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Toxic keratopathy due to the accidental use of chlorhexidine, cetrimide and cialit

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Abstract. Due to economical reasons some ophthalmologists are using an irrigating solution made by the hospital pharmacy instead of the commercially available solutions. These irrigating solutions come in bottles which are identical to the ones used for other solutions. During the last three years bottles were accidentally mixed up five times. Consequently, bottles containing solutions such as chlorhexidine, cetrimide, chlorhexidine/cetrimide and cialit solutions were used during cataract surgery. This resulted in immediate corneal edema which, in its turn resulted in a bullous keratopathy. Four patients underwent a penetrating keratoplasty. In one patient the cornea was covered with a conjunctival flap. Light microscopy of the corneas included epithelial edema, loss of keratocytes, and a disrupted and sometimes absent endothelial cell layer.

Introduction

Properly made irrigating solutions are usually safe for the corneal endothelium. The right chemical composition, PH and osmolarity can contribute to the prevention of damage in the structures of the eye. The addition of drugs to the irrigating solutions immediately before use, for instance sulfite-containing epinephrine, may be harmful to the endothelial cells. The majority of eye surgeons use commercially available irrigating solutions. These commercially available solutions are delivered in bottles completely different in size and shape from the bottles used by the hospital pharmacy. Due to economical reasons some ophthalmologists are using an irrigation solution made by the hospital pharmacy.

These irrigating solutions come in bottles which are identical to the ones used for other solutions. Quite often the caps and the labels are of the same colour or identical. During the last three years bottles were accidentally mixed up five times. Consequently, bottles containing solutions such as chlorhexidine, cetrimide and cialit solutions were used during cataract surgery.

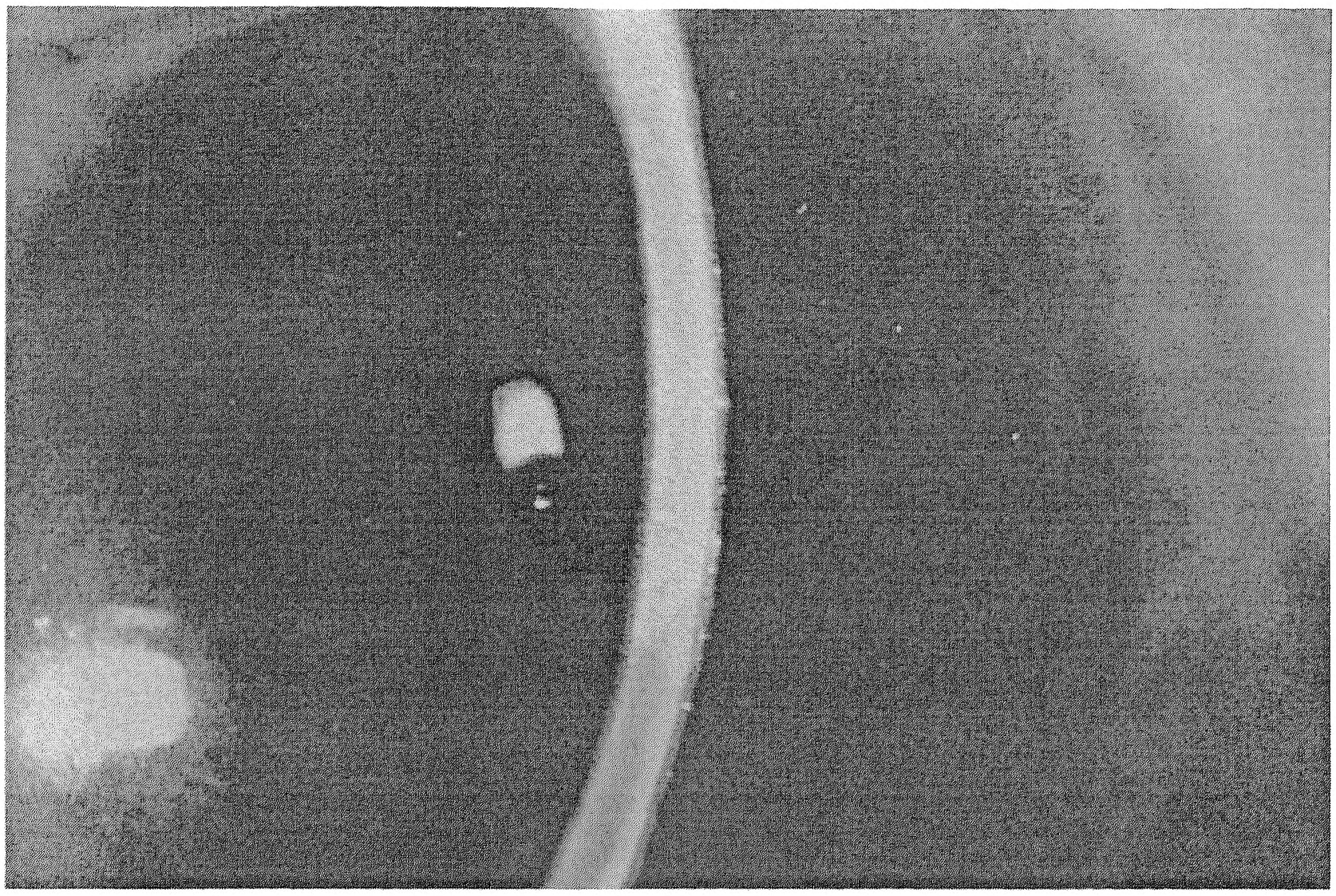

Fig. 1. Slitlamp photograph of the first patient, six months after exposure to chlorhexidine. A central epithelial defect is present but not visible. Note that stromal edema is almost absent.

Chlorhexidine and cetrimide are widely used antiseptic agents. Cialit (Sodium-2-ethyl thiobenzoixazole-5-Carboxylate) is used for the preservation of the ossicles of the middle ear. In this study we describe five patients with toxic keratopathy due to the use of these solutions.

Patients

The first patient is a 81-year-old white female who underwent an extracapsular cataract extraction in 1990. An anterior chamber maintainer was used. The infusion bottle contained chlorhexidine 1:1000 solution instead of irrigating solution. The cornea immediately became cloudy. After the mistake was discovered the surgeon irrigated the eye for more than ten minutes with a proper irrigating solution. Postoperatively her eye was red and she complained of ocular discomfort and a blurred vision. A persistent epithelial defect, corneal epithelial edema, slight stromal edema, peripheral anterior synechiae, a strongly dilated pupil and secundary glaucoma developed (Fig. 1).

Despite all kinds of therapy, including drops, ointments and bandage contactlenses, the central epithelial defect did not heal. Eighteen months after the cataract surgery a penetrating keratoplasty was performed. The donor cornea

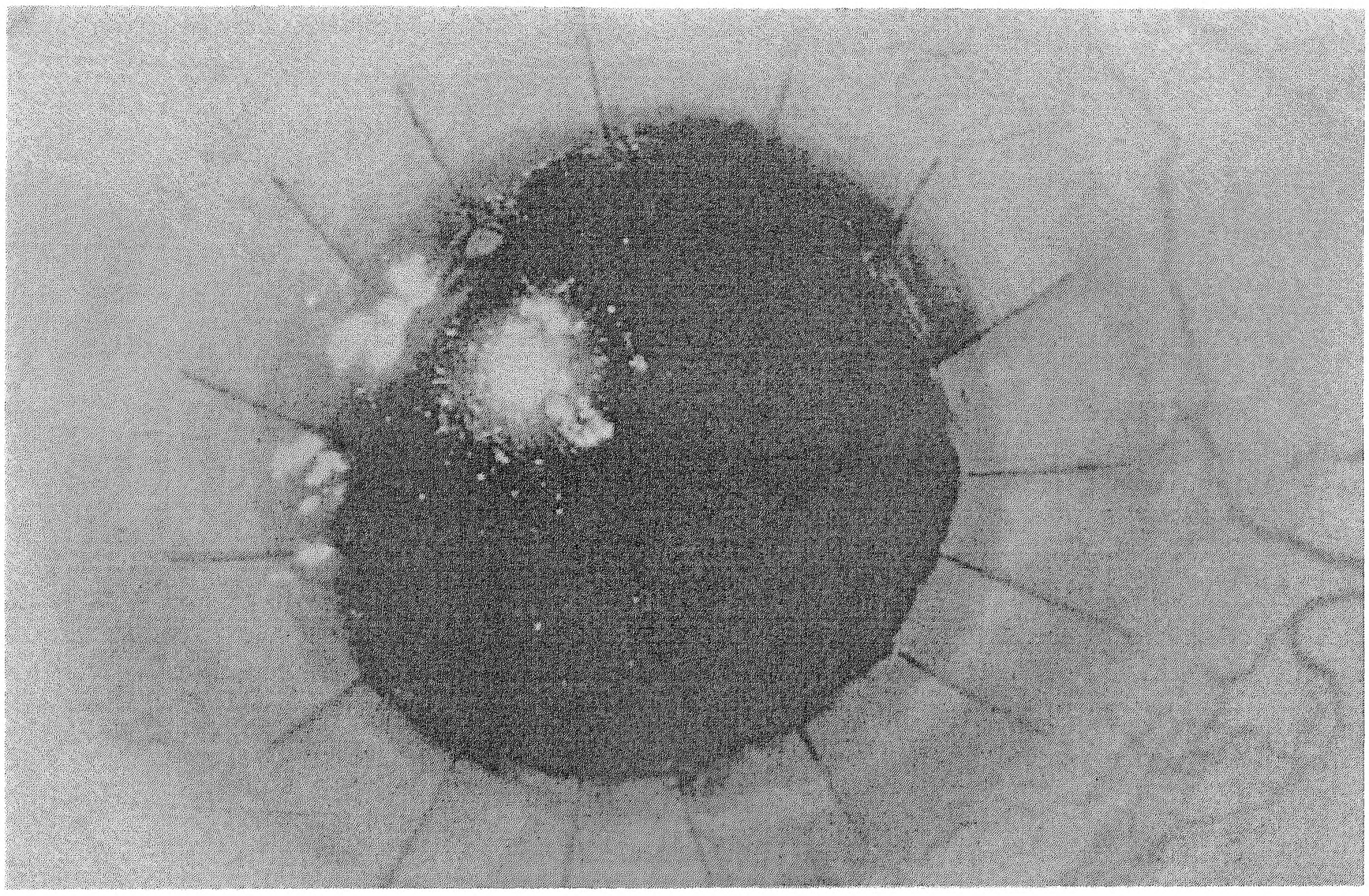

Fig. 2. Patient 1. Clear graft three months after penetrating keratoplasty.

epithelialized uneventfully (Fig. 2). The excised corneal button revealed no epithelial and no endothelial cells.

Her secundary glaucoma could not be controlled with eye drops. Twice a filtering procedure was performed. Two years after the cataract surgery, vision was light perception only due to glaucomatous damage to the optic nerve. The graft remained clear.

The second patient is a 69-year-old white male who underwent an extracapsular cataract extraction in 1990. After irrigating the anterior chamber with 'irrigating solution' the cornea became cloudy. The surgeon rightly concluded that something was wrong with the irrigating solution and requested a new bottle. With the new bottle the eye was irrigated for five to ten minutes. The cornea did not clear up. The supervisor was asked to come to the operation room. She checked the label on the two bottles and discovered that both bottles contained chlorhexidine 1:666 solution instead of anterior chamber irrigating solution. After the operation the patient complained of ocular discomfort and blurred vision. Hyperaemia of the conjunctiva, chemosis, a large persistent epithelial defect, slight stromal edema, Descemet's folds and a maximal dilated pupil developed. Flare and cells were present in the anterior chamber.

The epithelial defect persisted for two years, stromal edema increased and deep vessel ingrowth became visible into the cornea. In 1991 a bacterial ulcer

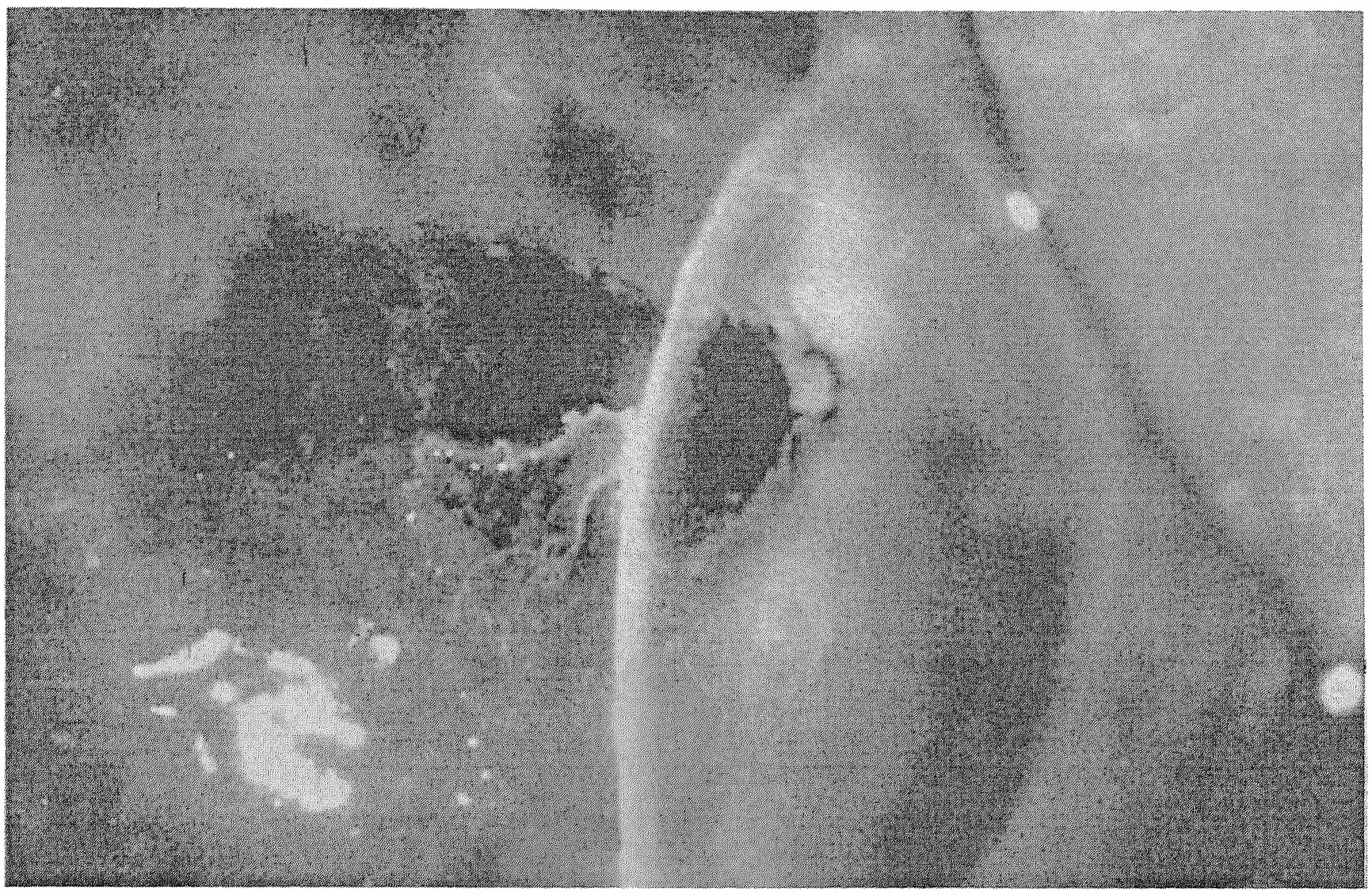

Fig. 3. Slitlamp photograph of cornea of the third patient three months after exposure to cetrimide. An epithelial defect in the centre of the cornea with calcium deposits is visible. Note the absence of marked stromal edema.

developed in the persistent epithelial defect. Secundary glaucoma caused a severe damage of the optic nerve. No visually evoked potentials were recordable. Two years after the cataract surgery the cornea was covered with a conjunctival flap.

The third patient, a 87-year-old white male with macular degeneration of both eyes underwent a cataract extraction in 1992. During irrigation-aspiration the lens capsule ruptured and a second bottle with irrigating solution was used. This second bottle unfortunately contained cetrimide 1:1000. In less than 30 seconds the cornea became cloudy. The eye was immediately irrigated with a balanced salt solution for ten minutes. Postoperatively the eye was red and the patient complained of blurred vision. A persistent epithelial defect developed in the centre of the cornea with calcium deposits (Fig. 3).

Although epithelial edema and bullae developed, only slight stromal edema could be observed (Fig. 3). Four months after the cataract surgery a penetrating keratoplasty was performed. Light microscopy revealed an epithelial defect and epithelial edema. Bowmans layer was absent in some areas. There was no marked loss of keratocytes. Descemet was intact and a damaged thin endothelial cell layer was present. One year after the keratoplasty the

Table 1. Visual acuity and follow up of five patients with toxic keratopathy

Cataract operation (year)	Irrigating solution	Follow up (months)	Visual acuity
1990	chlorhexidine	36	l.p.
1990	chlorhexidine	31	l.p.
1992	cetrimide	16	0.3
1992	cetrimide	13	0.3
1993	cialit	12	0.7

graft was clear. Visual acuity was 0.3 due to the macular degeneration. His secundary glaucoma was controlled with eye drops.

The fourth patient is a 71-year-old white male who underwent an extracapsular cataract extraction in 1992. The anterior chamber was irrigated with cetrimide 1:1000. A bullous keratopathy, stromal edema and a dilated pupil developed. The iris became atrofic and periferal anterior synechiae developed. A penetrating keratoplasty was performed seven months after the accident. Light microscopy revealed an epithelium of very variable thickness. In the centre it was very thin. In the perifery of the cornea some fibrous tissue was found between the epithelium and Bowmans layer. Granulocytes were observed in the superficial stroma. Descemet was intact. Between Descemet's membrane and the extremely attenuated endothelial cells (if present at all) a posterior collagenous layer was present. The patient developed secundary glaucoma. Three months after the keratopathy a filtering procedure with Mytomicine C was performed. Six months after the keratoplasty, vision was 0.1 with S+16 and 0.3 with pinhole. The eye had a tension of 11 mm Hg by applanation tonometry. The graft was clear.

The fifth patient is a 80-year-old white female who underwent an extra capsular cataract extraction in 1993. The anterior chamber of the eye was irrigated with cialit 0.02%. Cialit (Natrium-2-ethyl-mercury thiobenzoixazole-5-Carboxylate) is used for the preservation of the ossicles in the middle ear. The cornea immediately became cloudy. A penetrating keratoplasty was performed for bullous keratopathy with marked stromal edema four months after the cataract operation. Light microscopy of the cornea revealed a thin epithelial layer with intercellular edema and bullae between epithelium and Bowman's layer. In the anterior half and the perifery of the stroma keratocytes were discerned. The posterior half of the stroma was almost completely

devoid of keratocytes. Descemet's membrane was normal. The endothelial cell layer was completely atrofic. Eight months after the keratoplasty, vision was 0.7 with S-1.50=C+3.50;125°. The graft was clear. The intraocular pressure was 10 mm Hg by applanation tonometry.

Visual acuity of our five patients is summarized in Table 1.

Discussion

In this study we present five patients with severe corneal damage due to the accidental use of chlorhexidine, cetrimide and cialit solutions in the anterior chamber of the eye. These solutions are toxic to endothelial and epithelial cells in the rabbit [1–2]. Endothelial and epithelial toxicity has been demonstrated by Hamed *et al.* in two patients and by Varley *et al.* in one patient after preoperative preparation of the face with Hibiclens [2–3]. Hibiclens contains a mixture of 4% chlorhexidine gluconate, 4% isopropyl alcohol, purified water, FD & C Red #40, adjusted to a PH of 5.0 to 6.5. The authors observed a persistent epithelial defect, epithelial and stroma edema and cornea clouding after the exposure to Hibiclens. In Varley's patient light and electron microscopy revealed epithelial edema with bullous changes, marked loss of keratocytes, a thickened Descemet's membrane and an attenuated, disrupted endothelial cell layer [3]. Although in our patients chlorhexidine and cetrimide solutions were irrigated in the anterior chamber the solution left the eye through the surgical opening and it is likely that some irrigating solution might have been in direct contact with the corneal epithelium. However the corneal endothelium has been continuously in contact with the irrigating solution and we think it likely that the corneal lesions are mainly due to damage at the endothelial side. Apparently, chlorhexidine and cetrimide could penetrate into the corneal stroma after disruption of the endothelial cell layer.

In three of our five patients the corneal stroma was not very edematous for a long time after the exposure, although the endothelial cell layer was severely damaged, disrupted or absent (patients 1, 2 and 3). This is remarkable and cannot be explained easily. Visual acuity in Varley's patient was 0.25 [3] 6 days after the exposure. Two weeks after the event the corneal stroma became diffusely edematous but not very edematous. The corneas of Hamed's patients were hazy two weeks after the incident and became progressively more opaque over a follow-up period of 3 and 18 months respectively. The extent of corneal edema was not mentioned specifically in this paper. Corneal hydration is regulated by a barrier function and an ionic transport of the endothelium and epithelium, the swelling pressure of the stroma, the intraocular pressure and evaparation of water from the corneal surface.

Due to the severely damaged endothelium and absent epithelium the barrier functions and ionic transport are lost. The intraocular pressure has little effect on the stromal thickness and was within normal limits anyway.

The persistent epithelial defect will enhance evaporation of fluid from the cornea but this cannot explain the limited stromal swelling, because in the course of time, although the epithelial defect persisted, the corneas became more edematous. It might be possible that a direct toxic effect of chlorhexidine 1:1000 to the stroma prevented swelling. To test this hypothesis four human corneas with scleral rim endothelial side up were filled with chlorhexidine 1:1000, two of them during two minutes and the other two during ten minutes. The cornea's were then rinsed with BSS and submerged in MEM tissue culture medium. In the MEM tissue culture medium these cornea's swelled enormously.

It is possible that in the living eye a fibrinous layer adherent to the abnormal endothelium might prevent severe stromal edema during the first weeks. Such a layer has been found in the rabbit [2]. We think this is the most likable explanation. Four of our five patients developed secundary glaucoma. Only the fifth patient, with a relatively short follow-up, did not (yet) develop glaucoma. Two patients lost their vision due to secundary glaucoma (Table 1).

Cataract surgery is usually a very succesful procedure. About 35.000 eyes are operated in the Netherlands annualy. Between May 1990 and January 1993 approximately 100.000 cataract operations were performed. It is estimated that sixty percent of the operations (60.000) were performned with commercially available irrigating solutions (Alcon BSS, Landsberg). These commercial solutions come in specially designed bottles. These bottles were not accidentally mixed up with other bottles during surgery. Forty percent of the cataract operations (40.000) were performed with an irrigating solution made by the hospital pharmacy and were delivered in bottles which are identical to the ones used for other solutions. These bottles were accidentally mixed up five times. During the European Corneal Conference it became clear that according to our colleagues the situation in our country is unique. In the majority of countries bottles different in size and shape are used for intraocular irrigating solutions. It seems very sensible and even highly desirable to adopt to that practice.

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