

Treatment of lipid keratopathy with the argon laser

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SUMMARY Twenty-two patients with lipid keratopathy were treated with argon laser photocoagulation to the feeder vessels. Two were grafted just over a week after treatment and the corneal discs examined histologically. The remainder of the patients were followed up for at least a year. In 6 cases the visual acuity improved, in 3 deteriorated, and in 10 did not change. The density and extent of the lipid deposition were diminished in 50% of cases. The commonest complications were bleeding into the lipid keratopathy and iris damage. The only serious problem was a disciform type of lipid keratopathy that flared up after treatment. Suggestions are made on improvements in the technique of laser application.

Many patients with chronic corneal inflammatory disease are left with a vascularised scar and secondary lipid deposition. Not only is this unsightly, but it may spread across the pupil, diminishing vision and causing troublesome photophobia. Treatment may be considered under 2 main headings: primary preventive and secondary measures to deal with established disease. Primary measures include adequate early treatment of keratitis to prevent infiltration and vascularisation—for example, adequate long-term topical steroid administration in herpes simplex and zoster keratitis (with suitable antiviral cover in the former)—and the investigation and treatment of any systemic lipid anomaly. Established lipid keratopathy is more of a problem. Direct removal of superficial deposits may be attempted by keratectomy, but, when they are deeper, lamellar or penetrating corneal grafting is necessary.

Obviously the results of grafting are particularly poor in a vascularised host. Much attention has been concentrated in the past on the occlusion of these new vessels in the hope that further lipid deposition may be prevented, some resorption occur, and the host made safer for grafting. The methods have included peritomy, severing or cautery of the vessels at the limbus,¹ β radiation,²⁻⁶ thiotepa,^{7,8} and cryotherapy.⁹ All these methods were assessed by Ey *et al.*¹ in the inhibition of induced vascularisation in rabbits, and they found the most effective were β radiation, thiotepa, and topical steroid. The latter is known to reduce cellular infiltration, diminish fibroplastic

repair and postinflammatory vascularisation, and reduce capillary permeability associated with inflammation of the cornea.¹⁰⁻¹² More recently, renewed attempts have been made to occlude the new vessels unresponsive to steroid with the argon laser.¹³⁻¹⁵ Cherry *et al.*¹³ treated 4 patients with lipid keratopathy and had a short-term success in closure of new vessels in all cases, but regrowth occurred in 3 patients after 6 months. We felt that by modifying the technique used for closure of small new vessels in diabetic retinopathy¹⁶ we might have something useful for early cases of keratopathy, further lipid deposits being prevented and existing lipid absorbed by macrophages passing into adjacent corneal lymphatics. However, in the more advanced cases we recognised that major irreversible structural changes had occurred in the cornea and that full recovery would be impossible.

We proposed to give due consideration to possible dangers to iris, lens, and retina during the trial. We decided to try to obtain the discs from patients grafted soon after corneal lasering.

Materials and methods

Patients with all degrees of lipid keratopathy were drawn on a voluntary basis from those attending the Western Ophthalmic Hospital and Moorfields Eye Hospital. A history and full examination were carried out and the following recorded: history and aetiology of keratitis, drug treatment, visual acuity, the extent, density, and vascularisation of lipid deposits, iris appearance, and lens clarity. They were reassessed every 3-6 months, and most patients were screened for any systemic lipid anomalies.

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Colour photographs were taken on the photo slit-lamp every 6 months at $\times 2$ magnification with identical settings, lighting conditions, and film. A careful grading was made on the density and extent of lipid deposits. Density was recorded as mild, moderate, or severe, and the extent was expressed as a fraction of the total area of the cornea. Corneal fluorescein angiography was carried out on all patients prior to treatment and thereafter every 6 months to 1 year. Vascularisation was scored as mild, moderate, or severe and a note added on the size of the stem. Earlier patients were recorded at $\times 1$ magnification on 35 mm film but later at $\times 2$ magnification on film and videotape by the technique described by Marsh and Ford.¹⁷ The videotape was particularly useful because it could be immediately and repeatedly replayed to identify vascular filling pattern and closure.

Prior to treatment with a coherent radiation 900 argon laser 1% amethocaine was instilled; the patient was cautioned to be very still and stare constantly at the fixation light. To a certain extent the instrument settings and technique varied and underwent evolution as we progressed. The aperture setting varied from 50 μm to 100 μm depending on the size of the vessels to be treated, but it was important to have the machine checked regularly for correct focusing of the beam. The intensity necessary to occlude the blood column varied from 0.2 to 0.8 watts and again depended on the state of repair of the machine, although we found it better to start at a low level and slowly increase. We used 0.1 s exposures, the slowest speed possible consistent with comfort. The illumination of the slit was kept as low as possible and the delivery system angled to the cornea so that rays were directed away from the pupil to the periphery of the iris. It was best to constrict the pupil prior to treatment.

We preferred to begin treatment just behind the limbus, occluding all the main feeder tracks seen on the angiograms (this tended to 'trap' blood columns in the cornea). Next we occluded the main veins, just corneal to the limbus, which expanded and darkened these columns, facilitating further photocoagulation. They were progressively closed or blackened towards the centre of the cornea. After we closed the large veins we returned to the larger arteries in which flow had been considerably slowed. Smaller aperture settings and more power were necessary to close them all along their course. We next tackled any remaining small vessels and found it best to treat them initially at 'cross-over' points and then fill in intermediate sections.

All treatments were recorded. We found it best to arrange 3 treatment sessions in a day owing to the tendency of anastomotic channels to open up $\frac{1}{2}$ –1 hour after initial laser treatment. So we started early in the morning, and applied the second at midday and

the last in the late afternoon. In cases of profuse vascularisation patients were initially brought back for treatment every 2 weeks. As successful closure was achieved patients returned approximately every 3 months for assessment, including repeat of angiography and further treatment as necessary.

Efficacy of treatment was judged by improvement in visual acuity, a reduction in density and extent of the lipid, and by disappearance of vascularisation. Thus, these details were carefully recorded at each visit and photographed. In 2 cases histology was obtained after laser application.

Case 1 was a 27-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Ten days later a corneal penetrating graft was carried out with immediate transfer of the disc to fixative.

Case 2 was a 30-year-old man with a history of keratitis and dense vascularised central lipid keratopathy. Photographs and angiogram were taken and laser was applied to the vessels. Eleven days later a penetrating graft was carried out with immediate transfer of the disc to refrigerated fixative.

Both discs were fixed for at least 1 hour in 2.5% glutaraldehyde buffered in 0.1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH 7.4. After initial fixation each disc was briefly washed in cacodylate buffer containing 7.5% sucrose, and the areas exposed to laser irradiation were then isolated under a dissecting microscope. Samples of irradiated and unirradiated areas of both discs were postfixed for 1 hour in 2% osmium tetroxide in 0.2 M sodium cacodylate, dehydrated through a graded series of ethanol concentrations in water, and then embedded in Epon via epoxypropane. Semithin sections (0.75–1 μm thick) were cut on glass knives and stained with alcoholic toluidine blue.

Results

Twenty-two patients were treated with laser and of them 19 were followed up for a minimal period of a year. One patient failed follow-up after 3 months and 2 received corneal transplants 1 week after treatment.

The keratopathies could be broadly classified by morphology into several types: (a) central; (b) eccentric disciform; (c) marginal; (d) diffuse interstitial; and (e) diffuse deep. Table 1 shows the distribution of patients to these groups and their aetiology.

Table 2 shows the results of treatment in the 19 patients with minimum follow-up of 1 year. It can be seen that there was improvement in visual acuity in 6 cases, deterioration in 3, but no change in 10. The density of the lipid was reduced in 9 cases, increased

Table 1 Distribution of keratopathy

Aetiology	Central disciform	Eccentric disciform	Marginal	Diffuse interstitial	Diffuse deep
HS	4	5	2	1	
HZ	1	1			
Rosacea	0	1			
Trauma	0	1			
Idiopathic	0	1			2

HS=herpes simplex. HZ=herpes zoster.

in 3, but remained the same in 7. The extent of the lipid was reduced in 11, increased in 1, and there was no change in 7. Recurrence of vessels was troublesome in 7, easily handled in 4, and not a problem in 8.

COMPLICATIONS

During lasering 6 patients developed peaking of the pupil and 7 bled into the area of keratopathy. Both of these complications had usually resolved after 2 weeks and seemed not to lead to any serious long-term problems. Most patients tolerated the treatment very well, though some found fixating difficult. Occasion-

ally, when a large vessel near the surface was treated, a hole was punched out of the overlying cornea, through which blood found its way to the surface. However, these lesions healed very well over the following days. Great care was taken to avoid hitting the iris, but it was impossible to achieve this at all times. When it was hit several reactions occurred depending on the strength and timing of the shot. Firstly, nothing appeared to happen; secondly, a sudden spurt of cells and debris appeared in the adjacent aqueous drifting upwards, often accompanied by the production of an air bubble on the iris and a faint popping sound. If a major radial artery to the sphincter was hit peaking occurred.

The commonest late complication occurring in nearly all cases was iris atrophy. This obviously lay under the treated area and was chiefly stromal. The pigment epithelium was visibly breached in a few cases only. In 2 the pupil was permanently peaked. These complications rarely gave rise to a visual or cosmetic problem. There was no biomicroscopically observable lens defect as a result of treatment in any of the cases (the longest follow-up period being 5 years). So far as we are aware, the retina was not

Table 2 Results of laser therapy in 19 cases of lipid keratopathy

Case	Distribution of lipid	Density	Extent of cornea	Vascularity	Stem	Amounts of laser (sittings)	Density	Extent	Visual acuity (Snellen's)	Vascularity
1	Marginal	Mild	1/9	Mild	Several	114 (2)	Less	Less	Same	A little recurrence
2	Marginal graft host junction	Moderate	1/10	Moderate	Narrow	1154 (3)	Much less	Much less	Same	No recurrence (Fig. 1)
3	Graft host junction	Moderate	1/8	Moderate	Narrow	868 (3)	Less	Same	Same	Minimal recurrence
4	Eccentric disciform	Severe	1/3	Moderate	Several	4023 (14)	Less	Less	Same	Constant recurrence
5	Eccentric disciform	Severe	1/2	Moderate	Multiple	2411 (5)	Same	Same	Same	Constant recurrence
6	Failed follow-up at 3 months									
7	Eccentric disciform	Moderate	1/4	Profuse	Broad	891 (1)	Less	Less	Same	Some recurrence
8	Eccentric disciform	Moderate	1/6	Mild	Narrow	68 (2)	Much less	Much less	Improved	Minimal recurrence (Fig. 2)
9	Eccentric disciform	Moderate	1/2	Moderate	Narrow	859 (3)	Much less	Much less	Improved	Minimal recurrence
10	Eccentric disciform	Severe	1/4	Moderate	Narrow	577 (2)	Same	Same	Same	Some recurrence
11	Eccentric disciform	Severe	1/4	Moderate	Several	2562 (4)	Same	Less	Slightly improved	Minimal recurrence
12	Eccentric disciform	Severe	1/3	Moderate	Several	2180 (4)	Slightly less	Less	Same	Minimal recurrence
13	Central disciform	Moderate	1/4	Moderate	Multiple	9417 (14)	Worse	Worse	Worse	Constant recurrence
14	Central disciform	Severe	1/4	Moderate	Narrow	331 (2)	Worse	Same	Same	Constant recurrence
15	Central disciform	Severe	1/6	Moderate	Several	1865 (3)	Same	Less	Same	Minimal recurrence
16	Central disciform	Severe	1/3	Profuse	Narrow	2592 (5)	Worse	Same	Worse	Constant recurrence
17	Central disciform	Moderate	1/6	Moderate	Multiple	3302 (7)	Same	Less	Worse	Some recurrence
18	Deep diffuse	Mild	1/4	Moderate	Narrow	704 (4)	Same	Same	Better	Some recurrence
19	Deep diffuse	Mild	1/4	Profuse	Narrow	2791 (5)	Same	Same	Better	Some recurrence
20	Superficial diffuse	Severe	1/2	Profuse	Multiple	9889 (13)	Much less	Less	Better	Constant recurrence

struck, though this was difficult to assess in some patients with dense opacities.

Two cases got obviously worse after treatment, and both were severe disciform types. The first, however, lost most of his vascularisation and was successfully grafted after 3 years. The second, unfortunately, developed a very serious disciform keratitis. This was partly accounted for by his failure to take his steroid drops after treatment, and his scarring became very dense.

HISTOPATHOLOGY

Both cases showed a similar distribution of vessels in the peripheral cornea with the anterior two-thirds of the stroma predominantly involved. Also in both patients the stromal lamellae were irregular, and centrally a marked erosion of this layer had occurred, resulting in a total central corneal thickness in case 1 of only 280 μm . Descemet's membrane was abnormally thick for individuals in their late 20s, and in some areas discrete deposits of lipid were observed within this structure close to its anterior surface (Fig. 1e, f). The endothelium in these specimens appeared relatively normal, but macrophages were often observed in contact with its aqueous aspect.

The interpretation of the irradiated areas is complicated by the secondary tissue reactions that have occurred during the postexposure periods. The most significant changes were observed in the more superficial layers of the stroma. The topography of the damage would suggest a highly localised primary damage site associated with limited heat flow from the vessels that absorbed laser irradiation. However, the lamellar structure of the stroma, with vast regions of extracellular collagen, results in an amplification of secondary tissue responses, with tissue displacement through the presence of oedema and macrophages.

Two types of reaction were seen associated with blood vessels in the superficial stroma, namely, haemorrhages (Fig. 2) and blood stasis in areas of capillary closure (Fig. 2). Many areas of haemorrhages were observed, and these were presumably coincident

with certain areas of irradiation. The haemorrhages were of various sizes, and haemolysing red blood cells could often be seen in the abnormally distended spaces between adjacent lamellae. Blood cells were particularly prominent in the region of Bowman's membrane and were often found between this layer and the basal cells of the epithelium. In many areas the disruptive effects of blood cells, macrophages, and oedema had resulted in gross distortions of the regular array of the basal cells such that they resembled those in the limbus (Fig. 3). In other areas the distortion was so gross that islands of epithelial cells were observed deep within the stroma, and some were undergoing division here.

Only 2 areas were found with incompletely healed epithelial erosions, which suggested that significant bleeding to the surface of this cornea was rare and that most sites were repaired within 10 days of exposure.

Vessels showing blood stasis with haemolysing blood cells and areas of capillary closure were usually less superficial and did not have changes in the adjacent tissues that would suggest that they were sites of irradiation. These changes in deeper vessels were probably due to interrupted flow in feeder or drainage systems. Many of these vessels were surrounded by macrophages and were abnormally swollen, both of which reactions caused further distortion of the adjacent lamellae.

In all areas where oedema and macrophages were present, but especially in the superficial layers, active keratocytes were also observed, and most of these had the rounded appearance of embryonic cells.

Discussion

We achieved some success in reducing the extent and density of the keratopathies. As expected, the early milder and marginal cases did best. The very advanced central types were devascularised, however, and made easier for grafting. We were very heartened by the one diffuse dense superficial keratitis which improved considerably. Aside from the small number

Fig. 1a, b Preoperative photograph and angiogram of patient 2 with lipid deposit at graft host junction. c, d Postlaser photograph and angiogram of patient 2 one year later. e, f Light micrograph of central cornea showing erosion of stroma and the presence of both neovascular complexes and lipid deposits. The marker is 100 μm . High-power light micrograph of the posterior cornea in 1e showing lipid deposits within Descemet's membrane and a macrophage in contact with the endothelium. The marker is 10 μm .

Fig. 2a, b Preoperative photograph and angiogram of patient 7 with lipid deposition in eccentric disciform keratitis. c, d Postlaser photograph and angiogram of patient 7 one year later. e Light micrograph of the anterior cornea showing the presence of red blood cells within the stroma resulting from small haemorrhages, and red cell packing in non perfused vessels (arrowed). The marker is 50 μm .

Fig. 3a, b Light micrograph of anterior cornea showing distortion of Bowman's membrane and the presence of numerous red blood cells trapped between the stromal lamellae. Light micrographs of both an occluded (arrowed) and (c) reopened (arrowed) vessel in case 1, both showing the presence of red blood cells between the lamellae of the adjacent stroma. The marker is 25 μm .

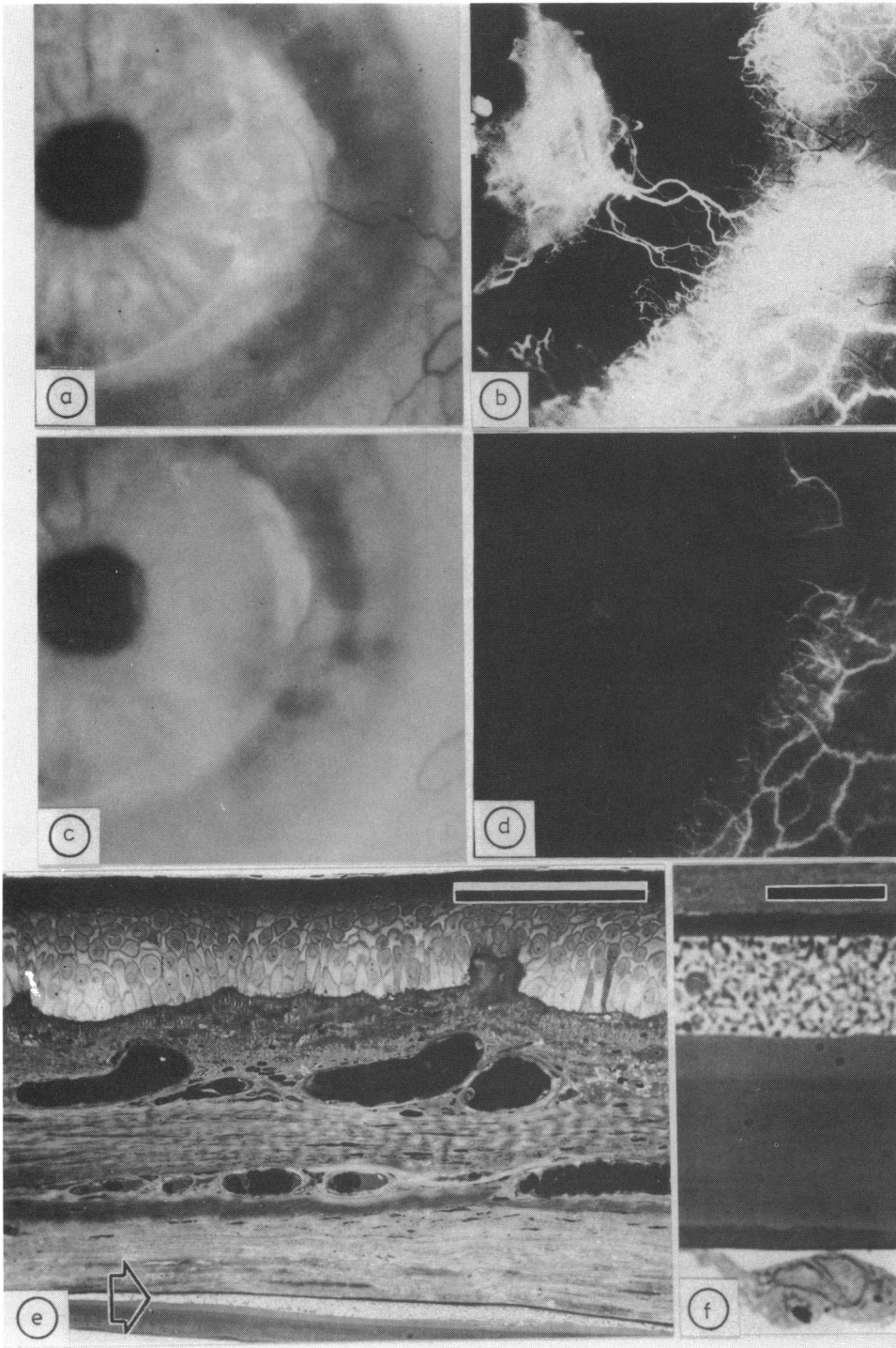


Fig. 1

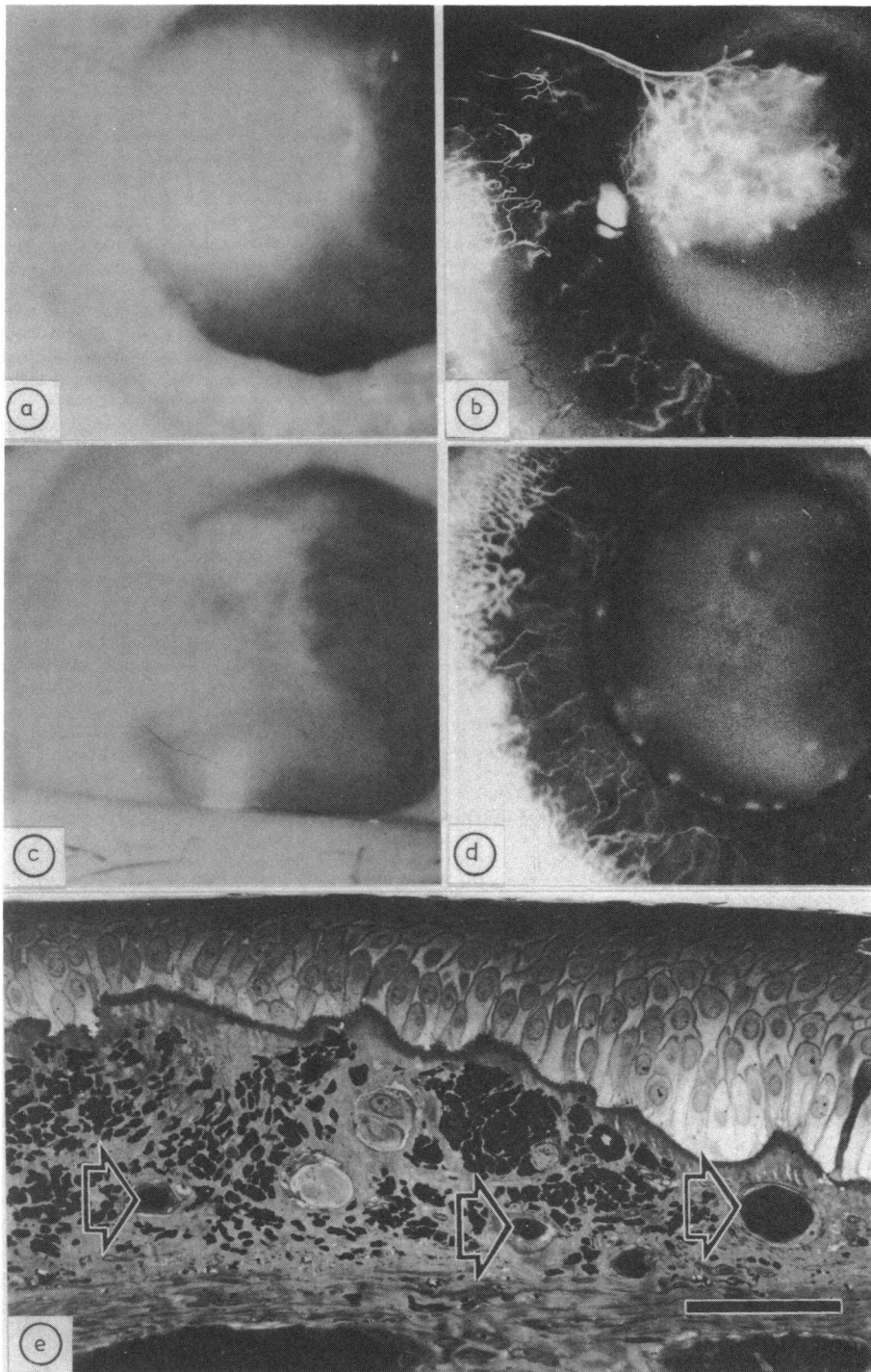


Fig. 2

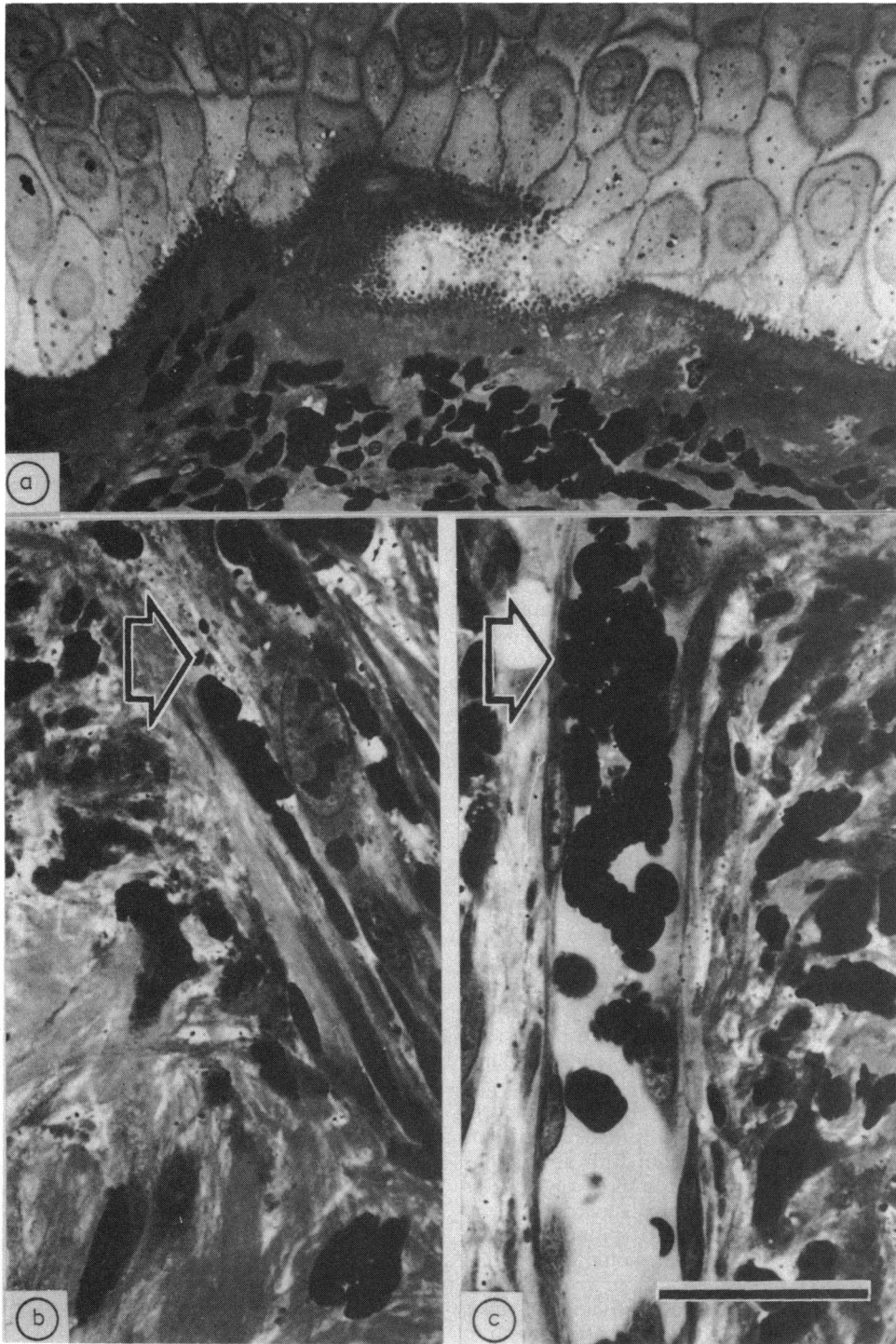


Fig. 3

of cases with improved Snellen's visual acuity many were subjectively better and their symptoms of photophobia improved. It is also notable that a large number failed to progress, contrary to the normal natural history.

The mechanisms of laser-induced vascular occlusion are not fully understood, and elucidation of this problem was not an objective of the present investigation. However, in general our observations support the conclusions drawn from similar studies on argon laser irradiation of retinal vessels.¹⁸ In essence, whatever the secondary mechanisms of vessel closure, they are dependent upon absorption and degradation of laser energy by haemoglobin. The focal irradiance on the vessels must be high to deposit sufficient energy within them to achieve damaging thermal profiles at the vessel wall. Thus attempts to close capillaries with 120 μm spot size exposures were always unsuccessful, because the area absorbing was always too small a portion of the total area irradiated. Once sufficient energy had been deposited within an irradiated vessel to induce temporary blood stasis further coagulation became relatively easier, because the cooling effect of flowing blood was lost. However, we found in our study, as in previous investigations, capillaries remained patent in areas of irradiation even when extensive necrosis of the capillary wall had occurred. Moreover evidence of intracapillary thrombosis and true fibrin deposition was rare, while small haemorrhages were common. Until detailed investigations of thermally induced occlusive processes are undertaken to optimise the required effect such surgical procedures remain empirical and depend upon the experience of the surgeon.

We are clearly concerned about the complications. Corneal transmission of short argon lines of emission is poor; thus dissipation in the cornea may be harmful.¹⁹ The human iris appears to be fairly resilient, and the commonest side effect is a temporary rise in intraocular pressure, with minimal disturbance of the blood/aqueous barrier.²⁰ We found it important to suppress the postlaser inflammatory response with topical steroid and to continue a low maintenance dose to suppress reopening of vessels. However, the iris is so close to the lens that transmission of heat from iris tissue to the lens is readily made.²¹ The lens becomes progressively pigmented with aging; thus there is an increase in absorption at short wavelengths and a greater potential for the dissipation of heat here.²² The retina may be damaged by 2 means: either an accidental direct burn, which should not occur if the beam is accurately directed; or by repetitive exposure to blue light, which has been shown to cause damage in animal eyes.²³ The complications seem to be acceptable in the short-term barring the severe iris damage, but our follow-up had to be carefully super-

vised, and multiple applications and visits were necessary in the very vascular lesions.

We can make suggestions on improvements in the technique so that there is added safety. The first is to make a very short focal length to the treatment beam by introducing a convex lens in front of the mirror of the slit-lamp to cause a widely diverging beam to develop after the point of focus, thereby decreasing the irradiance at deeper tissues. (Recently a new contact lens has become available for better lasering of lipid keratopathy. It is an Abraham lens, provided by Coherent Incorporated, UK. It is basically a scleral contact lens with an added strong convex lens cemented to its surface in one quadrant. It has an antireflective coating. The convex lens makes it possible to achieve a more convergent beam and thus avoid excessive iris damage. The contact lens also provides facilities for steadying the eye during treatment. We have found it extremely easy to use.) Secondly, the cornea, lens, iris, and retina absorb more light at short wavelengths; possibly it would be better to use a blue dye for delineating the vessels and a red laser to occlude them.

What is required now is a carefully controlled long-term study. We have started such an investigation with random allocation of cases to 3 groups: (a) has orally administered candicin; (b) has laser treatment only; and (c) has combined candicin and laser treatment.

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