Brit. J. Ophthal. (1976) **60**, 312

Pathology of practolol-induced ocular toxicity

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Practolol is a potent beta-adrenergic receptor blocking drug widely used in the management of angina pectoris, cardiac dysrhythmias, and systemic hypertension. Its immediate side-effects are usually trivial but latterly, as a result of prolonged administration, there have been several reports of more serious complications affecting multiple systems. Skin rashes, chiefly psoriasiform and erythematous with associated hyperkeratosis of the plantar, palmar, and digital surfaces, appear to be the most common disturbance (Felix, Ive, and Dahl, 1974; Wright, 1975), but conduction deafness (Wright, 1975) and intestinal obstruction secondary to a peculiar sclerosing peritonitis (Brown, Baddeley, Read, Davies, and McGarry, 1974; Meyboom, 1975), are also well known. Dryness of the mouth and nasal passages has been described and, exceptionally, a syndrome comparable to systemic lupus erythematosus with fever, nephropathy, and joint pains has been observed (Raftery and Denman, 1973).

The incidence of ocular lesions attributable to practolol is second only to that of skin changes. After a brief preliminary report (Wright, 1974), the clinical features of the eye changes were recorded in detail (Wright, 1975), and it was noted that all patients presented with the signs and symptoms of a dry eye which later progressed to an unusual form of conjunctival fibrosis. In some patients corneal opacities and severe ulceration developed. Although the pathogenesis is far from clear, immunological mechanisms may be involved. Several workers (Amos, Brigden, and McKerron, 1975; Rahi and Garner, in press) have identified antibodies with an affinity for the intercellular component of squamous epithelium as well as antinuclear factors and autoantibodies to smooth muscle.

We report here the ocular pathology in six patients with lesions attributable to practolol toxicity together with the results of antibody-labelling studies.

Case reports

CASE 1

A 75-year-old man, with angina following myocardial infarction, was treated with practolol for two and a half years. After two years' medication he developed skin eruptions and dry eyes with subconjunctival fibrosis causing entropion and requiring surgery to the lids on the right side. Subsequently the patient died as a result of further, sudden myocardial infarction.

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Histopathology

Sections of the enucleated globe showed moderately severe acanthosis of the conjunctival epithelium and complete absence of goblet cells with mild leucocytic infiltration of the underlying connective tissue (Fig. 1). On one side there was also some acanthosis of the corneal epithelium associated with destruction of Bowman's membrane and the formation of a subepithelial vascular pannus. Over much of the cornea, however, the epithelium was reduced in thickness and showed widespread cystic degeneration of the basal cells (Fig. 2*a*, *b*). Other parts of the eye were essentially normal.

Antibody labelling studies by an immunoperoxidase technique described by Taylor and Burns (1974) showed immunoglobulin in the intercellular spaces of the acanthotic conjunctival epithelium and also between individual epithelial cells of the cornea (Fig. 3*a*, *b*). The antibody belonged principally to the IgG class, although weak staining was also achieved with a peroxidase-labelled antiserum to IgM. There was no antibody staining in the non-pigmented epithelium of the ciliary body.

CASE 2

A 65-year-old man had had several myocardial infarcts and had been taking practolol regularly for over three years. After two and a half years on the drug he developed bilateral conjunctival irritation and subsequently was admitted to hospital with malaise and a psoriasiform skin rash. The ocular lesions progressed to cause filamentary keratitis with extensive conjunctival scarring and obliteration of the fornices. There was a complete absence of tear flow and six months later he developed corneal abrasions with severe ulceration which, on the left side, went on to perforate. At this juncture practolol administration was stopped but, although the skin rash resolved, the eye lesions did not improve. Six months after the drug had been withdrawn the patient died.

Histopathology

The right eye was removed post mortem and showed extreme corneal thinning with the formation of a Descemetocoele. In this area there was gross stromal lysis with moderate lymphocytic and vascular invasion.

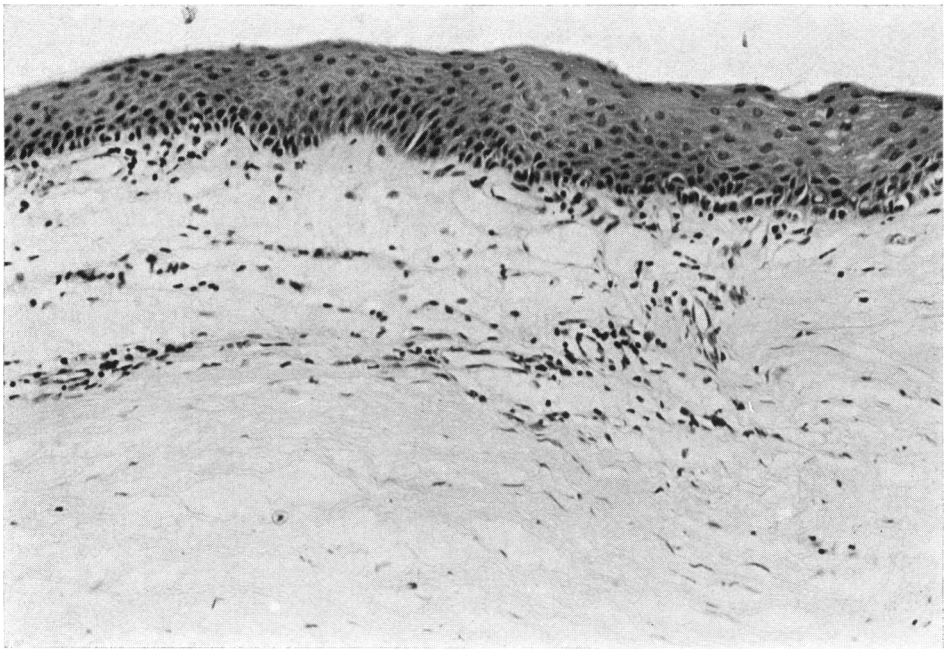

FIG. 1 *Case* 1. *Section of bulbar conjunctiva showing acanthotic thickening of epithelium with loss of goblet cells and mild lymphocytic infiltration of underlying collagenous stroma. Haematoxylin and eosin.* ×185

Towards the limbus there was again marked inflammation with the formation of granulation tissue, fibrinous exudation, and loss of much of the covering epithelium (Fig. 4). The bulbar conjunctiva was similarly inflamed with such epithelium as remained showing acanthosis and loss of goblet cells. Antibodies of both IgG and IgM classes were demonstrable between individual epithelial cells using peroxidase-conjugated antisera. A mild non-granulomatous iridocyclitis was also present together with some patchy degeneration of the retinal pigment epithelium. Other changes could be ascribed to post-mortem autolysis. Examination of the conjunctiva from the left eye also showed an intense inflammatory reaction with desquamation of all but the basal layer of epithelium. Goblet cells were absent.

The lacrimal gland showed massive fibro-fatty replacement of the parenchyma with a moderate degree of lymphocytic and plasma cell infiltration (Fig. 5). Only a few scattered islands of ductal epithelium remained and there was no sign of secretory tissue. Immunoperoxidase-labelled antibody staining showed immunoglobulin within the plasma cells, but its presence around residual glandular elements was equivocal because of artefacts caused by post-mortem diffusion. Samples of peritoneum, pleura, and pericardium were also examined and found to be very lightly infiltrated with lymphocytes with mild to moderate degrees of fibrous thickening.

CASE 3

A 72-year-old woman, who was confused, deaf, and a poor historian, developed a skin rash, dry eyes, conjunctival scarring, breakdown of the corneal epithelium, and gradual loss of corneal stroma after taking practolol regularly for several years. She had also had several episodes suggestive of small-bowel obstruction due to sclerosing peritonitis, and she eventually died from cardiac failure.

Histopathology

A biopsy of the conjunctiva seven months before death showed mild lymphocytic infiltration of the stroma and IgG/IgM antibody between the cytoplasmic membranes of the overlying squamous epithelium. The epithelium was slightly acanthotic with increased stratification and there was complete absence of goblet cells.

Examination of the eyes post mortem showed much epithelial and stromal ulceration of the central cornea with leucocytic infiltration and vascularization of the surrounding tissue. Residual corneal epithelium at the edges of the ulcers was mildly dysplastic (Fig. 6) and the acanthotic epithelium of the conjunctiva included foci of cystic degeneration. Both eyes also showed moderately severe non-granulomatous iridocyclitis, while immunoperoxidase staining not only confirmed the presence of antibody in the epithelial surfaces of the conjunctivae and corneae but also showed immunoglobulin within the lens epithelium.

Changes in other tissues included varying degrees of fibrous thickening of the pleural, pericardial, and peritoneal surfaces associated with diffuse lymphocytic infiltration (Fig. 7). No lacrimal gland tissue could be found but the parotid, submandibular, and minor salivary gland elements of the buccal mucosa showed only trivial foci of lymphocytic infiltration and no apparent tissue damage. Also, although antibody could be demonstrated in the intercellular spaces of the squamous epithelium of the buccal mucosa, tongue, oesophagus, and skin, there were no associated tissue changes.

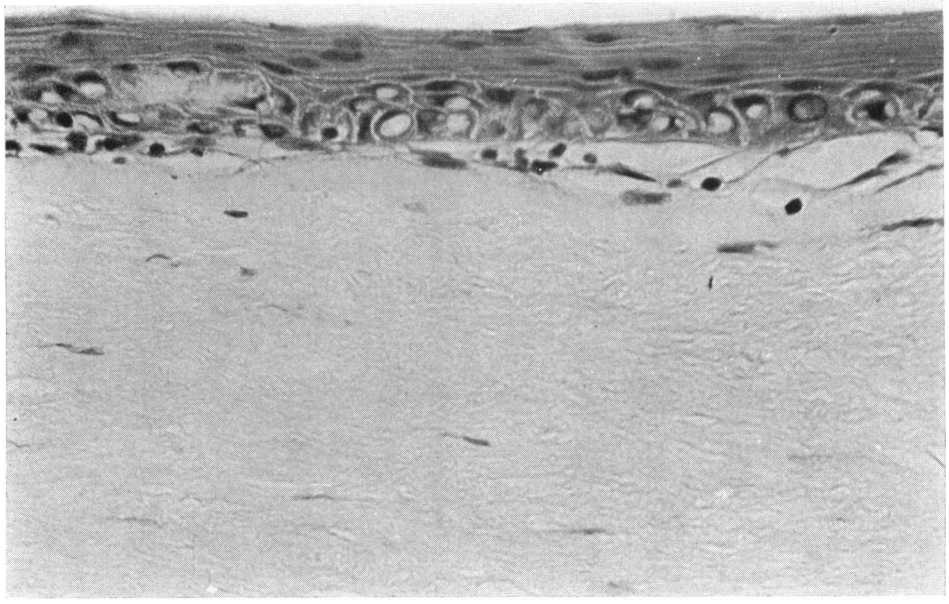

FIG. 2a *Case* 1. *Basal layers of corneal epithelium show cystic degeneration and there is a little subepithelial vascular ingrowth*

Decalcified sections of the inner ear showed neither antibody fixation nor epithelial abnormality.

CASE 4

A 65-year-old man, who had been taking practolol regularly for two years presented with iritis and increased intraocular pressure. Two months later he developed a marginal corneal ulcer in the right eye which failed to respond to carbolization and treatment with cysteine and steroids. Consequently a tarsorrhaphy was performed, but even this did not prevent the ulcer progressing to create a small perforation. The ocular tension continued to be raised and rather less than one year after ocular lesions first developed the right eye had to be enucleated.

Histopathology

There was marked vascular congestion and leucocytic

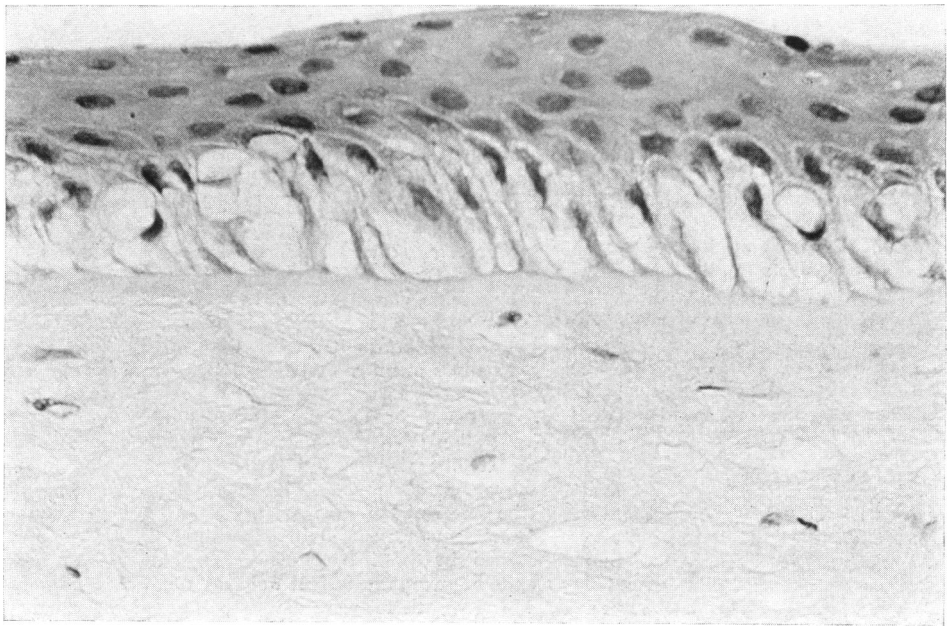

FIG. 2b *Another part of the same cornea showing intense basal cell oedema and cystic degeneration. Haematoxylin and eosin.* ×455

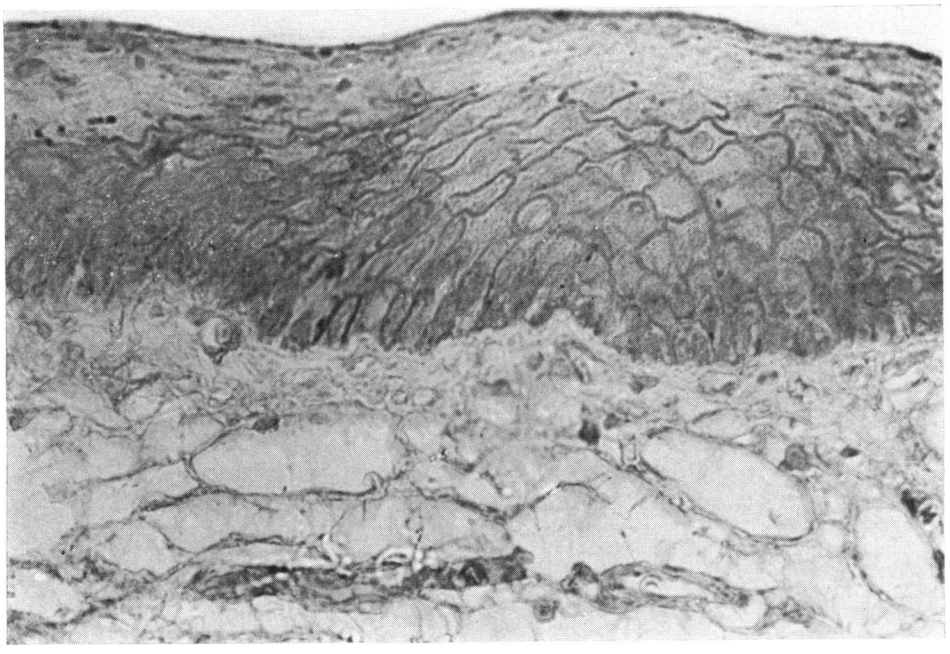

FIG. 3a *Case* 1. *Immunoperoxidase labelling of antibody located in the intercellular spaces of the acanthotic cells of the conjunctival epithelium.* ×455

infiltration of the bulbar conjunctiva associated with acanthosis of the overlying epithelium, loss of goblet cells, and considerable subepithelial fibrous tissue proliferation. The epithelium of the cornea showed cystic degeneration and absence of Bowman's membrane over a wide area with vascularization of the peripheral stroma. There was also deep stromal ulceration between the centre of the cornea and the inferior limbus with a small perforation. The iris was partially bound to the margins of the perforation and back of the cornea and there was a moderate degree of chronic iridocyclitis. The lens was cataractous with anterior subcapsular fibrosis related to the formation of posterior synechiae: rupture of the lens capsule was also seen. No significant abnormality was seen in the posterior segment of the globe.

Immunoperoxidase studies showed the presence of

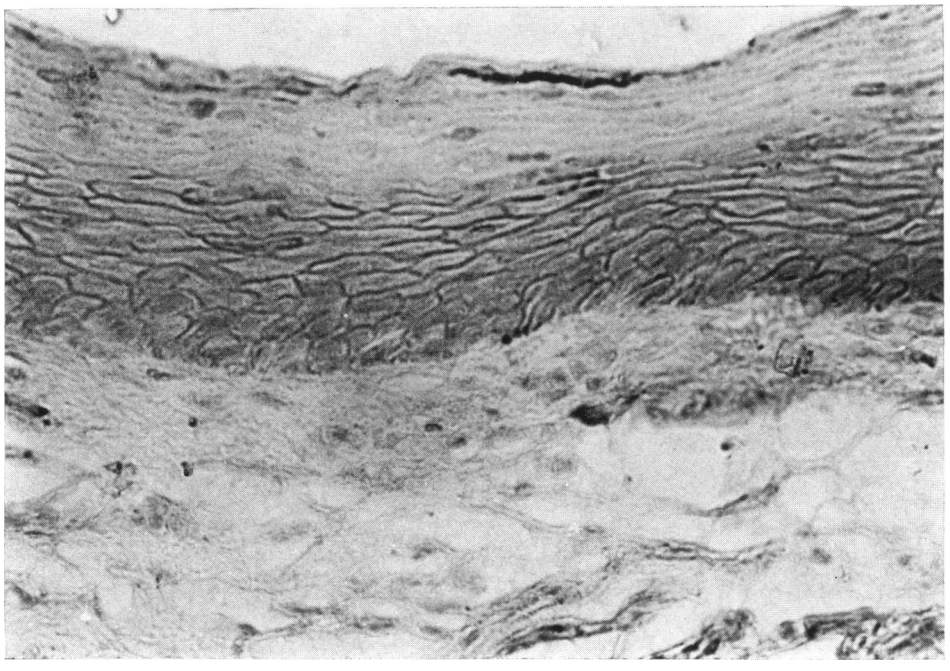

FIG. 3b *Similar preparation showing predominance of antibody fixation in the basal and prickle cell layers.* ×455

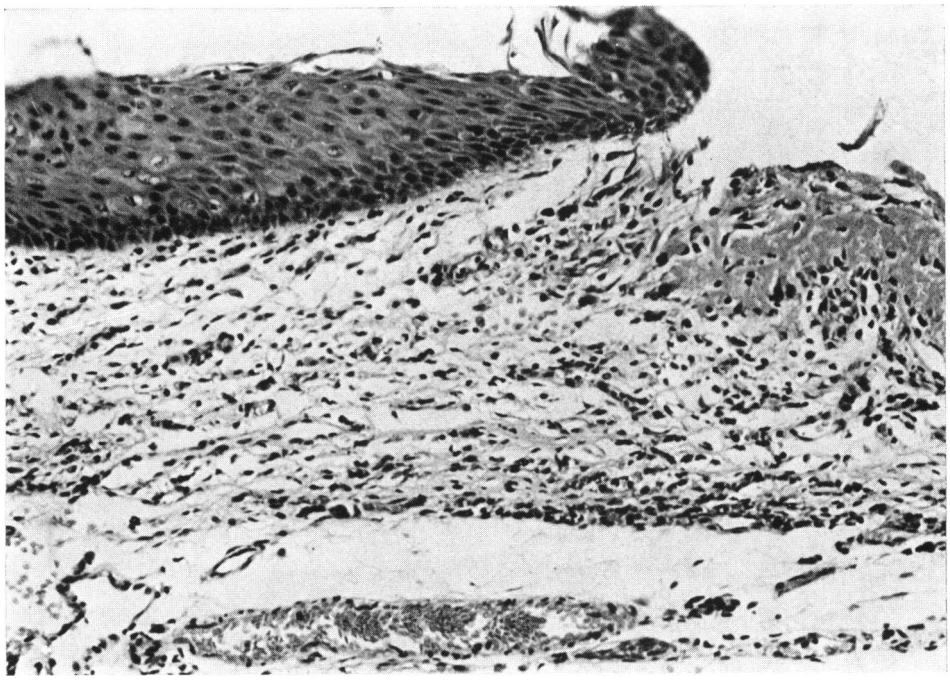

FIG. 4 *Case 2. Section of enucleated eye showing edge of deep corneal ulcer. Residual epithelium is acanthotic and there is much lymphocytic infiltration of underlying collagenous lamellae. Haematoxylin and eosin.* ×185

weak but unequivocal IgG antibody between the cells of the conjunctival and corneal epithelium.

CASE 5

A 65-year-old woman, with angina following myocardial infarction, was treated with practolol for four years. She developed hyperkeratotic skin lesions after one year and her eyes became sore after three years on the drug. Reduced tear flow with subconjunctival fibrosis developed leading to large, persistent epithelial erosions and rapidly maturing cataracts. The left cornea was covered with a conjunctival flap after intracapsular

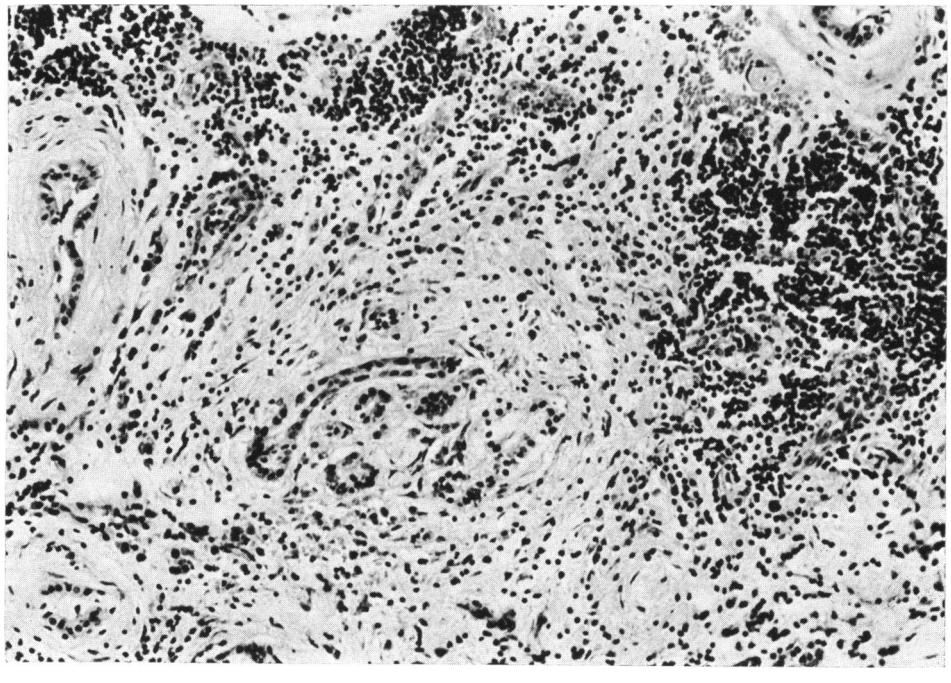

FIG. 5 *Case 2. Section showing lymphocytic and plasma cell infiltration of lacrimal gland associated with replacement of secretory acini by fibrous tissue. Only scattered collecting ductules remain. Haematoxylin and eosin.* ×185

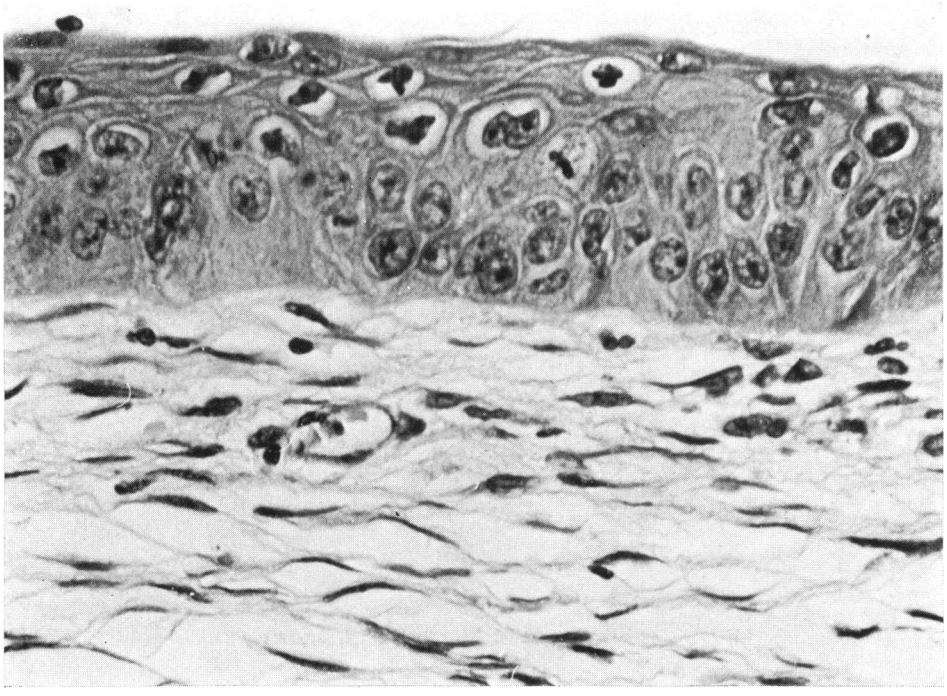

FIG. 6 *Case 3. Normal regular arrangement of corneal epithelium is disturbed and degenerate cells present in superficial layers. Bowman's membrane has been destroyed and there is fibrovascular proliferation beneath epithelium. Haematoxylin and eosin.* ×455

removal of the cataract. The right eye was managed with a soft contact lens.

Histopathology

Biopsy of the conjunctiva of the right eye showed marked acanthosis and spongiosis of the epithelium with absence of goblet cells and pronounced chronic inflammation of the underlying stroma (Fig. 8). There was also polymorphonuclear leucocytic infiltration of the epithelium but immunoperoxidase studies showed only weak antibody fixation in the intercellular spaces. Subsequently examination of the lens and a portion of iris from the left eye showed cataractous lens changes and mild iritis. Immunoglobulin, as revealed by immunoperoxidase-labelled antibody, was present beneath the capsule of the lens and in the iris stroma. In neither structure, however, was there any evidence of complement (C'_3) fixation.

Electron microscopy

There was no apparent cellular abnormality in the conjunctival epithelium apart from the absence of goblet cells and the presence of polymorphonuclear leucocytes (Figs 9, 10). The cytoplasmic membranes of individual squamous cells were intact, the desmosomal junctions in particular being normally formed and undisturbed. Similarly the hemidesmosomal junctions between the basal epithelium and the basement membrane appeared to be healthy (Fig. 11).

CASE 6

A 57-year-old man, with widespread arterial disease and hypertension, was treated with practolol for two and a half years. At the end of two years he had developed hyperkeratosis of his hands and a generalized psoriasiform skin eruption. The eyes became sore shortly afterwards with dryness, subconjunctival fibrosis, large persistent epithelial erosions of the corneae, and rapidly maturing cataract. Both eyes were treated with large doses of corticosteroids, while the left cornea was covered with a conjunctival flap and an intracapsular cataract extraction was carried out. He subsequently had several episodes of small-bowel obstruction due to fibrosing peritonitis, but these settled on conservative treatment.

Histopathology

Limited scrapings of the corneal epithelium of the right eye failed to show any morphological abnormality, although immunoperoxidase staining showed the presence of IgG antibody and the C'_3 component of complement between individual epithelial cells. Examination of the conjunctiva four months later showed an acanthotic epithelium devoid of goblet cells. Immediately beneath the epithelium there was considerable plasma cell and lymphocytic infiltration associated with reactive fibrosis. Immunoperoxidase studies of unfixed and washed tissue confirmed the presence of IgG/IgM antibody in the interepithelial spaces, but staining for complement (C'_3) was entirely negative.

Discussion

The conjunctival lesions associated with prolonged practolol administration take the form of thickening and acanthosis of the epithelium with loss of goblet

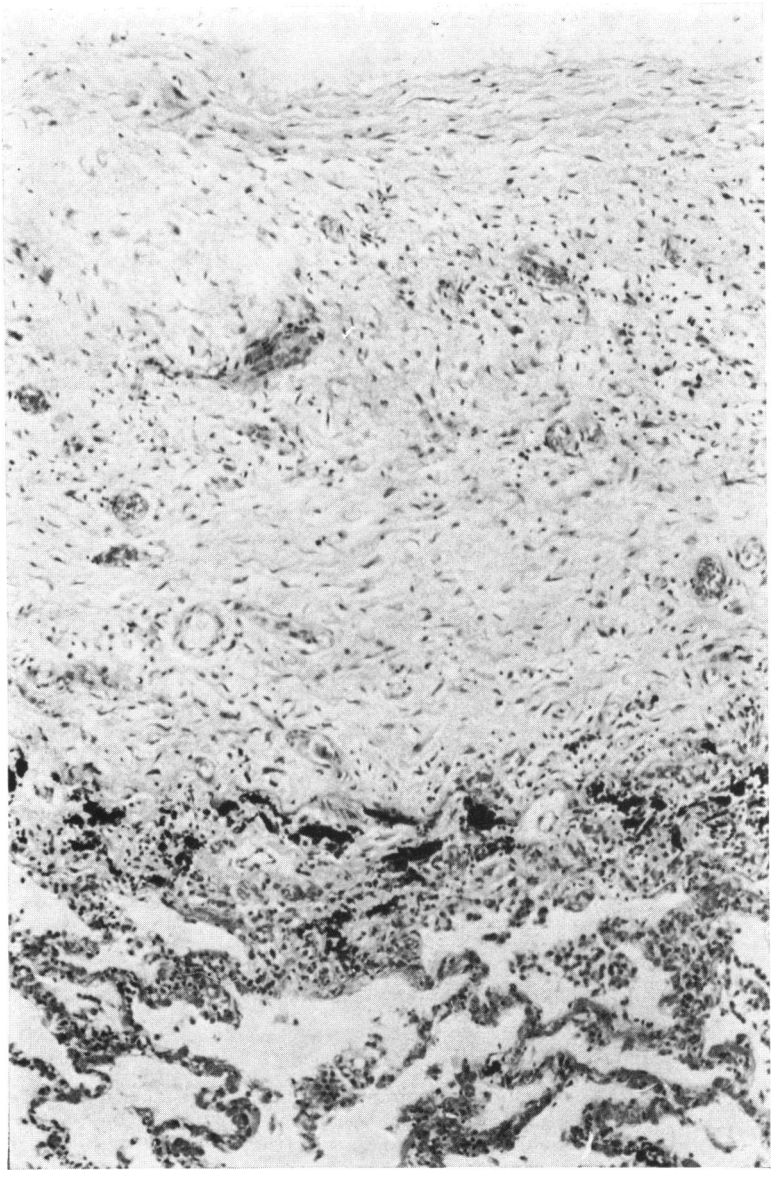

FIG. 7 *Case 3. Section of lung showing marked fibrous thickening of the overlying plasma. Scanty lymphocytes also present. Haematoxylin and eosin.* ×230

cells and chronic inflammatory changes leading to fibrosis in the underlying stroma. The corneal epithelium appears to be less obviously affected but may show cystic degeneration, while in two of the present cases there was pronounced epithelial and stromal ulceration progressing to perforation. Stromal or subepithelial vascularization was a feature of corneae showing epitheliopathy and ulceration. In part it is probably appropriate to attribute the epidermalization of the conjunctival epithelium to inadequate flow of tears, since dryness of the eye is a constant clinical finding in patients with ocular lesions (Wright, 1974; 1975).

In neither of the two cases examined post mortem could any functional lacrimal gland tissue be found. The absence of secretory IgA in the limited tear secretion (Wright, 1975; Rahi and Garner, in press) also emphasizes the failure of lacrimal gland function. Nevertheless, xerophthalmia alone is not usually associated with the measure of subepithelial fibrosis seen in the conjunctivae of eyes damaged by practolol, which suggests that the lesion might represent a combination of deficient tear flow and a primary change in the tissues of the conjunctiva. Disappearance of goblet cells, which was noted in all specimens, would probably

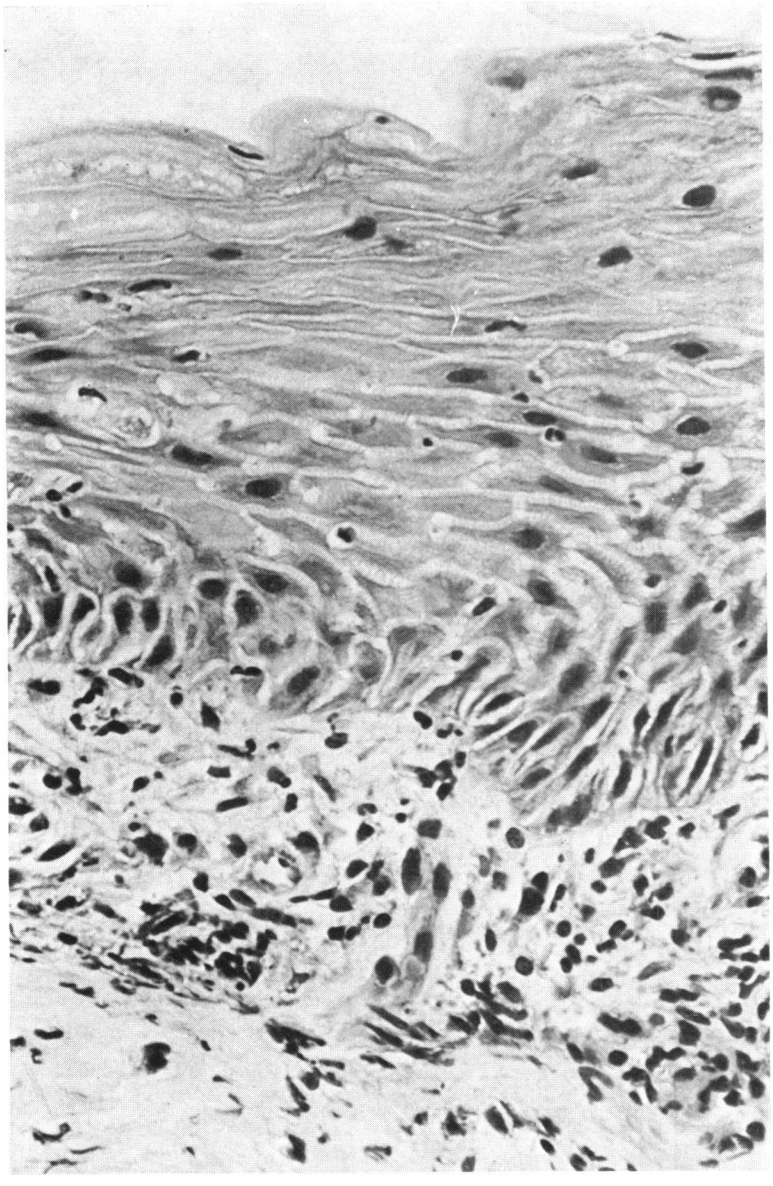

FIG. 8 *Case 5. Spongiosis of acanthotic conjunctival epithelium associated with presence of lymphocytes, plasma cells, and proliferating fibroblasts in underlying stroma. Haematoxylin and eosin.* ×455

contribute to the epithelial changes in the cornea since the mucus secretion of the conjunctiva is intimately concerned with the maintenance of corneal hydration (Lemp, Dohlman, Kuwabara, Holly, and Carroll, 1971; Dohlman, 1971). The immediate cause of the goblet cell loss is not clear but the parallel with pemphigus, benign mucous membrane pemphigoid, and Stevens-Johnson syndrome suggests that it is related to degenerative and reactive changes in the squamous epithelium. Similarly, although ulceration of the cornea is likely to be facilitated by xerosis, it is also possible that intrinsic changes in the corneal epithelium are involved, spongiosis and intraepithelial cyst formation, comparable to that observed as a result of practolol medication, having been recorded in a variety of corneal conditions in which there is defective epithelium (Tripathi and Bron, 1973). Necrosis, or 'melting' of the corneal stroma, might be a further index of an abnormal epithelium (Slansky and Dohlman, 1970).

As yet, however, the cause of the intrinsic epithelial defect is uncertain. The finding of the immunoglobulin between individual epithelial cells is reminiscent of pemphigus, in which similarly located antibodies have been described. In pem-

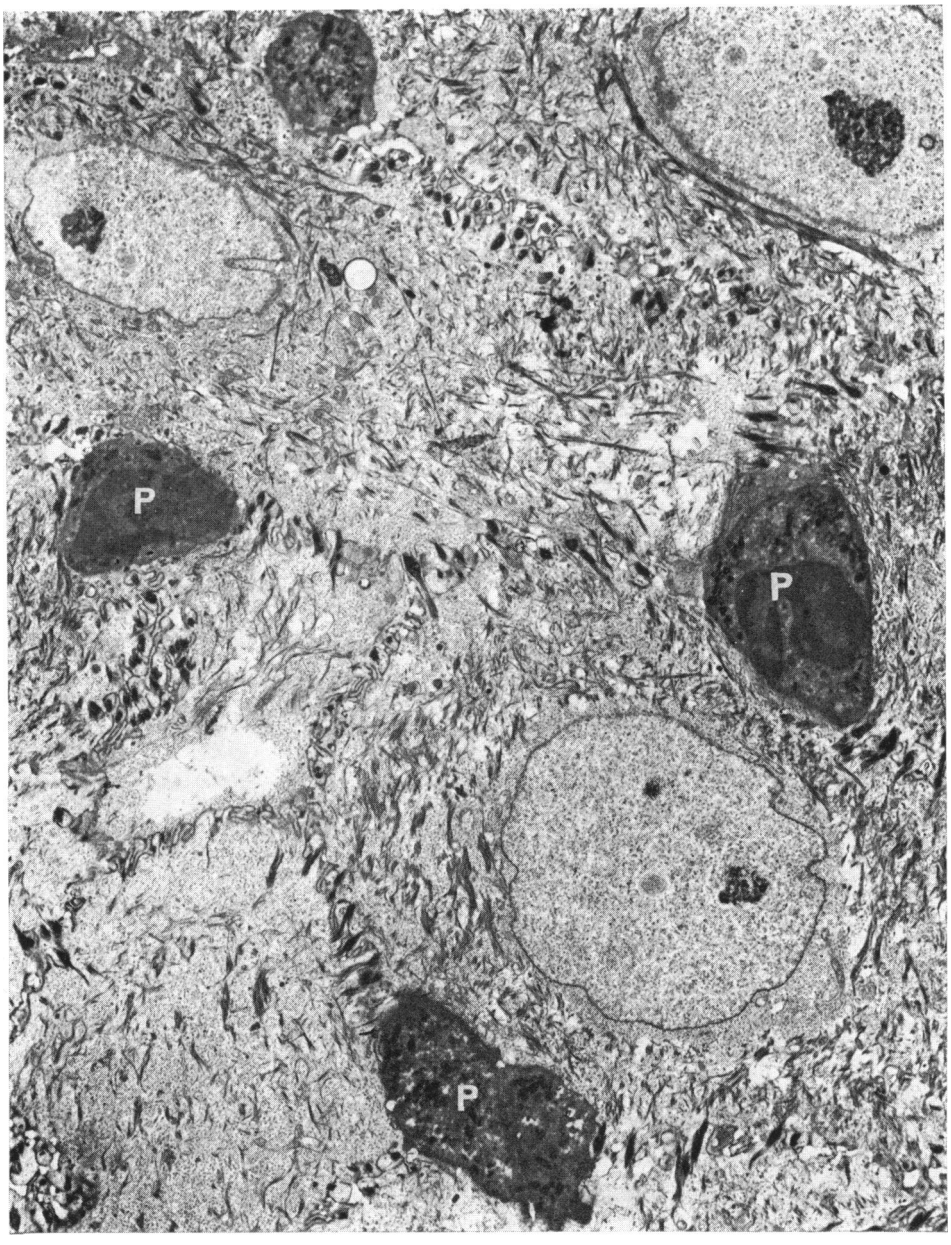

FIG. 9 *Case 5. Electron micrograph of acanthotic squamous cells in conjunctiva showing intact intercellular junctions. Scattered polymorphonuclear leucocytes (P) are present in intercellular spaces.* ×4000

phigus the antibody appears to be directed against the intercellular desmosomal attachments and exacerbations of the disease are commonly preceded by a rise in antibody titre (Sams and Jordan, 1971), while repeated injections of antiserum directly into the skin of monkeys have been claimed to provoke acantholysis (Beutner, 1973). On the other hand, some workers (Amos and others, 1975) consider the reported evidence for the toxic properties of pemphigus antibodies to be unconvincing and suggest that the antibody could be merely a cytophilic immunoglobulin which attaches in a non-specific manner to squamous epithelium. Apart from analogous uncertainties, the autoantibodies associated with practolol toxicity differ from those in pemphigus in combining with a component of the intercellular space which is removed by trypsin digestion, whereas the affinity of pemphigus antibody for epidermal cell membranes is not affected by trypsinization (Amos and others, 1975). Moreover, bullous skin eruptions comparable to pemphigus are not a feature of the

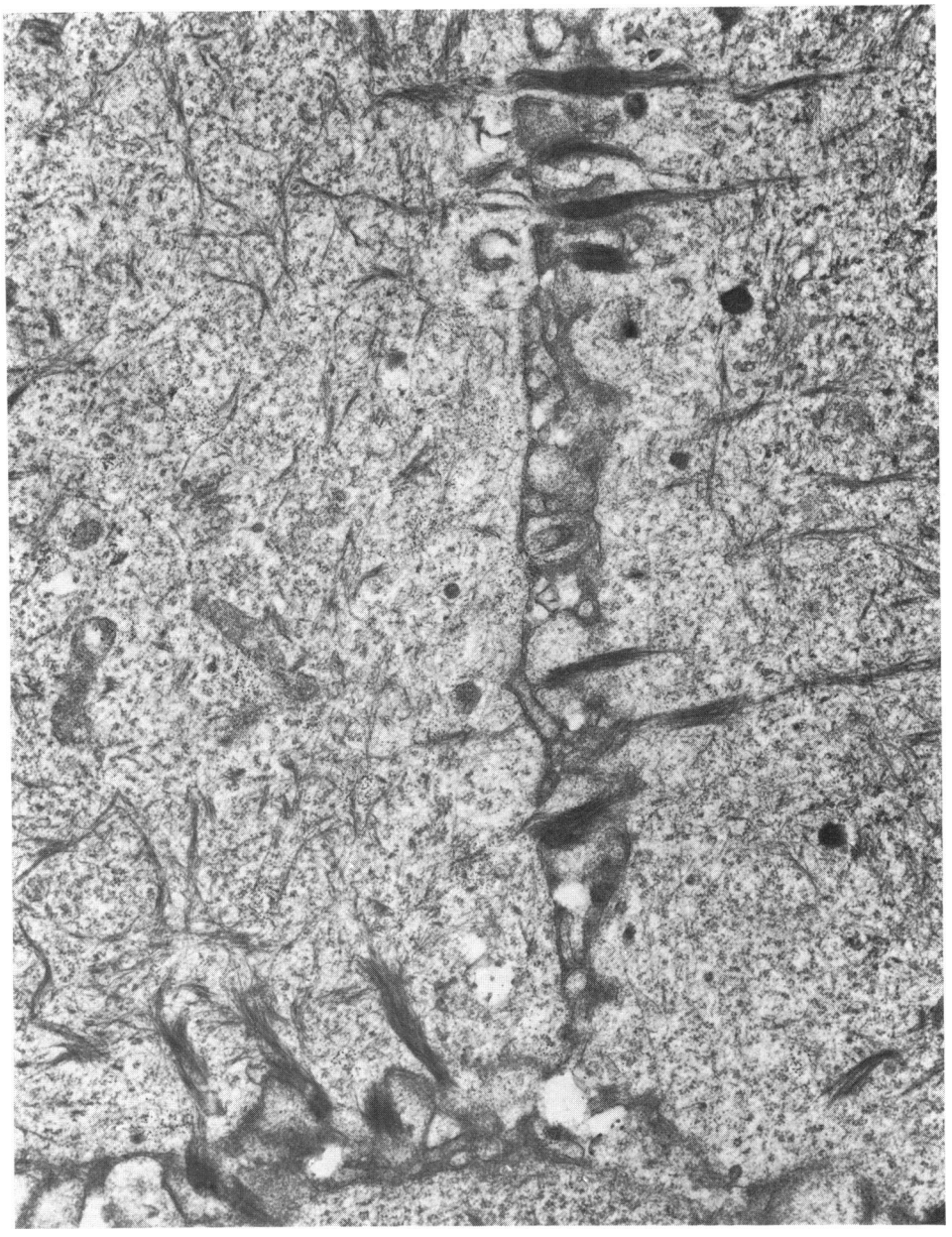

FIG. 10 *Case* 5. *Electron micrograph showing normal complement of intact desmosomal junctions between cells of conjunctival epithelium.* ×16 500

rash associated with practolol administration (Felix and others, 1974; Wright, 1975). In addition, despite our finding that fixation of immunoglobulin to epithelial cell membranes was present in unfixed tissue subjected to prolonged washing, and thus unlikely to be an artefact due to non-specific fixation of protein diffusing from the adjacent blood vessels, we were unable to demonstrate complement fixation in such tissue. This suggests that *in-vivo* activation of complement does not occur and that, consequently, the antibodies are probably not cytotoxic. In which case the formation of auto-antibodies in patients with practolol-induced ocular disease is more likely to be secondary to epithelial damage than its cause, although the possibility that the effect of the lymphoid response was impeded by topical corticosteroid application should not be overlooked.

The cause of the lacrimal gland damage is also uncertain. The presence of antinuclear factor, the evidence of reduced salivary secretion in many, the report of joint pain in occasional patients

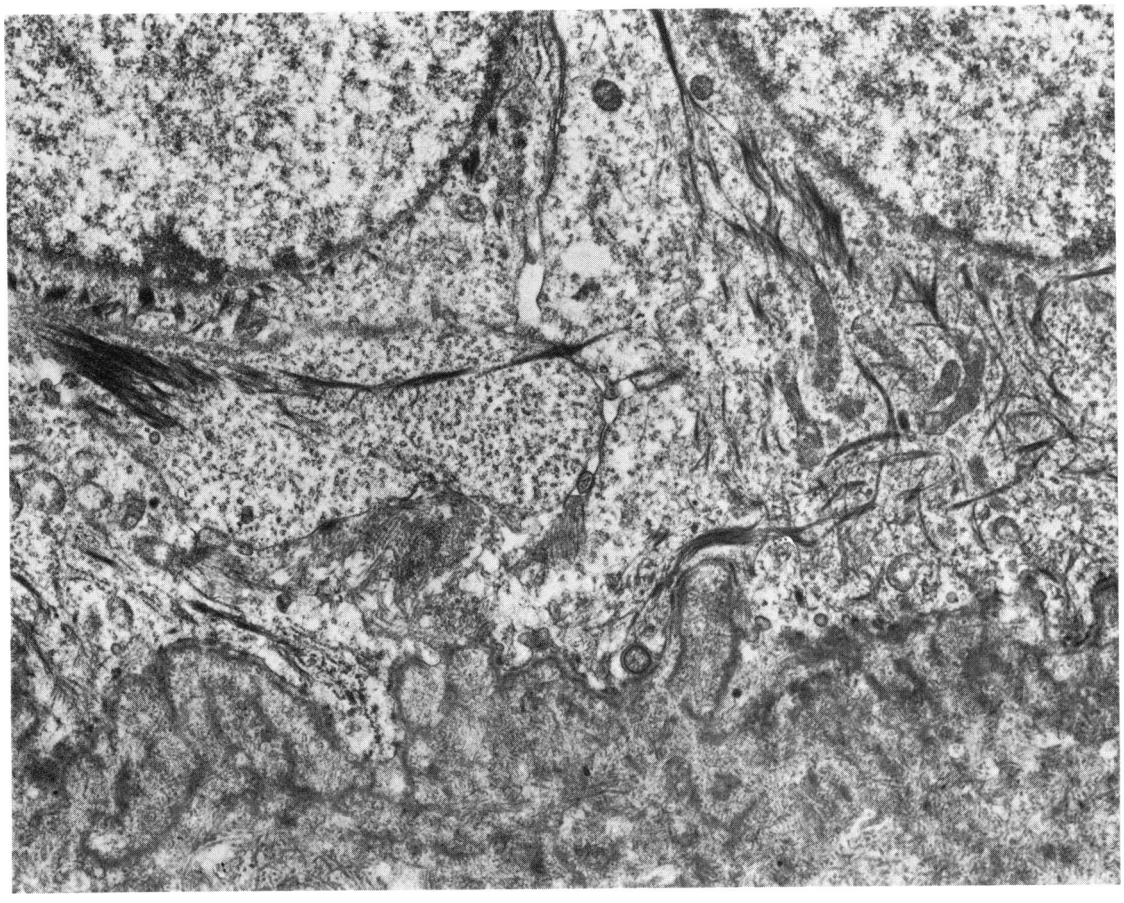

FIG. 11 *Case 5. Electron micrograph of junction between basal epithelium and its basement membrane showing absence of any structural abnormality.* ×12 500

(Raftery and Denman, 1973), and the histological evidence of lymphocytic infiltration of the gland are superficially suggestive of a Sjögrenoid lesion. Alternatively, in contrast to a predominantly immunological reaction it may be that direct drug-induced toxicity is responsible (Wright, 1975). But here again, although experiments in laboratory animals indicate that practolol is prone to accumulate in the lacrimal gland parenchyma, the drug appears to be well tolerated by these animals, neither immune response nor lacrimal damage accruing.

Because the incidence of oculodermal toxicity in patients receiving practolol is of a quite low order it is probable that an individual idiosyncrasy, possibly genetically determined, is involved.

Of the two cases in which the lens was studied one was cataractous and both showed some fixation of antibody in the subcapsular epithelial region. The absence of detectable complement fixation, however, suggests that the uptake was possibly non-specific and probably inconsequential.

The finding of fibrous thickening of the peritoneum, pleura, and pericardium in cases 2 and 3 is analogous to the serosal lesions described by Windsor, Kurrein, and Dyer (1975), although in our cases the degree of thickening was insufficient to produce such intractable abdominal symptoms as those described in other reports (Brown and others, 1974; Meyboom, 1975; Windsor and others, 1975).

Summary

The ocular side-effects of prolonged practolol administration concern the cornea and conjunctiva and are related to deficient tear secretion and the formation of an autoantibody which has an affinity for the intercellular zones of squamous epithelium. Histopathological study of six cases, including a review of the necropsy findings in two, showed destruction of lacrimal gland tissue, epidermalization of the conjunctival epithelium, with epithe-

liolysis and stromal ulceration of the cornea leading to perforation in two patients. Immunoperoxidase studies showed fixation of specific antibody in the corneal and conjunctival epithelium but, in the one case in which the tissue could be adequately studied, complement fixation could not be demonstrated. Possibly, therefore, the immune response in patients with practolol-induced ocular damage is secondary to the epithelial disturbance rather than its cause.

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