We report an unusual case of corneal epithelial toxic effects associated with perfluorocarbon liquids (PFCLs). The clinical and histopathologic findings are described. An elderly man underwent vitreoretinal surgery for a complicated retinal detachment. Perfluorodecalin was used to repair the retina. It was left in situ for 8 weeks and removed via the pars plana. One month after removal of heavy liquids the patient developed a nonhealing corneal epithelial defect associated with limbitis. Perfluorodecalin was found under the superior conjunctiva. A conjunctival biopsy revealed the presence of vacuoles in the conjunctival stroma surrounded by an inflammatory response that consisted of lymphocytes, macrophages, and giant cells. On surgical removal of the PFCL from the subconjunctival space, the epithelial defect healed. The histopathologic and clinical evidence suggest that the inflammatory response and corneal epithelial ulceration were caused by the prolonged presence of PFCL in the subconjunctival space. To the best of our knowledge, PFCLs have not previously been reported to cause corneal epithelial defects or incite an inflammatory response in the human eye.

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Perfluorocarbon liquids (PFCLs) were first used in 1984 by Zimmerman and Faris to reposition experimentally detached retinas. Although PFCLs are considered to be biologically inert, toxic effects may be caused by impurities containing unsaturated carbon bonds, compounds with nitrogen bonds, and compounds containing hydrogen and fluoride. The PFCLs currently used for complicated vitreoretinal surgery are highly purified. There are very few clinical reports on the effects of PFCL on the anterior segment of the eye. Wilbanks et al. reported 5 cases of endothelial toxic effects caused by the prolonged presence of PFCL in the anterior chamber. Adverse effects of PFCL on the corneal epithelium have not been reported. We report a case of corneal epithelial toxic effects and inflammatory response resulting from the presence of PFCL in the subconjunctival space after vitreoretinal surgery.

From the Princess Alexandra Eye Pavilion (Drs Ramaesh, Bhagat, and Singh) and the Neuropathology Laboratory, Department of Pathology, Western General Hospital (Dr Wharton), Edinburgh, Scotland.

A 75-year-old man underwent a 3-port pars plana vitrectomy, cataract extraction, membrane peeling, injection of perfluorodecalin, and an endolaser procedure in the surgical management of retinal detachment complicated by proliferative vitreoretinopathy. The PFCL was left in situ and removed after 8 weeks using 2 pars plana incisions, one for infusion and the other for active aspiration via a Charles flute needle. Both sclerotomies were temporal and were closed with 6-0 vinyl. Three months after removal of the PFCL, the cornea developed an oval, persistent, central epithelial defect associated with limbitis (Figure 1). Corneal sensation was normal, and infective causes of corneal ulceration were excluded by corneal scraping and culture; however, PFCL was observed in the superior subconjunctival space (Figure 2). The conjunctiva was incised, the PFCL was washed out, and a conjunctival biopsy was performed. After removal of the PFCL, the corneal epi-
thelium showed evidence of gradual healing. Eight months later the defect had healed, leaving stromal scarring. The retina remained attached.

**HISTOPATHOLOGIC FINDINGS**

Histological examination of the conjunctival biopsy specimen revealed many conspicuous vacuoles of varying sizes within the subepithelial tissue (Figure 3). Most of the vacuoles seemed empty, although some contained pale-staining nonbirefringent material that was probably PFCL. The vacuoles were surrounded by lymphocytes, macrophages, and giant multinucleated cells (Figure 4). Immunostaining for CD68 antigens was positive in the perivacuolar cells, confirming their macrophage lineage (Figure 5). Electron microscopy showed large vacuoles within the macrophages, representing engulfed PFCL (Figure 6). In addition, there was a chronic inflammatory cell infiltrate composed of lymphocytes and plasma cells. The lymphocytes were of mixed variety, consisting of T and B cells, and stained

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Figure 1. An anterior segment photograph showing the epithelial defect.

Figure 2. Accumulation of perfluorocarbon liquid in the superior subconjunctival space.

Figure 3. Fine vacuoles are present in the subconjunctival space, surrounded by a mononuclear cell infiltrate. Overlying conjunctival epithelium is intact (hematoxylin-eosin, original magnification ×270).

Figure 4. Larger vacuoles in the subconjunctival space surrounded by foreign body–type macrophages. Multinucleated cells and plasma cells are visible in the surrounding chronic inflammatory cell infiltrate (hematoxylin-eosin, original magnification ×270).
positive for CD3+ and CD20+ antigens. The conjunctival epithelium overlying the infiltrate showed no evidence of ulceration.

**COMMENT**

The long-term tolerance of intraocular PFCL is poor.3,5 It is usually removed at the end of surgery but can be left in the eye for limited periods without any toxic effects.3,5 Millsap et al6 did not document any PFCL-related retinal toxic effects when PFCL was left in the human eye for up to 4 weeks. In monkey eyes, PFCLs were found to be nontoxic to the retina for periods up to 22 weeks.7 In the latter model, retinal toxic effects were manifested by inflammatory cell infiltration and photoreceptor damage.

Animal studies have also shown corneal endothelial cell loss and edema in eyes in which PFCL (perfluoro-n-octane) was left in situ for a prolonged period.8 After 2 weeks of corneal contact with perfluorotributylamine, endothelial cell loss, stromal infiltration, and corneal vascularization were noted in animal experiments.3

Wilbanks et al4 reported 4 cases of corneal endothelial toxic effects from prolonged PFCL-endothelial contact. Of 5 eyes that had residual PFCL in the anterior chamber, 4 developed corneal edema in the area of PFCL-endothelial contact. The period of PFCL-endothelial contact ranged from 4 to 13 weeks. In the remaining eyes, deep corneal vascularization without edema in the area of contact was noticed after 12 months.

Only in 1 eye did removal of heavy liquid from the anterior chamber reverse the corneal edema; others required penetrating keratoplasty.4 In our case, a nonhealing, persistent corneal epithelial defect associated with limbitis developed because of the presence of PFCL in the subconjunctival space. Histological examination of the conjunctiva demonstrated vacuoles surrounded by lymphocytes, macrophages, and foreign body giant cells. The vacuoles in the conjunctiva represent spaces occupied by the PFCL; the cellular reaction is caused by the PFCL. This, along with the presence of engulfed PFCL within the macrophage (seen as a vacuole on electron microscopy), suggests that PFCL may not be entirely inert. It is noteworthy that the PFCL used in this procedure was highly purified and the toxic effects were likely caused by the PFCL rather than any impurities. The healing of the corneal epithelial defect on removal of the PFCL demonstrates a possible cause-effect relationship.

We believe the PFCL accumulated under the conjunctiva during removal and was trapped in the subconjunctival space. The mechanism of cellular injury caused by PFCLs remains to be determined. Wilbanks et al4 proposed that the corneal endothelial toxic effects may be caused by alteration in surface tension or impedance of normal metabolic exchange between the cells and the aqueous. The nonhealing, indolent nature of the corneal epithelial defect in our case may suggest lowered limbal stem cell activity because of the presence of PFCL in the subconjunctival space.

The corneal epithelial ulceration and the conjunctival reaction in the case we reported was probably caused by the prolonged presence and toxic effects of PFCL within the tissues. Accumulation of PFCL in the subconjunctival space and subsequent corneal-related complications can be avoided by thorough inspection of the conjunctival space after removal of PFCL.

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Corresponding author: Jas Singh, MSc, FRCS(Edin), Princess Alexandria Eye Pavilion, Chalmer’s Street, Edinburgh EH3 9HA, Scotland.

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