furthermore, examination of the fetuses by a skeletal staining with alizarin red S revealed
Fig. 1. A comparison of the normal skeletal examination (A) vs. a short rib found in rabbit number three (B) by staining with alizarin red.

Table 1. The effect of intraperitoneal injection of 20 mg. per kilogram per rabbit divided in 6.15 mg. doses per rabbit per day from day 16 to 18 of pregnancy of 10 pregnant rabbits

<table>
<thead>
<tr>
<th>Exp Rabbit No.</th>
<th>Maternal death</th>
<th>No. of fetuses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp. Rabbit No.</td>
<td>Weight (Kg.)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>4.30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3.80</td>
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<tr>
<td>3</td>
<td>3</td>
<td>3.85</td>
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<td>4</td>
<td>4</td>
<td>3.95</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3.95</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>4.40</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>4.50</td>
</tr>
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<td>8</td>
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</tr>
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<td>10</td>
<td>4.00</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>4.21</td>
</tr>
</tbody>
</table>

no malformations except for one short rib in one fetus from rabbit No. three (Fig. 1).

Discussion. Ara-A is a relatively new, very potent antiviral agent. It is metabolized primarily to the hypoxanthine arabinoside, a compound which is also an active antiviral agent. The therapeutic benefit of Ara-A is limited by its low solubility, so that topically it is not more active than IDU. Because of this low solubility and penetration, Ara-A was given systemically rather than topically. Animal studies indicate that it can be given subconjunctivally in effective antiviral doses with little toxicity. Also, effective systemic doses of Ara-A produced no hematologic toxicity and relatively few other systemic effects in animals. Due to the low solubility of this compound, the dose of 6.5 mg. per rabbit per day represents the maximum amount that could be given to the pregnant rabbits.

Under the conditions of this study, such as dose of drug, duration of exposure, volume and method of injection, neither teratogenic nor embryocidal effects of Ara-A were observed.

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Residual pilocarpine effects on outflow facility after ciliary muscle disinsertion in the cynomolgus monkey. Paul L. Kaufman and Ernst H. Bárány.

Outflow facility responses to pilocarpine were determined in ten cynomolgus monkey eyes after disinsertion of the ciliary muscle from the scleral spur. The effect of a large intravenous dose given on one occasion was compared to the effect of intense topical treatment for 18 to 24 hours on another occasion. The effect of the two modes of treatment differed from eye to eye, but were similar in the individual eye. In some eyes facility rose while in others it fell. The average effect of both treatments was very small.

The acute outflow facility-increasing effect of pilocarpine in the monkey eye is mediated essentially in total by ciliary muscle contraction. However, it has been suspected that there may be a second, slower developing, presumably endothelial, point of attack on facility.

In cynomolgus monkeys, the acute pilocarpine effect is almost completely abolished by surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur. We have treated such eyes intensely with topical pilocarpine for 18 to 24 hours before facility measurement to search for a slow effect.

Materials and methods. Ten cynomolgus monkeys (Macaca fasciculata) which had undergone unilateral ciliary muscle disinsertion and retrodisplacement were studied.

Acute pilocarpine experiments. The acute effects of intravenous and intracameral pilocarpine on gross outflow facility were determined, following a small systemic dose of atropine, by twollevel constant-pressure perfusion. The drug sequence and dosages were: intramuscular atropine sulfate 0.05 mg per kilogram; intravenous pilocarpine-HCl 2.0 mg per kilogram; intracameral pilocarpine-HCl 20 μg.

Subacute pilocarpine experiments. After several intervening perfusions, spaced approximately five to seven weeks apart, the animal was anesthetized with intramuscular CL-744 (Parke-Davis, Detroit, Mich.) 5 to 10 mg per kilogram, placed supine on a table, and a lid speculum inserted. Pilocarpine-HCl, 1.0 to 1.6 mg, was applied to the central cornea of the "disinserted" eye as one or several 2 μl drops. Where more than one drop was given the drops were separated by at least two minutes. The speculum was left in place for at least five minutes after the last drop. This procedure was repeated every six to eight hours over an 18- to 24-hour period. (The pilocarpine doses used are several times supramaximal in terms of accommodation in iridectomized cynomolgus and cause intense miosis lasting for more than eight hours in normal cynomolgus.) Facility was then determined approximately one hour after the last pilocarpine dose, four to six values being obtained over about 25 to 40 minutes. The average baseline facility of two to four previous perfusions, excluding the acute pilocarpine experiment, was taken as baseline.

Effect of perfusion. Thirteen "disinserted" eyes, three of which were in the above group, underwent acute pilocarpine testing as described. At a later date, they were perfused again without prior systemic administration of atropine. After baseline facilities were measured, 10 μl of mock aqueous humor was injected into the inflow tubing in the same manner as the pilocarpine solution. Five minutes later the chamber contents were mixed by blowing cold air on the cornea.

REFERENCES