Currently, nearly all pharmacologic treatment of primary open-angle glaucoma (POAG) is topical. The shortcomings of topical therapy are well known, but new technology is aimed at overcoming them.

PROBLEMS WITH BIOAVAILABILITY AND WITH ADHERENCE
The drawbacks of topical glaucoma therapy may be divided into two areas. First, it is difficult to get molecules to the target receptors through the myriad barriers of the eye. The cornea is lipophilic at its surface but hydrophilic in the stroma. Molecules that cross the epithelium easily cross the stroma poorly and vice versa. The majority of the instilled drug is rapidly cleared through the nasolacrimal duct, where the agent becomes available to the systemic circulation and may produce systemic side effects. The conjunctiva and episclera have robust vascular and lymphatic systems that clear topical drugs. Because of poor penetration and short residence time on the ocular surface, topical drops must have high concentrations of the active agent for adequate levels to reach the aqueous humor. These elevated concentrations increase the incidence of local and systemic toxicity.

The other problem is that adherence to pharmacologic therapy is poor. Patients use only a fraction of the drops prescribed, and they fail to refill their prescriptions. They have difficulty adequately instilling their drops. In addition, pharmacy benefit managers erect barriers to refilling prescription eye drops when needed.

PRIOR EFFORTS TO IMPROVE MEDICAL EFFICACY
Despite the difficulties associated with topical treatment, patients often prefer medical therapy to surgical intervention. In addition, pharmacologic treatment is adjustable in ways the surgery is not, an important consideration in the management of a disease that may evolve over decades. Novel ways to administer drug therapy that answer some of the objections would be welcome. Industry has offered products to achieve this goal, albeit in modest ways. The most obvious are changes in the vehicle to increase residence time and

Figure 1. The proprietary platform from QLT Inc. consists of novel plugs, insertion tools, and a handheld plug-detection device.
allow greater absorption (eg, Timoptic XE [Aton Pharma Inc.] and BetopticS [Alcon Laboratories, Inc.]).

**SUSTAINED-RELEASE SYSTEMS**

The issue of poor adherence might best be addressed by sustained-release delivery systems. Ocusert, a sustained-release device for pilocarpine, was introduced more than 3 decades ago. It had poor commercial success, however, perhaps because it lasted only 1 week and had to be inserted in the inferior fornix by the patient.4 This product is no longer available.

QLT Inc. (Vancouver, British Columbia, Canada) and Vistakon Pharmaceuticals, LLC (Jacksonville, FL), have investigated punctal plugs as delivery systems for latanoprost and bimatoprost, respectively. The goal is to develop a product that will maintain drug levels for 3 months or longer with excellent retention of the plug. The Vistakon system was unable to lower IOP more than placebo, and the program does not appear to be active.5 QLT Inc. has made progress with its platform to lower IOP, and development continues6 (Figure 1).

**IMPLANTABLE DRUG DELIVERY PLATFORMS**

The appeal of products such as Ocusert and punctal plug delivery systems is that they avoid invasive procedures, but they still must overcome the biological barriers to the aqueous humor. They do so by increasing residence time. Other platforms attempt to bypass one or more of the barriers.

The subconjunctival space is an appealing location for a sustained-release product. A drug placed here would have reduced access to the systemic circulation, and hydrophilic drugs might be utilized in far lower concentrations.

Robin et al found that anecortave acetate effectively lowered IOP for a prolonged period in a small number of patients with steroid-induced glaucoma when the drug was administered as a juxtascleral depot.7 Subsequent studies demonstrated that anecortave could be effective in POAG. Although these findings confirmed that drugs in the subconjunctival space could effect a sustained reduction in IOP, large-scale studies failed to confirm a consistent and reliable effect. This may have been due to poor bioavailability of the agent or to difficulties in accurately placing the drug. Nevertheless, further investigations have been abandoned.

Dumitrescu et al prepared a sustained-release form of timolol in polymer microspheres. A single subconjunctival injection in normotensive rabbits produced average pressure lowering of more than 25% compared with controls over a 10-week period. The total dose adminis-
tered was 0.125 µg, much less than the amount of timolol in a single drop of a commercial solution.8

Elhayek et al encapsulated latanoprost in poly(lactide-co-glycolide) microparticles, which were suspended in a solution that formed a polymer in situ. When 50 µL containing 500 µg of latanoprost was injected beneath the conjunctiva in rabbits, latanoprost-free acid could be detected in the aqueous humor for up to 9 weeks.9

DeVore et al studied the release of latanoprost from collagen matrices in vitro. They analyzed both a collagen wafer containing latanoprost and an in situ polymerizing form of collagen with latanoprost. These systems demonstrated a sustained release of latanoprost for 30 days.10

A REFILLABLE DELIVERY SYSTEM

Many patients with POAG will eventually require surgery, and the success of trabeculectomy is highly dependent on the condition of the conjunctiva. Consequently, physicians may be reluctant to employ therapies that require repeated insults to the conjunctiva, such as injections or the placement of drug-eluting substrates. A refillable subconjunctival reservoir might answer some of these objections.

Humayun and coworkers have developed the MicroPump (Replenish, Inc., Pasadena, CA; not available in the United States). This microelectromechanical systems pump is placed beneath the conjunctiva in a procedure similar to the placement of a glaucoma drainage device (Figure 2). The port may be placed in either the anterior chamber or the vitreous. The reservoir can be repeatedly refilled with a 3- to 9-month supply, and it is compatible with a number of drugs. The implant is designed to have a lifetime of 5 to 10 years.11

CONCLUSION

Systems capable of delivering medication to the eye more efficiently and with less systemic exposure than topical therapy would likely increase the efficacy of pharmacologic treatment in glaucoma. These systems have the potential to reduce toxicity while eliminating concerns about adherence. Although they are in their infancy and technological barriers remain, none seems insurmountable, which suggests that an alternative drug delivery system will be available in the future.

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