

FLUOROURACIL THERAPY FOR PROLIFERATIVE VITREORETINOPATHY AFTER VITRECTOMY

WALTER H. STERN, M.D., AND GEOFFREY P. LEWIS, B.A.

San Francisco, California

PAGE A. ERICKSON, B.A.

Santa Barbara, California

CHRISTOPHER J. GUERIN, B.S.

San Francisco, California

DON H. ANDERSON, PH.D., AND STEVEN K. FISHER, PH.D.

Santa Barbara, California

AND

JAMES J. O'DONNELL, M.D.

San Francisco, California

Fluorouracil effectively inhibits epiretinal membrane formation and traction retinal detachment after vitrectomy surgery. When 0.5 mg of fluorouracil was administered intraocularly every 24 hours for seven days, traction retinal detachment two weeks after the intraocular injection of 200,000 cultured retinal pigment epithelial cells occurred in 12 of 12 control eyes but in only six of 14 eyes treated with fluorouracil ($P < .001$). Four weeks after cell injection, eight of 12 eyes treated with fluorouracil had traction retinal detachments whereas 12 of 12 control eyes did ($P < .001$). The height of the traction retinal detachment four weeks after intraocular injection of 200,000 cultured retinal pigment epithelial cells was reduced 50% in eyes treated with 0.5 mg of fluorouracil every 24 hours for seven days compared to control eyes ($P < .001$).

When the number of injected retinal pigment epithelial cells was increased to 400,000 cells and 1.25 mg of fluorouracil was administered intraocularly every 24 hours for seven days, traction retinal detachment two weeks after injection occurred in 15 of 15 eyes in the control group but in none of ten eyes in the treated group. Four weeks after cell injection, eight of eight eyes in the control group and five of five eyes in the fluorouracil-treated group had detachments and the mean height of the detachments in the two groups was equal.

Autoradiography of the epiretinal membranes in eyes injected with

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From the Department of Ophthalmology, University of California, San Francisco, and the Veterans Administration Medical Center, San Francisco, California (Drs. Stern and O'Donnell, Mr. Lewis, and Mr. Guerin); and the Department of Biological Sciences, University of California, Santa Barbara, Santa Barbara, California (Drs. Anderson and Fisher and

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Reprint requests to Walter H. Stern, M.D., 4150 Clement St., San Francisco, CA 94121.

200,000 cultured retinal pigment epithelial cells and labeled for two hours with tritiated thymidine showed that 0.8% of the epiretinal cell nuclei were labeled two weeks after cell injection but that no labeled cells were present in the fluorouracil-treated eyes. Tritiated thymidine labeling of epiretinal cells in the fluorouracil-treated eyes was first noted three weeks after the cell injection. The presence of tritiated thymidine labeling in the fluorouracil-treated eyes correlated with an increase in the number of epiretinal cells and an increase in the incidence of traction retinal detachment.

Continued epiretinal membrane formation after vitrectomy surgery for proliferative vitreoretinopathy is a problem for which there is as yet no satisfactory solution. We previously described an experimental model of epiretinal membrane formation in the aphakic rabbit eye undergoing vitrectomy and subsequent injection of tissue-cultured retinal pigment epithelial cells.¹ In this model, the growth of cells on the inner retinal surface results in a funnel-shaped traction retinal detachment of the medullary rays. We used this model to determine the efficacy of fluorouracil as an inhibitor of epiretinal membrane growth and traction retinal detachment so that we could extrapolate the results to the clinical treatment of proliferative vitreoretinopathy.

MATERIAL AND METHODS

The methods, except for the drug injection schedule, were those previously described¹ and thus require only a brief summary.

Animals—We used New Zealand albino rabbits, 2.5 to 3.5 kg each in weight. The data for this report were derived from 50 eyes obtained from male and female rabbits. The animals were killed at various times to provide histologic data and, therefore, in the later weeks of the study the control and the fluorouracil-treated groups contained fewer eyes.

Retinal pigment epithelium tissue culture—We used albino rabbits of the inbred B-J strain to provide a uniform

source of tissue-cultured retinal pigment epithelial cells. We grew retinal pigment epithelium as a monolayer cell culture in minimal essential medium with 10% fetal calf serum in a 37 C, 5% carbon dioxide incubator. We passed the culture serially and expanded the colony with additional flasks. For these experiments we used cells in passages two through five.

We harvested cells from confluent cell flasks and adjusted the volume of injected cells for each experiment; these ranged from 0.1 to 0.25 ml so that the desired number of cells was injected in each experiment. A trypan blue test indicated that 98% of the cells were viable just before injection (measured by exclusion of dye from the cells).

Surgical technique—We sedated the animals with intramuscularly administered ketamine HCl (20 mg/kg of body weight) and xylazine HCl (2 mg/kg of body weight), and used 0.3 ml of intramuscularly administered atropine to reduce bronchial secretions. We inserted an intravenous line and maintained anesthesia with sodium pentobarbital (25 mg/ml) administered as needed. We dilated the pupils with 10% phenylephrine, 1% cyclopentolate, and 1% atropine.

We performed a pars plana lensectomy and vitrectomy as previously described.¹ At least two weeks after lens extraction and vitrectomy, we examined the fundi by indirect ophthalmoscopy and if we found no retinal detachment or other

abnormality, we injected the eyes with the cultured cells.

Injection of retinal pigment epithelial cells—Immediately after harvesting the retinal pigment epithelial cells from the tissue-culture flasks, we sedated the animals and performed a fluid-gas exchange with a 50% sulfur hexafluoride-air mixture as previously described. The animals were divided into two groups. In Group 1, we injected 200,000 cultured retinal pigment epithelial cells. In Group 2, we injected 400,000 cultured retinal pigment epithelial cells in phosphate-buffered saline. The animals were kept sedated and on their sides for two hours before we began injecting fluorouracil.

Drug injection—In Group 1 (200,000 cells), we injected 0.5 mg of fluorouracil in a volume of 0.05 ml of balanced salt solution two hours after cell injection. The drug was injected through the clear cornea into the gas-filled eye with a tuberculin syringe with a 30-gauge needle. We administered 0.5 mg of fluorouracil every 24 hours for the next six days for a total of seven injections of fluorouracil and a total of 3.5 mg of intraocular fluorouracil.

In Group 2 (400,000 cells), we injected 1.25 mg of fluorouracil in 0.05 ml of balanced salt solution beginning two hours after cell injection and every 24 hours thereafter for six consecutive days, for a total of seven intraocular injections and a total intraocular dosage of 8.75 mg of fluorouracil.

After the initial intraocular fluorouracil injection, we performed the later intraocular injections with a similar technique. We sedated the rabbits and slowly injected the fluorouracil through the clear cornea into the gas- or fluid-filled eye. The sulfur hexafluoride-air mixture was usually completely absorbed after seven days.

Twelve control eyes in Group 1 and 15 control eyes in Group 2 that had undergone lensectomy, vitrectomy, and the

injection of either 200,000 or 400,000 cells were injected with 0.05 ml of balanced salt solution instead of fluorouracil. The intraocular injection schedule and the technique were unchanged. Each repetition of the experiment was done with a single batch of cultured cells divided among two control and two treated eyes.

Clinical evaluation—The eyes were examined periodically by indirect ophthalmoscopy and retinal drawings were made. We described the detachment height by noting the degree of elevation of the medullary rays. We graded the elevation of the medullary rays from 0 to 4 with 0 being no retinal detachment and 4 being a vertical funnel-shaped detachment. For analysis, the detachment height score represented the average of all the control eyes or all the fluorouracil-treated eyes at the different times studied.

Histologic examination—We enucleated eyes in both groups from one to four weeks after cell injection. Two hours before killing the animals, we injected 100 μ Ci of tritiated thymidine into the vitreous cavity of the gas- or fluid-filled eye. At the end of the incubation we enucleated the eyes, removed the corneas, and placed the eyes in a phosphate-buffered, 1% glutaraldehyde, 1% paraformaldehyde mixture (pH 7.1) overnight. The next morning, the specimens were rinsed in several changes of phosphate buffer for one hour. With a razor blade, we removed the remaining anterior segments just posterior to the iris and cut the specimen in half in a plane parallel to the medullary rays just below the optic nerve. This provided a cross section of the eye and permitted us to observe the extent of the detachment of the medullary rays of the retina. We then photographed the specimens.

The tissue was postfixed in 2% osmium tetroxide, washed in distilled water, de-

hydrated in a graded ethanol series, placed in propylene oxide, and then embedded in Araldite 6005. We studied the tissue sections by light and electron microscopy.

Autoradiography—We prepared light microscopic autoradiograms by dipping 1- μ m sections in a 1:1 solution of water and NTB-2 nuclear track emulsion (Eastman Kodak) maintained at 43 C and exposing them in light-tight boxes for about one week (at 6 C). Autoradiograms were stained with a methylene blue-azure II mixture and counterstained with basic fuchsin.

We determined the percentage of tritiated thymidine-labeled epiretinal pigment epithelial nuclei from two days to four weeks after cell injection by counting the number of labeled vs unlabeled epiretinal cells resembling myofibroblasts. The number of cells counted in each eye ranged from 470 to 820. These counts were made from at least four nonoverlapping sections of the epiretinal cells.

RESULTS

Clinical findings and gross anatomy—All 12 control eyes in Group 1 developed traction retinal detachments after one week (Fig. 1). In contrast, there were no detachments after one week in 14 Group 1 eyes treated with fluorouracil. Two weeks after cell injection, six of 14 treated eyes in Group 1 had developed traction retinal detachments; by four weeks, eight of 12 treated eyes had developed traction retinal detachments. There was a significant difference ($P < .001$ determined by the Newman-Keuls specific comparison test) between the detachment rates of the control and the treated eyes during the four-week trial.

The detachment height of the control and fluorouracil-treated eyes in Group 1 differed significantly. The control eyes after one week showed an average de-

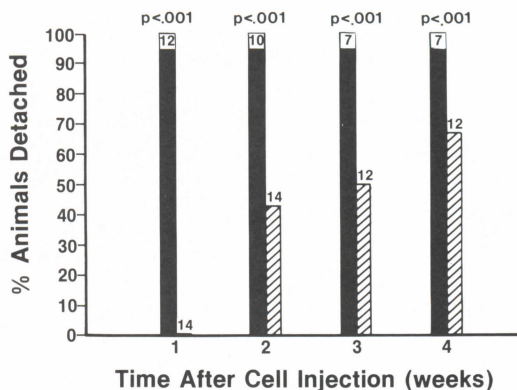


Fig. 1 (Stern and associates). Group 1. Cumulative frequency of traction retinal detachment after injection of 200,000 cultured retinal pigment epithelial cells is significantly decreased as much as four weeks after intraocular injection of 0.5 mg of fluorouracil every 24 hours for seven days. Solid bars, control eyes; diagonally lined bars, fluorouracil-treated eyes.

tachment height score of 2.25 vs a detachment height score of 0 in the treated eyes (Fig. 2). By three weeks, control eyes had reached a maximum detachment height score of 4.0 vs 1.7 in fluorouracil-treated eyes. After four weeks, the detachment

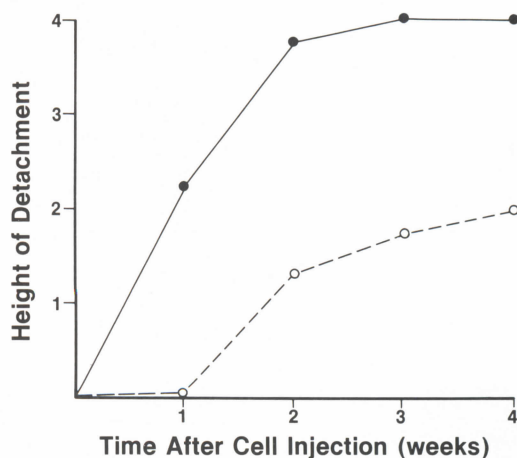


Fig. 2 (Stern and associates). Group 1. Height of retinal detachment after injection of 200,000 cultured retinal pigment epithelial cells is decreased by 50% four weeks after intraocular injection of 0.5 mg of fluorouracil every 24 hours for seven days ($P < .001$). Solid circles, control eyes; open circles, fluorouracil-treated eyes.

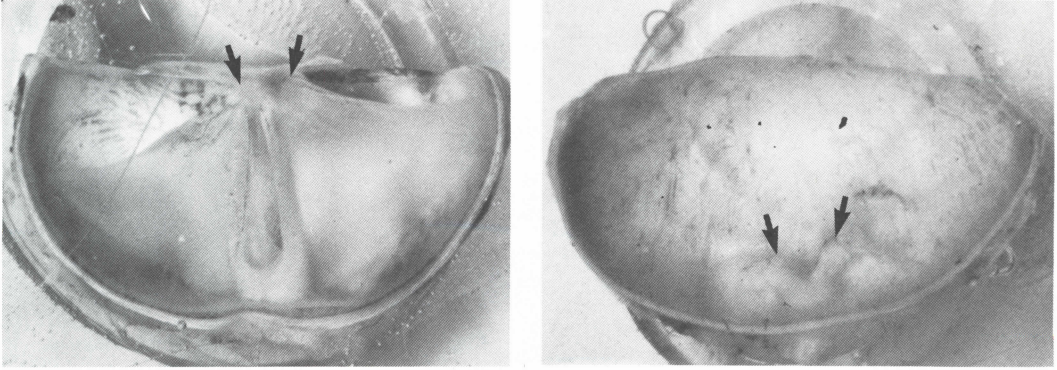


Fig. 3 (Stern and associates). Group 1. Gross specimens illustrating traction detachment of the nerve fiber bundles (arrows) four weeks after injection of 200,000 cultured retinal pigment epithelial cells in a control eye (left) and an eye treated with 0.5 mg of fluorouracil every 24 hours for seven days (right).

height score of the treated eyes was one-half that of the controls ($P < .001$) (Figs. 2 and 3).

All 15 control eyes in Group 2 developed traction retinal detachments after one week (Fig. 4). There were no traction retinal detachments after two weeks in the ten Group 2 eyes treated with fluorouracil. Three weeks after cell injection, eight of nine treated eyes in Group 2 had developed traction retinal detachments;

this increased to five of five treated eyes four weeks after cell injection.

The detachment height in the control and fluorouracil-treated eyes in Group 2 differed significantly (Fig. 5). Control eyes at two weeks showed a maximum detachment height score of 4.0 vs a 0 detachment height score for fluorouracil-treated eyes ($P < .001$). After three weeks, the detachment height score in the

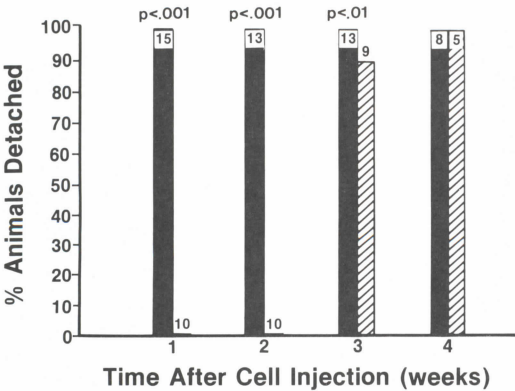


Fig. 4 (Stern and associates). Group 2. Cumulative frequency of traction retinal detachments after injection of 400,000 cultured retinal pigment epithelial cells is significantly decreased for two weeks by the intraocular injection of 1.25 mg of fluorouracil every 24 hours for seven days. Solid bars, control eyes; diagonally lined bars, fluorouracil-treated eyes.

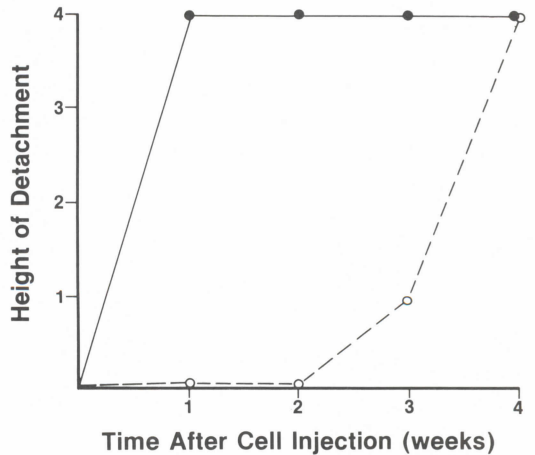


Fig. 5 (Stern and associates). Group 2. Height of retinal detachment four weeks after intraocular injection of 400,000 cultured retinal pigment epithelial cells is similar in control eyes (solid circles) and in eyes treated with 1.25 mg of fluorouracil every 24 hours for seven days (open circles).

fluorouracil-treated eyes had increased to 0.9 and after four weeks it further increased to 4.0, equal to that of the control eyes.

Histologic findings—Injection of cultured retinal pigment epithelial cells onto the retinal surface resulted in a multilayered epiretinal membrane composed of spindle-shaped cells (Fig. 6). The cells possessed all of the ultrastructural features of myofibroblasts including indented nuclei, extensive rough endoplasmic reticulum, prominent Golgi complexes, microfilament bundles with densifications, basal laminae, adherens junctions, and hemidesmosomes. The only difference in the histologic patterns of Group 1 (200,000 cells) and Group 2 (400,000 cells) eyes one week after cell injection was the presence of more cells in Group 2 eyes. Intraocular injection of fluorouracil in eyes containing epiretinal membranes resulted in a dramatic decrease in the number of epiretinal cells throughout the four-week study in both groups of eyes (Figs. 7 and 8). The epiretinal cells in the fluorouracil-treated eyes in Groups 1 and 2 had one or more of the following ultrastructural characteristics: distended nuclear envelope endoplasmic reticulum, distended mitochondria, ruptured plasma membranes, autophagic vacuoles, multivesicular bodies, and electron-

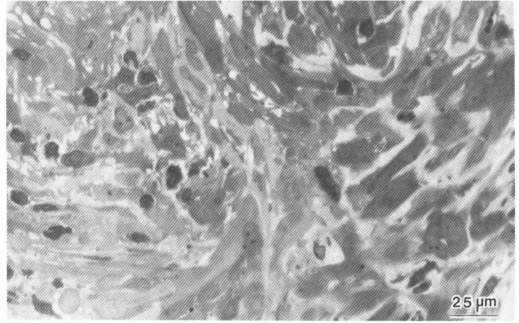


Fig. 6 (Stern and associates). Light microscopy shows a typical area of epiretinal membrane 14 days after injection of 200,000 cultured retinal pigment epithelial cells ($\times 530$).

dense inclusions. Additionally, many epiretinal cells were lacking one or more of the following: ribosomes, microfilaments, basal lamina, adherens junctions, and hemidesmosomes (Fig. 9).

Autoradiographic findings—We determined the percentage of epiretinal pigment epithelial cell nuclei labeled with tritiated thymidine in Group 1 control eyes at seven different times after the injection of the cultured cells (Fig. 10). From a peak of 23.6% labeled cells at two days, there was a sharp decline in the percentage of labeled cells so that at four weeks 3.2% of the cells were labeled.

We determined the percentage of cells labeled with tritiated thymidine at two weeks, three weeks, and four weeks in

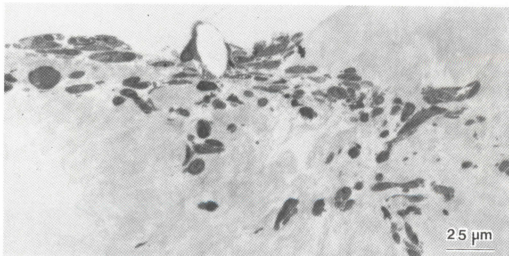


Fig. 7 (Stern and associates). Light microscopy shows the largest grouping of epiretinal membrane cells 14 days after injection of 200,000 cultured retinal pigment epithelial cells and fluorouracil therapy (0.5 mg of fluorouracil every 24 hours for the first seven days) ($\times 530$).

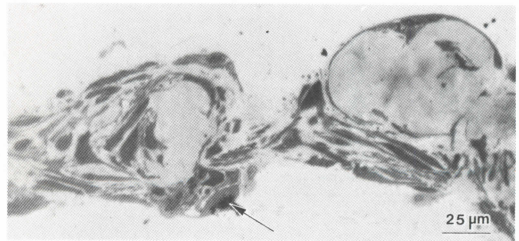


Fig. 8 (Stern and associates). Light microscope autoradiogram of an epiretinal membrane 28 days after injection of 200,000 cultured retinal pigment epithelial cells and fluorouracil therapy (0.5 mg of fluorouracil every 24 hours for the first seven days). The arrow points to a cell nucleus labeled with tritiated thymidine ($\times 530$).

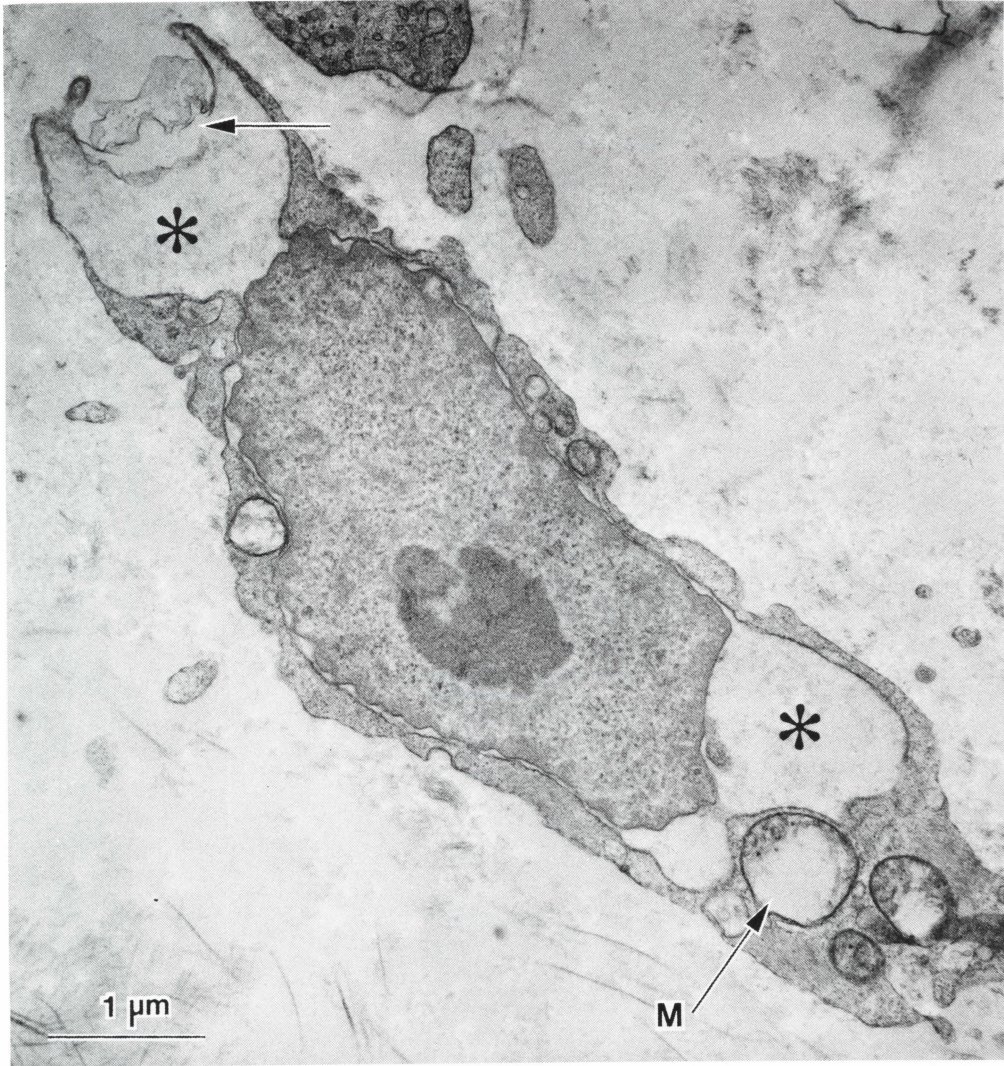


Fig. 9 (Stern and associates). Electron microscopy shows a cultured retinal pigment epithelial cell 14 days after intraocular injection and fluorouracil therapy (0.5 mg of fluorouracil every 24 hours for the first seven days). The asterisks indicate a distended nuclear envelope and endoplasmic reticulum; the arrows indicate ruptured plasma membranes. Ribosomes are absent from this cell and the mitochondria (M) are distended ($\times 20,000$).

the eyes in Group 1 treated with fluorouracil. Before two weeks, fluorouracil-treated eyes contained insufficient epiretinal cells to perform quantitative autoradiography. Two weeks after cell injection, no labeled cells were present in the epiretinal membrane, at three weeks 4.8% of the cells were labeled, and at four

weeks 0.94% of the epiretinal cells were labeled.

DISCUSSION

Retinal detachment complicated by proliferative vitreoretinopathy remains a significant problem because of the development of contractile membranes that

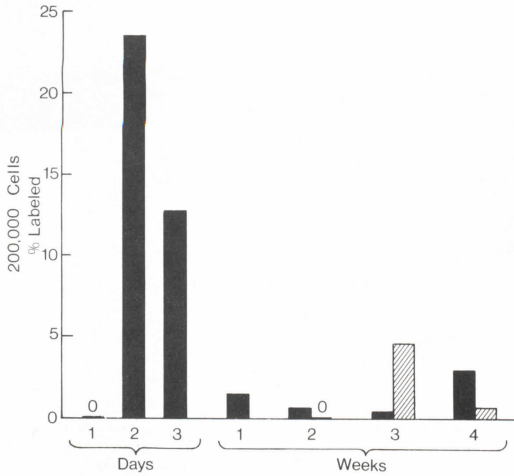


Fig. 10 (Stern and associates). Histogram relating the percentage of epiretinal pigment epithelial cell nuclei labeled with tritiated thymidine to the time after injection of the cells onto the retina. Solid bars, untreated eyes; diagonally lined bars, eyes treated with 0.5 mg of fluorouracil every 24 hours for seven days. Before two weeks, fluorouracil-treated eyes contain insufficient epiretinal cells for quantitative autoradiography.

keep retinal breaks open, form new retinal breaks, and disrupt the adhesion between the sensory retina and retinal pigment epithelium.

Techniques developed to deal with intraocular cellular proliferation on tissue surfaces within the eye include scleral buckling,² pars plana vitrectomy,³ vitrectomy and epiretinal membrane dissection,⁴ and intraocular liquid silicone injection, either alone or combined with vitrectomy and membrane dissection.⁵ A recent review of surgical results in which vitrectomy, scleral buckling, and membrane dissection were used in the management of posterior penetrating injuries indicated that of the 35 eyes that could not be repaired surgically, 26 were lost because of intraocular cellular proliferation.⁶ Although silicone injection combined with pars plana vitrectomy increases the anatomic success rate in severe proliferative vitreoretinopathy to 57%,⁵ liquid silicone does not inhibit cellular

proliferation (noted by Fastenberg and associates⁷ and Stern and associates, unpublished data).

Because of the importance of vitrectomy surgery in removing traction on the retina, removing vitreous opacities, and providing access to the vitreous cavity and retina for a variety of surgical procedures, vitrectomy will continue to be the primary approach to the treatment of proliferative vitreoretinopathy. Nonetheless, additional methods are needed to prevent epiretinal membrane formation and contraction after vitreous surgery.

Recent studies have focused on pharmacologic techniques for inhibiting intraocular cellular proliferation. Tano and his associates⁸⁻¹⁰ demonstrated that intravitreal injections of dexamethasone and triamcinolone acetonide are capable of partially inhibiting experimental intravitreal fibroblast proliferation and subsequent traction retinal detachment in the rabbit eye with an intact vitreous. Weiss and Belkin¹¹ reported a significant reduction of intraocular cellular proliferation with the use of both intravitreal and systemic penicillamine after experimental penetrating injury.

We studied the effect of various drugs, including triamcinolone acetonide, penicillamine, methotrexate, and fluorouracil, on the formation of epiretinal membranes and traction retinal detachment in aphakic rabbit eyes that underwent vitrectomy surgery. Of these drugs, the most effective and least toxic drug to the eye was fluorouracil.¹²

In Group 1 eyes (200,000 cells), it was necessary to inject 0.5 mg of fluorouracil intraocularly every 24 hours for seven consecutive days in order to achieve a nontoxic, yet clinically significant effect.¹³ These doses differed significantly from that used in the rabbit eye with an intact vitreous and lens in which a single injection of 1 mg of fluorouracil exerts a significant effect on the production of traction

retinal detachments produced by 250,000 cultured fibroblasts.¹⁴ In this model, however, cells are inhibited from migrating freely by the intact vitreous and the half-life of the injected fluorouracil (as well as those of other drugs such as corticosteroids) is greatly extended by the intact vitreous and lens.^{15,16}

Fluorouracil acts by irreversibly binding with the enzyme thymidylate synthetase, thus interfering with DNA synthesis. The drug is most effective on rapidly proliferating cells.¹⁷ We have shown that cultured retinal pigment epithelial cells have an initial low rate of proliferation when placed in the eye; this rate then increases rapidly during the next 24 to 48 hours before tapering off to a continued low level of proliferation.^{1,13} Even at a borderline toxic dose of fluorouracil (0.5 mg daily for seven days), proliferation of the injected retinal pigment epithelial cells was not prevented completely four weeks after intraocular cell injection (shown by the increased number of cells present on the internal limiting membrane, by the presence of cells labeled with tritiated thymidine in epiretinal membranes, and by the increased rate of traction retinal detachment). Even cells that are not dividing are still capable of contracting.¹⁸ This may explain why it was more difficult to inhibit the formation of traction retinal detachment in eyes in Group 2 that received injections of 400,000 cells.

Nonetheless, fluorouracil may prove to be beneficial in the treatment of proliferative vitreoretinopathy for several reasons. By delaying the onset of proliferation, fluorouracil may allow an increasingly strong adhesion to develop between the sensory retina and the retinal pigment epithelium. Not all of the cells present on the retinal surface in eyes with proliferative vitreoretinopathy may possess the same ability to contract and proliferate in such a short time as cultured

cells transplanted onto the retinal surface in experimental eyes; therefore, fluorouracil at the presently used or lower intraocular concentration may prove to be an effective antiproliferative drug. Additionally, proliferative vitreoretinopathy clinically seems to be a self-limiting disease in which growth and contraction of epiretinal membranes apparently cease after several months. Fluorouracil may encourage the stable phase at a much earlier period. Also, fluorouracil has been used systemically to treat a variety of neoplasms. Its systemic side effects are well established,¹⁹ allowing accurate assessment of systemic toxicity that might result from its intraocular use. Our studies on the ocular toxicity of fluorouracil are available elsewhere.¹³ If fluorouracil finds a role in the treatment of proliferative vitreoretinopathy, it will probably be as part of a broad therapeutic regimen that includes scleral buckling, vitrectomy, the use of a temporary or permanent intraocular tamponade to assist in the management of retinal traction and open retinal breaks, and other anticontractile and antiproliferative drugs.

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