LETTERS TO THE EDITOR

Sir,

Dangers of Direct Injection of Antimetabolites into Filtration Blebs

We read the letter by Caballero and Clearkin¹ regarding their use of a single 0.4 ml injection containing 10 mg (25 mg/ml) 5-fluorouracil (5-FU) into the potential space between Tenon's capsule and the conjunctiva.

However, we write to urge great caution with the use of antimetabolites injected directly into the filtration bleb when there is a patent sclerostomy, even one covered by a scleral flap. Surgeons with less experience than Drs. Caballero and Clearkin run the risk of injecting concentrated 5-FU directly into the bleb drainage area, which has direct access to the anterior chamber. In addition, if the conjunctiva has been closed (unlike the technique used by Caballero and Clearkin) the pressure in the bleb could, depending on the volume of 5-FU used, rise higher than that in the eye. Also, the intraocular pressure immediately following filtration surgery may be near 0 mmHg and may potentially reach a negative pressure depending on the traction forces on the eye. In this situation, 5-FU or any other antimetabolite may be pushed or sucked into the eye, theoretically achieving a very high concentration in the anterior chamber. In addition to its direct antimetabolic effect, commercially available 5-FU is solubilised using sodium hydroxide, resulting in a solution with an alkaline pH near to 9 which may enter the eye.

We have also heard accounts of other surgeons injecting antimetabolites, including 5-FU and even mitomycin C, directly into the filtration area between Tenon's capsule and the sclera after conventional filtration surgery or laser sclerostomy. This practice considerably increases the chance of concentrated solutions of antimetabolites entering the anterior chamber. Derick and coworkers² have described the catastrophic results when the equivalent of one drop (50 µl) of mitomycin C (0.5 mg/ml) is injected into the anterior chamber of the eye.

The advantage of injecting antimetabolites into the filtration area is to achieve maximal concentrations in the desired area with relative sparing of other areas, including the corneal epithelium. This can be achieved much more safely by the intraoperative application of sponges soaked in the antimetabolite at the appropriate concentration, which is then rinsed out before the eye is opened.³ Comparisons of the pharmacokinetic data for the intraoperative technique⁴ versus injections^{5,6} suggest that intraoperative

technique with washout is much safer than injections into the bleb site.

We agree that the peak concentration of 5-FU is in many ways more relevant than the total dose, as suggested by Ball,⁷ and this is supported by our cell culture studies which have shown that human Tenon's fibroblasts can be growth-arrested for several weeks by 5-FU or mitomycin C *in vivo*^{8,9} and *in vitro*¹⁰ after exposures as short as 5 minutes. As such, the clinical results obtained by Drs. Caballero and Clearkin¹ and Ball,¹¹ who inject 5-FU directly into the bleb site, should be reproducible by 5-minute exposures to appropriate concentrations of 5-FU or mitomycin C.¹² On the basis of these results we now use single-dose intraoperative exposures to either 5-FU or mitomycin C at different concentrations which are only occasionally supplemented with post-operative injections,¹³⁻¹⁵ depending on the patient risk factor profile and clinical course.

In conclusion, we would like to advise great caution with regard to the practice of injecting concentrated 5-FU directly into the filtration area after glaucoma filtration surgery. Clinicians are advised that they run the risk of injecting concentrated 5-FU directly into the anterior chamber with this technique, with potentially serious complications. Additionally, in the light of present knowledge, mitomycin C should never be injected into the filtration bleb area after surgery.

P. T. Khaw, K. A. Baez, M. B. Sherwood, R. A. Hitchings,
M. H. Miller and N. S. C. Rice

Glaucoma Unit

Moorfields Eye Hospital/Institute of Ophthalmology

Bath Street

London EC1V 9 EL, UK

and

University of Florida

Gainesville

Florida, USA

References

1. Caballero JC, Clearkin LG. Complications of 5-FU after trabeculectomy. *Eye* 1990;6:428-31.
2. Derick RJ, Pasquale L, Quigley HA, Jampel H. Potential toxicity of mitomycin C. *Arch Ophthalmol* 1991;109:1635.
3. Chen C-W, Huang H-T, Bair JS, Lee C-C. Trabeculectomy with simultaneous topical application of mitomycin C in refractory glaucoma. *J Ocul Pharmacol* 1990;6:175-82.
4. Kawase K, Matsushita H, Yamamoto T, Kitazawa Y. Mitomycin concentration in rabbit and human ocular tissues after topical administration. *Ophthalmology* 1992;99:203-7.

5. Rootman J, Tisdall J, Gudauskas G, Ostry A. Intraocular penetration of subconjunctivally administered 14 C-fluorouracil in rabbits. *Arch Ophthalmol* 1979;97:2375-8.
6. Kondo M, Araie M. Concentration change of fluorouracil in the external segment of the eye after subconjunctival injection. *Arch Ophthalmol* 1988;106:1718-21.
7. Ball SF. Concentration change and activity of fluorouracil in the external segment of the eye after subconjunctival injection. *Arch Ophthalmol* 1989;107:1276-7.
8. Khaw PT, Ward S, Porter A, Grierson I, Hitchings RA, Rice NSC. The long-term effects of 5-fluorouracil and sodium butyrate on human Tenon's fibroblasts. *Invest Ophthalmol Vis Sci* 1992;33:2043-52.
9. Khaw PT, Sherwood MB, MacKay SLD, Rossi MJ, Schultz GS. Five-minute treatments with fluorouracil, floxuridine, and mitomycin have long-term effects on human Tenon's capsule fibroblasts. *Arch Ophthalmol* 1992;110:1150-4.
10. Khaw PT, Doyle JW, Sherwood MB, Grierson I, McGorray S, Schultz GS. Five-minute exposures to 5-fluorouracil and mitomycin-c have prolonged localised tissue effects. *Arch Ophthalmol* 1993 (in press).
11. Loftfield K, Ball SF. 5-Fluorouracil (5-FU) in primary trabeculectomy: a randomised trial. *Invest Ophthalmol Vis Sci (Suppl)* 1991;32:745.
12. Khaw PT, Doyle JW, Sherwood MB, Smith MF, McGorray S. Effects of intraoperative 5-fluorouracil or mitomycin-c on glaucoma filtration surgery in the rabbit. *Ophthalmology* 1993 (in press).
13. Kitazawa Y, Kawase K, Matsushita H, Minobe M. Trabeculectomy with mitomycin: a comparative study with fluorouracil. *Arch Ophthalmol* 1991;109:1693-8.
14. Skuta GL, Beeson CC, Higginbotham EJ, Lichter PR, Musch DC, Bergstrom TJ, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992;99:438-44.
15. Lanigan LP, Stuermer J, Hitchings RA, Khaw PT. Single intraoperative exposures to 5-fluorouracil: early results. *Ophthalmology* 1993 (in press).

Sir,

Hulbert and Vernon¹ have performed a valuable service in reminding ophthalmologists who treat diabetic retinopathy of the importance of preserving as much of the visual field as possible. However, I suspect that they may be advocating dangerous undertreatment of patients with proliferative diabetic retinopathy.

Most authors recognise that 'complete treatment' of proliferative retinopathy by panretinal photocoagulation requires approximately 1800-2000 laser burns of 500 μ m size. This was the basis of laser treatment applied in the Diabetic Retinopathy Study² and forms the guidelines for present-day management of proliferative diabetic retinopathy.³ Patients with aggressive retinopathy may well, of course, require much more laser treatment.

Hulbert and Vernon advocate the use of 200 μ m spot size laser burns and comment in their guidelines that 'between 3000 and 3500 carefully applied burns induces regression in all but severe cases'. Using a 200 μ m spot size it would require 12 500 laser burns to cover the same area of retina as the 'conventional' 2000 burns of spot size 500 μ m. They therefore appear to be advocating consider-

ably less laser treatment than is currently the norm, and I suspect this could well be a dangerous undertreatment. Furthermore, as far as I am aware, this form of treatment has never been tested in controlled studies and as such should, in my opinion, be regarded with caution.

J. M. Gibson, MD, FRCS, FROphth
East Birmingham Hospital, NHS Trust
Bordesley Green East
Birmingham B9 5ST, UK

References

1. Hulbert MFL, Vernon SA. Passing the DVLC field regulations following bilateral pan-retinal photo-coagulation in diabetics. *Eye* 1992;6:456-60.
2. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative retinopathy: clinical applications of Diabetic Retinopathy Study (DRS) findings. DRS Report no. 8. *Ophthalmology* 1981;88:583-600.
3. Bloom SM, Brucker AJ. Laser surgery of the posterior segment. Philadelphia: Lippincott, 1991:25-51.

Sir,

I am grateful to Mr. Gibson for re-emphasising the importance of delivering sufficient laser photocoagulation to induce neovascular regression in proliferative diabetic retinopathy. I had hoped that this would be covered by Guideline 5 in our paper.¹ We are, of course, aware that our suggestions (specifically designed for individuals who require a driving licence) result in a smaller area of retina being photocoagulated. Our experience, as outlined in the tables,¹ would indicate that, based on the degree of severity of retinopathy of patients referred to our clinic, many do not require our 'standard retinal ablation' to induce stability of their disease. Titrating treatment in these patients, provided there are adequate facilities for follow-up, would not appear to prejudice the end result; thus a decision to deliver 2000 burns at 500 μ m spot size in a patient who does not need that volume of photocoagulation is clearly unjustified. Conversely, patients with rapidly progressive, aggressive retinopathy (which would fall into the severe category) must be treated with more extensive photo-ablation.

Stephen A. Vernon, FRCS, FCOphth
University Hospital
Queen's Medical Centre
Nottingham NG7 2UH, UK

References

1. Hulbert MFL, Vernon SA. Passing the DVLC field regulations following bilateral pan-retinal photo-coagulation in diabetics. *Eye* 1992;6:456-60.