A PROSPECTIVE, RANDOMIZED STUDY OF 5-FLUOROURACIL AND FILTRATION SURGERY*

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INTRODUCTION

PRIOR STUDIES SUGGEST THAT GLAUCOMA PATIENTS WHO ARE APHAKIC, BLACK, OR young have a poorer prognosis following filtration surgery than the average patient.[1-6] In addition, those eyes with previous conjunctival surgery, inflammation, or neovascular glaucoma often do poorly.[7-11] Scarring of the conjunctiva and Tenon's capsule is the most common cause of failure of filtration. Theoretically, an agent that inhibits proliferation of fibroblasts following surgery might prevent excessive scarring and decrease the number of surgical failures. 5-Fluorouracil (5-FU), a pyrimidine analog which inhibits fibroblast proliferation in tissue culture, has recently been used for this purpose.[12]

Heuer et al[13,14] reported a success rate of 69% to 81% in poor prognosis patients undergoing filtration surgery when 5-FU was administered subconjunctivally in the postoperative period. Furthermore, the use of this agent in the laboratory has made it possible to achieve filtration in primates, a feat previously unobtainable.[15-17] However no control groups have been included in prior clinical studies and no effective dosage levels have been determined. Therefore, we undertook a randomized, prospective study comparing the use of small subconjunctival doses of 5-FU to no antimetabolite therapy in patients with a poor prognosis for filtration surgery.

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MATERIALS AND METHODS

PATIENT SELECTION

Between April 1984 and April 1986, 26 of 40 eligible patients were enrolled from the clinical practices of two of the authors (JMR and DBW). The remaining 14 patients, most of whom had undergone multiple procedures, refused randomization. Twelve additional patients were treated with 5-FU under this protocol after April 1986. The study protocol and consent forms were approved by the Investigational Review Board and Hospital Scientific Research Committee.

Patients eligible for this study included those with a prior failed filtration procedure, aphakia, prior conjunctival surgery, or inflammatory or neovascular glaucoma. We also included primary filtering procedures in black patients between the ages of 10 and 50 and in white patients between the ages of 10 and 40. Patients with no light perception, those unable to give informed consent, pregnant or nursing females, those unable to cooperate for subconjunctival injection or follow-up examination, or those who had received prior systemic or topical corticosteroid therapy were excluded from the study.

The average age of the control group (n = 12) was 50. Five patients were black, seven were white, nine were male, and three were female. In the 5-FU group (n = 14), the average age was 49. Six patients were black, eight were white, seven were male, and seven were female.

SURGICAL PROCEDURES

All filtration procedures, except one, were done with a limbus based flap to minimize leakage of aqueous humor from the surgical wound. Eighteen patients had posterior lip sclerectomies and eight had trabeculectomies. This percentage was similar in the experimental and control groups. Following the procedure, 2 mg of dexamethasone sodium phosphate were injected subconjunctivally. Topical atropine 1% and antibiotics were also given at the time of surgery. All patients received a similar topical medical regimen in the postoperative period. This included topical dexamethasone 0.1% solution or prednisone acetate 1% solution, dexamethasone ointment, atropine sulfate solution, and a topical antibiotic. Each physician maintained his typical routine of topical care and modified it when needed (ie, patching for corneal abrasion or shallow anterior chamber, increased steroid dosage for increased inflammation, etc).

PATIENT EVALUATION

At a minimum all patients were examined for the first 7 postoperative

days and at 14 to 16 days, 6 weeks, 3, 6, and 12 months. Patients' examinations included measuring for intraocular pressure (Goldmann applanation tonometry), anterior chamber depth, and morphology of the conjunctival bleb (flat, microcystic, or Tenon's cyst). The cornea and conjunctiva were stained with fluorescein to detect corneal abrasions and wound leaks. Humphrey or Goldmann visual fields were obtained preoperatively and postoperatively at 6 or 12 months if possible. The number of glaucoma medications used preoperatively and postoperatively was also recorded. Baseline preoperative intraocular pressures were obtained immediately prior to surgery. Postoperative intraocular pressures were recorded either on the date of failure (intraocular pressure > 21 mm Hg on maximum medication) or from 6 to 18 months postoperatively in the successful group. The anterior chamber was defined as follows: flat, if the cornea touched the lens, posterior capsule, intraocular lens, hyaloid or vitreous face; shallow, if there was peripheral contact between the iris and cornea; and formed, if the cornea was not touching the iris.

5-FLUOROURACIL INJECTIONS

Patients selected for treatment with 5-FU received 7 injections of 0.5 ml (5 mg) 5-FU prepared from the commercially available injection (Fluorouracil®, Roche, 50 mg/ml) diluted to 10 mg/ml with nonpreserved saline 0.9%, USP. Injections with a 30-gauge needle began postoperatively as soon as a water tight wound was established. Injections were given daily unless a wound leak occurred. In all uncomplicated cases the injections were completed by the ninth postoperative day. The site of injection, anesthetized by two drops of topical proparacaine 0.5%, was located at 90 to 180 degrees from the filtration bleb. The 5-FU was generally given as far into the fornix as possible. A follow-up injection was given during the second postoperative week.

STATISTICAL ANALYSIS

Preoperative and postoperative intraocular pressures were compared between the 5-FU group and the control group. Success rates were compared by life table analysis. Successful surgery was defined as intraocular pressure measurements that were consistently 21 mm Hg or less, regardless of whether the patient was taking glaucoma medication. We chose intraocular pressure measurements as the criterion of success because meaningful comparisons of visual fields could not be made. Comparison of preoperative and postoperative visual acuity, bleb morphology, and complication rates was also made. All comparisons were based on unpaired

t-tests and analysis of variance. Comparison by diagnostic category was not performed because of the small number of patients in each group.

RESULTS

Summaries of the patient data are listed in Tables I to III. Three patients in the control group had other factors that influenced their outcome. Patient 5 developed a cyclodialysis cleft with a resulting intraocular pressure of less than 5 mm Hg. Patient 6 had a bleb needling procedure of a Tenon's cyst during the second postoperative week. Patient 12 had a suprachoroidal hemorrhage with an intraocular pressure of greater than 50. The data from these patients is included in the analysis.

Mean preoperative intraocular pressure in the 5-FU group (n = 14) was 38.4 ± 3.08 mm Hg (standard error of the mean [SEM]), while the preoperative intraocular pressure in the control group (n = 12) was 41.2 ± 5.0 mm Hg ($P > 0.6$). Mean postoperative intraocular pressure at 6 to 18 months was 14.4 ± 1.4 mm Hg for the 5-FU group, and 30.7 ± 3.9 mm Hg for the control group ($P < 0.01$). These results are summarized in Fig 1. Using the level of intraocular pressure of 21 mm Hg or less as a criterion for success, we found that 25% (n = 3/12) of the control group had a successful outcome after 9 months; while in the same period 92% (n = 13/14) of the 5-FU group was well controlled. By 12 months, an additional 5-FU patient had failed, resulting in a cumulative survival rate of 74.3%. Fig 2 shows cumulative probability of success over time for the 5-FU and control groups. A pairwise comparison between the control and 5-FU group showed that the 5-FU patients maintained a higher success rate throughout the study ($P < 0.001$).

Visual acuity results were not significantly different between the two groups. In the control group, three patients lost significant vision: patient 5 had a retinal detachment from diabetic retinopathy, patient 6 developed a cataract, and patient 12 had a suprachoroidal hemorrhage. Patient 7 in the 5-FU treatment group had progressive visual loss due to severe diabetic retinopathy.

Bleb morphology was also compared (Fig 3). In the control group, 10 of 12 patients had flat blebs at 6 months. One of 12 had a Tenon's cyst, and 1 of 12 had a diffuse microcystic bleb. In the 5-FU group, 10 of 14 had diffuse microcystic blebs, 3 of 14 had a Tenon's cyst, and 1 of 14 had a flat bleb.

In addition, we compared the number of preoperative glaucoma medications with the number of postoperative medications required to control the intraocular pressure. These results are summarized in Table III and

TABLE I: SUMMARY OF PATIENT DATA

PATIENT NO.	SEX	AGE	RACE	PRIOR OCULAR PROCEDURES	DIAGNOSIS	INTRAOCULAR PRESSURE	
						PREOP	POSTOP
Control group							
1	F	54	W	0	Neovascular glaucoma	48	40
2	M	31	B	4	Juvenile glaucoma	40	30
3	M	29	B	0	Juvenile glaucoma	40	29
4	F	68	W	1	Aphakic open angle glaucoma	20	18
5	F	58	W	2	Neovascular glaucoma	65	8
6	M	61	W	1	Primary open angle glaucoma	43	18
7	M	34	B	0	Juvenile glaucoma	22	33
8	M	43	B	2	Juvenile glaucoma	26	31
9	M	67	B	1	Primary open angle glaucoma	27	27
10	M	64	W	1	Neovascular aphakic glaucoma	30	34
11	M	30	W	0	Neovascular glaucoma	68	42
12	M	64	W	1	Congenital aphakic glaucoma	65	60
5-FU group							
1	F	54	W	1	Neovascular glaucoma	35	19
2	M	31	B	5	Juvenile glaucoma	36	14
3	M	29	B	0	Juvenile glaucoma	40	14
4	F	52	W	1	Primary open angle glaucoma	54	7
5	F	68	W	1	Aphakic glaucoma	21	15
6	M	70	W	1	Aphakic glaucoma	22	12
7	M	30	W	0	Neovascular glaucoma	42	24
8	M	55	W	1	Neovascular aphakic glaucoma	54	5
9	F	26	W	2	Neovascular glaucoma	28	21
10	F	39	B	1	Juvenile glaucoma	55	11
11	F	42	B	2	Inflammatory angle closure glaucoma	36	10
12	M	43	B	1	Juvenile glaucoma	30	17
13	F	78	B	1	Chronic open angle glaucoma	34	18
14	M	64	W	1	Neovascular aphakic glaucoma	51	14

TABLE II: SUMMARY OF PATIENT DIAGNOSIS DATA

	CONTROL GROUP			5-FU GROUP		
	PHAKIC	APHAKIC	TOTAL	PHAKIC	APHAKIC	TOTAL
Primary open angle glaucoma	2	1	3	2	2	4
Secondary angle closure glaucoma	0	0	0	1	0	2
Juvenile open angle glaucoma	4	1	5	4	0	4
Neovascular glaucoma	3	1	4	3	2	5
Total	9	3	12	10	4	14

TABLE III:
COMPARISON OF GLAUCOMA MEDICATIONS REQUIRED TO CONTROL INTRAOCULAR PRESSURE

PATIENT NO.	VISUAL ACUITY*		BLEB MORPHOLOGY	NUMBER OF MEDICATIONS	
	PREOPERATIVE	POSTOPERATIVE		PREOPERATIVE	POSTOPERATIVE
Control group					
1	CF 5′	CF 5′	Flat	3	3
2	20/50	20/60	Flat	4	4
3	20/20	20/20	Flat	4	4
4	20/50	20/50	Cystic	2	2
5	HM	NLP	Flat	1	0
6	20/50	20/400	Flat	4	4
7	20/30	20/20	Flat	3	0
8	20/20	20/30	Flat	3	3
9	20/70	20/80	Flat	4	4
10	20/100	20/100	Tenon's cyst	2	2
11	CF	CF	Flat	2	2
12	20/50	CF	Flat	4	2
Total				36	30
5-FU group					
1	CF 3′	CF 5′	Tenon's cyst	3	2
2	20/60	20/60	Cystic	4	0
3	20/20	20/20	Cystic	4	0
4	20/50	20/60	Cystic	2	0
5	20/40	20/40	Cystic	2	2
6	20/40	20/30	Cystic	4	1
7	20/100	CF	Tenon's cyst	2	2
8	HM	HM	Cystic	3	0
9	20/30	20/70	Flat	2	2
10	20/100	20/100	Cystic	3	0
11	20/20	20/20	Cystic	2	0
12	20/30	20/30-2	Cystic	4	3
13	20/100	20/70	Cystic	4	0
14	20/100	20/100	Tenon's cyst	2	2
Total				41	14

*CF, counting fingers; HM, hand motion; NLP, no light perception.

Fig 4. The average number of medications taken by patients in the control group did not change significantly, whereas in the 5-FU group patients took an average of three glaucoma medications preoperatively and one medication postoperatively.

COMPLICATIONS

Fifty percent (n = 7) of the 5-FU group had corneal epithelial defects and one patient had a delle. There were two wound leaks and one flat anterior

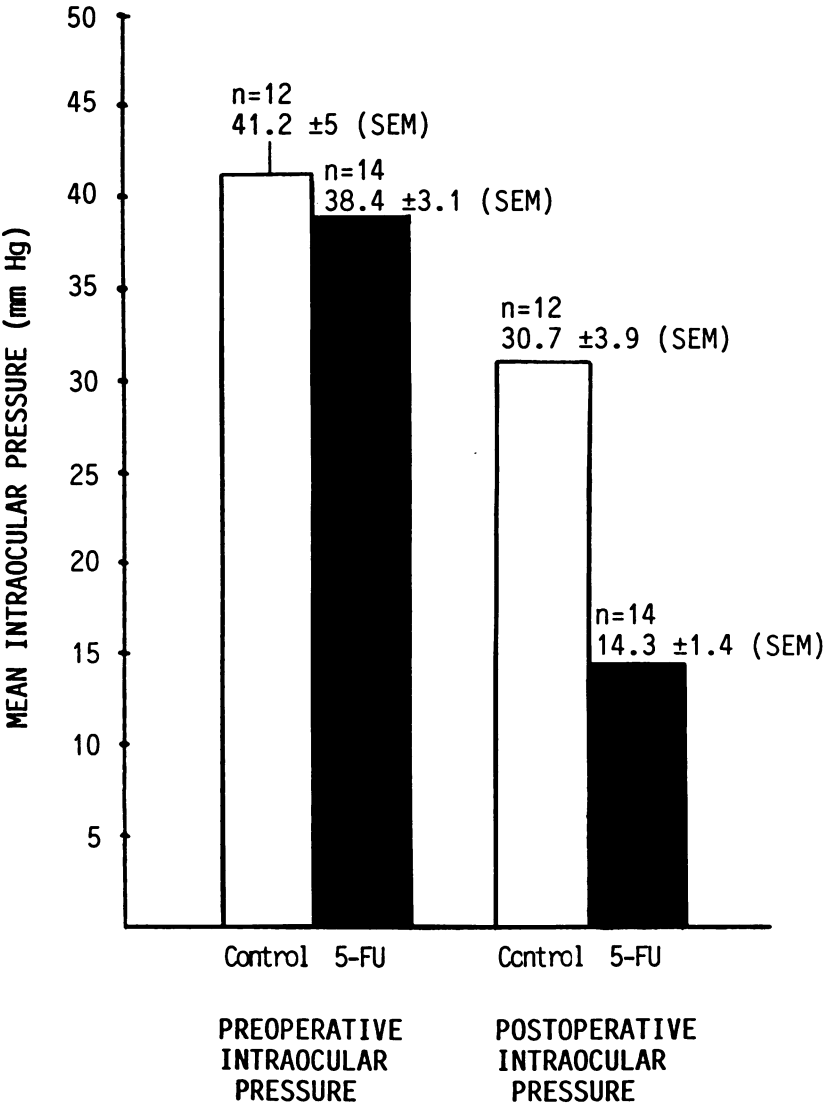

FIGURE 1
Analysis of preoperative and postoperative intraocular pressure.

chamber in this group, which responded well to pressure patching. In the control group, there were two epithelial defects, one wound leak, one flat anterior chamber, and one suprachoroidal hemorrhage.

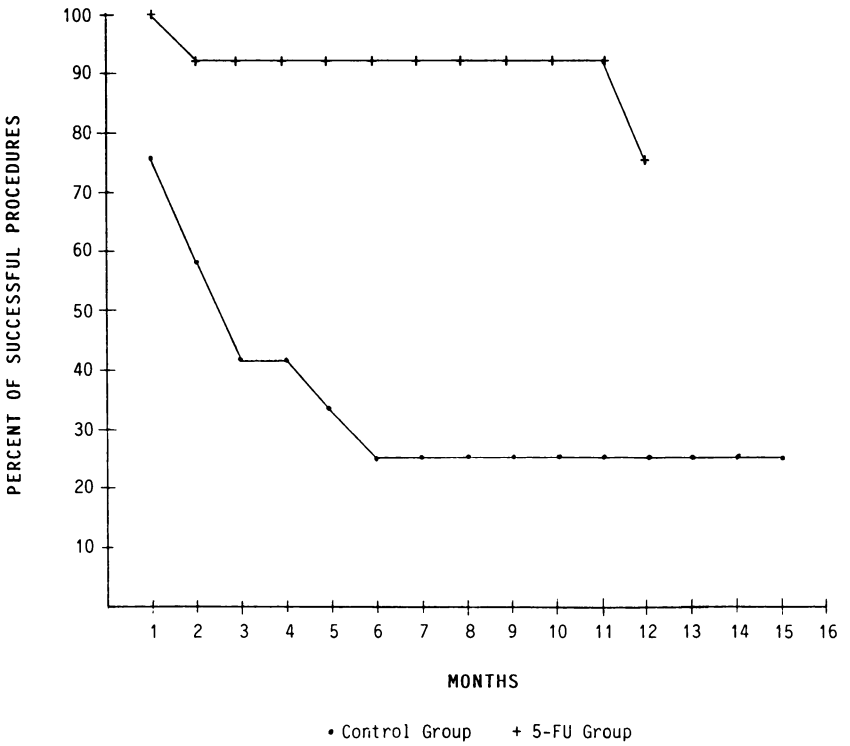

FIGURE 2
Cumulative probability of success.

NONRANDOMIZED PATIENTS

Twenty-six patients were referred to us specifically for 5-FU treatment and thus could not be randomized and were not entered into the study. They were treated with 5-FU according to the protocol. Length of follow-up ranged from 2 to 16 months (mean, 5 months). Distribution of the diagnosis was similar to that seen in the randomized group. Average preoperative intraocular pressure was 36 ± 2.0 mm Hg (SEM) and postoperatively 17.2 ± 1.7 mm Hg (SEM). The cumulative probability of success was 79% after 12 months and 53% after 16 months. Fifteen blebs were graded as diffuse microcystic, 10 were flat, and 1 had a Tenon's cyst. Four of the six failures occurred in patients with flat blebs. The patient with the Tenon's cyst also failed. Eight of 26 (30.8%) had epithelial defects, 5 of 26 (19.2%) had wound leaks, 1 of 26 had a suprachoroidal hemorrhage and 1 of 26 had a hyphema.

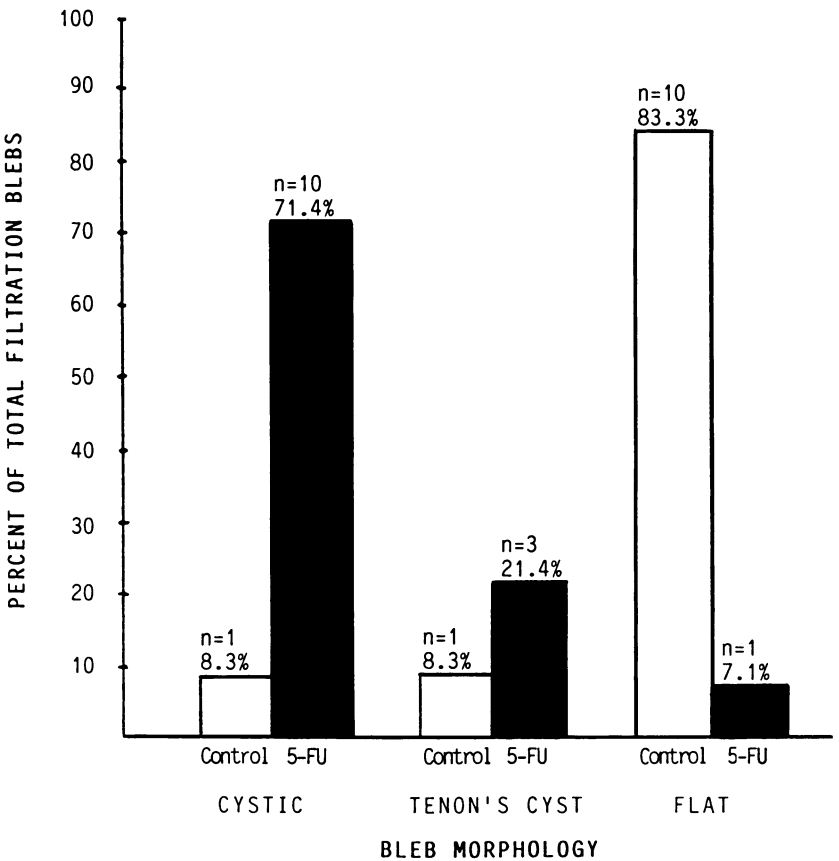

FIGURE 3
Bleb analysis.

DISCUSSION

Subconjunctival injection of 5-FU in the postoperative period following filtration surgery is an effective means of promoting filtration and inhibiting conjunctival scar formation. The low success rate of the control group in our study confirms the impression that these patients have a poor prognosis for filtration after glaucoma surgery without adjunctive therapy. In addition, despite the fact that we used less than one-half the dose of 5-FU employed in the study by Heuer et al,[13,14] our success rate is similar.

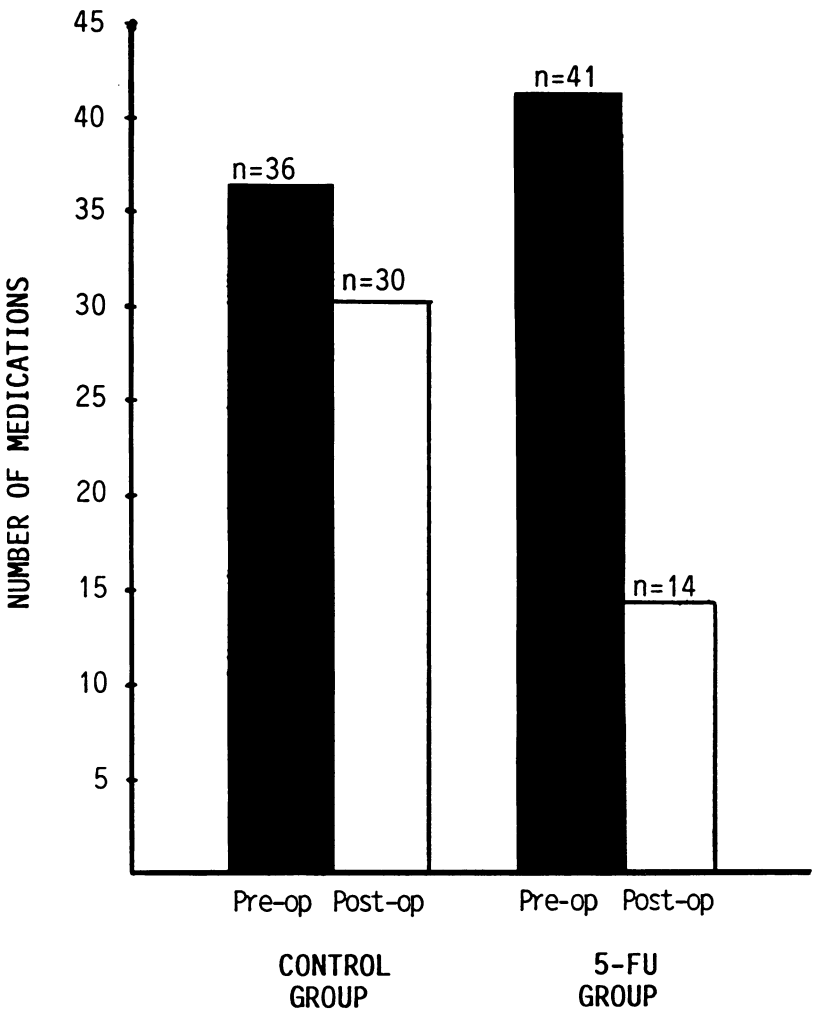

FIGURE 4
Analysis of preoperative and postoperative medications.

Obtaining patients for a randomized study such as this is difficult. Patients may refuse randomization and demand 5-FU treatment because of the severity of their disease. Many times, as noted above, they were referred by other physicians specifically for 5-FU treatment. In addition to randomization problems, masking is difficult. A series of placebo injections was not considered reasonable because of the potential risks of

infection, inflammation, and hemorrhage. Furthermore, we found no patients willing to receive placebo injections. However, the 5-FU group was so much more successful than the control group that the inherent bias in our study does not seem significant.

Evaluation of whether 5-FU is a valuable adjunctive therapy is also complicated by the fact that intraocular pressure alone is an inadequate measure of success. It does not take into account loss of vision, other surgical complications perhaps caused by the medication, prolonged discomfort, and the extended hospital study that are required. However, because intraocular pressure measurements are reproducible and because elevated pressure is felt to be the most likely cause of continued visual loss in patients with severe glaucoma, we, like Heuer et al,[13,14] have used it as the major criterion of success. An additional measure of the efficacy of this procedure is found in the fact that the intraocular pressure was controlled postoperatively by significantly less medication in the 5-FU group. Fifty percent of the 5-FU group was controlled without medication after surgery, while only 16.7% of the control group was controlled without medication.

It was not possible to analyze the efficacy of 5-FU in subgroups, because of the limited number of patients. It is the authors' impression, however, that patients with non-regressed neovascularization of the iris did the poorest with filtration surgery regardless of whether 5-FU was used. This may be due to continued or stronger stimulus for fibrous proliferation well after the period of 5-FU administration.

Differences in bleb morphology suggest that increased filtration is the mechanism by which eyes treated with 5-FU have lower postoperative intraocular pressures. Patients treated with 5-FU have an increased tendency to form diffuse microcystic blebs or Tenon's cysts, while a bleb failed to persist in the majority of cases in the control group. Tonography and/or fluorophotometry could be used to verify the mechanism of decreased intraocular pressure in the future.

A major goal of our study was to determine whether a small dose of 5-FU would result in fewer complications. It is clear that the discomfort to the patient, expense, and length of hospital stay are significantly reduced in patients who are treated only half as long. However, evidence is also convincing that a lower dose of 5-FU is associated with the same incidence of some complications as with a higher dose, such as epithelial defects which occurred in 50% of our 5-FU group, not significantly different than that found by Heuer et al.[13,14] Although our patients did not have any severe sequelae from the epithelial defects, serious corneal complications such as bacterial and sterile ulceration as well as perforation

have recently been reported.[18]

Our rate of wound leaks (14%), while higher than in the control group (8%), is not significantly different. It is however, considerably less than that first reported by Heuer et al (41%). There are many potential explanations for this besides the fact that we used a lower dose of 5-FU. One may be the fact that the patients had fewer injections and therefore, less manipulation of the eye. In addition, we chose not to begin our injections until a water-tight wound had been established. Absence of wound leaks may enhance success of this procedure and decrease complications such as flat chambers, cataract formation, corneal decompensation, prolonged inflammation, and suprachoroidal hemorrhage.

Further research into alternative delivery systems such as liposome and depot drug administration is needed. In addition, other agents that interrupt different portions of the healing process, such as steroids, beta-aminopropionitril, penicillamine, and fluorouridine should be investigated.

SUMMARY

Our study shows that use of a small dose of subconjunctival 5-FU provides significantly lower postoperative intraocular pressure than does no antimetabolite treatment. Morphology of the postoperative blebs suggests that increased filtration results in lower intraocular pressure in the 5-FU group. Corneal epithelial defects were as common with a low dose as with higher doses previously described.

REFERENCES

1. Bellows AR, Johnston MA: Surgical management of chronic glaucoma in aphakia. *Ophthalmology* 1983; 90:807-813.
2. Heuer DK, Gressel MG, Parrish RK, et al: Trabeculectomy in aphakic eyes. *Ophthalmology* 1984; 91:1045-1051.
3. Merritt JC: Filtering procedures in American blacks. *Ophthalmic Surg* 1980; 11:91-94.
4. Schwartz AL, Anderson DR: Trabecular surgery. *Arch Ophthalmol* 1974; 92:134-138.
5. Stewart RH, Kimbrough RL, Bachh H, et al: Trabeculectomy and modifications of trabeculectomy. *Ophthalmic Surg* 1979; 10:76-80.
6. Gressel MG, Heuer DK, Parrish RK: Trabeculectomy in young patients. *Ophthalmology* 1984; 91:1242-1246.
7. Kolker AE, Hetherington J Jr: *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas*. 5th ed, St Louis, CV Mosby, 1983, p 509.
8. Epstein DL: *Chandler and Grant's Glaucoma*, 3rd ed, Philadelphia, Lea & Febiger, 1986, p 362.
9. Herschler J, Agness D: A modified filtering operation for neovascular glaucoma. *Arch Ophthalmol* 1979; 97:2339-2341.
10. Parrish R, Herschler J: Eyes with end-stage neovascular glaucoma; natural history following successful modified filtering operation. *Arch Ophthalmol* 1983; 101:745-746.

11. Allen RC, Bellows AR, Hutchinson BT, et al: Filtration surgery in the treatment of neovascular glaucoma. *Ophthalmology* 1982; 89:1181-1187.
12. Blumenkranz M, Ophir A, Claflin A: A pharmacologic approach to non-neoplastic intraocular proliferation. ARVO Abstracts. *Invest Ophthalmol Vis Sci* (Suppl) 1981; 20:200.
13. Heuer DK, Parrish RK, Gressel MG: 5-fluorouracil and glaucoma filtering surgery. *Ophthalmology* 1986; 93:1537-1546.
14. ———: 5-fluorouracil and glaucoma filtering surgery. *Ophthalmology* 1984; 91:384-394.
15. Gressel MG, Parrish RK, Folberg R: 5-fluorouracil and glaucoma filtering surgery: 1. An animal model. *Ophthalmology* 1984; 91:378-383.
16. Regan EF: Scleral cautery with iridectomy: An experimental study. *Trans Am Ophthalmol Soc* 1963; 61:219-227.
17. Barany EH, Linner E, Lutjen-Drecoll E, et al: Structural and functional effects of trabeculectomy in cynomolgus monkeys: Light microscopy. *Albecht von Graefes Arch Klin Exp Ophthalmol* 1972; 184:1-28.
18. Knapp A, Heuer DK, Stern GA, et al: Serious corneal complications of glaucoma filtering surgery with postoperative 5-fluorouracil. *Am J Ophthalmol* 1987; 105:183-187.

DISCUSSION

Dr George L. Spaeth. Doctor Ruderman and colleagues have undertaken an important study. They are to be congratulated for trying to limit variables and bias while investigating a subject in which there has been disappointingly little progress, how best to preserve vision in patients with glaucomas refratory to more established methods of treatment. Mother nature has been extraordinarily secretive in revealing or allowing to be understood why certain individuals are so resistant to treatment.

I applaud the authors for their efforts and their contribution. However I am still not convinced that there has been a substantive qualitative improvement in the prognosis of patients who are the victims of our continuing inability to manipulate satisfactorily the way tissues heal.

In an otherwise superbly designed study one area was not controlled; a systematic difference in the management and pattern between the control and treatment groups could have caused the results found by the authors. Specifically, the postoperative use of topical steroids was apparently handled differently by the different surgeons, the medications being altered depending upon inflammation and other factors. The ideal way in which to use topical corticosteroids in the postoperative period following glaucoma surgery has not yet been established, but it is clear that different treatment programs have different effects. For example, with the use of "Maxitrol" four times daily in the postoperative period cysts of Tenon's capsule develop in approximately 20% of cases, but when the frequency is increased to hourly use, the frequency of Tenon's capsule cyst increases to 100% (personal observation). This goes along with the recent report by Lank and colleagues of a biphasic effect of topical steroids on fibroblast activity. Unfortunately, from a clinical point of view we do not know just how much topical steroid is going to be inhibitory and how much will facilitate fibroblast proliferation in the individual patient we are treating. I ask Doctor Ruderman, "How much difference was there in the way that topical steroids were used, and do you believe there was

a systematic difference in this regard?"

Doctor Ruderman stated that visual field examinations could not be used to follow this group of patients. A second question is, "Why were visual fields unable to be used to follow these patients?" Doctor Ruderman properly points out that judging success merely on the basis of intraocular pressure lower than an arbitrary figure is not really a satisfactory way of defining success in glaucoma patients. The goal, after all, is enhancement or preservation of the patient's quality of life; inconvenience, discomfort, expense, and loss of visual function are far more important than the level of intraocular pressure. The authors correctly state that in many similar studies the results are judged solely in terms of effect on intraocular pressure. Unfortunately, they have perpetuated this state of affairs. We now know that arbitrary levels of intraocular pressure are of little value in determining the natural history of visual function in patients with glaucoma.

Additionally, one could challenge the author's statement that "elevated pressure is the most likely cause of continued visual loss in patients with severe glaucoma . . ." Most surely, intraocular pressure elevation is a critical factor, and it is appropriate to direct our attention to it, but other factors can be as or more important, as for example, in neovascular glaucoma, where the prognosis is more related to the condition of the patient's diabetic vascular disease rather than to the glaucoma.

Eight of the 26 cases in this study were listed as "juvenile glaucoma," their ages ranging from 29 to 43 years. These patients have been included as ones in which prognosis for successful filtration is poor. This differs with my experience. I believe patients this age do well with glaucoma surgery. Therefore, it is some what surprising that the results were not more favorable. Only 7 of the 26 cases were aphakic. It is these aphakic cases in which the results are so dismal.

It was of concern that the results in the 26 nonrandomized cases were far less favorable than in the randomized group. Only 53% of these cases had controlled intraocular pressure at the end of 16 months. Furthermore, around 20% had wound leaks and 31% had epithelial defects. This seems like a high complication rate for a success rate that is still not very gratifying.

Which brings up the essential question, which is, "Does the increased risk of using 5-FU justify the increased benefit?" The answer to that is still not established. Three of Heuer et al's original patients had corneal endothelial scarring. Knopp and colleagues reported two bacterial ulcers, a sterile corneal ulcer, and a corneal perforation. In aphakic patients a significant number of trabeculectomies or other procedures will succeed. However, in aphakic patients needing repeat surgery for glaucoma, 5-FU may well be justified.

Additionally, there are alternatives which are now available. An old operation that has been neglected in phakic patients is cyclodialysis. In my experience it has a fairly high success rate in phakic patients. In aphakic glaucoma the Nd:YAG laser cyclophotocoagulation is a viable alternative, and several centers are reporting up to 75% success rate using the Schockett procedure.

We need better understanding of the causes of failure of filtration procedures. We need better understanding of how to manipulate these causes in each individ-

ual case. Certainly, there are different causes in different patients.

In summary, the authors are to be congratulated on performing a difficult and important study. They had made what I believe to be several important advances: (1) 5-FU does seem to be effective in establishing a lower final intraocular pressure, (2) a small dosage of 5-FU is probably more appropriate than that initially recommended, and (3) the 5-FU should not be started until it is clear that no leaks are present and that the initial surgery is healing well. It is possible that even smaller doses of 5-FU will still be effective. If this is the case, it may become a standard part of many surgical procedures in patients with glaucoma refractory to standard surgical techniques.

DR JULES BAUM. Both Doctor Ruderman and colleagues and Doctor Spaeth have discussed the problem of corneal epithelial defects. 5-Fluorouracil is a toxic drug. We have seen over the past year 5-FU administered systemically for nonophthalmic conditions, with the patients coming to us with photophobia. They exhibit epithelial edema which disappears when the drug is stopped. Based on our experimental antibiotic pharmacokinetic studies, the authors use of a subconjunctival injection of 5-FU should deliver a much higher concentration of drug to the corneal epithelium than when given by systemic administration and the authors did observe epithelial defects. Might it be best to consider giving the subconjunctival drug at a different location? I believe you stated you were giving it inferiorly. You might be able to deliver a much lower dose if it were given at a superior location, away from the bleb. This modification might reduce the incidence of epithelial defects.

DR DONALD DOUGHMAN. I have a criticism of the study design. You mentioned in one of your closing slides that you did not give a sham or placebo injection. You did not do so because your IRB committee felt that the complications do not warrant this. First, I'm not impressed that subconjunctival injections are necessarily dangerous. We give them a lot in anterior segment disease for many reasons such as, delivering antibiotics and steroids. I don't know of any time we ran into a major complication. But even so, to presume that it would be a complication in the controls but beneficial to the experimental group obviously expresses a bias that the treatment will work, but has complications that are too risky for controls. This is obviously a flawed study design and not truly a prospective controlled study. I would like you to comment.

DR JON M. RUDERMAN. I would like to thank Doctors Spaeth, Baum, and Doughman for their excellent comments. Regarding Doctor Spaeth's questions on steroid use and why it was not uniform, it was very difficult to establish a uniform method of giving steroids. The indication for giving steroids depends not only on intraocular inflammation but also on inflammation of the conjunctiva. We tried to limit the variable as to whether or not the patient received 5-FU. The vast majority of our patients received Decadron four times a day. Strict control over its

dosage would have been difficult and would have altered our normal postfiltration treatment.

Regarding the inclusion of the younger patients, this is a debatable subject. There is considerable literature suggesting that young patients, especially very young patients, do not do as well with filtering surgery. Our younger patients were split almost evenly between the two treatment groups. If this diagnostic group as a whole tended to succeed or fail, it should not affect one group more than the other. Our juvenile glaucoma patients did much more poorly in the control group than in the 5-FU group.

Regarding the lower success rate in the nonrandomized group, there are two possible explanations for this. One is that our nonrandomized patients simply had much more severe disease. They were often referred in specifically for 5-FU treatments. Many of these patients had undergone three, four, or five previous operations. Often there was a very short period of time between their previous procedure failure and our procedure. We are dealing with a different group of patients than those who accepted randomization. The second reason for the lower success rate in the nonrandomized patients is that with life table analysis of success the failure of a patient with longer follow-up would be weighed more heavily. One patient failed at 16 months because he had inflammatory glaucoma and had recurrent inflammation. This failure might skew the results.

Regarding Doctor Baum's suggestion of giving subconjunctival drug closer to the bleb, originally, we gve the medication far inferiorly because we noticed less reflux of the drug. By changing the location of the injection, as Doctor Spaeth pointed out, perhaps we can use an even lower concentration of 5-FU. I think that it certainly would be worth comparing different areas of injection and trying to find out how it affects drug concentration. There are also other medications, specifically 5-fluorouridine, which is 100 times more powerful than 5-FU in terms of fibroblast inhibition. It might be that very low concentrations of this medication injected near the bleb might be useful.

Doctor Doughman criticized our study design because not all patients received some form of injection. He raised the possibility that the injection itself could account for the increased rate of success. Before we started the study, I asked a number of patients whether they would enter a study in which they would receive a number of subconjunctival injections if the injection might be a placebo. No patient was willing to undergo injections without getting 5-FU. In addition, we felt very uncomfortable giving postoperative injections with saline because of the slight but added risk of infection, hemorrhage, or creating wound leaks. It is true that the ideal controlled study would use placebo injections, but we felt that ethical and practical problems prevented use of control saline injections.