CHRONIC PROGRESSIVE CONJUNCTIVAL CICATRISATION

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SUMMARY

The aim of this review is to demonstrate the spectrum of conditions encompassed by the term 'chronic progressive cicatrising conjunctivitis', to discuss mechanisms of conjunctival scar tissue formation and to describe the sequelae and therapeutic options in this potentially blinding condition. Chronic progressive cicatrising conjunctivitis is found in association with some mucocutaneous disorders (cicatricial pemphigoid, linear IgA disease), as part of paraneoplastic syndromes and after long-term treatment with certain systemic and topical medications (pseudo-pemphigoid). Recent studies on the conjunctiva of pemphigoid patients indicate that macrophages may play a pivotal role in chronic progressive conjunctival cicatrisation. They mediate the transition from inflammation to scar tissue by secretion of fibrogenic cytokines. There is evidence that similar mechanisms are involved in the other fibrosing conjunctival disorders. Sequelae of chronic conjunctival cicatrisation include the obstruction of lacrimal and meibomian glands, tear film alterations, trichiasis, keratopathy and blindness. Present possibilities and future options for the treatment of this condition are discussed.

Lids, tears, mucous and epithelial surfaces interact to produce a complex physico-chemical system that ensures an optimal corneal environment. Cicatrisation of the conjunctiva may cause imbalance of this system, resulting in changes which are incompatible with a corneal clarity and normal eyesight.

Many types of conjunctival inflammation resolve without any scarring. Purulent conjunctivitis, for instance, even when recurrent, usually leaves no scars. Other disorders (Table I), including all types of membranous conjunctivitis, can be associated with cicatricial changes.[1] Most types of cicatrising conjunctivitis are characterised by an acute phase of tissue injury with subsequent scarring. Cicatrisation is thus temporally limited after withdrawal of the noxious factors, leading to a static fibrous scar. Alternatively a chronic progressive course can be found with mucous membrane pemphigoid, linear IgA disease, as part of certain paraneoplastic syndromes and after long-term treatment with systemic and topical medications.

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Table I. Conditions associated with cicatrising conjunctivitis

Physical
Heat
Ionising radiation
Chemical
Infection
Trachoma
Membranous conjunctivitis (bacterial and viral)
Oculocutaneous disorders
Erythema multiforme
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Mucous membrane pemphigoid
Linear IgA disease
Bullous pemphigoid
Epidermolysis bullosa
Dermatitis herpetiformis
Pemphigus group
Chronic atopic keratoconjunctivitis
Other associated systemic disorders
Rosacea
Sjögren's syndrome
Inflammatory bowel disease
Graft-versus-host disease
Immune complex diseases
Paraneoplastic syndromes
Drug-induced
Systemic
Topical (pseudopemphigoid)

CHRONIC PROGRESSIVE CICATRISING CONJUNCTIVITIS

Benign Mucous Membrane Pemphigoid

Benign mucous membrane pemphigoid or cicatricial pemphigoid is a relatively rare disease, affecting more women than men with presentation usually in the seventh decade.[2,3] It is characterised by blisters or bullae of the mucous membranes and skin, with a tendency to scar formation.[4] Conjunctival involvement, which is often asymmetrical, occurs in approximately 70% of patients with this disorder.[5,6] Blisters are rarely seen in the eye, but it is the invasion of the submucosa by newly formed connective tissue with subsequent contraction which is regarded as the essential destructive process in the conjunctiva.[7]

On the basis of findings from animal and immunohistochemical studies[2,8–15] a proposed pathogenesis for lesions in cicatricial pemphigoid has been described.[16] Circulating antibodies, which may be found in up to 40% of patients,[13] bind to an antigen of the basement membrane, resulting in the biopsy finding of linear deposits of immunoglobulin. Complement fixation occurs and an inflammatory infiltrate consisting of polymorphonuclear leucocytes, macrophages, lymphocytes, plasma cells and mast cells forms in the subepithelial tissue.[2,17–21] The number of neutrophils and macrophages within subepithelial tissue reflects clinical disease activity.[21] Fibroblast activation (see below) and hyperproliferation of fibroblasts[22] lead to subsequent scar tissue formation.

Early ocular symptoms are those of any non-specific chronic conjunctivitis and may include conjunctival irritation, hyperaemia and discharge.[1] An early clinical sign is the involvement of canthal structures,[23] leading to shallow canthal recesses and in the medial canthus to a loss of architecture with flattening or obliteration of the normal conjunctival folds, plica and caruncle (Fig. 1).[24] Other early signs are conjunctival thickening and white lines of subepithelial fibrosis, which usually involve first the lower fornix (Fig. 2). Progression of the subepithelial fibrosis results in shrinkage of the fornices and, as the process continues, in the formation of symblephara with their sequelae.[2] Conjunctival ulceration (Fig. 3) may occur as part of an acute manifestation of the ocular disease and is followed by further, rapid progression of cicatrisation.[25]

The diagnosis of benign mucous membrane pemphigoid is based on clinical findings and on the immunopathological findings at biopsy. In addition to the conjunctival findings, extraocular involvement may support the diagnosis of presumed cicatricial pemphigoid. Sites which can be affected by benign mucous membrane pemphigoid include the oral (Fig. 4) and nasal mucosa, the larynx, oesophagus, vagina, urethra and anus. Involvement of the skin and scalp is found in about 20% of patients.[26] The linear deposition of immunoglobulin and/or complement in the ocular or extraocular mucous membranes shown by direct immunofluorescence (Fig. 5) is regarded as diagnostic.[26] This finding is characteristic but non-specific,[12] and its absence does not exclude cicatricial pemphigoid. Furthermore, immunoglobulin deposition at the conjunctival basement membrane can disappear after several months (W. Bernauer, P. Wright and J. N. Leonard, unpublished data) – a phenomenon which was described by Fern and coworkers when pemphigoid patients were treated with dapsone.[27]

Linear IgA Disease

Linear IgA disease primarily affects the skin, resulting in a rash with spontaneous blistering but without cutaneous scarring.[26] The skin lesions may look similar to those seen in dermatitis herpetiformis or bullous pemphigoid.[28] Mucous membrane involvement in linear IgA disease is frequent and can lead to ocular lesions indistinguishable from those of benign mucous membrane pemphigoid.[29,30] In many patients, however, eye involvement is asymptomatic and the course of the ocular disease seems to be less aggressive than in classical benign mucous membrane pemphigoid associated with IgG basement membrane zone antibody deposition.[1,29]

Homogeneous linear deposits of IgA along the dermal-epidermal junction in uninvolved skin and along the subepithelial basement membrane of affected mucous mem-

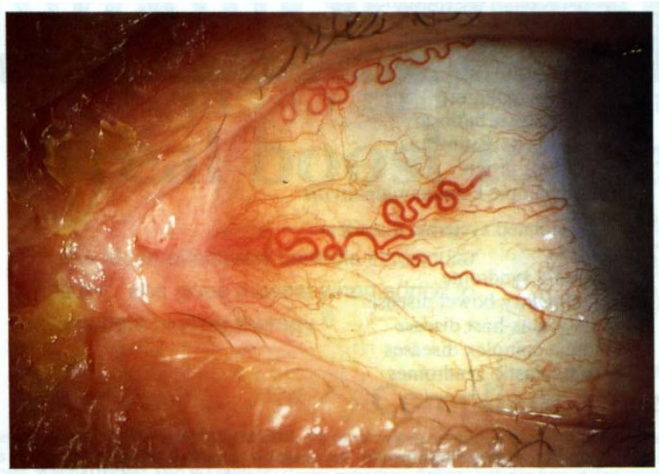

Fig. 1. *Chronic cicatricial pemphigoid, early disease. Note the loss of inner canthal architecture.*

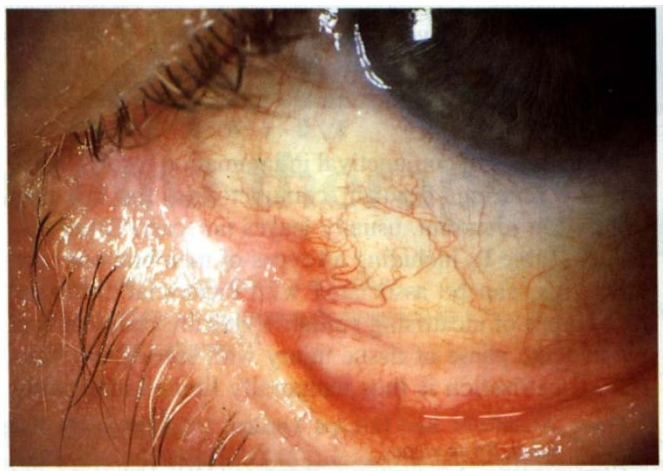

Fig. 2. *Subacute cicatricial pemphigoid. Note symblepharon formation, fornix foreshortening and white striae of subconjunctival fibrosis.*

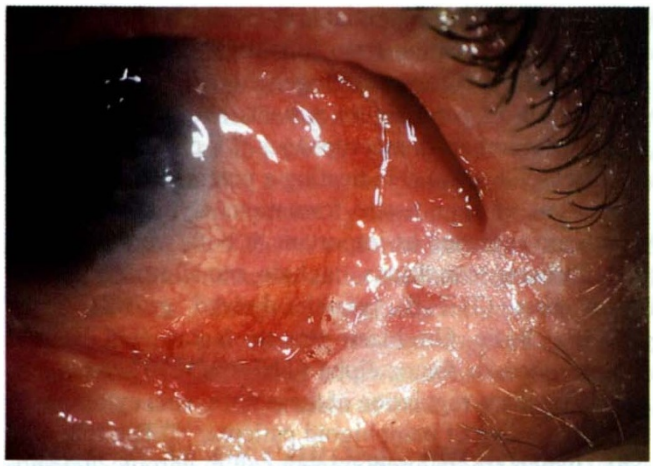

Fig. 3. *Acute ocular pemphigoid in a 73-year-old man with a history of dysphagia and skin involvement who had had ocular symptoms for 1 year. Note the conjunctival swelling, ulceration and symblepharon formation.*

branes (Fig. 5) is the characteristic immunofluorescence finding of this condition.[13,28]

Other Mucocutaneous Disorders

Although there are sporadic reports of conjunctival scarring in pemphigus vulgaris, bullous pemphigoid and dermatitis herpetiformis[7,14,31] these conditions do not show the chronic progressive course characteristic of benign mucous membrane pemphigoid or linear IgA disease.

Epidermolysis bullosa only rarely involves the mucous membranes but can lead to cicatricial conjunctival changes[4,32] that are often localised and non-progressive.[1]

Erythema multiforme and its severe forms, Stevens–Johnson syndrome and toxic epidermal necrolysis, are acute, generally self-limiting vascular diseases in which delayed type hypersensitivity mechanisms are involved. Skin lesions, papules and blisters develop in association with inflammation of mucous membranes.[26] The latter may lead to conjunctival adhesions which are soft and lack the dense fibrous subconjunctival component seen in mucous membrane pemphigoid.[24,33] Recurrent episodes of conjunctival inflammation in patients with Stevens–Johnson syndrome have been reported,[34] but progressive scarring does not usually occur once the acute stage has subsided.[35]

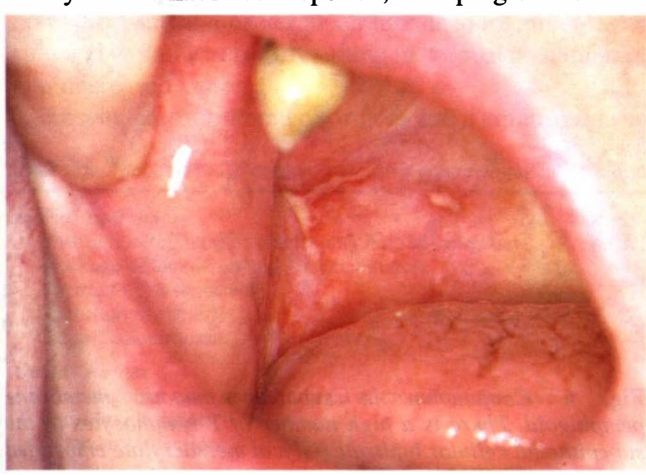

Fig. 4. *Oral lesions in benign mucous membrane pemphigoid.*

Paraneoplastic Disorders

Cicatrising conjunctivitis was recently reported in patients with malignant lymphoma,[36] chronic lymphatic leukaemia[36] and bronchogenic squamous cell carcinoma.[37] Anhalt and coworkers coined the term 'paraneoplastic permphigus' for this entity. The immunohistochemical findings were similar to those found in pemphigus vulgaris[36,37] or pemphigoid.[36]

Drug-Induced Conjunctival Cicatrisation and Pseudopemphigoid

Conjunctival cicatrisation as an adverse effect of systemically administered drugs is extremely rare. It has been reported for patients taking oral iodides or bromides when calomel (mercurous chloride) was simultaneously instilled topically[38] and for patients treated with the systemic beta-receptor blocking drug practolol.[39,40]

The effect of long-term treatment with topical antiglaucomatous medication on the ocular surface has also been studied and reviewed.[41,51] Clinical effects include tear film alterations,[41,45] various types of conjunctivitis,[41,47] epithelial metaplasia,[44] conjunctival dyschromia[41,52] and conjunctival cicatrisation.[1,41] Fibrosing changes, manifest as obstruction of the lacrimal system, were first described after instillation of furmethide.[53] Kristensen and Norn[54] suggested an association between mucous membrane pemphigoid and use of topical therapy, and Patten and coworkers introduced the term 'pseudopemphigoid' for chronic progressive conjunctival cicatrisation following long-term topical therapy.[55] Since then several reports of severe drug-induced conjunctival cicatrisation mimicking mucous membrane pemphigoid have appeared.[1,13,56–60] Drugs which were believed to be involved in progressive

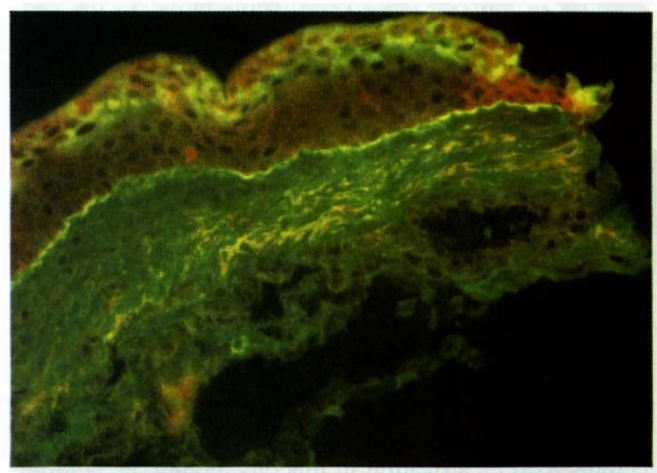

Fig. 5. *Chronic cicatricial pemphigoid: immunofluorescence photograph of a conjunctival biopsy specimen. The snap-frozen tissue has been cryostat-sectioned and stained with fluorescein-labelled anti-human IgA. Note the line of homogeneous fluorescence of the epithelial basement membrane zone, signifying the presence of deposits of IgA in this region (original magnification × 100). (Courtesy of Dr. J. N. Leonard and Mr. G. Haffenden.)*

conjunctival cicatrisation included echothiophate iodide,[55,59] guanethidine with or without adrenaline,[1,55,59] timolol,[59] pilocarpine,[58,59] dipivefrine,[59] demecarium[58] and idoxuridine.[57] In contrast to these severe forms of conjunctival cicatrisation, asymptomatic foreshortening of the inferior conjunctival fornix was recently reported as a frequent complication in association with chronic exposure to glaucoma medications, irrespective of type.[61]

It is believed that drug-induced conjunctival shrinkage represents a spectrum of disease ranging from a self-limiting toxic form to a progressive 'immunological' form.[60] This progressive 'immunological' form, which is progressive after withdrawal of the topical drug (= pseudopemphigoid) may be clinically and pathologically indistinguishable from cicatricial pemphigoid.[13,59,60] The mechanisms by which it is induced are not clear,[62] but the fact that different classes of topically administered medications are associated with drug-induced pemphigoid and the failure of *in vitro* studies to show a stimulation of fibroblasts by antiglaucomatous drugs or their preservatives[63] favours the hypothesis that a mechanical factor may be involved. Direct chronic tissue damage and/or the chronic low-grade inflammation after long-term application of drugs[48,51] may render components of the basement membrane zone immunogenic, giving rise to an autoimmune reaction resulting in the same sequence of events as in cicatricial pemphigoid. Alternatively, chronic low-grade inflammation and tissue damage may trigger the onset of pemphigoid in disposed patients. The fact that none of the reported patients with pseudopemphigoid had extraocular mucous membrane involvement does not support this hypothesis, but it should be considered that conjunctival and extraocular basement membranes may have different antigenicity.

Clinically, drug-induced conjunctival cicatrisation initially involves the lower fornix,[61] in contrast to the early changes of mucous membrane pemphigoid. In the later stages pseudopemphigoid is indistinguishable from cicatricial pemphigoid and can only be diagnosed with some certainty on the basis of the medical history and the fact that pseudopemphigoid may be unilateral. Direct immunofluorescence to assess immunoglobulin deposition at the basement membrane zone has been shown to be positive in some cases of pseudopemphigoid.[13,59,60] Conjunctival biopsy is thus not helpful in the differentiation of pseudopemphigoid from cicatricial pemphigoid.

MECHANISMS OF CHRONIC PROGRESSIVE CONJUNCTIVAL CICATRISATION

Recent studies have investigated possible mechanisms of conjunctival cicatrisation in mucous membrane pemphigoid.[21,22,64] A chain of events, starting with the induction of submucosal inflammation, leads eventually to hyperproliferation of fibroblasts and new tissue formation. The transition from inflammation to scar tissue in the conjunctiva of pemphigoid patients seems to be mediated by the same mechanisms as those in wound healing and fibrosing diseases.[21]

Macrophages are essential for wound healing[65] and can promote the transition from inflammation to new tissue formation by secretion of fibrogenic growth factors.[66] The conjunctiva of pemphigoid patients shows significantly increased numbers of macrophages,[19–21] particularly when the disease is active,[21] indicating a potential cause for the promotion of scar tissue formation. Cytokines factors which are regarded as important in both wound healing and fibrosing conditions, include transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and tumour necrosis factor alpha (TNF-α).[66,67] There is evidence for an up-regulation of these fibrogenic cytokines in the conjunctiva of pemphigoid patients.[21,64] The role of T cells, which are the predominant cell in chronic and subacute conjunctival pemphigoid[21] (Fig. 6), is not completely understood. It seems that they are not essential for scar tissue formation, as shown in experiments of T cell depletion[68] and in studies with nude mice, which have a profoundly impaired T cell system.[69] The role of T cells appears to be mainly regulation and perpetuation of the repair process.[70]

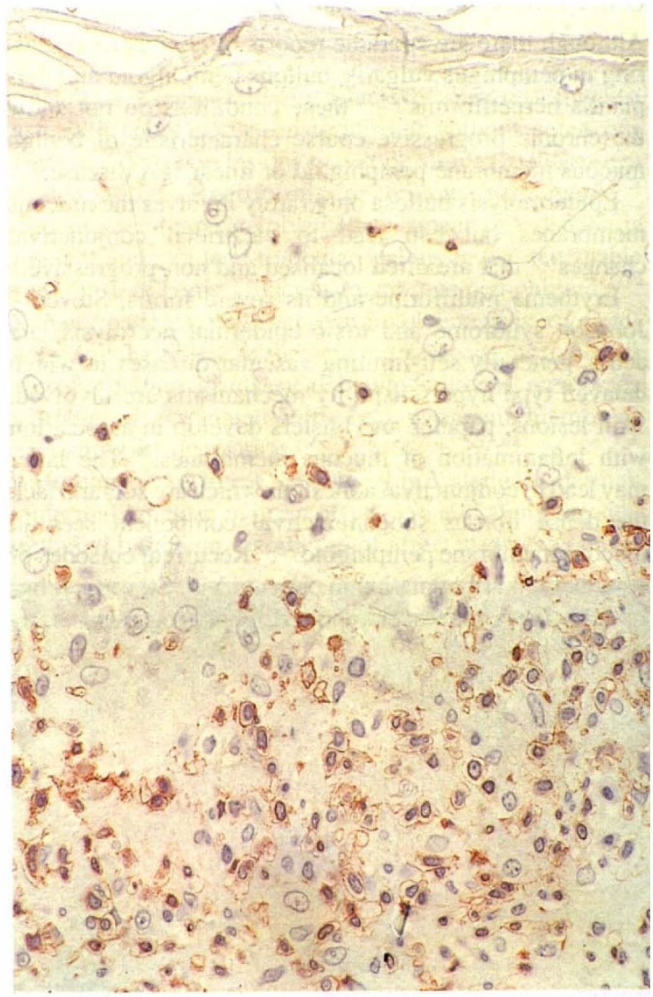

Fig. 6. *Conjunctiva in subacute mucous membrane pemphigoid. There is a high number of T lymphocytes in the subepithelial cellular infiltrate (Glycol methacrylate embedded section; anti-CD3 antibody, immunoperoxidase reaction; original magnification × 500).*

The conjunctival cellular infiltrate characteristic of many chronic conjunctival disorders, including pseudopemphigoid and low-grade conjunctivitis following long-term treatment with antiglaucoma drops, involves the same cell types as in patients with chronic and subacute conjunctival mucous membrane pemphigoid.[48,71–73] This suggests that it is not primarily the composition of the cellular infiltrate but differences in the secretory activity of these cells which determine the clinical characteristics of these diseases. Fibrogenic cytokines may be the crucial soluble factors involved in the aetiology of cicatrising conjunctivitis, but further investigations are required to define the relative importance of each of these cytokines.

SEQUELAE OF CHRONIC PROGRESSIVE CONJUNCTIVAL CICATRISATION

The sequelae of chronic progressive conjunctival cicatrisation for the eyelids and ocular surface are listed in Table II, and discussed in more detail below.

Eyelids

Aberrant eyelash growth secondary to damage to cilia follicles is a frequent early complication of chronic cicatrising conjunctivitis.[2] Progression of conjunctival scarring and symblepharon formation causes entropion with trichiasis and, when left untreated, leads to lagophthalmos, abnormal blinking and exposure.[1,4,7,74]

Ocular Surface

Scarring of lacrimal ductules and obstruction of meibomian glands alter the composition of tears. Inflammation and cicatrisation of the conjunctiva lead to loss of goblet cells, loss of the normal microvillous structure and a reduction of glycocalyx production. These changes, together with the abnormal spreading effect of the affected lid margin, result in an unstable precorneal tear film.[75]

The abrasive effect of misdirected lashes and the altered precorneal tear film cause mechanical damage and drying. Squamous metaplasia follows prolonged drying of the conjunctiva and often involves the canthal regions in ocular pemphigoid.[44] Secondary infections are a frequent complication of ocular pemphigoid.[2] Secondary corneal epitheliopathy and bacterial keratitis lead to corneal scarring and vascularisation, resulting in corneal opacification and decreased vision.

Absent tears, obliterated fornices and a keratinised surface mark the end stage of progressive conjunctival cicatrisation (Fig. 7).

Table II. Sequelae of chronic progressive conjunctival cicatrisation

Eyelids and annexe
Obstruction of lacrimal glands and meibomian glands
Blockage of canaliculi and lacrimal puncta
Aberrant eyelash growth
Distortion of the lids
Cicatricial entropion
Ocular surface
Loss of goblet cells and of normal microvillous structure
Tear film alteration
Secondary infection
Trichiasis
Keratopathy

MANAGEMENT OF CHRONIC PROGRESSIVE CONJUNCTIVAL CICATRISATION

General Considerations

It is our experience and that of other authors[76] that untreated ocular cicatricial pemphigoid has a variable course that is not always progressive. The requirement of therapy is dependent on disease activity, which should be monitored with standard position photographs and drawings. Episodes of acute disease manifested as conjunctival hyperaemia, oedema, active subconjunctival fibrosis and occasionally conjunctival ulceration result in rapid shrinkage of the conjunctiva.[25] Progression of scarring is more likely to occur in advanced stages of cicatricial pemphigoid.[3] Superadded bacterial conjunctivitis, toxic or allergic reaction to medication or preservatives, trichiasis and exposure can all cause similar inflammatory activity and such aetiologies should be excluded before the inflammatory signs are attributed to the disease process itself.

These principles also apply to other conditions of chronic progressive conjunctival cicatrisation. Topical treatment should be withdrawn in suspected drug-induced fibrosis and any subsequent progression of inflammation and scarring carefully monitored. If discontinuation of ocular medication is not possible, it should be continued with unpreserved preparations. Unpreserved topical medication is favoured in patients with chronic progressive conjunctival cicatrisation to avoid further potential damage to the ocular surface.

Immunosuppressive Therapy

There is no known specific treatment for chronic progressive conjunctival cicatrisation including cicatricial pemphigoid. Studies in recent years have focused on the use of various types of immunosuppression for the treatment of this condition.[2,5,76–82]

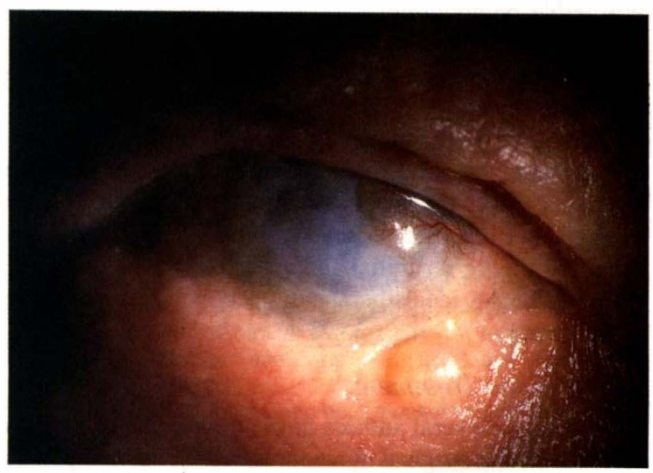

Fig. 7. *End stage in progressive conjuctival cicatrisation. Note the absence of tears, obliterated fornices and a keratinised surface.*

Immunosuppression with Topical Treatment. There is general agreement that topical corticosteroids are ineffective on a long-term basis for controlling the progression of conjunctival scarring in pemphigoid patients.[2,4] However, the use of intensive topical steroid therapy in patients with acute mucosal ulcerations seems to be beneficial with regard to rapid healing and reducing the amount of subsequent scarring.[23] We therefore prescribe unpreserved topical steroids when conjunctival inflammatory signs are present.

Conclusive studies on the effect of topical treatment with the newer generation of immunosuppressive drugs (cyclosporin A and FK 506) are not yet available for ocular pemphigoid.[83]

Immunosuppression with Systemic Treatment. Generalised immunosuppression is currently believed to be the only effective treatment able to halt the process of progressive conjunctival cicatrisation.[2,16,82] Our experience with such therapy tallies with that of other authors, who found that the inflammatory, rather than the cicatricial, features consistently responded to generalised immunosuppression.[27] Control of inflammation, therefore, does not always fully control the scarring process. Despite this limitation, systemic immunosuppression is a valuable tool in the management of certain patients with chronic progressive conjunctival cicatrisation.

Systemic corticosteroids are of definite value in the treatment of the acute manifestations of ocular cicatricial pemphigoid.[25] According to Hardy and coworkers[5] an equivalent of 40 mg prednisone per day was necessary to control disease progression in patients with active mucous membrane pemphigoid. However, this dose is unacceptable for long-term therapy because of steroid-induced side effects. We currently use systemic steroids in an initial dose of 80 mg prednisone in combination with cyclophosphamide for the treatment of acute, rapidly progressive manifestations of ocular cicatricial pemphigoid.

Diaminodiphenylsulphone (dapsone) and the systemic cytotoxic immunosuppressive agents cyclophosphamide and azathioprine have been shown to be effective in treating active pemphigoid.[1,27,76,78,79,82] Cyclophosphamide is regarded as the most effective drug in the treatment of cicatricial pemphigoid and is mainly used in the acute inflammatory phase.[2,82] Dapsone is less toxic and is therefore favoured for the treatment of milder forms of progressive disease.[2,16,35] The role of oral cyclosporin A in the treatment of progressive conjunctival cicatrisation is not clear. Foster reported on seven patients treated with this drug (10 mg/kg as initial therapy), of whom only one responded.[2] An ideal therapeutic regimen has yet to be established.

Symptomatic Treatment

Lid Surgery. Several authors have stressed the disastrous effect of ocular surgical procedures in general, and plastic surgical procedures in particular, when carried out in patients with active cicatricial pemphigoid.[1,2,84] It is believed that conjunctival trauma triggers the disease process, resulting in an inflammatory flare up with rapid cicatrisation. Whenever possible surgery should thus only be performed when control of the disease process has been achieved. Procedures which avoid direct trauma to the conjunctiva are preferred. Biopsy of the fornix conjunctiva is contraindicated.

Trichiasis secondary to isolated aberrant eyelashes should be treated with electro- or cryoepilation; the latter is the more effective. Cryoepilation of large areas should be avoided, because of potential exacerbation of the disease and the possibility of losing vertical lid height.

Entropion repair is preferably achieved by procedures which avoid direct trauma to the conjunctiva (i.e. Jones-type procedure for the lower lid, anterior lamellar repositioning for the upper lid). Successful mucous membrane grafts have been reported in cicatricial pemphigoid,[2] but the extensive trauma to the conjunctiva greatly increases the risk of disease promotion.

Management of Ocular Surface Problems. The general therapeutic principles for external eye disease apply to the management of ocular surface changes secondary to chronic progressive conjunctival cicatrisation.

An unstable precorneal tear film when present should be treated with artificial tears, preferably as an unpreserved formulation. Specific substitution of the mucous component layer is desirable in many patients but is not possible. Lid abnormalities should be treated to allow normal spreading of tears. Punctal occlusion can be performed if the puncta are not already occluded by scarring.

Bacterial conjunctivitis and blepharitis should be treated and oral tetracycline or doxycycline may be helpful in meibomitis.

The use of bandage contact lenses in the management of corneal epithelial breakdown is limited by tear film alterations and secondary anatomical changes. Botulinumtoxin-induced therapeutic ptosis[85] is only useful if restriction of lid motility, secondary to scarring, is minimal. Infectious keratitis should be treated according to sensitivity testing with the least toxic drugs.

Retinoic acid for the treatment of keratinisation is helpful in conditions where the primary inflammatory process has resolved, for example after acute Stevens-Johnson syndrome.[86] Its use in active cicatrising conjunctivitis may cause additional inflammation or epithelial breakdown as an adverse effect of its irritative properties.

PROSPECTS

Specific treatment of chronic progressive conjunctival cicatrisation would be desirable. The development of specific therapy remains impossible until we understand the basic immunological process, namely the initiation of autoaggression. Focusing on the mechanisms of conjunctival scar tissue formation with evaluation of fibrosing growth factors may identify new and more satisfactory therapeutic possibilities for the prevention of scar tissue formation. Future therapeutic regimens for the treatment of chronic progressive conjunctival cicatrisation may include blockers of fibrogenic cytokines or of their recep-

tors. This would offer a new approach not only in the treatment of cicatrising conjunctivitis, but also for adjunctive therapy in glaucoma filtration surgery.

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Key words: Basement membrane, Cicatricial pemphigoid, Cicatrising conjunctivitis, Iatrogenic disease, Linear IgA disease, Pemphigoid, Wound repair.

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