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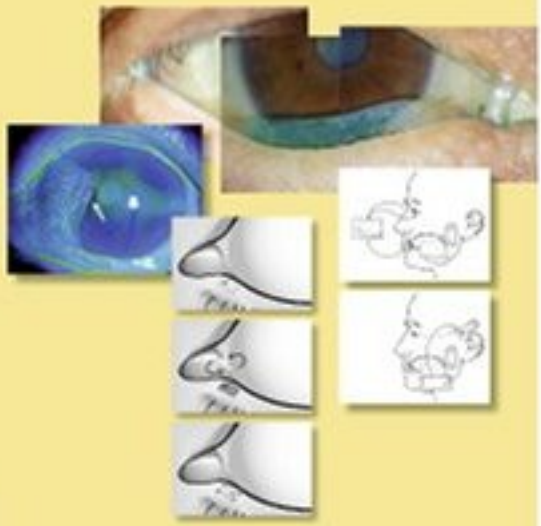
Surgery for the Dry Eye

Scientific Evidence and Guidelines for the Clinical Management of Dry Eye Associated Ocular Surface Disease

Editors
G. Geerling
H. Brewitt



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Surgery for the Dry Eye

Developments in Ophthalmology

Vol. 41

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W. Behrens-Baumann, Magdeburg

Surgery for the Dry Eye

Scientific Evidence and Guidelines for the Clinical Management of Dry Eye Associated Ocular Surface Disease

Volume Editors

Gerd Geerling, Würzburg
Horst Brewitt, Hannover

101 figures, 71 in color, and 32 tables, 2008

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Gerd Geerling
Klinik für Augenheilkunde
Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11
DE–97080 Würzburg

Horst Brewitt
Ubbenstrasse 11
DE–30159 Hannover

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List of Contributors

L. Baldeschi
Department of Ophthalmology
Academic Medical Center
University of Amsterdam
Meibergdreef 9
NL-1105 AZ Amsterdam
(The Netherlands)

H. Brewitt
Ubbenstrasse 11
DE-30159 Hannover
(Germany)

A.J. Bron
Clinical Research Unit
Nuffield Laboratory of
Ophthalmology
Walton Street
Oxford OX2 6AW (UK)

J.R.O. Collin
Moorfields Eye Hospital
162 City Rd
London EC1V 2PD (UK)

C. Cursiefen
Augenklinik
Friedrich-Alexander-Universität
Erlangen-Nürnberg
Schwabachanlage 6
DE-91054 Erlangen (Germany)

G. Geerling
Klinik für Augenheilkunde
Julius-Maximilians-Universität
Würzburg
Josef-Schneider-Strasse 11
DE-97080 Würzburg (Germany)

H.W.A. Henderson
The Royal Free Hospital
Pond Street
London NW3 2QG (UK)

J. Herold
Maxillofacial Department
Royal Sussex County Hospital
Brighton BN2 5BE (UK)

C. Hicks
220 Onslow Road
Shenton Park
Western Australia 6008
(Australia)

K. Hille
Ortenau Klinikum
Offenburg-Gengenbach
Ebertplatz 12
DE-77654 Offenburg (Germany)

C. Hintschich
Augenklinik der
Ludwig-Maximilians-Universität
Mathildenstrasse 8
DE-80336 München (Germany)

T. Inatomi
Department of Ophthalmology
Kyoto Prefectural University of Medicine
Kajii-cho 465, Hirokoji-agaru, Kawaramachi-dori
Kamigyo-ku, Kyoto 602-0841
(Japan)

T. Kaercher
Dossenheimer Landstrasse 48
DE-69121 Heidelberg (Germany)

S. Kinoshita
Department of Ophthalmology
Kyoto Prefectural University of Medicine
Kajii-cho 465, Hirokoji-agaru, Kawaramachi-dori
Kamigyo-ku, Kyoto 602-0841
(Japan)

F.E. Kruse
Augenklinik
Friedrich-Alexander-Universität
Erlangen-Nürnberg
Schwabachanlage 6
DE-91054 Erlangen (Germany)

S. Lakhani
Principal Optometrist
Moorfields Eye Hospital
162 City Road
London EC1V 2PD (UK)

M.A. Lemp
4000 Cathedral Ave. N.W. #828B
Washington DC 20016 (USA)

R. Linderoth
Karolinska Institute
St. Erik's Eye Hospital
SE-11282 Stockholm (Sweden)

C. Liu
Sussex Eye Hospital
Eastern Road
Brighton BN2 5BF (UK)

A.K. Mircheff
Department of Physiology and Biophysics
Keck School of Medicine,
University of Southern California
Los Angeles, Calif. (USA)

J. Murube
Clinica Murube
San Modesto 44-1
ES-28034 Madrid (Spain)

B. Nölle
Klinik für Augenheilkunde
Universitäts Klinikum
Schleswig-Holstein
Campus Kiel
Hegewischstrasse 2
DE-24105 Kiel (Germany)

F. Paulsen
Institut für Anatomie und
Zellbiologie
Martin-Luther-Universität Halle-
Wittenberg
Grosse Steinstrasse 52
DE-06097 Halle/Saale (Germany)

P. Raus
MIRO Centrum voor Ooglidchirurgie
en Esthetiek
Rondplein 23
B-2400 Mol (Belgium)

G.E. Rose
Moorfields Eye Hospital
162 City Road
London EC1V 2PD (UK)

S. Sahlin
Karolinska Institute
St. Erik's Eye Hospital
SE-11282 Stockholm (Sweden)

S. Schrader
Klinik für Augenheilkunde
Universitäts Klinikum Schleswig-
Holstein
Campus Lübeck
Ratzeburger Allee 160
DE-23538 Lübeck (Germany)

P. Sieg
Klinik für Kiefer- und
Gesichtschirurgie
Universitäts Klinikum Schleswig-
Holstein
Campus Lübeck
Ratzeburger Allee 160
DE-23538 Lübeck (Germany)

D. Tan
Singapore National Eye Centre
11 Third Hospital Avenue
Singapore 168751 (Singapore)

J. M. Tiffany
Nuffield Laboratory of Ophthalmology
University of Oxford
Walton Street
Oxford OX2 6AW (UK)

F.H.W. Tost
Klinik und Poliklinik für
Augenheilkunde
Ernst-Moritz-Arndt Universität
Ferdinand-Sauerbruch-Strasse
DE-17475 Greifswald (Germany)

S. Tuft
Moorfields Eye Hospital
162 City Road
London EC1V 2PD (UK)

N. Yokoi
Department of Ophthalmology
Kyoto Prefectural University of
Medicine
Kajii-cho 465, Hirokoji-agaru,
Kawaramachi-dori
Kamigyo-ku, Kyoto 602-0841
(Japan)

To our teachers in life: Parents, Professors, Patients and Partners

Surgery for the Dry Eye?

'Perhaps our eyes need to be washed by our tears once in a while, so that we can see Life with a clearer view again.' (A. Tan)

Our understanding of anatomy and physiology of the ocular surface has substantially expanded during recent decades. Especially the importance of the tear film for a healthy cornea and conjunctiva has become more and more obvious. All adnexal structures, the tear system, the lids and the orbit as well as neuronal and cellular components of the ocular surface itself are involved in tear production and maintenance. They mechanically and immunologically protect the cornea and conjunctiva, but also provide essential nutrients for the surface epithelia.

Any part of this complex functional unit may be altered either primarily or secondarily to other disease and this can lead to tear film and ocular surface changes called 'dry eye', which in turn often is an equally complex and multifactorial disorder. It includes mild forms, e.g. due to involutional changes of the lacrimal apparatus – one of the most frequent diagnoses in everyday ophthalmic practice – as well as rarer, but also more severe forms of the disease, which may for example be due to thermal and chemical burns. The more severe the disease, the more challenging therapy usually is, since the indication is not only comfort, but may be tectonic and optical.

In this book all aspects of this complex disorder and its treatment are discussed, with a major part focusing on surgical concepts. To suggest that surgery in this context may be a therapeutic option makes eyebrows rise frequently.

- Is there an indication for surgery at all in dry eyes?
- Are all forms of dry eye suitable for surgery?
- Are there any techniques – other than punctal occlusion – available?
- Is there a substantial chance – if not to cure – to alleviate the consequences of dry eye with surgical means?

The anatomical and functional unit of the ocular surface and the ocular adnexae is the key to these questions. Especially in *secondary* ocular surface disease, due to abnormalities of the ocular adnexa major pathomechanisms include *exposure, abrasion and malnutrition* resulting from conjunctival scarring, fornix shortening and severe aqueous deficiency. These conditions can all lead to epithelial defects, which – due to impaired wound healing – persist and progress. Hence, dry eye cannot only lead to severe discomfort or pain but also to visual impairment or even blindness. Surgery in primary and secondary ocular surface disease/dry eye not only has to prevent disease progression but also has to attempt symptomatic and visual rehabilitation.

However, the same pathomechanisms involved in the evolution also often prevent successful surgical rehabilitation of the disease. Surgery for dry eyes therefore not only aims to enhance lubrication, but also to improve function of cornea, conjunctiva, eyelids and even the orbit, since these are vital parts of the ocular surface functional unit. Hence this book not only describes techniques of tear drainage occlusion or salivary gland transplantation, but also details procedures for fornix reconstruction, correction of lid malpositions and exposure keratopathy and techniques for visual rehabilitation of corneal blindness, e.g. keratoplasty or keratoprosthesis. The functional unit of the ocular surface and the common context of tear film abnormality provide the red thread to these forms of clinical management.

Up-to-date concepts and techniques of a panel of well-established international experts in the field lay the theoretic foundations and describe the interactions of the ocular adnexae and surface, provide up-to-date guidelines on the diagnosis and medical management of ocular surface disease in dry eye and underlying adnexal disorders. Currently available published evidence and evolving techniques to correct exposure, fornix shortening and aqueous deficiency are discussed, which we hope the reader and hopefully eventually the patient suffering from dry eye will find useful. Based on this potpourri of evidence and new concepts, we are convinced that the answer to the initial questions is a firm “Yes”!

Acknowledgements

This book is the result of a collaborative effort from ophthalmologists specialized in external eye disease and ophthalmic-plastic reconstructive surgery, as well as maxillofacial surgeons and basic scientists. We are indebted to all authors for their excellent contributions, which have provided the interdisciplinary update of surgery in dry eyes we aimed for.

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'Put my tears into thy bottle. Are those things not noted in your book?' (Psalm 56, V 8)

Gerd Geerling, Würzburg
Horst Brewitt, Hannover
April 2008

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The Normal Tear Film

John M. Tiffany

Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, UK

Abstract

Purpose: To survey briefly current knowledge on the normal preocular tear film. **Methods:** Sections deal with: (1) Formation of the film, its physical dimensions and rates of inflow and outflow of tears, and briefly the pathways of nervous control of tear production in the main lacrimal gland and accessory lacrimal tissue. (2) The protein and electrolyte composition of the aqueous part of the tears derived from the lacrimal gland, as well as the accessory secretions of the meibomian glands and conjunctiva; the 'soluble' or gel-forming mucins from the conjunctival goblet cells are described as well as the membrane-spanning epithelial mucins of the glycocalyx which take part in wettability and mucus binding. (3) The functions of the film, including acting as a nutritional route for the anterior epithelium of the cornea, and its protective roles in ocular lubrication and in scavenging and eliminating invading debris and microorganisms, plus specific antibacterial and immune functions. (4) Problems of structure and stability of the film are discussed, and (5) the wide variety of tests of tear function and quality, with discussion of which tests are suitable for the clinical environment, and which laboratory-based tests can be useful in assessing the individual patient. **Results:** The preocular tear film plays a vital role in nourishing, lubricating and protecting the ocular surface. Many tests can be applied in either the clinical or the laboratory setting, to determine whether the tears of the individual patient exert their physiological and antimicrobial functions at the normal level. **Conclusions:** Knowledge of the normal functions of the film provides a basis for later consideration of clinical and surgical treatment of the dry eye.

Importance of Film

In the open eye, the exposed surfaces of cornea and sclera are covered with a very thin film of tear fluid. This has both protective and nutritional properties; its thickness changes due to evaporation while the eye is held open, and during prolonged eye-opening the film may break up to expose surface epithelial cells directly to the air. The tear break-up time (TBUT) is an important clinical

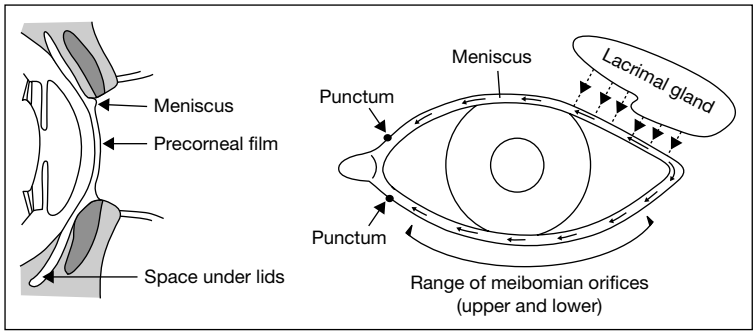

Fig. 1. Position of tear film. Left, sagittal section indicating different regions of the tear film. Right, front view showing position of main lacrimal gland and other structures influencing the tear film.

parameter in defining the normality of function of the eye. During normal life, break-up will perhaps occur only comparatively rarely, as blinking is very rapid and is a nearly automatic response to symptoms of drying. However, normal life for many people now includes prolonged periods of computer or other visual screen use, and it is known that the blink rate falls when paying close attention. Hence the tear film may break up between blinks. The Corneal Protection Index (CPI), defined as the ratio of TBUT to the length of the interblink, can be used to indicate the boundary between normal and dry eye.

Position and Extent of the Tear Film

The term 'tear film' is normally used to describe the film of fluid covering the corneal surface and contained between the lid margins (fig. 1). In fact we should also include the film overlying the exposed bulbar sclera; however, because this surface is rough and irregular it is much harder to obtain information about its nature by the usual reflectance-based methods used for the cornea, so this area is often ignored. At present we cannot even say with certainty that a uniform and continuous tear film is present over all the exposed sclera. However this area is not negligible – in upward gaze it may contribute 60% or more of the total exposed area. It is also neglected because it is of much lower importance than the cornea in the visual process, and because, having its own blood supply, it recovers more readily from injuries and infections.

The exposed area is quite closely dependent on interpalpebral height, which in turn is determined by the direction of gaze (exposure is considerably greater in upward than in downward gaze, as the upper lid follows the movement of the globe). Thus in downward gaze not all the cornea is exposed, along

with a small area of sclera, while in upward gaze we may see all the cornea plus a variable amount of sclera both above and below the limbus as well as larger lateral areas. A rough linear relationship between area and palpebral height is often used: Area (cm^2) = 0.28 × (height in mm) − 0.44 [1]. A more precise value can be obtained by computer analysis of images of the eye, allowing separate estimation of the areas of exposed cornea and sclera [2]. Typical values for the area in normal level gaze are 2–3 cm^2, of which 45–55% is cornea. These figures help to strengthen the recommendation to those doing much computer work, to keep the screen as low as possible to minimise ocular exposure and drying because of the reduced blink rate.

The total area of the human conjunctival sac has been estimated as 16 cm^2 [3]. If all this is covered by a layer of gelatinous mucus with a water content of about 90%, say averaging 1 μm thick, 1.44 μl of fluid would be contained. Where the lids overlie the globe, it is possible that two such layers on the apposed surfaces will be in contact, giving an effective fluid thickness of 2 μm. However, it seems unlikely that in this case there would be free flow of fluid (e.g. fresh tear fluid entering the upper conjunctival sac through the tear ductules) although fluid transport could occur through a 'squeegee' mechanism in blinking.

Formation of the Film

As the lids close during the blink, the upper and lower menisci are pushed ahead of them and sweep up the fluid forming the preocular film, rather like a windscreen wiper. In the opening phase of the blink, the viscosity of the tears causes fluid to be pulled out of both menisci to create a new film, but opposed to this is the negative pressure due to the concave tear meniscus. As long as the lids are moving, fluid is spread, but when the lids become stationary there is within 0.3–1 s a settling down or rearrangement whereby fluid is pulled back into the meniscus while the bulk of the spread film remains intact. The region closest to the meniscus is however considerably thinned and if fluorescein is instilled, a 'black line' can be seen around the rim of the tear film. This line is so thin that it contains too little dye to fluoresce, and it acts as a barrier to diffusion or flow of fluid into or out of the film in the interblink period. Hence the film is effectively isolated from the rest of the lacrimal system while the eye is open, and is subject to different influences such as evaporative loss at these times. The isolated film has been referred to as 'perched' because it covers the exposed eye but is in a sense independent of the ocular adnexa [4].

Volume of Various Compartments

We can distinguish three distinct components of the fluid in the lacrimal sac: the film itself, lying between the lid margins; the continuous line of meniscus

around the lid margins, joining at the outer canthus and around the caruncle, and the fluid under the lids.

It is still not clear what volume of tears lies under the lids, or whether this should be included as part of the tear film. In the normal eye the lid margins glide in contact with the globe during a blink, and it is thought that there is a slight curvature inwards of the margin of the upper lid to give a 'windscreen wiper' action sweeping the film forward as the lids close. This would suggest that the exposed and the under-lid compartments remain separate; but King-Smith et al. [5] discuss the possibility that the two compartments are connected but that during the blink the upper meniscus changes position, being swept down by the advancing lid margin.

Recent experiments on adding saline to severely dry eyes showed that fluid was absorbed (presumably under the lids) before any lid margin meniscus became visible, implying that the two compartments are connected [6]. The mean under-lid volume was calculated to be 5–6 μl. The volume of tears in the combined upper and lower menisci can be calculated from their total length (about 50 mm) and cross-sectional area, assuming that their profile is a quadrant of a circle; using a mean value of 0.365 mm for the radius of curvature, the normal meniscus volume is about 2.9 μl [7]. The volume of the preocular film clearly depends on its thickness (see below), but taking commonly-agreed limits of 3 and 10 μm and an area of 2 cm^2, the volume is 0.6–2.0 μl with a mean probably about 1.0 μl. Hence the total volume of tear fluid in the external eye is roughly 10 μl. This does not include additional small amounts such as the fluid over the caruncle.

Clearly there is considerable personal variation in this figure – differences in form of the lid margins, slight inward or outward turning of the lids relative to the globe, positioning of the puncta and height of the palpebral opening can all affect the contained tear volume.

Thickness of Precorneal Film

Estimates of tear volume involve knowing the thickness of the film. This is not easy to measure, although several methods have been used over the years. Simple methods include isolating an area of tear film by pressing the end of a wide-mouthed syringe onto the eye and measuring the volume of fluid sucked off [8], absorbing fluid over a known area by placing a disc of absorbent paper on the eye [9], or measuring fluorescence intensity after adding a known amount of fluorescein to the film [10]. More recently the variation of intensity of light reflection has been analysed in three ways (varying angle, frequency or wavelength). Ocular coherence tomography can measure corneal thickness with and without a contact lens and estimate the film thickness by difference. All these methods are summarised by King-Smith et al. [5]. Some estimates of tear film

Table 1. Some reported thicknesses of the precorneal tear film [data from 6]

Method	Thickness μm
Absorbent discs	7
Fluorometry	4
Angle-dependent fringes	34–45
Wave-front fringes	2.7
Ocular coherence tomography	3.3

thickness by these methods are given in table 1. The film thickness over the anterior surface of a contact lens is generally thinner than the precorneal film, and less stable, although this varies with the contact lens material and depends on factors such as degree of contamination of the lens surface by tear components.

Volume Flow of Tears Into and From the Eye

The volume of tears in the external eye at any moment is a balance between the rate of inflow of fluid from the lacrimal gland, from the accessory lacrimal tissue and by permeation of water from the corneal epithelium through aquaporin-controlled channels. Removal of fluid is principally by drainage through the puncta following each blink, and by evaporation from the open eye. When the lids close, the upper and lower puncta press on each other and prevent outflow, but as the lids open there is a drop in canalicular pressure and fluid is sucked into the puncta from the marginal lacrimal lake [11]. Evidence for absorption of water by the corneal or conjunctival epithelium is lacking, although it is suggested that some or all of that passing down the canaliculi is absorbed before it reaches the nose [12].

There is considerable variation in the rate of inflow of tears. It has often been suggested that in the quiet eye there is a 'basal rate' of flow, augmented by different degrees of stimulation; one variant is that the basal secretion is produced by the accessory lacrimal tissue (about 10% of the total) and stimulated reflex or psychic tears by the main lacrimal gland, but there appears to be no firm evidence for this. Another view is that all secretion is stimulated, that in the quiet eye being produced simply in response to opening of the eye. Most clinical estimates of tear flow rate are based on the Schirmer test and its variants; these are described below in 'Clinical Tests'. Published values of the 'unstimulated' flow rate are usually around 1.2 μl/min or roughly 1.2 ml/day (assuming a 16-hour waking cycle, since tear output is largely inhibited during sleep), with a turnover rate of 16%/min [10]. However, using the Fluorotron Master instrument, a much lower value was found of 0.15 μl/min (about

0.15 ml/day from each eye) with a turnover rate of 8.2%/min [13]. Stimulated flow rates are much greater – up to 50 or 100 times more; 40–50 μl in <1 min has been reported with nasal stimulus by ammonia [14]. Since the myoepithelial cells which surround the acini of the lacrimal gland contract in this process, it seems possible that some of the released tears are preformed and the actual secretory process may be somewhat slower than at first appears. It is not clear whether there is a 'maximum' rate of secretion; sustained rates are generally less than the 40–50 μl/min already mentioned.

Regulation of Tear Production

The innervation of the lacrimal gland is complex. The reflex arc is particularly important, involving fibres from the fifth cranial nerve in the cornea, conjunctiva or surrounding tissues. There is also innervation by both the parasympathetic and the sympathetic systems, inducing positive and negative control of secretion respectively. The parasympathetic route indicates some of the complexity: starting from the lacrimatory nucleus in the brainstem of the facial nerve (cranial nerve VII), parasympathetic fibres follow the greater superficial petrosal nerve to the pterygopalatine ganglion; the conventional view is that from there the secretory fibres of the lacrimal nerve follow the zygomatico-cotemporal nerve and join the lacrimal nerve of the ophthalmic division of cranial nerve V and enter the lacrimal gland. However, there is evidence that a number of rami orbitales pass from the pterygopalatine ganglion and some of these travel directly to the lacrimal gland [15].

The innervation of the accessory lacrimal tissue is even less well known, but it is assumed that it is controlled in the same way as the main lacrimal gland, as they are histologically very similar.

Composition of the Tears in the Conjunctival Sac and Origins of Secretions

Several different collection techniques have been used, but usually collection is from the lower meniscus, or sometimes from the conjunctival surface of the slightly everted lid, or among the folds in the lower fornix. Some workers have used absorbent sponges placed in the lower fornix, which is effective but has the disadvantage of picking up mucus as well as fluid tears. It is still not possible to collect from the actual film, e.g. by blotting the ocular surface, without some damage to epithelial cells and contamination by cellular contents. One should be clear whether the aim is to collect stimulated or unstimulated tears. Stimulation of flow may be by bright lights, a cold stream of air on the cornea, tickling inside the nose or tweaking nasal hair, or by exposure to specific

lacrimatory substances such as onion vapour, ammonia or chloracetophenone. If unstimulated tears are needed (for example, for osmolarity measurement), with collection at the slit-lamp, one must avoid passing the light beam across the pupil. We can classify the various components of the secretion as intrinsic or accessory in origin.

Intrinsic Secretions

Intrinsic secretions are produced in the main lacrimal gland (and presumably also from accessory lacrimal tissue since there is no apparent histological difference between the two types of tissue).

Aqueous Component

The aqueous part of the tears forms the bulk of the lacrimal secretion; it is actively secreted, and linked to the secretion of proteins (see below, (Major Proteins'). Although there is some input via aquaporin-controlled water channels in the corneal or conjunctival epithelium, its main source is the lacrimal tissue, where it is produced by the acinar epithelium and collected by the ductules. There is some modification and reabsorption in the ductules before delivery via the main lacrimal ductules to the outer upper fornix. It is possible by everting the temporal portion of the upper temporal lid and by finger pressure prolapsing the lacrimal gland slightly into the fornix to see one or two of the orifices, and if fluorescein is added then clear rivers can be seen in the fluorescing tears indicating the position of their orifices. During sleep or prolonged eye closure, the output of both proteins and water from the lacrimal gland changes (see below, 'Major Proteins').

The rate of secretion of lacrimal fluid varies considerably between the quiet eye and active stimulation (see 'Volume Flow of Tears into and from the Eye'). The ageing lacrimal gland suffers progressive fibrosis and loss of functional acinar tissue so its output gradually falls, creating tear film conditions similar to the earlier stages of the aqueous-tear-deficient form of dry eye.

Salts

Electrolytes are actively secreted by acinar and ductal epithelium of the lacrimal gland, and can be seen from the relative proportions of various ions not to be a serum filtrate (table 2) [16]. The pH of tears usually lies within the range 7.2–7.6 but may be higher on prolonged eye-opening through loss of CO_2; the value in neonates is about 6.8. Tears exert a buffering action due to their content of bicarbonate ion, proteins and other components, although the turnover rate has also been shown to be part of the response to pH challenge [17].

The osmolarity of the tears is determined almost entirely by their electrolyte content, since the molarity of even the major proteins is low in comparison. For

Table 2. Ionic composition of normal human tears [data from 16]

Ion	Concentration mmol · l^{-1}
Na^+	128.7
K^+	17
Ca^{2+}	0.32
Mg^+	0.35
HCO_3^-	12.4
Cl^-	141.3

Table 3. Major protein composition of normal human tears

Protein	Approx. molecular size, Da	Concentration mg · ml^{-1}
Lysozyme	14,000	2.07
Lipocalin ('tear-specific prealbumin')	17,500	1.55
Lactoferrin	90,000	1.65
sIgA	385,000	1.93
Albumin	68,000	0.04
IgG	53,000	0.004

normal unstimulated tears the generally accepted value is 302 ± 6 mosm · kg^{-1} [18].

Major Proteins

Human tears contain four major proteins (each 15–20% or more of total protein) – lysozyme, lactoferrin, lipocalin and secretory IgA (table 3). The protein of unknown function previously referred to as 'tear-specific prealbumin' is now known as tear lipocalin, a member of the lipocalin superfamily of small proteins with lipid-binding properties [19]. There is some evidence for interactions between lipocalin and both lysozyme and lactoferrin [20]. Lysozyme, lactoferrin and lipocalin are secreted by the acinar tissue of the lacrimal gland. The secretory form of IgA, in contrast, is produced by interstitial plasma cells embedded in the gland but external to the acini; the IgA dimer, consisting of two monomeric IgA molecules held together by a J or joining piece, are transported through the acini and the secretory component characteristic of completed sIgA is added (fig. 2). Control of secretion of lacrimal gland proteins

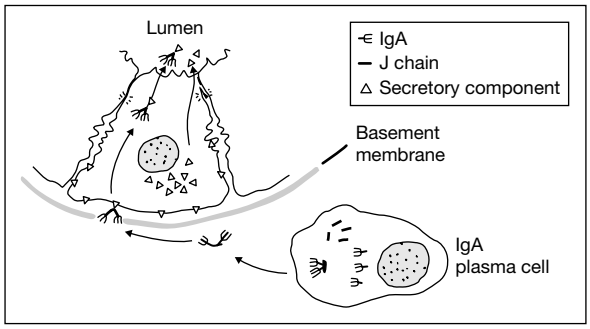

Fig. 2. Assembly of sIgA in lacrimal gland. IgA and J chain are synthesised and assembled in the plasma cells and transported through the acinar epithelial cells where they pick up the secretory component and are secreted into the ductal lumen. This process is independent of the secretion of water, electrolytes and tear proteins by the ductal cells.

appears to be linked to that of water: when output of water falls, so also does production of the proteins, and the concentrations of lysozyme, lactoferrin and lipocalin appear fairly constant. During sleep, as mentioned above, fluid secretion declines, and after about 2 h may approach zero. Output of sIgA, however, continues as the plasma cells producing this protein are not under the same control as the lacrimal gland, and the same amount of sIgA in a greatly reduced volume of aqueous appears as a steep concentration rise. At the same time, polymorphonuclear leukocytes accumulate, with the result that the tear film under the closed lids becomes much reduced in volume, sludgy and turbid, and has been described as being in a state of subclinical inflammation [21].

IgG and serum albumin are frequently also reported in tears, but since their levels vary with severity of disease or irritation it is considered that these proteins are not normal constituents but indicate leakage from conjunctival blood vessels.

The accessory lacrimal glands, making up 10% of all lacrimal tissue, are distributed at a number of sites within the conjunctiva. They have historically been named as the glands of Wolfring, Krause, etc. but appear to be histologically identical to the main lacrimal gland and to have similar innervation [22]. All the major lacrimal proteins have been identified immunochemically in this tissue [23]. Although the reflex response to irritation is less pronounced, the tissue can produce enough lacrimal fluid to maintain an adequate tear film in the quiet eye even in the absence of the main lacrimal gland.

Accessory Secretions

Several components are added to the aqueous tears within the conjunctival sac, and it is the combination of all these which produces the physiologically functional tear film and influences its formation and stability.

Lipids

A complex mixture of lipids is delivered from the meibomian glands opening on the lid margin at the mucocutaneous junction. These glands are large, tubuloacinar structures lying within the tarsal plate and related to the sebaceous glands of skin; although the surrounding tissue is richly innervated, no specific fast-acting nervous stimulation is known, and they appear to be free-running, secreting lipid continuously. As with sebaceous glands of skin, modification of systemic hormonal status may affect output, but the response is on a scale of months. Compression of the tarsal plate in blinking causes a small amount of oil to be squeezed out of each gland, but repeated heavy or forcible blinking can deplete the supply within the duct of the gland so that delivery is reduced until synthesis catches up with excretion. Conversely, during sleep there is no squeezing of the glands, so the elastic ducts fill up until some critical pressure is reached and excess leaks out onto the closed lid margins, where it either flows or is rubbed away, or forms flakes on the lashes [24].

In the lid-opening phase after a blink, a fresh air/water interface is rapidly generated, and oil (or at least the more surface-active components) spreads onto the tear film, probably forming a largely monomolecular film. It is thought that this initial spreading is followed by a second phase in which a fluid but less surface-active fraction spreads over the first to produce a multilayered oil film structure. Its thickness can be estimated from its interference colours (e.g. as seen with the Keeler Tearscope®); normal thickness is in the range 40–90 μm. The surface tension gradient created within the film by this spreading may cause Marangoni flow, pulling aqueous tears from the upper and lower menisci and thickening the overall tear film.

The meibomian oil contains several phospholipids, principally phosphatidylcholine and phosphatidylethanolamine, which with a small amount of free fatty acids and cholesterol make up the surface-active fraction. The non-polar fraction consists largely of wax esters (fatty acid + long-chain fatty alcohol) and cholesterol esters; branching in many of the acyl chains ensures that the melting range of the mixture is close to lid-margin temperatures [25]. Together, they form a layer shown to retard the evaporation of water from the surface of the tear film. Recently a model has been proposed for the structure of the oil film [26].

Lipids of non-meibomian origin have also been found in the tears, although reports are still incomplete. A mixture of non-polar lipids, mainly triacylglycerides, a small amount of phospholipid, and a substantial proportion of unidentified glycolipids has been described [27]. Since no free lipids are found in tear fluid, it is presumed that these are bound to lipocalin, which is the only major protein with strong lipid-binding characteristics [28].

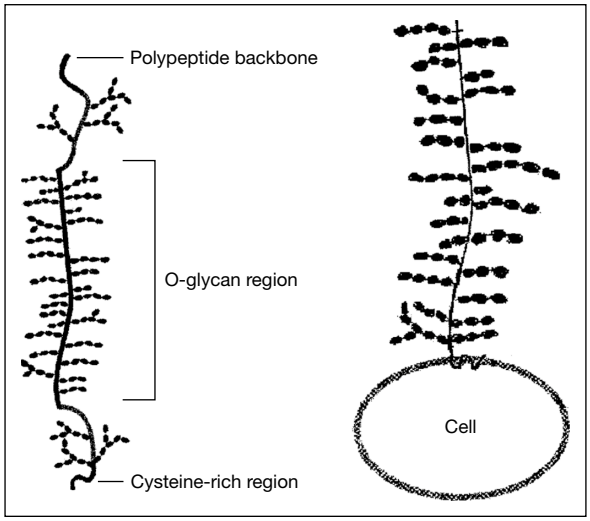

Fig. 3. Structure of different classes of mucin. Left, soluble type (e.g. MUC5AC gene product); the central section contains tandem repeats of polypeptide and O-linked glycans forming the 'bottle-brush', while the ends have cysteine-rich regions which cross-link to other molecules to build the gel. Right, representation of a membrane-spanning epithelial-bound type (e.g. MUC1) which does not form gels.

Mucins

Mucins are a complex class of glycoproteins with a very high carbohydrate content; their main characteristic is the 'bottle-brush' structure of a polypeptide backbone with many 'tandem repeats' of amino acid sequences and a high proportion of serine, threonine and proline, with a large number of oligosaccharide side chains O-glycosidically linked to Ser or Thr. They are the products of the family of MUC genes, and are of two main types: secreted or 'soluble' mucins of which the most important in the eye is MUC5AC, a gel-forming mucin produced in conjunctival goblet cells, and epithelial mucins, where the polypeptide backbone has a membrane-spanning region anchoring it to the plasma membrane of epithelial cells of cornea or conjunctiva, such as MUC1 [29] (fig. 3). The epithelial mucins (principally MUC1, 4 and 16) form the glycocalyx visible in transmission electron micrographs of the ocular surfaces, and a major function appears to be the anchoring of a gelatinous layer of secreted mucin so that a lubricating layer is present on all the surfaces gliding over each other during blinks or ocular movements. Mucins typically contain more than 50% carbohydrate, and water makes up more than 90% of mucin gel.

Minor Components and Small Molecules

Tears contain a large number of small molecules and minor components which can protect the corneal surface or which are produced in response to specific conditions such as inflammation. Defensins are a family of small proteins (M_r about 8,000) with antimicrobial properties (see below, 'Antimicrobial Protection'). Several cytokines associated with inflammation (IL-1α and IL-1β, IL-6 and IL-8) have been identified in normal tears [30]. However it is not always clear whether these factors are derived from the lacrimal gland or secreted by the conjunctival epithelium, or by leakage from the surrounding blood vessels. Enzyme activity of various kinds can be detected in tears, although the amount of the appropriate protein may be very low. Thus, catalase, superoxide dismutase, and glutathione peroxidase have been reported, among others, and are presumed to have an antioxidant protective role [31].

A number of systemic drugs can be detected in the tears. The actual source (conjunctival vessel leakage, transport through corneal epithelium, or lacrimal gland secretion) is not always obvious. If corneal, this could imply a specific membrane-associated transport mechanism, or an ability to pass the tight intercellular junctions, and this latter is thought to be related to the lipid solubility of the drug. Thus, phenobarbital, carbamazepine and methotrexate, which all have reasonable lipid solubility, have been detected in tears at levels comparable to those in serum, whereas ampicillin is less lipid-soluble and is found only at a very low level compared to serum [32]. Acetaminophen is excreted in the tears at comparable levels to serum [33]. It is known that systemic cytosine arabinoside can cause keratitits, and this is thought to follow secretion into the tears. Rifampicin and its metabolites appear in tears, which may be coloured red-orange and cause staining of contact lenses.

Functions of the Film

Nutritional Aspects

Because of the requirement for transparency, the cornea has no blood supply. Delivery of gases and nutrients by diffusion from blood vessels at the limbus would be too slow, so these are supplied directly from the tear film; the film acts as a coupling medium for oxygen from the air (as is clear from the comparative performance of contact lenses with differing D_k values). A similar function takes place on the endothelial side of the cornea from the aqueous humour of the anterior chamber. In the open eye the tears, being in contact with air, are assumed to be saturated with oxygen (i.e. 155 mm Hg); however, when the eye is closed, oxygen must be supplied by diffusion from the blood in the conjunctival vasculature (55 mm Hg), so the metabolic status of the corneal

epithelium changes markedly between the two states [34]. It should be noted that in the closed eye the coupling medium to the cornea must actually be the film of tear fluid filling the space under the lids. The thickness of this is not exactly known, and it is also assumed that there is a relatively thick mucous layer filling most of this space, caused by the apposition of the mucous layers covering both cornea and tarsal conjunctiva.

The tears transport oxygen to the corneal epithelium, and remove metabolic carbon dioxide. Comparatively few other nutrients are found in significant quantities. It is suggested that glucose is supplied to the cornea entirely from the posterior or endothelial side, and that the corneal and conjunctival epithelia are impermeable. Tear glucose levels are low, and little changed in diabetics; reports of higher levels may be due to local tissue damage and assay of released glucose. Lactate and pyruvate are also found, indicative of the metabolic activity of corneal tissue. The growth factors EGF and TGF-α have also been detected [35].

Protective Roles

These can briefly be classified in two distinct areas:

Physical Protection

Many threatening or noxious attacks on the eye are averted by the rapid blink reaction, or by aversion (head turning or brow lowering); some lighter invading materials such as airborne dust, hairs or bacteria may be reflected from the surface of the tear film, especially hydrophilic particles which have been observed to bounce off the oil film [36]. The mucous gel coating of ocular surfaces traps, absorbs and immobilises many particles and microbes, and removes them from the eye as part of the mucous thread which is swept down into the lower fornix and eventually extruded onto the skin of the inner canthus [37]. The lubricating action of the mucous layer also prevents shearing damage to the surface epithelium at the high speeds (as high as 20 cm/s) achieved during the blink [38].

Lipocalin is the principal lipid-binding protein in tears, and a role for this protein has been suggested in scavenging excess lipid from the ocular surface or the surface of the mucous layer to avoid the development of non-wettable patches that would lead to tear film break-up [39]. As yet this has not been supported by analytical studies.

Antimicrobial Protection

Several of the components of tears have antimicrobial functions. Lysozyme is well known for its muramidase activity in the outer cell wall of Gram-positive bacteria, while both lactoferrin and lipocalin have iron-sequestering properties

which inhibit siderophilic bacteria [40, 41]. Secretory IgA exerts immunological protection after priming of the plasma cells against specific microorganisms and viruses; priming can be via mucosa-associated lymphoid tissue in the conjunctiva or elsewhere [42, 43]. Recently a group of small protective peptides known as defensins have been identified in the tears by immunochemical means. Several members of the α and β families of defensins were identified in normal tears, lacrimal gland, and inflamed conjunctiva. These have a broad spectrum of antimicrobial activity (bacteria, fungi and viruses) and are claimed to accelerate epithelial healing [44].

All these factors need to be considered in relation to ocular surgery, especially physical aspects such as the placement of inflow ductules and puncta/canaliculi for drainage, avoidance of distortion of surface or conformation of lids on globe, and the removal or remodelling of conjunctiva.

Structure and Stability of the Precorneal Film

Many structural models of the preocular tear film have been proposed over the last 50 years. These are mainly based on the three-layered structure of Wolff [45], which has a layer of gelatinous mucus in contact with the epithelial surface (since modified largely on the basis of electron-microscopical evidence to include the surface glycocalyx), the bulk of the thickness made up of an aqueous solution of the proteins and other water-soluble molecules, and a surface layer of meibomian oil. More recently, a model has been proposed for the rat involving only two layers, in which the bulk of the film was aqueous/mucous plus an oil layer, with no differentiation into separately identifiable aqueous and mucous layers [46]. A somewhat similar model is suggested for the mouse [47]. It is not clear whether either of these models should also be expected for the human, and space does not allow an extensive review of the aspects of all the available models. Despite much work on the human tear film and in many species of animal, we have not yet arrived at one consistent model which can satisfactorily explain all aspects of formation, stability and function of the film.

In view of the nutritive and protective properties of the tear film, it is clearly desirable for it to cover the exposed surface of the eye throughout the eye-open period between blinks. Evaporation can be measured, but we should remember that most evaporative loss will be from the film, while the bulk of the available fluid is in the menisci or under the lids, and it is from these compartments that samples are collected for analysis [7].

Hence local changes in osmolarity may be greater than usually thought, and corresponding effects on film stability may be masked.

The main test of tear film stability is the break-up time (BUT), i.e. the time taken after the last complete blink for signs of rupture and dewetting of the film to be detected. Tests differ in whether they are invasive (instillation of fluorescein to show break-up as black spots, FBUT) or non-invasive (detection of distortions of the reflected image of a grid from the cornea, NIBUT), and the value taken to indicate the borderline between normal and unstable or dry eye may vary according to method: between 5 and 180 s (ca. 5–20 s for FBUT [48], or ca. 10–30 s for NIBUT [49]). However, other factors such as number of repeat measurements, time of day or racial characteristics of the subject can also influence the outcome [50]. Perhaps the most reliable use of BUT is in assessing the effectiveness of clinical treatment. FBUT is widely considered to have poor repeatability, although this may depend on the quantity of fluorescein introduced, since this can itself affect tear film stability. NIBUT also shows considerable variation when the same subject is measured on successive days, and also for repeated measurements on the same day, although this may be due to increased tearing in response to holding the eye open for long periods. Nevertheless, BUT is a valuable guide to tear film stability. It is considered satisfactory to take the mean of three successive measurements (in the case of FBUT, adding as little fluorescein as possible).

Tests on Tears

There are many tests which can be used to assess tear film composition or function. These may be classified as subjective, where some element of judgement is required on the part of the observer, such as in grading the extent or severity of a sign, on some predetermined scale such as 0–4, as −/+ or + to +++; or objective, involving use of methods or equipment capable of giving a more precise value. A further division is between those tests which can be carried out under clinical conditions (although the results may be interpreted elsewhere), and those where samples are examined in the laboratory or the patients themselves are examined outside the clinic.

Clinical Tests

Apart from the basic tear break-up test, these include estimating tear volume from the Schirmer paper strip test [51]. The recommended Schirmer strip is of Whatman No. 41 filter paper 5 mm wide and 35 mm long, with the terminal 5 mm bent to hook over the lid margin. The test can be applied in various forms, which measure different aspects, but the nomenclature is confusing. The test can be with or without anaesthetic. Schirmer's original test (Schirmer I)

is without anaesthetic and does not include stimulation, other than that due to the inserted paper. The 5-min wetting length is taken to represent the basal unstimulated flow. A wetted length of 15 mm or more is taken to indicate normal production. A variant of this is the Jones test [52] which also measures the basal rate, but uses anaesthetic and is carried out in subdued lighting conditions to minimise reflex tearing. The normal response is a wetted length of 10 mm or greater. If the basal rate is normal but the reflex response to stimulation is thought to be defective, Schirmer II can be applied, which uses anaesthetic but includes stimulation of reflex tearing by nasal irritation with ammonia vapour, onion vapour or a cotton applicator. A reading of 5 mm or less in 5 min is indicative of aqueous-deficient dry eye. There are numerous variants of the original Schirmer tests; despite many reservations about its meaning, it is still generally accepted that it gives useful information. The cotton-thread test is a variation of the Schirmer test, using a loosely-twisted thread which is less irritating to the eye (and less likely to provoke reflex secretion); the steady-state output of the lacrimal gland is being assessed, whereas without anaesthetic (and hence with the irritation of insertion of the paper) the reflex response of the lacrimal gland is probed. The disadvantage of the thread method is that because it does not provoke tearing, it measures only the fluid already available in the conjunctival sac [53].

The normality of tear volume is also estimated from meniscus height [54] or meniscometry [55] where meniscus curvature is calculated from reflection of a striped target.

The measurement of evaporation itself is possible under clinical conditions, but no commercial instrument exists. One instrument, which calculates evaporation rate from the rate of rise of humidity inside an eyecup, is currently used in assessment of dry eye patients in the clinic [56].

The use of the Fluorotron Master to measure turnover time or clearance rate of tears from the eye has been mentioned above in ‘Volume Flow of Tears Into and From the Eye’.

The thickness of the lipid layer is assessed from the interference colours seen on reflection of light using an instrument such as the Keeler Tearscope [57]. Meibometry, in which the lid margin is blotted with a tape and the change in transmission of the tape due to the oil picked up is measured, can give information about the availability of oil, and if the lid margin is first cleaned of oil, about delivery from the glands [24, 58]. This is in fact the only currently available objective measure of meibomian gland output.

Laboratory Tests

These are generally more time-consuming or involve the use of more complex equipment than clinical tests. Samples of tears or other secretions must be

taken, paying attention to the collection site or conditions. Thus the protein composition may be analysed by high-performance liquid chromatography, although this will show only the major proteins and not minor components, which may have to be detected by assaying collected column effluent fractions for enzyme activity or other functions. Alternatively, polyacrylamide gel electrophoresis can give detailed information about the protein composition of tears.

Tear osmolarity is a good indicator of high rates of evaporative loss, and can be measured on collected tear samples. The Clifton nanolitre osmometer (depression of freezing-point principle) is still considered the 'gold standard' method despite its many practical difficulties; the Wescor vapour pressure osmometer is simpler and could be used in the clinic, but may have a considerable reading error with tear samples <1 μl, which one must use to avoid reflex lacrimation and dilution of the tear film during collection [59]. A simple, rapid and very sensitive commercial instrument is promised, but was not available at the time of writing.

Tests of Quality

Whereas one can, by detection of deviations from normal composition, conclude that the tears are of less than the required quality to maintain stability and function, it is much harder to devise tests to establish whether the performance of a sample of whole tears is of the required quality. Perhaps the only such test is tear ferning. A small sample of fluid tears (about 2 μl) is placed as a droplet on a clean microscope slide and allowed to dry, then examined under the microscope [60]. Viewed at $\times 50$ to $\times 100$, feathery patterns of salt crystals are seen, and the degree of complexity of these correlates well with other measures of tear quality or performance. Although often called the 'mucus ferning' test, it is in fact less dependent on mucus content than on the balance of electrolytes [61], but much more exploratory work needs to be done before it can be considered altogether reliable.

Compositional tests as indicated in 'Laboratory Tests' can be applied to show that some assumed 'best' or 'normal' assembly of components is present. But this is complicated in that it changes to some extent with age or other physiological states (e.g. the menstrual cycle). Vital staining can also give information about the completeness of the film. Thus, in the same way that fluorescein is used to indicate breaks in the epithelial surface, staining with rose bengal is considered to depend on breaks in the mucous layer covering the ocular surface, revealing the unprotected and presumably unlubricated epithelial surface beneath [62].

Physical properties such as viscosity or surface tension can be measured if adequate volumes of tears are available, and can indicate the normality of the tears [63, 64].

Conclusions

The normal tear film is metabolically functional, protective, and nutritive. Problems arise if its stability is compromised by anatomical factors such as the improper meeting of lids or the closeness of their fit to the globe, blockage of the drainage routes, surface roughness or epithelial damage. Inflammation involves the secretion into the conjunctival sac of many additional components, of both tissue and serum origin, and these can materially alter the physiological functioning of the tears. These factors must all be taken into consideration in planning surgical procedures.

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John M. Tiffany
Nuffield Laboratory of Ophthalmology, University of Oxford
Walton Street, Oxford OX2 6AW (UK)
Tel. +44 1865 248 996, Fax +44 1865 794 508
E-Mail john.tiffany@eye.ox.ac.uk

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Functional Anatomy and Immunological Interactions of Ocular Surface and Adnexa

Friedrich Paulsen

Department of Anatomy and Cell Biology, Martin Luther University
Halle-Wittenberg, Halle/Saale, Germany

Abstract

Background: This chapter gives an overview about the structures and physiology of the ocular surface and its adnexa and focuses in a second part on the possible meaning of eye-associated lymphoid tissue (EALT) in a context with the development of dry eye. **Methods:** Sections deal with (1) anatomy of the ocular surface, lacrimal gland, eyelid and nasolacrimal ducts. (2) The meaning and importance of the lacrimal functional unit and the function of the mucosal innate immune system are briefly summarized. (3) Finally, the occurrence and the possible function of EALT is discussed with regard to tolerance induction and dry eye. **Results:** The epithelial surface of the eye and its specialized glandular infoldings produce the components of the tear film, which include water, protective antimicrobials, cytokines, lipids as well as mucins and trefoil factor family (TFF) peptides. Antimicrobials, mucins and TFF peptides perform a number of essential functions which, collectively, provide protection of the ocular surface. Their production changes in cases of dry eye. The development of EALT is a common feature frequently occurring in symptomatically normal conjunctiva and nasolacrimal ducts. **Conclusions:** The production of antimicrobials, mucins and TFF peptides can be linked with cell signaling, tear film rheology, and antimicrobial defense at the ocular surface. Changes in the production of such peptides and proteins in cases of dry eye support the assumption that these peptides and proteins are involved in the pathophysiological events that occur at the ocular surface and lacrimal apparatus. Whether special types of bacteria, viruses, or other factors, e.g., immune deviation, are responsible for the development of EALT in humans requires further investigation in prospective and experimental studies.

Anatomy

The ocular surface and its adnexa comprise the cornea, the conjunctiva with bulbar, fornical and palpebral parts, the main lacrimal gland, the glands of

the eyelids, i.e. meibomian, Moll's, and accessory lacrimal glands and the nasolacrimal system with the upper and lower puncta, the paired lacrimal canaliculi, the lacrimal sac and nasolacrimal duct. The nasolacrimal ducts collect the tear fluid from the ocular surface and convey it into the nasal cavity whereas all other structures contribute to formation of the preocular tear film. The tear film serves to protect and lubricate the ocular surface, as well as to provide the major refractive surface for the visual system.

The preocular tear film (see chapter 1 by J.M. Tiffany) contains water, protective antimicrobials, cytokines, lipids, and mucins and can be divided in three components: a lipid component, an aqueous component, and a mucus component. The lipid component is secreted by the meibomian glands in the eyelid and forms the superficial layer of the tear film. The aqueous component contains electrolytes, water, and a large variety of proteins, peptides and glycopeptides and is primarily secreted by the lacrimal gland as well as the accessory lacrimal glands (glands of Krause; glands of Wolfring) of the lids. The mucus component is the product of conjunctival goblet and epithelial cells, corneal epithelial cells and acinar as well as excretory duct cells of the lacrimal gland, which have recently been shown to produce mucins (fig. 1).

Ocular Surface

The apical surface of the ocular surface epithelia, both corneal and conjunctival (fig. 2a, b), provide a specialized interface between the tear fluid and the epithelium that stabilizes the fluid layer. That interface includes the undulating membrane ridges on the apical cell's apical membrane, termed microplicae, and emanating from their apices, a layer termed the glycocalyx. Membrane-bound mucins (MUCs 1, 4 and 16) of corneal and conjunctival epithelial cells are present in the glycocalyx layer (figs 1b, c, 2a, b); soluble mucins (MUC5AC) from conjunctival goblet cells (figs 1b, 2b) [for review, see 1] as well as MUCs 5B and 7 from lacrimal glands are in solution in the tear film [2–5]. Both MUC5B and MUC7 have been shown to bind bacteria [for review, see 1] and contribute to innate immunity of the tear film. Beside MUC5AC, conjunctival goblet cells secrete the trefoil factor family (TFF) peptides TFF1 and TFF3 [6]. TFF peptides are, together with mucins, typical constituents of mucus gels that influence the rheological properties of the tear film, promote migration of corneal epithelial cells, have antiapoptotic properties, and induce cell scattering [for review, see 7]. Conjunctival and corneal epithelial cells are able to react against pathogens by the production of inducible antimicrobial peptides [8, 9]. Moreover, in certain disease states the corneal cells are able to produce TFF3 [10].

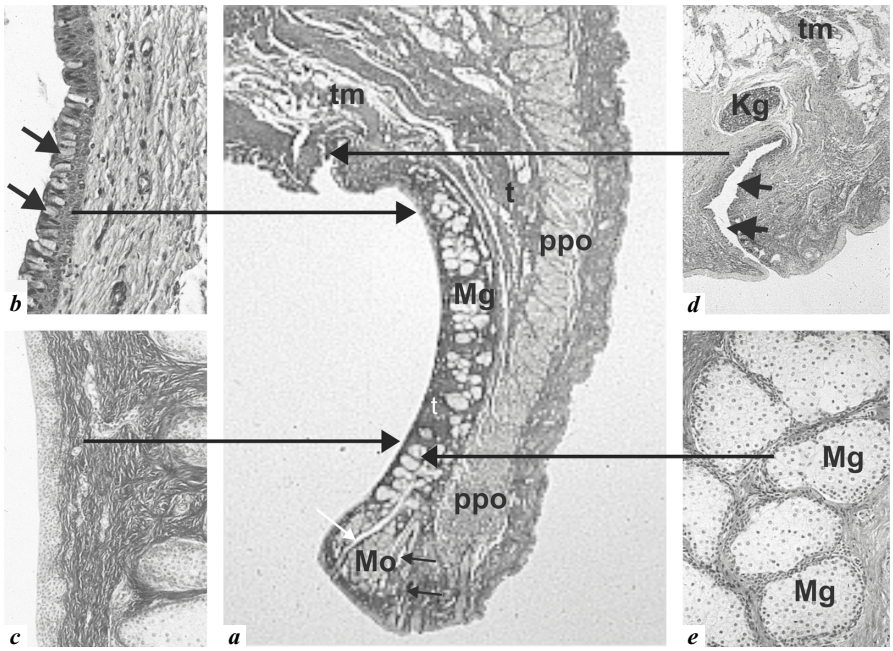

Fig. 1. Structures of the eyelid. ***a*** Overview. Sagittal section through a eyelid. tm = Tarsalis muscle; t = tarsus; ppo = palpebral part of orbicularis muscle; Mg = Meibomian gland; white arrow = excretory duct of Meibomian gland; Mo = Moll's gland; black arrows = sections through eyelashes. ***b–e*** Representative magnifications of the areas marked by a large black arrow in figure 1a. ***b*** Conjunctival epithelium in the area of the tarsal plate near the fornix. The epithelium consists of columnar epithelial cells with integrated goblet cells (arrows). Tight connective tissue of the tarsus underlies the epithelium. ***c*** Conjunctival epithelium in the area of the tarsal plate near the rim of the eyelid. A non-cornified squamous epithelium covers the underlying tarsal plate. Parts of the Meibomian gland are visible. ***d*** The magnification shows an accessory lacrimal gland (Krause's gland; Kg). Iris excretory duct opens into an infolding of the fornical conjunctiva (arrows). Parts of the tarsalis muscle (tm) are visible above the gland. ***e*** Magnification of a part of a Meibomian gland (Mg) revealing its sebaceous character. The gland is embedded in the tarsal plate.

Lacrimal Gland

The lacrimal gland is anterior in the superolateral region of the orbit, and is divided into two parts by the levator palpebrae superioris muscle. The lacrimal gland consists of acini that are built of a luminar lining of columnar epithelial cells that are surrounded by a basal layer of myoepithelial cells and an enclosing basement membrane (fig. 2c). The human lacrimal gland is a tubuloalveolar gland of serous type. Intercalated and 6–12 interlobular ducts drain the secretions

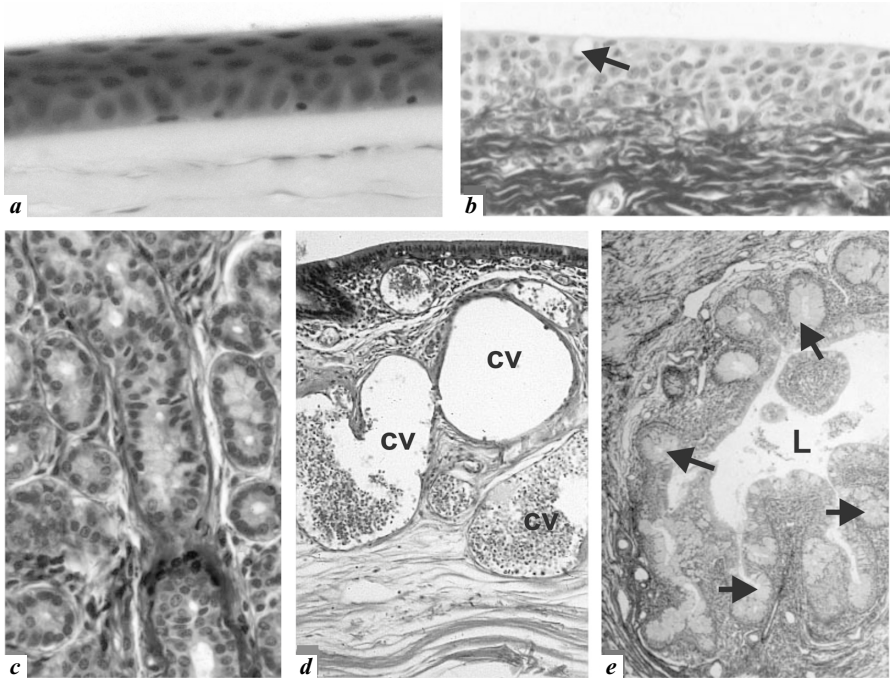

Fig. 2. Histological section through the epithelial lining of the cornea (***a***) and the conjunctiva (palpebral part near eyelid rim) (***b***). The arrow in ***b*** marks a small goblet cell. ***c*** Cross section through the lacrimal gland revealing acini that are built of a luminar lining of columnar epithelial cells that are surrounded by a basal layer of myoepithelial cells and an enclosing basement membrane. ***d*** Cross section through the subepithelial connective tissue of the lacrimal sac. Blood from a subepithelially located capillary network is collected by postcapillary venules that drain into widely convoluted capacitance veins (cv). Note the columnar epithelium. ***e*** Cross section through the lacrimal sac. Goblet cells show a characteristic arrangement of several cell groups in the upper part of the lacrimal sac forming mucous glands (arrows). L = Lumen of the lacrimal sac.

into the conjunctival fornix beneath the temporal bone. The tubules discharge without any characteristic excretory duct system (histologic distinction from serous salivary glands) into the interlobular ducts. The connective tissue between the acini contains accumulations of lymphocytes as well as many plasma cells mainly secreting IgA and being part of the eye-associated lymphoid tissue (EALT). As already mentioned, the lacrimal gland produces electrolytes, water, and a large variety of proteins, peptides and glycopeptides. Of these, recent research regarding tear film rheology and innate immunity focus on production of different constitutively and inducible antimicrobial peptides,

such as β-defensins [for review, see 9], surfactant proteins A and D [11, 12] as well as MUCs 4, 5AC, 5B and 7 [2, 3] that are secreted into the tear film.

Eyelid

The 'skeleton' of the eyelid is a collagen plate called the tarsus (fig. 1a). It contains a row of branched alveolar sebaceous glands, unrelated to the eyelashes. These tarsal or Meibomian glands have punctate openings along the free edge of the eyelid close to its posterior margin (figs 1a, e). They produce a lipid material whose synthesis is dependent on neuronal, hormonal, and vascular factors. This lipid material is fluid, spreads easily, is a surfactant as well as an aqueous barrier and must remain functional after a blink. To satisfy these requirements, the Meibomian lipids have a specific composition. Even after delivery it may be modified by lipases produced by ocular bacteria, and modifications in the lipid components can lead to unique disease states [for review, see 13]. Sexual hormones, especially androgens, seem to play a decisive role in Meibomian physiology [14].

Near the anterior margin of the eyelids there are two or three rows of stiff hairs – the eyelashes (fig. 1a). In the middle of the lid is the cross-striated orbicularis oculi muscle, the fiber bundles of its palpebral part overlapping one another like tiles on a roof (fig. 1a). The tendon of the cross-striated levator palpebral muscle is inserted into the tarsus; beneath it is the smooth tarsalis muscle (figs 1a, d). The tone of the latter is determined by autonomic nervous impulses and is supposed to adjust the width of the palpebral opening. The apocrine ciliary glands (Moll's glands) open close to the eyelashes (fig. 1a). These apocrine glands are active from birth in producing agents against pathogenic microorganisms in the eyelid shaft and on the ocular surface, i.e. lysozyme, β-defensin-2, adrenomedullin, lactoferrin, and IgA [15]. In the conjunctival fornix the eyelid also contains small accessory lacrimal glands (Krause's glands, Wolfring's glands). Although much smaller, these glands are histologically comparable to the main lacrimal gland (figs 1a, d). However, only less is known about the secretions of these small glands and their contribution to tear film physiology.

Nasolacrimal Ducts

A lacrimal system consists of the upper and the lower lacrimal canaliculus, the lacrimal sac and the nasolacrimal duct. The structures are surrounded by a wide ranging cavernous system (fig. 2d) and are embedded in the osseous canal between the maxilla and the lacrimal bone [16]. The internal wall of each lacrimal canaliculus is lined by a thick non-cornified epithelium resting on a basement membrane. The lacrimal sac and the nasolacrimal duct are lined by a double-layered epithelium with integrated goblet cells sometimes forming

characteristic mucous glands (fig. 2e). As a draining and secretory system, the nasolacrimal ducts play a role in tear transport by production of MUCs 2, 4, 5AC, 5B, and 7 [17], TFF peptides TFF1 and TFF3 [18] and non-specific immune defense [19]. Moreover, components of tear fluid are absorbed in the nasolacrimal passage and are transported into the surrounding vascular system [20]. This system is similar to a cavernous body that is subject to autonomic control and regulates tear outflow [21]. Tear duct-associated lymphoid tissue (TALT) is present in the efferent tear ducts [22]. Under normal conditions, tear fluid components are constantly absorbed into the blood vessels of the surrounding cavernous body. These vessels are connected to the blood vessels of the outer eye and could act as a feedback signal for tear fluid production, which ceases if these tear components are not absorbed [for review, see 23].

Lacrimal Functional Unit and Host Defense at the Ocular Surface

Lacrimal Functional Unit

The cornea possesses the richest sensory innervation of the body to detect noxious stimuli. The trigeminal sensory neurons (CN V) that innervate the eye vary in their chemical composition and electrophysiological properties, and can be classified according to the stimuli that activate them preferentially: mechanical forces, temperature, or irritant chemicals. Different classes of noxious stimuli (mechanical injuries, heat, extreme cold) activate to a different degree the various populations of sensory fibers of the ocular surface and evoke unpleasant sensations of distinct quality [for review, see 24].

It is recognized today that the tear film is secreted reflexively from the 'lacrimal functional unit' that is composed of the ocular surface tissues (cornea and conjunctiva, including goblet cells and Meibomian glands), the lacrimal glands (main and accessory), and their interconnecting sensory (CN V) and autonomic (CN VII) innervation [25]. This reflex secretion is initiated by subconscious stimulation of the highly innervated ocular surface epithelia. The human nasolacrimal ducts are integrated in this reflex arc, as shown by recent investigations [21, 26].

Host Defense at the Ocular Surface

Some defense mechanisms of the innate immune system have already been mentioned above and it is beyond the scope of this chapter to deal with all of them. However, it should be mentioned that the defense of the ocular surfaces presents a unique challenge in that not only must integrity be maintained against microbial, inflammatory and physical assault, but it must be done while minimizing the risk of loss of corneal transparency. This puts severe limitations

on the degree to which scarring or neovascularization can occur in the cornea secondary to any infectious, inflammatory, immunological or wound-healing process. The defense system must be equally effective under two extremes of conditions: those found in the open eye and the closed eye environments. Distinctly different defense strategies are utilized in both open and closed conditions. The extraordinary effectiveness of this system is evidenced by the fact that despite continued exposure to a microbe-rich environment, the external ocular surfaces maintain a very low microbial titer and are highly resistant to breaching by all but a few pathogens [for review, see 27].

Eye-Associated Lymphoid Tissue as an Entrance Side for Immunological Events

EALT

The epithelia of the ocular surface, the corneal and conjunctival epithelia, the epithelium of the efferent tear ducts, the Meibomian glands, main and accessory lacrimal glands and lids make up a physiological system that was recently dubbed the lacrimal-ocular surface system (LOS) [28]. The LOS is organized to maintain the clarity of the cornea – a homeostatic set-point. Like the systems that represent epithelial interfaces between the internal and external environments, i.e., the gastrointestinal, integumentary and respiratory systems, the LOS system collaborates with the innate and adaptive immune system to respond to microbial invasion. The lacrimal glands, conjunctiva and efferent tear ducts constitute one venue of this collaboration area. These tissues are populated by IgA-producing plasma cells and their epithelia actively transport secretory IgA into the nascent tear fluid (fig. 3) [29].

Specific secretory immunity depends on sophisticated cooperation between the mucosal B cell system and an epithelial glycoprotein called the *secretory component* [30]. Initial stimulation of Ig-producing B cells is believed to take place mainly in organized mucosa-associated lymphoid tissue (MALT) [31]. It has become evident that MALT is characterized by considerable regionalization or compartmentalization, perhaps determined by the different cellular expression profiles of adhesion molecules and/or the local antigenic repertoire. Antigenic stimulation of B cells results in the generation of predominantly IgA-synthesizing blasts that leave the mucosae via efferent lymphatics, pass through the associated lymph nodes into the thoracic duct, and enter the circulation. The cells then return selectively to the lamina propria as plasma cells or memory B cells [32] by means of homing mechanisms (fig. 4).

Organized lymphoid tissue in the conjunctiva (conjunctiva-associated lymphoid tissue – CALT) and efferent tear duct system TALT [22, 23, 33–40] have

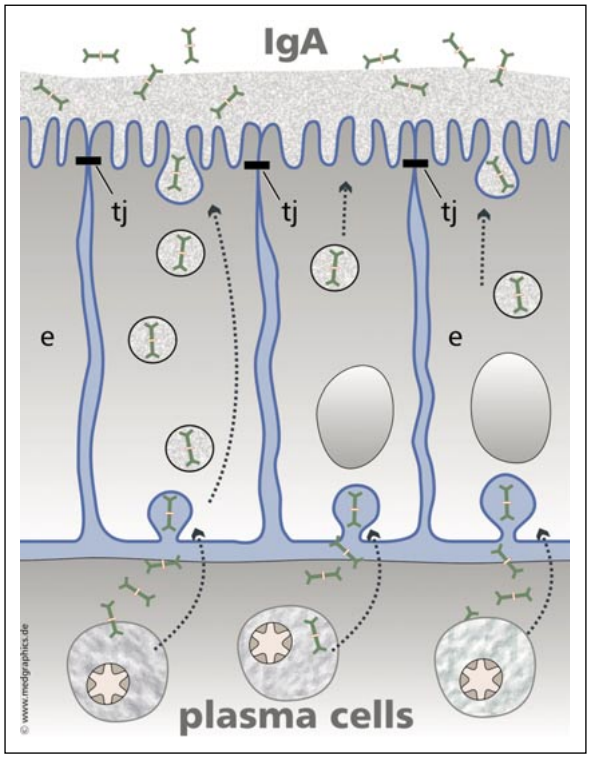

Fig. 3. Transepithelial transport and secretion of IgA. tj = Tight junction.

recently been termed collectively EALT [41]. However, aggregated follicles that fulfill the criteria for designation as EALT occur only in somewhat less than a third of conjunctivae and nasolacrimal ducts from unselected cadavers with no known history of disease involving the eye, efferent tear ducts, or nose [22, 23, 34]. In most cases, only lymphocytes and other defense cells are amply present subepithelially, i.e. inside the conjunctiva and efferent tear ducts that do not form aggregated follicles. It is as yet unclear whether special types of bacteria, viruses, allergic reactions, or other factors, such as some type of immune deviation, are responsible for the development of EALT in humans. However, when EALT is present, it can provide the basis from which primary low-grade B cell lymphoma of the MALT type may arise.

EALT as an Entrance Side for Immunological Events

Some organs of the human body (anterior eye chamber, brain, placenta, testicle) have a special immunological state of reduced activation of the specific

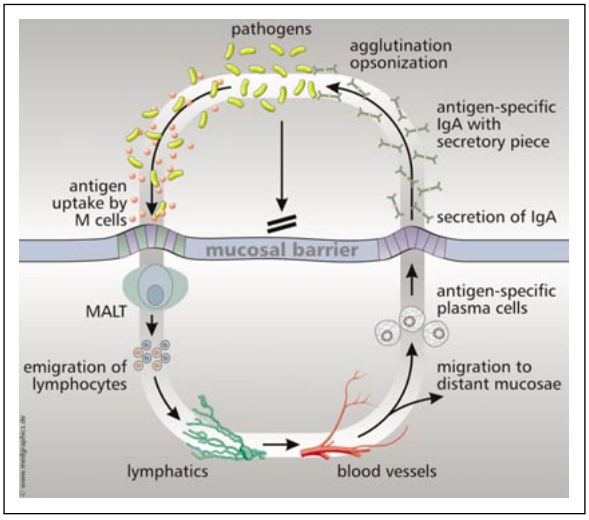

Fig. 4. Function of MALT (see text for details).

and non-specific immune system. This condition of local immune suppression, termed *the immune privilege*, is expressed in delayed or totally suppressed rejection of allogenic transplantations in these organs [42, 43]; this is illustrated by the maintenance of the immunophenotypic immature placenta in the maternal organism and in the survival of corneal and lens transplants in the anterior eye chamber. The biological functions of the immune privilege are evident: tolerance of a foreign antigen is obviously better in some organs than its rejection, and this can be achieved only at the expense of T-cell-mediated cytolysis of local cells. Such cell loss is not replaceable in poorly regenerative, postmitotic, or highly differentiated tissues. Therefore, some viruses survive in the central nervous system, as their elimination by T-effector cells would doubtlessly lead to neural cell death with subsequent severe neurological deficit or even individual death. A similar situation exists in the anterior eye chamber [44] and the testicle. Such immune suppression is not necessary in regenerative organs, like the liver or the skin, since all the cells needed for this process are able to proliferate and redifferentiate.

The mechanisms that maintain the immune privilege are non-uniform among different organs, and they are not understood in detail. Besides the classic concept of mechanical tissue barriers (i.e. the blood-brain, blood-testis and blood-retina barriers), we must consider the expression of so-called *death ligands* (CD95, TRAIL, TNF) that induce apoptosis of potentially dangerous T cells, as well as a special form of antigen presentation that produces immune

tolerance. Such *immune deviation* was first described in the anterior eye chamber [45]. There, injection of foreign antigen does not lead to a local T-cell reaction (type IV immune reaction) as it does at other body locations, but rather produces systemic tolerance against the inoculated antigen. In this way, antigens are not attacked in the anterior eye chamber, thus protecting the sensitive visual system against inflammatory damage. In this way, the immune privilege of the anterior eye chamber allows transplantation of allogenic lenses, artificial intraocular lenses, and corneae (although type IV immune reactions are possible after corneal transplantation in rare cases).

Such tolerance is known to be transferable by injection of splenocytes from an animal primed by inoculation of an antigen into a second animal, demonstrating that antigens from the anterior eye chamber receive a signal that produces immune deviation and that regulatory T cells have developed. In contrast to the spleen, the cervical lymph nodes do not play a critical role in the induction of immune deviation, as was shown in rats by Yamagami and Dana [46]. Nevertheless, the drainage routes of the antigens from the anterior eye chamber and the location of their origin, as well as the passage of the belonging antigen-presenting cells, are unclear. In particular, it is not clear what role is played by the conjunctiva and the nasolacrimal ducts, as well as the lymphoid tissues associated with them (CALT [33, 34, 39, 47–49] and TALT [22, 23, 37, 40]), in the immune privilege of the anterior chamber of the eye.

Egan et al. [50] demonstrated in mice that potent immunologic tolerance can be achieved by exposure of antigen (ovalbumin) via the conjunctival mucosa. They identified the submandibular lymph node as the principal lymph node in which antigen-bearing antigen-presenting cells are located and in which antigen-specific T-cell clonal expansion occurs following conjunctival application of antigen. Clonal expansion was maintained at an elevated level and the T cells were responsive in vitro during a 10-day period of daily ovalbumin application to the conjunctiva. However, despite continuous antigen application, the number of antigen-specific T cells steadily declined over the 10-day period, and by day 14, the remaining ovalbumin-specific T cells were refractory to secondary challenge with ovalbumin, indicating that they had become anergic in vivo. Egan et al. [50] concluded that the fact that antigen-presenting cells presenting ovalbumin were found only in the submandibular lymph node – and not in other lymph nodes, spleen, or nasal associated lymphoid tissue (NALT) – rules out the possibility that tolerance in this system was due to drainage of antigen through the efferent tear ducts and association with NALT or gastrointestinal-associated lymphoid tissue (GALT).

However, one important point is lacking in the suggestions of Egan et al. [50]: It has not yet been appreciated that antigens drained by the tear fluid itself, and not applied intraconjunctivally, would be able to induce immune deviation

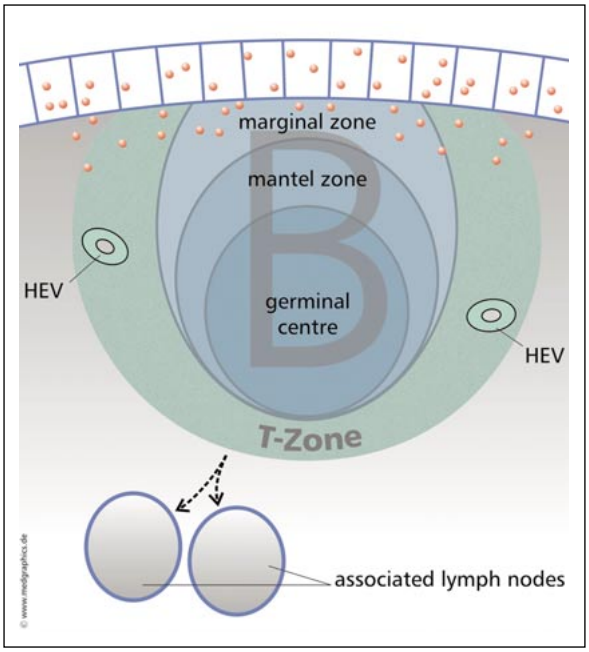

Fig. 5. Organization and components of MALT. Red spots indicate intra- (lymphoepithelium) and subepithelial lymphocytes. B = B-zone (blue); HEV = high endothelial venule in the T-zone (green).

via CALT and/or TALT. With regard to protection of the cornea against inflammatory destruction, this would be plausible and analogous to the process in the nervous system and the anterior eye chamber [45]. In comparison with gastrointestinal tract MALT (GALT), it is not known as yet whether M cells occur in human CALT and TALT, although they probably do, as their presence has been demonstrated in several animal species. M cells are highly specialized epithelial cells that facilitate uptake and transcytosis of macromolecules and microorganisms. Following transcytosis, antigens to cells of the immune system in lymphoid aggregates are released beneath the epithelium, where antigen processing and presentation and stimulation of specific B and T lymphocytes take place [51, 52].

According to a definition formulated by Isaacson [32] for MALT of the gut wall (i.e., Peyer's patches), MALT comprises four components (fig. 5): (1) organized MALT, (2) a lamina propria, (3) intraepithelial lymphocytes, and (4) an associated lymph node. Circulation of the lymphoid cells in these four components enables them to home to their original and other mucosal sites, where

they exert the effector function. Such a response may be dominated by sIgA release and may include cytotoxic T-lymphocyte action [52]. In this regard, the submandibular lymph node found by Egan et al. [50] might be the 'associated lymph node' of CALT and TALT, but not of NALT.

Activation of T lymphocytes has been observed in dry eye, which leads to the frequent occurrence of abnormal (pathological) apoptosis in terminally differentiated, acinar epithelial cells of the lacrimal gland [53]. Tears secreted to the ocular surface will then contain proinflammatory cytokines and will inflame the tissues of the ocular surface. Abnormal apoptosis has also been detected in the epithelial cells and lymphocytes of the ocular surface [53]. This ocular surface inflammatory response consists of inflammatory cell infiltration, activation of the ocular surface epithelium with increased expression of adhesion molecules, inflammatory cytokines and pro-apoptotic factors, increased concentrations of inflammatory cytokines in the tear fluid and increased activity of matrix-degrading enzymes in the tear fluid. It has been suggested that the reduction of circulating androgens plays a role in these processes [54, 55]. Treatment with locally applied cyclosporin A eye drops interferes with interleukin metabolism, especially of interleukin-6, thus creating a new treatment option that leads to remarkable improvement of the irritation symptoms and ocular surface signs in particular in severe cases of keratoconjunctivitis sicca.

Taken together, these findings support the conclusion that CALT and TALT play a role in the pathogenesis of dry eye. One can imagine that misdirected stimulation of EALT could result in a misguided form of immune deviation at the ocular surface. Within the scope of this event, T cells would no longer be hindered in inducing autoimmunity by apoptosis, finally resulting in the clinical picture of dry eye.

It should be mentioned, however, that a recently published article has placed our understanding of MALT in a different light concerning its functional significance. Alpan et al. [56] demonstrated that a systemic immune response to orally administered soluble antigens does not depend on the presence of functional GALT, but more likely on initiation of immune response by gut-conditioned dendritic cells. This finding suggests that MALT is not required for initiation of a primary immune response to antigens that have entered the body. If present, however, it seems to act in two ways: (1) It produces plasma cell precursors that later migrate into adjacent mucosa, mature to plasma cells, and produce sIgA for mucosal protection. (2) It allows uptake of antigens by M cells and presentation of these antigens to virgin T and B cells to initiate a primary immune response. Thus, MALT could represent a second pathway (a kind of safeguard of the adaptive immune system) for initiation of a immune response to antigens that have been incorporated into the mucus layer and, in the case of CALT or TALT, have entered the ocular surface and are drained with tear fluid.

It can be concluded that development of EALT is a common feature frequently observed in symptomatically normal nasolacrimal ducts. Whether special types of bacteria, viruses, or other factors, e.g., immune deviation, are responsible for the development of EALT in humans requires future investigation in prospective and experimental studies.

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Prof. Dr. F. Paulsen
Department of Anatomy and Cell Biology, Martin Luther University Halle-Wittenberg
Grosse Steinstrasse 52, DE–06097 Halle/Saale (Germany)
Tel. +49 345 557 1707, Fax +49 345 557 1700
E-Mail friedrich.paulsen@medizin.uni-halle.de

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Classification and Diagnosis of Dry Eye

Thomas Kaercher[a], *Anthony J. Bron*[b]

[a]Heidelberg, Germany and [b]Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, UK

Abstract

Background: Dry eye, or keratoconjunctivitis sicca (KCS), is divided into two subgroups, tear-deficient and evaporative. Each form calls for a different therapeutic approach and it is therefore essential to apply a combination of diagnostic tests in order to establish the exact diagnosis. **Material and Methods:** The diagnosis of KCS is based in part on the patient's history and symptoms and in part on the application of specific tests. Several non-invasive tests exist (e.g. slit-lamp examination, meniscometry, interferometry). Mildly invasive tests are the fluorescein tests, staining with lissamine green, meibometry and meibography. Markedly invasive tests include the Schirmer test and staining with rose bengal. Additional histological procedures are the ocular ferning test and impression cytology. **Results:** A combination of diagnostic tests leads to one of the two forms of KCS. Its severity is calculated according to grading systems, which exist for several tests. The longitudinal observation of the dry eye patient is provided on the basis of this same grading system, although limited reproducibility is reported for some tests. **Conclusion:** The diagnostic steps for dry eye patients can be efficiently arranged. In most of the cases, non-invasive or mildly invasive tests provide an accurate diagnosis.

Classification of Keratoconjunctivitis Sicca

The condition of keratoconjunctivitis sicca (KCS) is synonymous with that of dry eye. According to the International Dry Eye Workshop (DEWS) [1] the dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. It comprises two subgroups: tear- or aqueous-deficient dry eye (aqueous tear deficiency) is due to a failure of lacrimal function while evaporative dry eye is due, predominantly but not entirely, to lipid tear deficiency (fig. 1). Either form may cause damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort. A unifying mechanism

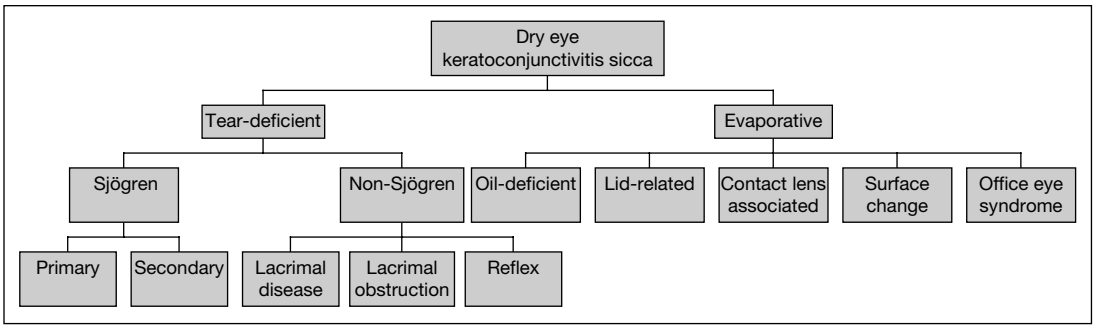


Fig. 1. Classification of dry eye.

is tear hyperosmolarity, which can directly cause damage to surface epithelial cells. However, an additional factor is the release of pro-inflammatory cytokines in the lacrimal gland and tears, which can both initiate autoimmune lacrimal damage, as in Sjögren's syndrome, or perpetuate chronic conjunctival inflammation.

The commonest form of tear-deficient KCS is non-Sjögren's dry eye, whose age-related form has a prevalence of about 15% in the older population. It is due to a T-cell infiltration of the lacrimal gland which reduces secretory function. Non-Sjögren's dry eye can be caused by other lacrimal diseases such as graft-versus-host disease and sarcoidosis, by lacrimal obstruction in cicatricial conjunctival diseases (e.g. ocular pemphigoid, Stevens-Johnson syndrome and trachoma) and also by reduced sensation at the ocular surface, leading to a loss of afferent reflex drive to the lacrimal gland. Sjögren's syndrome is a less common disorder, with a prevalence of about 0.2–0.5%. It is an autoimmune exocrinopathy giving rise to dry eye and dry mouth and affects other mucous membranes and even the central nervous system. Primary Sjögren's syndrome occurs in the absence of a defined connective tissue disorder, whereas secondary Sjögren's syndrome is accompanied by such a condition, such as rheumatoid arthritis, systemic lupus or Wegener's disease. In general, the onset of Sjögren's syndrome dry eye is earlier than that of non-Sjögren's dry eye and it evolves with greater severity.

The commonest form of evaporative dry eye is due to meibomian gland obstruction and this in turn has a strong association with skin disorders such as acne rosacea, atopic dermatitis (affecting the face) and seborrhoeic dermatitis. Evaporative dry eye can also result from lid-globe malposition (e.g. proptosis), contact-lens wear and occupational and environmental stresses. Thus it may be associated with low humidity due to air conditioning, with a reduction in blink rate while performing microscopy or with increased width of the palpebral aperture which occurs when working at a video display terminal. Such events may contribute to the office eye syndrome.

Diagnosis of Keratoconjunctivitis Sicca

The above definition of the dry eye accentuates the following features of the disease: (1) symptoms; (2) interpalpebral surface damage; (3) tear instability, and (4) tear hyperosmolarity. There are numerous tests for the diagnosis of dry eye and they vary with respect to their invasiveness. The selection and order of these tests is of paramount importance since each test may influence the outcome of the test which follows. In general it is recommended to start with the least invasive procedure and to end with the most invasive test. Occasionally it is necessary to perform some tests on a subsequent day. At the end of a battery of tests it should be possible to confirm the diagnosis, classify the form of dry eye, being conscious of its grade, and initiate appropriate therapy.

Symptoms and History

A record of clinical history and ocular symptoms is required. Several questionnaires have been developed for the assessment of dry eye [2–4]. A special questionnaire for the detection of psychosomatic alterations exists and can be applied additionally [5].

Important aspects of the patient's history are: (a) symptoms: burning sensation, foreign body sensation, tired eye, photophobia, epiphora, swelling of the lids; (b) onset of the symptoms, duration; (c) circadian rhythm; (d) environmental conditions at home and in the office (smoke, wind, humidity); (e) contact lens-associated problems; (f) cosmetics; (g) systemic diseases; (h) allergic diseases; (i) dermatologic diseases, and (j) drug history.

Examination of the Lids

The dynamics of blinking and of lid position should be observed whilst taking the history in order to prevent conscious alterations. Points of interest are: (a) frequency of blinking; (b) variation of blink intervals; (c) size of the palpebral aperture, and (d) adequacy of lid closure.

The position of the lids may influence the tear turnover, therefore care should be taken to identify the following malpositions: (a) entropion; (b) ectropion; (c) eversion of the lacrimal puncta; (d) cicatrical malposition; (e) dermatochalasis, and (f) swelling of the temporal aspect of the upper lid, implying enlargement of the lacrimal gland.

Slit-Lamp Examination

Slit-lamp biomicroscopy should evaluate the following anatomical structures and their alterations: (a) *Lid margins:* hyperaemia, telangiectasia, thickening, scarring, keratinization, ulceration, tear debris, abnormalities of the meibomian

Fig. 2. Tearscope.

orifices, metaplasia, character of expressed meibomian secretions. (b) *Eyelashes:* misdirection, malposition, encrustations, collarettes. (c) *Conjunctiva:* erythema, swelling, keratinization, papillary/follicular reaction, pinguecula, lid parallel conjunctival folds. (d) *Cornea:* infiltrates, scars, punctuate staining or ulcers, vascularization, pannus, and pterygium. (e) Additionally, the tear film should be analysed for: filaments, mucus, and cellular debris, meibomian foam.

Non-Invasive Break-Up Time

The non-invasive break-up time test was created to measure the stability of the precorneal tear film without any dye [6]. It involves projection of a target onto the convex mirror surface of the tear film and recording the time taken for the image to break up after a blink. The test was originally performed with a custom-built 'Toposcope' but has also been performed over a limited zone of the exposed precorneal film, using a keratometer. It can also be measured with the TearscopePlus™ (fig. 2) [7, 8] and is a non-invasive procedure (fig. 3).

Interferometry

Tear film interferometry is a non-invasive technique for grading the behaviour of the tear film lipid layer and estimating its thickness on the basis of the observed interference colours (fig. 4) [9, 10]. It is useful for selecting dry eye

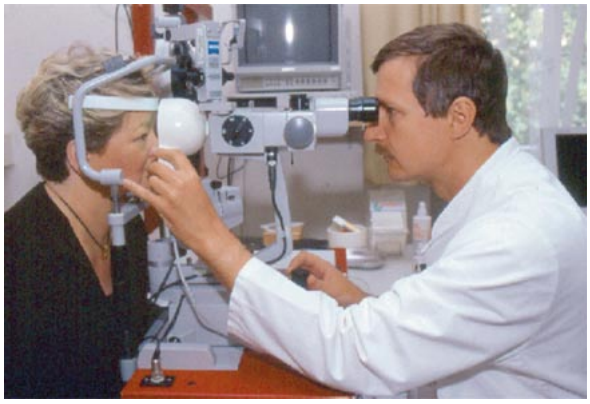


Fig. 3. Use of the Tearscope in combination with the slit-lamp.

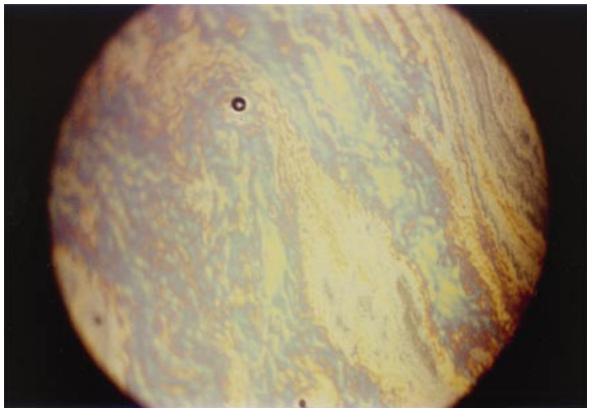


Fig. 4. Interference pattern of a thick globular lipid layer.

candidates for punctal occlusion. Apparatus which have been used for this purpose include the TearscopePlus and the Kowa DR-1.

A colour scale which has been used is as follows [9]: (a) greyish colours, uniform: normal; (b) greyish colours, non-uniform: normal; (c) yellow colours: dry eye; (d) brown colours: dry eye, and (e) blue colours: dry eye.

Reflective Meniscometry

Reflective meniscometry is a non-invasive method to measure the radius of the tear meniscus curvature (figs 5, 6). The radius is directly proportional to the

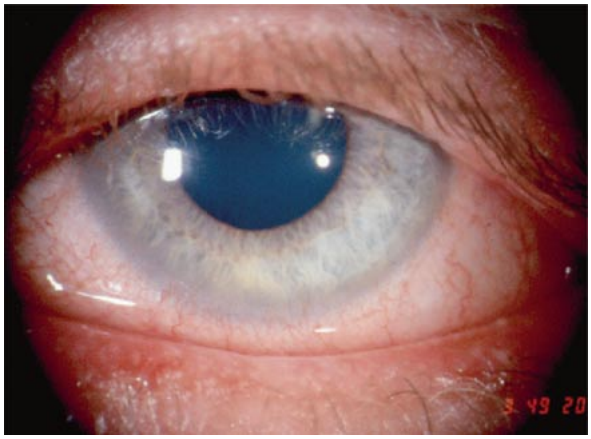


Fig. 5. Reflective meniscometry.

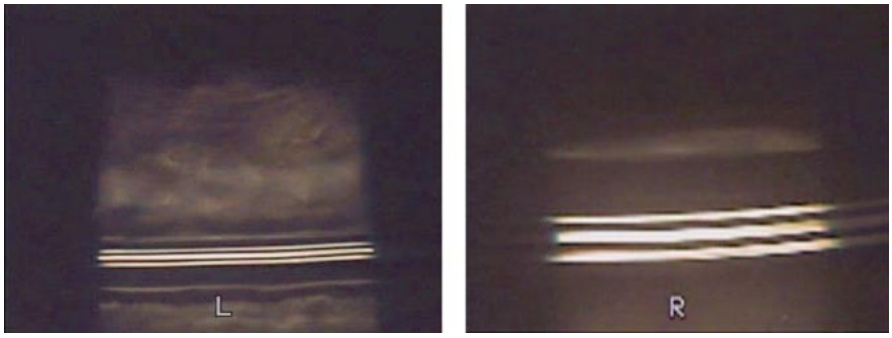


Fig. 6. Meniscometry: demonstration of the reduced size of the tear meniscus in aqueous-deficient dry eye (L) compared to a normal tear meniscus (R) using meniscometry (by courtesy of Dr. N. Yokoi).

tear meniscus volume and to the total tear volume of the tear sac [11]. A radius <0.25 mm indicates a hyposecretory dry eye.

Fluorescein Tests

Fluorescein sodium is used for several dry eye tests (fig. 7). They all are mildly invasive tests. At a concentration around 0.1%, the dye is highly fluorescent, staining the tear film and epithelial defects. Once the surface layer of epithelial cells is lost, the dye spreads rapidly in the intercellular space. Fluorescein is available in the form of fluorescein-impregnated paper strips or as a 1–2% solution in a sterile, unit dose sachet. Fluorescence is with the use of

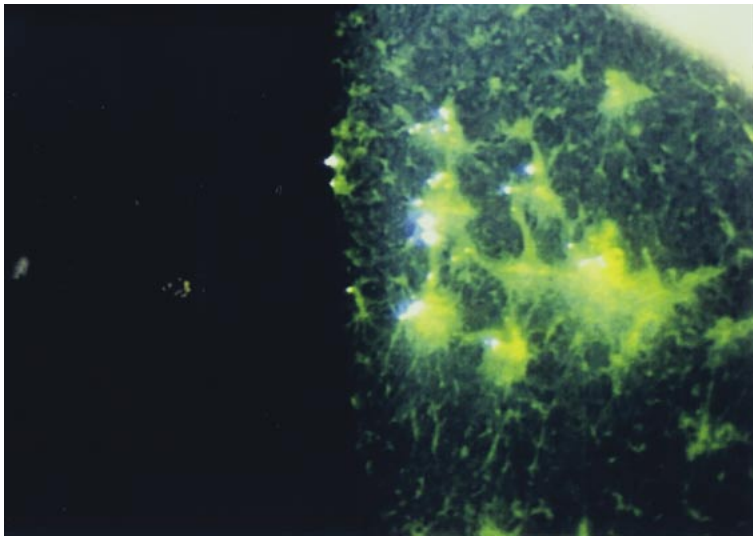


Fig. 7. Fluorescein staining.

a blue exciter filter in combination with a yellow barrier filter. Most slit-lamps are provided with an adequate blue light source and it is well worth purchasing a suitable Kodak Wratten 12 or 15 barrier filter.

To instil fluorescein from an impregnated strip, a drop of sterile saline is applied to the impregnated end and the excess discarded with a rapid flick. The moistened tip is then touched lightly onto the lower tarsal plate of the right and then the left eye, in sequence. Because 1–2% fluorescein is non-fluorescent, it is only appropriate to apply a small volume in order to achieve dilution and fluorescence. A suitable volume is 2–5 μl applied with a micropipette.

The fluorescein tear film break-up time records the rupture of the tear film after a blink. The tear film should be evaluated after a few blinks. The average of three measurements provides a representative measure of the tear film stability [12]. *Evaluation:* >10 s: normal; 5–10 s: marginal dry eye; <5 s: dry eye.

Fluorescein staining of the interpalpebral surface of the eye has a characteristic pattern in KCS, initially affecting the lower part of the exposed eye and later affecting the cornea and conjunctiva more extensively. In meibomian gland dysfunction the staining pattern is often disposed over the lower cornea, closer to the lower lid margin. A number of suitable grading schemes exist [1, 13–15]. The Oxford grading scheme [13] consists of a series of panels representing the cornea and the two zones of exposed conjunctiva, on which is displayed a pattern of dots representing increasing staining from grade 0 to 5 (fig. 8). The number of dots increases sequentially in a log-linear scale: from grade 0 to 1 there is a 1-log step,

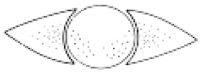
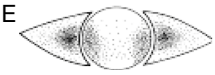
Panel	Grade	Criteria
A 	0	Equal to or less than panel A
B 	1	Equal to or less than panel B, greater than A
C 	2	Equal to or less than panel C, greater than B
D 	3	Equal to or less than panel D, greater than C
E 	4	Equal to or less than panel E, greater than D
>E	5	Greater than panel E

Fig. 8. Grading of corneal and conjunctival staining (Oxford scheme).

which means that 10 dye spots are detected per 1 zone in grade 1. Between grade 1 and 5 there is a 0.5-log unit increase of spots, which equals 32 dye spots in grade 2, 100 dye spots in grade 3 and 316 dye spots in grade 4, always counted per 1 zone. Grade 5 is detected, when the number of dye spots exceeds 316 per 1 zone. The individual scores for each of the 3 panels are added up to give the total score. The maximum staining score for the exposed conjunctiva and cornea is 15.

An important point to note is that if the recommended filter combination is used then grading with fluorescein can be carried out on both the cornea and conjunctiva and use rose bengal can be avoided. This prevents patient discomfort, since in the absence of an anaesthetic, rose bengal causes intense stinging on instillation (fig. 9). Staining of the epithelium can occasionally be obscured by the fluorescence of the tear film. Asking the patient to blink several times allows the staining pattern to be viewed more clearly.

The stained meniscus can be used to estimate the meniscus volume, either simply by measuring meniscus height using the width of the slit-lamp beam, or in a more sophisticated fashion, by reflective meniscometry [11] or by assessing its profile photographically in slit section [16]. A meniscus radius of curvatures <0.25 mm suggests a dry eye condition.

Fluorescein can also be used for measurements of tear turnover and of the tear fluorescein clearance [17].

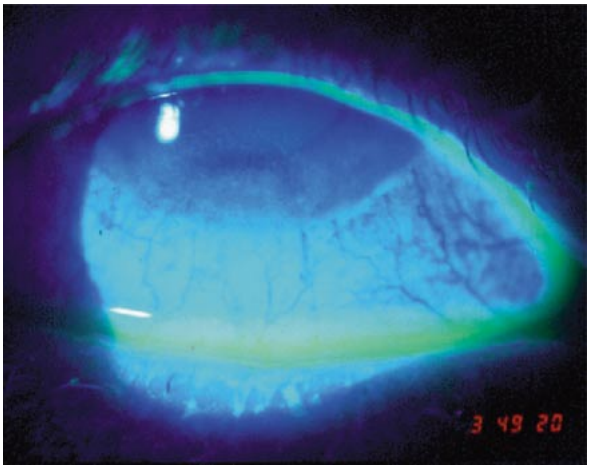


Fig. 9. Fluorescein meniscometry.

Meibometry

Meibometry is a mildly invasive quantitative method for measurement of the basal level of meibomian lipid on the lid margin. In this test, lipid is blotted onto a loop of plastic tape, which produces a strip of increased transparency. The change in transparency is quantified photometrically and provides an index of the uptake of lipid. The system can be calibrated to provide approximate estimate of the amount of lipid on the lid margin, without giving information about chemical composition [18]. An appropriate photometer is available at Courage & Khazaka Electronic GmbH (Cologne, Germany), together with the plastic tape for testing (fig. 10).

Schirmer Test

The Schirmer I test is one of the oldest tests available for dry eye diagnosis and is a measure of reflex tear secretion (fig. 11). It is performed in the unanaesthetised eye. It is highly invasive, and is therefore performed later in the diagnostic sequence. A standard filter paper is placed with its notched tip bent around the lower lid margin at the junction of the middle and outer third. With the eyes closed, the Schirmer paper is allowed to wet for a period of 5 minutes, after which the length of wetting is measured from the notch to the leading, wetted edge [15]. *Evaluation:* <6 mm: in the dry eye range; 6–10 mm: dry eye suspect; >10 mm: normal.

The Schirmer test can also be performed after instillation of a topical anaesthetic when it has been said to represent a ‘basal’ measurement, since sen-

Fig. 10. Meibometer and its use.

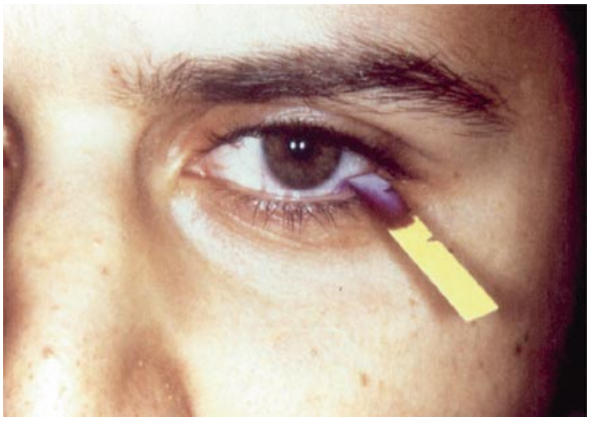


Fig. 11. Schirmer I test.

sory reflex stimulation from the eye is suppressed. This is called the Jones test. Although the test value is usually lower than that recorded by the Schirmer I test, the test has not been adequately validated [19]. If the Jones test is performed after nasal stimulation, it is named Schirmer II test. In Sjögren's syndrome in contrast to non-Sjögren's dry eye, it has been shown that the ability of nasal stimulation to increase the tear production of the anaesthetised eye is greatly reduced and is of diagnostic value [20].

Rose Bengal Staining

The rose bengal test is markedly invasive (fig. 12). Rose bengal is not a vital dye. It stains damaged cells which possess an abnormal mucin coat [21, 22]. It is

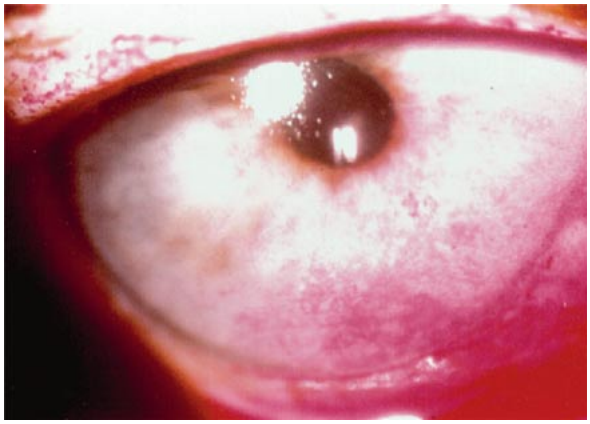


Fig. 12. Rose bengal staining.

intrinsically toxic and therefore causes marked stinging on instillation. If used in drop form, its use should be preceded by instillation a topical anaesthetic [14].

Rose bengal is available in drop form (1%) (Minims Rose Bengal, Chauvin) or as a dye-impregnated paper strip. Staining is a dose-dependent staining effect so that when the paper strip is used, and less dye is delivered, a weaker staining pattern is achieved.

Grading of staining using rose bengal uses the same approach as for staining and grading using fluorescein. The Oxford scale has been described above. The classic, van Bijsterveld schema [15] is also based on an estimate of staining on the cornea and the nasal and temporal part of the exposed bulbar conjunctiva. Each zone is graded from 0 to 3, and the maximum total score is 9. A score >3 is regarded as indicative of dry eye according to the van Bijsterveld schema. It should be noted that the visibility of rose bengal staining is greatest over the white of the bulbar conjunctiva. For grading purposes visibility on the cornea is reasonable when the background is a blue iris, but is poor against a dark brown iris.

Lissamine Green

Lissamine green (Lissaver Plus, Contopharma, Interlaken, Switzerland) stains the eye in a similar way as rose bengal, but it is less toxic and is consequently well tolerated [23, 24]. It is therefore recommended as an alternate test to the rose bengal test. However, the contrast of the dye is less sharp and the detection of the stained areas more difficult. Lissamine green is used in a 1.0% concentration. The test is mildly invasive, similar to fluorescein (fig. 13). The Oxford grading system and the van Bijsterveld system can be applied as described above.

Fig. 13. Lissamine green and its staining.

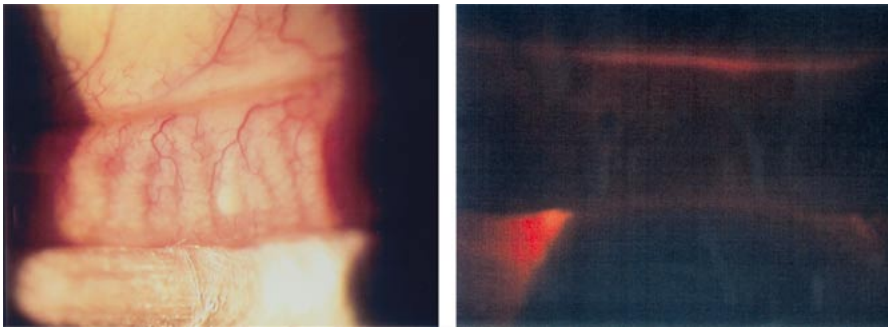


Fig. 14. Direct inspection (left) and transillumination (right) of the meibomian glands.

Meibography

Meibography involves the transillumination of the meibomian glands after eversion of the upper and lower lid (fig. 14). The glands are visible in silhouette and the absence of glands or 'drop-out' can be quantified. The manipulation of the lids stimulates reflex tearing and the test should be regarded as mildly invasive [25].

Ocular Ferning Test

If a tear sample taken from the lower tear meniscus is applied to a glass slide, a characteristic ferning pattern develops as the tears evaporate (fig. 15). This pattern can be viewed under the microscope at a 40–100× magnification and used as an index of dry eye. In dry eye states, the delicate fronded pattern becomes broken up and irregular and the appearances can be graded. Fern formation is influenced by the protein and electrolyte composition of the tears. Since only a small sample of tears is required for the test it is only mildly invasive. Grading is based on the regularity of arborization of the ferning pattern [26]. Classes 1 and 2 are regarded as normal, and classes 3 and 4 represent increasing degrees of dry eye.

Fig. 15. Ocular fern pattern of a grade 4 dry eye.

Impression Cytology

Impression cytology is a histological method of cytological examination without the disadvantages of an invasive excisional biopsy. The samples can be examined by light microscopical, electron-microscopical, immunological and molecular biological methods. Several methods of interpretation of the results exist [27, 28]. Important features of dry eye include squamous metaplasia (table 1), loss of goblet cells and accumulation of inflammatory cells. Ultrastructural signs include changes in the nuclear/cytoplasmic ratio and an increased frequency of 'snake-like' chromatin (figs 16, 17).

Osmolarity

The measurement of tear osmolarity (mosm/l) is regarded as a gold standard in the diagnosis of dry eye [29], however it is difficult to measure and no commercial instrument is currently available. Studies using the depression-of-freezing-point osmometer have suggested that a value of >312 mosm/l is diagnostic of dry eye. Newer techniques for routine clinical use are in development.

General Information and Recommendations

Diagnostic tests of dry eye states are in general intended for two groups of patients: those who come for the first visit with a suspected dry eye and those who have already undergone therapy elsewhere and wish further advice. In the

Table 1. Stages of metaplasia according to Tseng [28]

Stage 0: Nuclear-cytoplasmatic ratio 1:1
Stage 1: Nuclear-cytoplasmatic ratio 1:2, reduced goblet cells
Stage 2: Nuclear-cytoplasmatic ratio 1:4, no goblet cells, flattened epithelial cells
Stage 3: Nuclear-cytoplasmatic ratio 1:6, mild keratinization, metachromatic changes of the epithelial cells
Stage 4: Nuclear-cytoplasmatic ratio 1:8, moderate keratinization, keratin filaments
Stage 5: Advanced keratinization

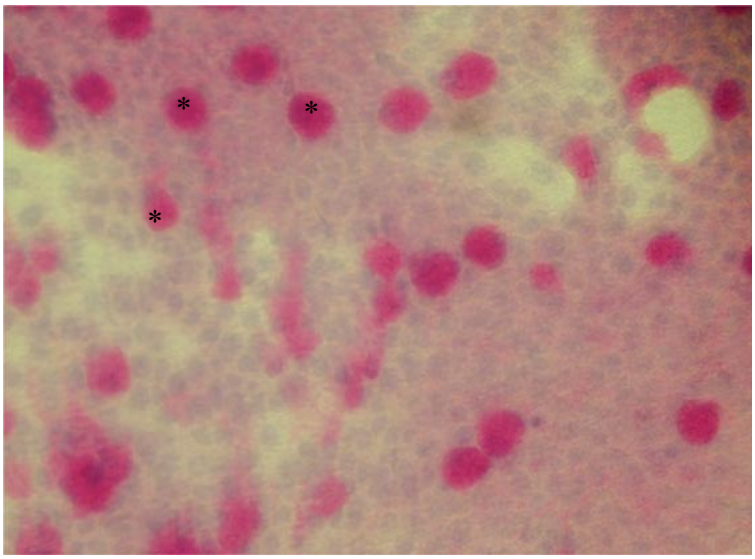


Fig. 16. PAS staining of normal impression cytology with goblet cells (asterisks) and a 1:2 nucleus-cytoplasm ratio (by courtesy of G. Geerling).

first group of patients the test series for dry eye can be started immediately. In the second group of patients it is recommended to stop the patients' preexisting therapy for 1 week and start the testing afterwards. This opens the pathway towards an exact diagnosis without any therapeutic interference.

For the routine diagnostic way of a suspected dry eye state it is advised to select a number of tests. Non-invasive procedures like questionnaires, symptoms and history and slit-lamp examination are among these and often are

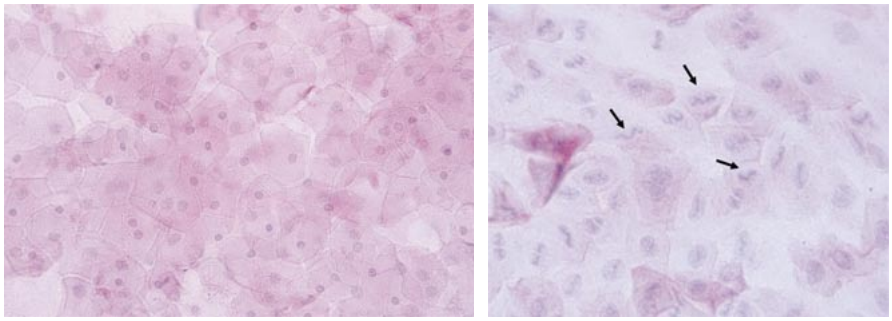


Fig. 17. PAS staining of metaplastic human conjunctiva with 1:12 nucleus-cytoplasma ratio (left) and snake-like condensed nuclei (right, arrows) (by courtesy of G. Geerling).

called low-tech diagnostic. Considering patients' comfort and economic aspects, simple tests should always be used. These tests provide already a reliable information of the dry eye condition. A questionnaire has a surprisingly high sensitivity of 77% with a specificity of 81% [30]. In combination with data from other non-invasive methods, sensitivity and specificity can even be raised. Slit-lamp characteristics like an irregularity of the black line or hyperaemia of the conjunctiva result in a sensitivity of 92% and a specificity of 81% [30]. Simple low-tech diagnostic is therefore the basis of the dry eye testing.

Besides that, a battery of dry eye tests exist which are mildly or markedly invasive. The order of tests is of critical importance since one test may influence the result of the next. Therefore it is recommended to start with the least invasive test and to end with the most invasive procedure. Some tests are mutually exclusive, which means that in a certain patient only a selection of dry eye tests is performed.

Within this system of tests (table 2) with increasing invasiveness, intervals of 5 min are recommended between invasive tests. This is the time necessary for restoration of the original meniscus height [31]. For the routine dry eye patient a sequence of tests giving the essential information for the classification should be selected (table 3).

After having selected the appropriate combination of tests, the grading and interpretation of these tests gains importance. It is essential to know the information we can get from a certain test in order to classify our patient's dry eye form as tear-deficient or evaporative. If you suspect a hyperevaporative dry eye the non-invasive BUT and meibography should be measured. Meniscometry and Schirmer I test are specifically indicative for the hypovolemic dry eye. The same tests give us sufficient information about the severity of the ocular surface disease. Staining with Lissamine and fluorescein allow a more precise quantification of the severity and are therefore recommended (Tab. 4). The interpretation is based on a

Table 2. Available diagnostic procedures for the dry eye patient, their differential diagnostic accuracy and the degree of invasiveness

Test	Hypovolaemic	Hyperevaporative	Invasiveness
Symptoms and history	x	x	NI
Examination of the lids		x	NI
Slit-lamp examination	x	x	NI
Non-invasive break-up time		x	NI
Interferometry		x	NI
Reflective meniscometry	x		NI
Fluorescein tests			
Break-up time		x	MI
Staining	x	x	MI
Meniscometry	x		MI
Clearance	x		MI
Meibometry		x	MI
Schirmer	x		HI
Jones	x		HI
Schirmer II	x		HI
Rose bengal staining	x		HI
Lissamine green staining	x		MI
Meibography		x	MI
Ocular ferning test	x		MI
Impression cytology	x		MI
Osmolarity		x	HI

NI = Non-invasive; MI = mildly invasive; HI = highly invasive.

Table 3. Recommended sequence of tests for the routine dry eye patient

Test	Function
Non-invasive break-up time	tear film stability
Meniscometry	tear volume
Lissamine green staining	ocular surface
Meibography	anatomical structures
Fluorescein staining	ocular surface
Schirmer I test	tear volume

Table 4. Importance of recommended dry eye tests

Test	Diagnostic aim
Non-invasive BUT	LTD (hyperevaporative dry eye)
Meibography	LTD (hypovolemic dry eye)
Meniscometry	ATD (hypovolemic dry eye)
Schirmer I test	ATD (hypovolemic dry eye)
Lissamine green staining	grading of the dry eye, either form
Fluorescein staining	grading of the dry eye, either form

grading system of the tests mentioned above. This system allows us to distinguish normal from marginal dry eyes or manifest dry eye patients.

Once the diagnosis is confirmed and the grade of the disease established the patients need follow-up examinations. The course of the KCS under therapy is documented. We get the best information from a repetition of the tests which have been selected initially. This pathway of examination provides reliable information about the course of the disease and forms the basis for longitudinal observations. However, we have to take into account that certain tests like fluorescein and rose bengal staining show limits with respect to their reliability at different times [32]. Nevertheless, these tests are necessary to provide exact information about the localization of ocular surface defects, whereas the non-invasive tests give us broader information about the whole ocular surface. The diagnosis of dry eye is therefore based on the data of different tests with increasing invasiveness arranged in a way to minimize interference between the tests and on the grading of the results which permit a selection of the appropriate therapy and a long-term observation of the patient.

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Thomas Kaercher, MD
Dossenheimer Landstrasse 48
DE–69121 Heidelberg (Germany)
Tel. +49 6221 400888, Fax +49 6221 412203, E-Mail thomas.kaercher@meibomius.de

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Medical Management of Dry Eye Disease

Stephen Tuft, Shreeti Lakhani

Moorfields Eye Hospital, London, UK

Abstract

Purpose: To describe the medical options for the management of dry eye disease, including the use of contact lenses. **Methods:** The normal behaviour of the tear film and the mechanism of dry eye disease are briefly discussed to provide a rationale for treatment. A guideline for the medical management of disease includes general environmental measures, the treatment of exacerbating factors and associated disease, the selection of tear substitutes, and the role of contact lenses. Advances in the use of agents that stimulate the production of normal tear components and the use of anti-inflammatory agents are presented. **Results:** The basic mechanisms of many of the treatment options used to treat dry eye disease are poorly understood. The evidence for the relative merits of a large range of available treatments is weak. Although the choice of treatment is in part determined by the severity of disease, a reliable algorithm for the sequence of introduction of agents has yet to be developed. **Conclusions:** Medical management plays a major role in the initial treatment and control of symptoms of dry eye. Empiric evaluation of the effect of the large range of options still has a major role for the management of individual patients.

The initial management of dry eye disease relies on the use of artificial tear substitutes and the conservation of natural tears. Most artificial tears are lubricants with an electrolyte content that is only an approximation of normal tears. Viscosity agents are often added to artificial tears to increase the ocular surface residence time. An understanding of the complex interactions between aging, hormonal change, the environment, and the immune system has lead to new therapies to treat dry eye disease. Treatments that reduce associated conjunctival inflammation and stimulate the production of normal tear components may become increasingly important for the management of severe disease. An understanding of the behaviour of normal tears and the aetiology of dry eye is fundamental to the development of an effective treatment strategy.

Rational for Medical Management

Structure of the Tear Film

The tear film is part of a functional unit that comprises the tears, corneal and conjunctival epithelium, lacrimal glands, and lids. Disturbance of one or more of these interrelating structures can result in characteristic symptoms and signs of dry eye disease. This disease acts through the common disease mechanisms of hyperosmolar tears and surface drying that damages the epithelial cells, with associated inflammation and a susceptibility to infection. The terms dry eye disease, dysfunctional tear syndrome, and keratoconjunctivitis sicca are synonymous.

Tears are mechanically spread over the ocular surface by upper lid blinking, but the development of an effective tear film depends upon surfactant phospholipids in the surface layer and mucous in the basal layer that allows the fluid to adhere to the hydrophilic epithelial cells. The lubricating action of the tear film disperses the shearing forces on the epithelium caused by blinking. Finally, the tear film provides a smooth optical interface, transports metabolites, and freely transmits oxygen and carbon dioxide to the cornea.

The structure of the tear film consists of an outer lipid layer lying on an aqueous layer that contains mucus. The meibomian glands secrete the lipid, which is released from the glands by lid movement. The lipid layer is composed of two phases: (1) an outer surface non-polar phase that contains waxes, cholesterol esters, and triglycerides and (2) an inner polar aqueous-mucin phase that has surfactant properties. The inner polar phospholipids are bound to protein lipocalins within the aqueous layer that bind hydrophobic molecules and contribute to tear viscosity. The lipid layer reduces evaporation from the aqueous layer and dysfunction may result in an evaporative dry eye state [1].

The aqueous layer is secreted by the main and accessory lacrimal glands and consists of water, electrolytes, dissolved mucins, and proteins. It has antibacterial properties due to the presence of IgA, lysozyme and lactoferrin, and it contains growth factors (EGF, TGF-α, HGF) secreted from the lacrimal gland in response to injury [2]. It also contains leukocytes and pro-inflammatory cytokines that accumulate when tear production is reduced during sleep. The aqueous phase can physically wash away debris and toxic agents that may cause inflammation. Deficiency of this layer results in an aqueous deficiency dry eye [1].

Mucins are at their highest concentration internally in the aqueous phase and they serve to increase viscosity and anchor the aqueous phase to the glycocalyx of the external cells of the epithelium. Each mucin is a high-molecular-weight glycoprotein containing a protein core with radially linked carbohydrate

side chains. The protein core forms the basis of further classification (e.g. MUC1, MUC2, etc.). Human mucins are classified according to anatomical distribution as transmembrane or secretory, and the secretory mucins are further classified according to their physical properties as gel-forming or soluble. Secretory ocular mucins are principally produced by the conjunctival goblet cells (MUC5AC) but also by the lacrimal glands (MUC7). The glycocalyx of the superficial epithelial cells of the cornea and conjunctiva is formed of transmembrane mucins (MUC1, MUC2, and MUC4). MUC1 is essential to aid spreading of the secretory gel mucin produced by goblet cells and it also prevents pathogens binding to the ocular surface [3]. Damage to the mucus-binding complex will change the cell membrane from a hydrophilic to a hydrophobic surface and prevent normal tear film adherence. Loss of goblet cells and ocular surface mucus is a feature of cicatrising conjunctivitis, vitamin A deficiency, and chemical burns. Almost all of this complexity of structure is absent from artificial tears.

Mechanical Behaviour of the Tear Film

Fluids can be classified according to the way they behave under sheer stress. A perfect fluid has no resistance to shear stress and therefore lacks viscosity. Fluids that are not perfect are classified as either newtonian if their viscosity is constant for different rates of shear, or non-newtonian if they become less viscous over time when a shear force is applied. This property of non-newtonian fluids is termed thixotropy – these are fluids that are both viscous and elastic. Tears have thixotropic properties but most artificial tears do not. The linear charged polymers (carboxymethylcellulose and hyaluronic acid) are the only agents used in artificial tears that have shear-thinning characteristics of non-newtonian fluids. It has been proposed that tears behave like a fluid during blinking but more like a gel between blinks.

Regulation of Tear Film Components

Regulation of the stability of the tear film is under hormonal and neuronal control. Androgen receptors have been identified in meibomian tissue, while oestrogen and progesterone receptors have been identified in conjunctiva and lacrimal gland [4–7]. Postmenopausal women and the elderly may be relatively androgen-deficient and this may account for some of the involutional changes seen in periocular tissue. Androgens (testosterone) may also act as a natural

suppressor of inflammation [8]. Hormone treatments have been evaluated to treat some of the involutional changes associated with dry eye disease. Nerve fibres have been demonstrated adjacent to the lacrimal gland, goblet cells, and meibomian glands. The role of these fibres in maintaining the tear film is unclear although parasympathetic (acetylcholine- and VIP-dependent) fibres stimulate aqueous and protein secretion from the lacrimal gland, and VIP endings at the basement membrane may stimulate mucus secretion from the goblet cells.

Inflammation and Dry Eye Disease

A T-lymphocyte infiltrate is present in the conjunctiva and accessory glands of 80% of patients with dry eye disease. There is also an increased expression of HLA class II antigens, markers of apoptosis (Fas-Fas ligand), and inflammatory cytokines in the epithelium. Although this is thought to be a primary event in Sjögren's syndrome, secondary inflammation from surface friction during blinking is probably an aggravating factor in the majority of patients with dry eye disease. Inflammation may thus be both the cause and the result of dry eye, amplifying and perpetuating disease. The presence of inflammation is the rationale for the use of steroid and immunosuppression in the treatment of dry eye disease in patients with and without Sjögren's syndrome [9].

Guidelines for Clinical Management

Dry eye disease is generally not curable and management is structured around the control of symptoms and the prevention of surface damage. Clinical tests have a low sensitivity and specificity and they are not a reliable basis for management. Fortunately, in the great majority of patients the disease is not sight-threatening. The choice of treatment depends on the severity of the disease, and one or more of the following measures may be used alone or in combination. Initial treatment is with artificial tears that lubricate the surface and reduce lid friction, although they usually only provide relief for a short time period after drop instillation. The goal of treatment is to improve eye comfort and vision at a frequency of treatment that can be reduced to a minimum. Guidelines have been produced to indicate the level of management that is appropriate according to the severity of disease [1, 10–12]. There is a placebo effect and some patients wish to continue using artificial tears without clinical signs of dry eye. A benefit with regard to patient symptoms is more difficult to achieve than a resolution of ocular signs [13, 14].

General Measures

(1) Patient education. Discuss the nature of the condition to establish a realistic expectation of outcome, provide reassurance, and encourage compliance with treatment.

(2) Review of the home and work environment. Emphasize the importance of blinking when reading or using a video display unit. Eliminate dry air conditioning and wind if possible. A reduction in room temperature and central heating will minimize tear evaporation. Humidifiers are usually disappointing because they do not increase room humidity sufficiently. Working directives and open plan offices can limit the ability of employers to implement these recommendations. A local increase in humidity can be achieved with moist chamber goggles or side shields to glasses if this is cosmetically acceptable.

(3) Discontinue toxic topical treatments if possible. Numerous systemic treatments have been associated with symptoms of dry eye, e.g. thiazide diuretics, anticholinergics, tricyclic antidepressants, β-blockers, isotretinoin (13-*cis*-retinoic acid), and antihistaminines (loratadine, cetrizine). The excipients (e.g. benzalkonium chloride, EDTA) in drops used for other reasons, e.g. glaucoma medications, may aggravate surface damage. The preservative benzalkonium chloride can be particularly toxic to the epithelium.

(4) Aids should be provided for patients with a loss of dexterity (e.g. rheumatoid arthritis). Single unit dose dispensers for preservative free drops may not be appropriate. Stiff plastic dropper bottles can be held and squeezed in a nutcracker or an eyedrop bottle squeezer (available commercially).

Identify and Treat Associated Conditions

Local Factors Associated with Dry Eye

These factors include: (i) Posterior lid margin disease (blepharitis) may exacerbate evaporative dry eye. This may be associated with rosacea and allergic eye disease. (ii) Corneal exposure from lagophthalmos, lid margin defects, or seventh nerve palsy allows excessive evaporation. Abnormal globe position, lid retraction or exophthalmos from thyroid eye disease should be treated. (iii) Relative corneal anaesthesia with reduced reflex tearing following LASIK may precipitate dry eye symptoms.

Systemic Disease

A number of systemic conditions also cause ocular surface disease and severe dry eye, although dry eye disease is rarely the presenting symptom. These conditions should be investigated and treated appropriately, but the treatment of the associated dry eye disease is then usually still based on ocular signs rather than the underlying condition. These diseases include: (i) Sjögren's syndrome; (ii) rheumatoid arthritis; (iii) scleroderma (crest syndrome – calcinosis,

Reynaud's phenomenon, oesophageal hypomotility, sclerodactyly, and telangiectasia); (iv) systemic lupus erythematosis; (v) retroviral infection: infection with HTLV1, HIV, hepatitis C, or chronic Epstein-Barr virus (EBV) infection – EBV infection has been proposed as a trigger for the onset of Sjögren's syndrome, and (vi) cicatricial conjunctivitis (mucous membrane pemphigoid, Stevens-Johnson syndrome, atopic keratoconjunctivitis, graft-versus-host disease).

Tear Substitutes

These have a relatively simple formulation compared to normal tears and their delivery is periodic rather than continuous. Although continuous delivery pumps are available, they are usually restricted to the treatment of extreme dry eye. The relative contribution of their individual components to the overall desired effect – lubrication, replacing tear components, reducing osmolarity, or diluting inflammatory agents – is difficult to prove. Slightly alkaline pH drops are better tolerated than neutral or acidic drops [15]. Almost all artificial tears aim to replace the aqueous phase of the tear film. There are no mucus substitutes, and oils and lipids are only an approximation to the action of tear lipid layer. Simple electrolyte solutions and saline are rapidly lost from the ocular surface and attempts have therefore been made to increase the ocular surface residence time by adding macromolecules that increase the viscosity or gel properties of the solution, contribute a demulcent effect, and potentially combine with the mucus component of the tear film [16–18]. These viscous or gel agents are otherwise inactive components of the drop. For example, the ocular surface residence time of carboxymethylcellulose is significantly longer than smaller molecule hydroxypropylmethylcellulose, although it is uncertain whether this fact fully explains the difference in effect. Because relative efficacy or artificial tear drops is difficult to compare the principal categories are listed in alphabetical order below and in table 1.

(1) Acetylcysteine 5% drops are commercially available and are useful in patients with filamentary keratitis and mucous plaques secondary to dry eye. They are used 4 times daily and may cause stinging following instillation if there is epithelial disease. Acetylcysteine 10 and 20% is not available commercially and they have a limited bottle life even if kept refrigerated.

(2) Cellulose-based products have been the mainstay of artificial drop treatment for years. Except for carmellose they have a short ocular surface residence time.

(3) Carbomers 974P and 980 make a relatively viscous solution, which increases ocular residence time.

Table 1. Principal categories of artificial tears

Name	Primary agent	Product and manufacturer	Preservative	Comment
Acetylcysteine (mucolytic)	Acetylcysteine 5% + hypromellose 0.35%	Ilube (Alcon)	BAK	May sting Prevents mucous deposition
Cellulose derivatives	Carmellose (carboxymethylcellulose sodium 0.5 and 1%)	Celluvisc (Allergan)	Unpreserved	Good duration of action Deposits on lashes
	Hypromellose (hydroxypropylmethylcellulose HPMC)	Hypromellose 0.3% (Generic) Hypromellose 0.32% Artelac sdu Pharma Global)	BAK or unpre-served Unpreserved	Short duration of action
		Hypromellose 0.5% (Isopto Plain (Alcon))	BAK	Short duration of action Preservative limits frequency of use
		Hypromellose 1% (Isopto Alkaline)	BAK	Deposits on lashes Preservative limits frequency of use
	Hyetellose (hydroxyethylcellulose (HECL) 0.44% drops + sodium chloride 0.35%	Minims Artificial Tears (Chauvin)	Unpreserved	Short duration of action
	Dextran 70 0.1% and hypromellose 0.3% drops	Tears Naturale (Alcon)	BAK	Preservative limits frequency of use

Carbomers (polyacrylic acid)	Carbomer 980 0.2% gel	Gel Tears (Chauvin) Liposic (Bausch and Lomb) Viscotears (Novartis)	BAC Cetrimide Certrimide or unpreserved	Preservative limits frequency of use
	Carbomer 974P 0.25% gel	Liquivisc (Allergan)	BAK	Preservative limits frequency of use
Electrolyte solutions saline	Not declared Sodium chloride 0.9% drops	TheraTears and others[a] Minims sodium chloride (Chauvin)	Unpreserved Unpreserved	No data available Short duration of action
HP-guar	Hydroxypropyl - guar	Systane (Alcon)[b]	Polyquad® unpreserved	Preservative limits frequency of use
Oils and lipids	Yellow soft paraffin 80%, liquid paraffin 10%, wool fat 10% White soft paraffin 57.3%, liquid paraffin 42.5%, wool alcohols 0.2% White soft paraffin 60%, liquid paraffin 30%, wool fat 10% Castor oil Soy lecithin 1% Triglyceride Phospholipids	Simple (Generic) LacriLube (Allergan) Lubri-Tears (Alcon) Refresh Endura (Allergan) Clarymist: Liposic (Bausch and Lomb) Ocutears Lipospray (Santen)	Unpreserved Unpreserved Unpreserved Phenoxyethanol	Blurs vision
Polyvinyl alcohol	Polyvinyl alcohol (PVA) 1.4% drops	Liquifilm Tears (Allergan) Sno Tears (Chauvin)	BAK or unpreserved[c] BAK	Preservative limits frequency of use
Povidone	Polyvinylpyrrolidone 5% drops	Oculotect (Novartis)	Unpreserved	Short duration of action
Serum	Autologous serum (20–100%)	Not commercially available	Unpreserved	Effective for severely dry eye Production laboratory required

Table 1. (continued)

Name	Primary agent	Product and manufacturer	Preservative	Comment
Sodium hyaluronate	Sodium hyaluronate 0.1–0.2% (usually contains dextran)	Vismed Products (TRB Chemedica) Vislube (Cantor-Nissel) Hycosan (Bausch & Lomb) AQuify (Novartis) Blink (AMO) Oxyal (Santen) Hylo-Vision HD (Omnivision) Hyabak (Théa Pharma) Hyal drop (Chauvin)[b]	Unpreserved	Effective for severely dry eye

Note: Product names are examples and apply to the United Kingdom or Germany. Some products may not be generally available.

BAK = benzalkonium chloride.

Some large hospital-based manufacturing pharmacies produce non-preserved acetylcysteine, hypromellose, and polyvinyl alcohol.

[a]These products usually manufactured in the USA and imported (not evaluated by the FDA). [b]These products are CE marked and marketed as a device. [c]Also contains povidone 0.6%.

Preserved drops should not be used more than 4 times daily, which limits their use to mild dry eye states.

Artificial drops marketed within all countries of the European Union require a CE (Conformité Européene) marking which means the product complies with the essential requirements of the relevant European health and safety legislations. Artificial tears drops for dry eye must also be registered as a medicine in a member state. Drops that are marketed as 'comfort drops' for dry eye in contact lens wearers can be marketed as a device (a device only has a CE marking), which is a simpler and cheaper process than obtaining registration as a medicine. Artificial tears drops in this latter category cannot legally be provided to patients with dry eye who are not contact lens wearers, although this occurs widely. Artificial tears drops are also available over the Internet although details of their standard of manufacture, components, and effectiveness often are not provided.

(4) Electrolyte solutions are marketed to treat the 'electrolyte toxicity' from hypertonic tears. Their constituents are usually not provided. They may have added ω–3, flaxseed or evening primrose oil, and vitamins A or E of unknown effect. They are not CE marked and have not been evaluated by the FDA but are available on the Internet. Saline (0.9%) drops are effective but very short acting.

(5) Hydroxypropyl (HP) guar is not listed in pharmacopeias. It is marketed as Systane® (Alcon), which also contains polyethylene glycol 400 and propylene glycol. It is proposed that HP-guar becomes a viscous gel on combination with the patient's tears and binds to the hydrophobic epithelial surface to form a protective layer [19].

(6) Oils and ointments contain petrolatum mineral oil (paraffin) and wool fat. Castor oil emulsion is marketed as Refresh Endura™ (Allergan) in the USA. Ointments can be useful for extreme dry eye disease and they can be used at bedtime to supplement other treatments given during the day. They can blur vision, which limits their use in mild dry eye. Clarymist™ is a spray that contains soy lecithin 1.0% incorporated in liposomes. The phosphatidylcholine polar molecule consisting of a fatty acid component that is lipid-soluble and a charged phosphate group that is water-soluble. It is proposed that this mimics the function of the tear lipid layer.

(7) Polyvinyl alcohol and povidone are viscous additions to a balanced saline solution. They are available as non-preserved drops [20].

(8) Autologous serum (20–100%) contains surface-acting proteins, cytokines, and inhibitors of inflammation [21–23]. They are effective in severe dry eye disease such as graft-versus-host disease or ocular cicatricial pemphigoid and for in the management of associated epithelial breakdown [24]. Recent European legislation has limited the manufacture of blood products to accredited laboratories and blood banks. The manufacture is therefore expensive.

(9) Sodium hyaluronate is available from several manufacturers as unit doses or as a spray (Hycosan®, Vismed®, Hyabak®, HyloVision HD®) with a sufficient amount to last several weeks. It has a relatively long surface residence time and is particularly effective in the management of severe dry eye states [20]. Concerns have been raised that phosphate-buffered solutions of sodium hyaluronate can cause corneal calcium precipitation in severe dry eye disease.

The excipients (stabilizers, buffering systems, etc.) and preservatives in many formulations are a potential source of corneal toxicity, especially if there is delayed tear clearance after punctal occlusion [25]. Preservative-free drops are essential if there is severe dry eye, and the intensive use of drops containing benzalkonium chloride in severe dry eye can cause central corneal melt. It is recommended that non-preserved drops be used whenever possible, particularly if treatment is required more than 4 times daily.

Management of Dry Eye with Contact Lenses

Contact lenses can be used as an aid to manage dry eye disease or ocular surface exposure by preventing or reducing surface evaporation. They can help reduce surface discomfort from keratinisation or filamentary keratitis, and rigid lenses can overcome the effects of irregular astigmatism. Their use is normally reserved for patients with moderate to severe dry eye liable to epithelial breakdown and unresponsive to topical treatment, and their use is supplemented with ocular lubricants. In patients with Stevens-Johnson syndrome and ocular cicatricial pemphigoid, shallow fornices and symblepharon may mean that large diameter lenses cannot be used. Hydrogel, silicone hydrogel, and silicone rubber lenses have been evaluated, but there is an increasing interest in the use of rigid corneal and scleral lenses. For each lens the potential benefit of a reservoir of fluid trapped behind the lens and the mechanical protection provided has to be weighed against the increased evaporation from the surface of the lens, reduced tear flow, and the risk of infection. The key properties of lens fit, the resistance to spoliation, and the oxygen transmission of the available contact lenses are listed below and in table 2. Oxygen transmission is measured as the Dk/t of the lens – where Dk is the oxygen permeability of the lens material and (t) the lens thickness. To limit overnight corneal swelling to ≤4%, it has been estimated that a lens should have a Dk/t of $87.0 \pm 3.3 \times 10^{-9}$ units, where the units are (cm/s) (ml O_2/ml × mm Hg) [26].

Hydrogel Lenses

These are available in a wide range of parameters. The use of a thin lens made of a high water content material increases the oxygen transmission [27], although they are not recommended for overnight wear as they do not achieve the required Dk/t. The lens material may carry an electronic charge such that an ionic material attracts positively charged proteins, while non-ionic materials tend to attract lipids. If there is decreased tear production with a high concentration of protein and mucin in the tear film a non-ionic material may be preferable [27]. Omafilcon A (Proclear®, Coopervision) contact lenses have a high water content and incorporate phosphorylcholine that creates a biocompatible layer of synthetic lipid on the surface that makes the lens hydrophilic, increases the surface wettability, and reduces the rate of protein adsorption [28]. The Benz 3× lens material has similar properties (Igel®, Ultravision). High water content lenses can cause corneal dehydration by absorbing water from the tear film, and with a poor tear film the lens is prone to drying and discomfort [27]. For more severe dry eye conditions a thin low water content lens should be considered although they carry a greater risk of epithelial hypoxia [26].

Table 2. Contact lenses for the management of dry eye

Severity	Lens type	Advantages	Disadvantages
Mild	Hydrogels	Simple fitting Drape well Wide parameter range Comfortable to wear	Greater tendency to dehydrate Ionic materials prone to deposits Poor Dk/t
		e.g. Proclear Biocompatibles (Coopervision) 8.60/14.20, 60% WC, non-ionic, Dk/t 27–34	
Mild-moderate	Silicone hydrogels	Good Dk/t Simple fitting Suitable for EW Less dehydration, cf. Hydrogels	Limited parameters, cf. Hydrogels Can be uncomfortable Formation of mucin balls
		e.g. Purevision (Bausch & Lomb) 8.60/14.00, 35% WC, Dk/t 101 Focus Night & Day (CIBA Vision) 8.60/13.80, 8.40/13.80, 24% WC, Dk/t 175 Acuvue Oasys (Johnson & Johnson) 8.40/14.00, WC 38%, Dk/t 147 Biofinity (Coopervision) 8.60/14.00, 48% WC, Dk/t 160	
Moderate	Silicone rubber	High Dk/t No dehydration Suitable for EW	Limited parameters Prone to surface spoilage Challenging fit
		e.g. Silsoft, Bausch & Lomb BOZR 7.50–8.30, TD 11.30 and 12.50, high plus powers only, Dk/t >200	

Table 2. (continued)

Severity	Lens type	Advantages	Disadvantages
Moderate-severe	Limbal	Retention of lens shape Partial retention of tear reservoir Range of materials e.g. Limbal Lens, Moorfields made to order Typically BOZR 7.0–9.0, TD 12.5 mm	Lid sensation – not as comfortable, cf. Hydrogels Complex fitting Not ideal for EW
Severe	Scleral	Full retention of tear reservoir No dehydration Protection of ocular surface Comfortable to wear e.g. RGP sealed sclerals, Innovative Sclerals Typically 23 mm TD (full aperture), made to order	Unfamiliar fitting Can intimidate patients Not recommended for EW
	Collagen shields	Mould to shape of cornea Few deposit problems e.g. Bio-Cor, Bausch & Lomb, US Dissolution times 16, 24, and 72 h	Can be uncomfortable Reduction in vision Unpredictable dissolution rates Unable to assess eye underneath Expensive

BOZR = Back optic zone radius; TD = total diameter; EW = extended wear; WC = water content; Dk/t = measure of oxygen transmissibility for a −3.00 lens (in this table) [Dk/t of 87.0 ± 3.3 is required to limit overnight corneal swelling to 4%.

Silicone Hydrogel Lenses

These have high oxygen transmissibility due to the silicone component of the lens material, and because the water content can be reduced the potential for lens dehydration is also reduced [29]. They meet the minimum recommended oxygen transmission for overnight wear. The lens is less flexible than a hydrogel lens and sometimes may be less comfortable due to the higher modulus. Until recently, silicone hydrogel lenses were only available in a limited number of parameters. Second-generation silicone hydrogel materials such as Galyfilcon A (Acuvue® Advance™, Johnson & Johnson) and Iotrafilcon B (O_2 Optix™, CIBA Vision) have a higher water content and although they have a lower Dk/t their increased flexibility may increase comfort. These new lenses have a Dk/t of >130.

Silicone Rubber

Silicone rubber lenses have previously been used extensively for managing severe dry eye disease [30]. They have an extremely high oxygen transmissibility of 200–400 and can be worn overnight without hypoxia [31]. They do not contain water and cannot dehydrate but they are prone to surface spoliation. They can also tighten unpredictably after fitting, which can result in lens binding [27, 30]. They are semi-rigid and do not drape well over an irregular cornea. Two types of silicone rubber lenses have been marketed, Silflex® (Wöhlk) and Silsoft™ (Elastofilcon A, Bausch & Lomb). Unfortunately, Silflex® lenses have been withdrawn and Silsoft™ lenses are only available in high positive powers for aphakia or high hypermetropia.

Limbal Diameter Rigid Gas-Permeable Lenses (RGP)

Limbal diameter rigid lenses are particularly useful in cases of exposure or moderate to severe dry eye (e.g. Stevens-Johnson syndrome). They protect the entire corneal surface by retaining a tear reservoir. They flex less than silicone lenses so the chances of binding are reduced. The oxygen transmission is not as high as silicone rubber, but greater than hydrogels. Although they may not be as comfortable as hydrogel or silicone hydrogel lenses in mild dry eye, they do not dehydrate and may be more comfortable in severe dry eye [27].

Scleral Lenses

Scleral contact lenses have an important role in the management of severe dry eye disease, exposure, and trichiasis. With the introduction of RGP materials the first choice for fitting is with a non-ventilated design [32, 33]. They have a large diameter (typically between 16 and 23 mm) and the bearing surface for the lens is the sclera rather than the cornea. The lens retains a precorneal fluid reservoir of saline or non-preserved artificial tear solution that maintains

Table 3. Topical medication and contact lenses [modified from 27, with permission]

	Hydrogel[a]	Silicone hydrogel[a]	Silicone rubber	Corneals/limbals (RGP)	Sclerals
Ointment	No	No	Yes but ↓VA	Yes but ↓VA	Yes but ↓VA
Oil-based drops	No	No	Yes	Yes	Yes
Preserved Rx	Short term	Short term	Yes	Yes	Yes
Unpreserved Rx	Yes	Yes	Yes	Yes	Yes
Fluorescein	No	No	Yes	Yes	Yes

[a]Benzalkonium chloride binds to hydrogel lenses.

corneal hydration and physically protects the entire ocular surface. They can be comfortable to wear without adaptation because there is little movement and thus minimal lid sensation. Although fitting sets are available, specialist knowledge of their use is necessary. Overnight wear is possible although there is significant hypoxia, and this is only indicated if there is nocturnal exposure [34].

Collagen Shields

These have been evaluated for dry eye but are now generally unavailable. They contain porcine or bovine collagen and are packed dry and hydrated with saline before inserting. They can help re-epithelialisation of the severe dry eye, although they are not licensed for the treatment of dry eye. They dissolve over time although the rate can vary. They can be uncomfortable, vision is usually reduced to at least 6/36 and corneal visualisation is difficult [35]. The oxygen permeability of a new lens is similar to a hydrogel lens, but this increases dramatically as the lens dissolves [36, 37].

Contact Lens Selection

The type of contact lens used is dependent on the severity of the ocular surface disease and the aetiology. Table 2 summarises the different lens types and provides a guideline for lens selection dependent on the severity of dry eye. A silicone hydrogel lens can be used across the whole spectrum of disease as long as the fornices are not severely contracted. Table 3 shows the compatibility between eyedrops and contact lenses. If treatment with topical medication is required the use of a non-fenestrated scleral lens may prevent effective drug penetration.

Tear Stimulation

Cholinergic agonists (secretogogues) such as oral pilocarpine (Salagen® 5 mg orally q.i.d.) and cevimeline (15 mg t.i.d.) that act on the exocrine glands have been shown to reduce the symptoms of dry eye and dry mouth in patients with Sjögren's syndrome, although side effects such as flu-like symptoms, blurred vision, nausea, and sweating in about 40% of patients limits their usefulness [38, 39]. Diquafosol 2%, a topical analogue for the nucleotide receptor $P2Y_2$, has been shown to be capable of increasing the production of ocular surface aqueous and mucous, although it improves corneal signs better than symptoms [40–42]. Other topical agents (rebamipide, ecebet sodium, gafarnate) are being assessed as mucous production stimulators. Stimulated secretion of mucin MUC1 from corneal epithelium by topical eicosanoids (15(S)-HETE) has been demonstrated [43]. Topically applied eledoisin (Alcon-Cusi, Spain), a extract from octopus venom glands, stimulates tear flow as a vasodilator and a contraction agent of extravascular smooth muscle and may be useful in volume-deficient dry eyes due to palsy of the major petrosal nerve.

Anti-Inflammatory Agents

(1) Low-dose topical steroid is an effective supplementary treatment for the management of acute exacerbations of dry eye disease [44]. However, the risks of long-term treatment must be balanced against the potential benefits of increased comfort [45]. Intensive topical prednisolone 1% used 4 times daily for 6 weeks was reported to be helpful in severe dry eye associated with graft-versus-host disease [46].

(2) Topical ciclosporine A 0.05% (Restasis®, Allergan) is a safe, well-tolerated agent that reduces T-cell-mediated inflammation of lacrimal tissue [47]. Treatment is followed by a fall in indictors of inflammation (HLA-DR-positive cells, IL-6 levels, and apoptosis) in the tear film and conjunctiva. An increase in goblet cell numbers and reversal of squamous metaplasia has also been documented [48], with an improvement in tear flow as assessed by Schirmer's test [49].

(3) Systemic tetracyclines (doxycycline 50–100 mg daily) may help control any blepharitis associated with dry eye disease. It may act as an antibiotic to reduce lipase production that can break down meibomian lipids and exacerbate evaporative dry eye. They may also directly block some inflammatory cytokines and metalloproteinases in the tears.

Other Options

(1) Retinoic acid 0.05% has no demonstrated beneficial effect on dry eye disease apart from reversing squamous metaplasia and keratinisation.

(2) Zidovudine, an antiretroviral agent, has been reported to be effective in primary Sjögren's syndrome [50].

(3) Postmenopausal women taking oestrogens are at increased risk of developing dry eye disease [51]. Oral oestrogen replacement is not helpful and has potential systemic risks [52]. Although no benefit effect has been demonstrated for topical oestrogens, there may be an effect for combined oral oestrogen and androgen [53]. The role of topical androgens (e.g. testosterone 0.03%) on evaporative dry eye has not yet been fully evaluated.

(4) The effect of flaxseed (ω–3) oils taken orally or added to artificial tears is unproven.

(5) Trehalose is a natural disaccharide that protects cells against desiccation. It appears to be clinically effective against signs of dry eye but it is not available commercially [54].

(6) Patients following acupuncture feel better but lack any objective signs of improvement, suggesting a placebo effect [55].

Suggested Sequence for the Introduction of Medical Therapy

(1) Symptoms but no signs: (a) environmental measures; (b) preserved artificial drops.

(2) Mild conjunctival and corneal stain: (a) non-preserved drops of increased viscosity; (b) ointment at night.

(3) Confluent central corneal stain: (a) intensive frequency of non-preserved drops; (b) trial of topical anti-inflammatory treatment (cyclosporine A or steroid); (c) temporary punctual occlusion.

(4) Actual or potential epithelial breakdown: (a) intensive non-preserved drops; (b) topical anti-inflammatory treatment; (c) autologous serum (if available); (d) contact lens; (e) immunosuppression for autoimmune disease (rheumatoid arthritis, graft-versus-host disease, OCP, etc).

Conclusions

(1) Medical treatment is central to the management of dry eye disease. Environmental control has an important role in prevention of symptoms.

(2) Use non-preserved viscous preparations wherever possible for moderate to severe dry eye. As the ocular residence time of an agent is increased they tend to become more effective and the frequency of treatment can thus be reduced.

(3) The role of anti-inflammatory agents and topical immunosuppression needs to be better defined.

(4) Contact lenses have a role in the prevention of epithelial breakdown and visual rehabilitation in severely dry eyes.

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S.J. Tuft
Moorfields Eye Hospital
162 City Road, London EC1V 2PD (UK)
Tel. +44 207 566 2472, Fax +44 207 566 2019
E-Mail s.tuft@ucl.ac.uk

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Anti-Inflammatory and Immunosuppressive Concepts

Bernhard Nölle

Dept. of Ophthalmology, University Hospital Schleswig-Holstein,
Campus Kiel, Kiel, Germany

Abstract

Background/Purpose: Patients with symptomatic dry eyes are frequently seen by every ophthalmologist. Understanding of the plethora of factors involved in sicca syndrome is essential to substantially help the patient. Besides important and frequent topical treatment options, anti-inflammatory and immunosuppressive systemic treatment concepts sometimes play an additional role. **Material and Methods:** Relevant data of publications listed in Medline between 1966 and 2006 are analyzed. **Results:** Local treatment options are listed, immunosuppressive substances are shortly characterized with regard to action, side effects, and control parameters. An overview of new applicable biological substances is given. **Conclusions:** A variety of treatment options can be offered to patients with dry eyes. The spectrum ranges from lubricants to systemical immunosuppressive substances. At present no official guidelines replace individual strategies to treat the patient. An escalation of treatment options has to be performed with individual experience.

Ocular surface disorders do not have to be treated routinely by systemic immunosuppression, as various local treatment options are available and sufficiently effective in many patients. These are: (1) lid closure, enable or improve it surgically; (2) local corticosteroids, they suppress local inflammation, but may deteriorate dry eye symptoms and increase risk of local infections; (3) topical cyclosporin A (CsA) acts as an anti-inflammatory with rare side effects; (4) local lubricants, apply them frequently, but be aware of local toxicity resulting in intolerance to components of these drops (mostly preservatives); (5) vitamin-A-containing substances, they improve superficial epithelial cell layers; (6) autologous serum, it contains various cytokines and growth factors as useful adjunct for healing of epithelial defects; (7) therapeutic contact lens, apply it for superficial

epithelial defects, but take care of infectious complications; (8) punctum plugs, insert them or obliterate nasolacrimal duct, and (9) amniotic membrane transplantation for reconstruction of superficial layers of the cornea and conjunctiva.

Details of the above-mentioned local treatment options are outlined in chapters 4–9. The use of the various local treatment options were recently recommended by an international expert panel [1]. There is increasing evidence that dry eye problems beside other pathophysiological disturbances also show increased inflammatory cells and proinflammatory cytokines in the conjunctiva, lacrimal glands and tear fluid [2–5]. Topical anti-inflammatory substances are therefore a logical therapeutical adjunct. Glucocorticosteroids should be applied only for short time period (2–4 weeks) as they are effective within several days, but severe side effects are probable in long-term use [5–10]. Topical CsA is an anti-inflammatory substance with a slowly acting effect increasing within weeks to 6 months; this substance can be applied topically for a long time, as side effects are very rare [5, 11–15].

However, there are some systemic disorders with involvement of the ocular surface and adnexa, where the above-mentioned local treatment options are not sufficiently working. Among these systemic inflammatory disorders are atopic disorders, bullous mucocutaneous disorders with ocular involvement or inflammatory disorders due to collagenous or vasculitic systemic diseases. These systemic disorders may show heavy inflammatory involvement of the ocular surfaces and adnexa, therefore systemic anti-inflammatory treatment regimens are reasonable.

The main indications for any systemic immunosuppression are (1) to prevent eyes from becoming blind by inflammation, (2) to maintain the integrity of the eye, and (3) to reduce mortality caused by systemic inflammation. A prerequisite for any immunosuppression is to rule out infection as the possible cause of inflammation. Immunosuppressive treatment regimens are sometimes shown to be effective in randomized controlled studies, but quite often only uncontrolled case series are available to justify the treatment. In addition, the relative efficacy of different treatment regimens is not determined and interindividual variations of the effectiveness for the same substance is well known for various drugs. Therefore, at present each patient will be best treated with an individualized treatment regimen. In general, the use of alkylating substances often results in long-term drug-free remissions, but treatment with other substances needs to be continued long term or even indefinitely. A guideline gives advice how to manage this topic [16].

First-line anti-inflammatory treatment consists of corticosteroids, which can be applied topically, periocularly or systemically. Their anti-inflammatory capacity becomes evident within a few days. However, side effects, possible complications, or sometimes ineffectivity limit their application. Usually, in patients with liver insufficiency about 1 mg/kg/day prednisolone is applied, and in severe inflammation pulses of 1 g/day for 3–5 days are possible. The dose should be

Table 1. Immunosuppressive drugs

Type	Mechanisms	Examples
Alkylating	Binding to DNA, RNA, proteins	Cyclophosphamide Chlorambucil
Purine analogues	Inhibition of purine synthesis	Azathioprine Mycophenolic acid mofetil
Folic acid antagonism	Interference transport, $1C + CH_3$	Methotrexate
Pyrimidine analogues	Inhibition of pyrimidine synthesis	5-Fluorouracil
Alkaloids	Inhibition of mitosis	Vinblastine
Antibiotics	Inhibition of DNA synthesis	Daunorubicin
Immunophilins	Inhibition of calcineurin	Ciclosporin A, FK-506
Biologicals	Blocking of receptors	Basiliximab (anti-CD25) Infliximab (anti-TNF-α) Etanercept (anti-TNF-α) Adalimumab (anti-TNF-α) Rituximab (anti-CD20)

reduced stepwise (10 mg every 1–2 weeks, at the level of 40 mg/day reduce in 5-mg steps, at 20 mg/day in 2.5-mg steps, at 10 mg in 1-mg steps), reduction intervals can be prolonged from 1 to 4 weeks depending on the clinical course. During glucocorticosteroid treatment, monitoring of hypertension, body weight, blood glucose (every 3 months), serum lipids, density of bones (once a year) should be performed. Important and frequent side effects are (a) increased risk of infection, (b) fluid retention, (c) diabetes mellitus, (d) hyperlipidemia, (e) osteoporosis, (f) atherosclerosis, (g) glaucoma, (h) cataract, (i) anxiety, (j) sleepiness, (k) mood changes, (l) easy bruising, and (m) poor wound healing. As supplements to steroids, calcium 1,500 mg/day, vitamin D 800 IU/day, estrogens, if decreased or postmenopausal, and antiabsorbants should be added. Adverse effects of glucocorticosteroids are cushingoid changes (weight gain, moon facies, fat redistribution, acne) for doses >5–10 mg/day prednisone, suppression of adrenal glands, and delay of pubertal growth in children. Sometimes severe side effects such as pancreatitis, aseptic bone necrosis, IDDM, myopathy, or psychosis require immediate reduction of corticosteroids. In cases of concomitant use of NSAID, the risk of gastric ulceration increases. Long-term corticosteroid therapy is associated with an increase in mortality. If corticosteroids fail to induce improvement of the inflammation within 2–4 weeks or if a continuous dose of >10 mg/day is needed, then additional systemic immunosuppression with alternative drugs should be performed [16]. The immunosuppressive substances frequently applied in such human disorders are outlined in table 1.

Cyclophosphamide (Cyc) is a cytotoxic alkylating drug. It effects resting and dividing lymphocytes and results in a broad T- and B-cell impairment. The drug is well absorbed and metabolized in the liver. It is eliminated via the kidneys and therefore some metabolites can cause bladder toxicity. The main indications for Cyc are as antineoplastic drug in oncology, in autoimmune disorders especially SLE and Wegener's granulomatosis, uveitis and ocular cicatricial pemphigoid. Usually a dose of Cyc of 1–3 mg/kg/day is given. Pulse treatment every 3–6 weeks of about 600–1,500 mg is a possible alternative. The main side effects are bone marrow depression, rarely myelodysplasia, hemorrhagic cystitis, teratogenicity, ovarian suppression, testicular atrophy, azospermia, alopecia, nausea, vomiting, and opportunistic infections due to lymphopenia. Routine monitoring of blood cell count, platelets, urinalysis, every week initially and later every month is recommended [16].

Chlorambucil is a cytotoxic alkylating drug inducing crosslinking of DNA to proteins. It is metabolized in the liver to phenylacetic acid mustard. Inactive compounds will be eliminated in the urine. Indications are as antineoplastic drugs in oncology, Behçet's disease, uveitis especially due to Behçet's syndrome and sympathetic ophthalmia. The dosage should be 0.1–0.2 mg/kg/day for about 1 year. Alternatively a short-term (3–6 months) treatment is possible with initiation of 2 mg/day and an increase every week by 2 mg until complete suppression of inflammation or white blood cells are $<$2,400/μl or platelets $<$100,000/μl are reached. The side effects are bone marrow suppression, mostly reversible, but often prolonged, opportunistic infections (e.g., herpes zoster, *Pneumocystis carinii*), permanent sterility in men and amenorrhea in women, teratogenicity, increased risk of malignancy in the long term. Monitoring of blood cell counts every week initially, later monthly, in cases of short-term regimen every week is advised [16].

Azathioprine (Aza) interferes with adenine and guanine ribonucleotides resulting in reduced numbers of lymphocytes, mixed lymphocytes reactivity, IL-2 synthesis and IgM production. The substance is orally well absorbed; metabolism of Aza needs activity of xanthine oxidase, which can be inhibited by allopurinol. The main general indications are rheumatoid arthritis, organ transplantation, psoriasis, Reiter's syndrome, or systemic lupus erythematosus; in ophthalmology, chronic uveitis, uveitis in Behçet's syndrome and intermediate uveitis are frequent indications. The dosage ranges between 1 and 3 mg/kg/day, reduction is recommended when allopurinol is applied. The main side effects are reversible bone marrow suppression, increased risk of non-Hodgkin's lymphoma, hepatotoxicity 2%, and gastrointestinal intolerance 25%. Monitoring of blood cell counts and platelets at 4- to 6-week intervals and liver enzymes every 12 weeks is recommended. The dosage should be reduced if liver enzymes increase $>$1.5-fold, stop Aza application if the rise is $>$5 times of normal [16].

Mycophenolate mofetil (MMF) selectively inhibits inosine monophosphate dehydrogenase, it reduces lymphocyte proliferation, suppresses antibody synthesis, reduces cellular adhesion to vascular endothelium, and inflammatory cell recruitment. MMF shows renal elimination and has a high oral bioavailability. The main indications are transplantation of solid organs, uveitis, and scleritis. However, no controlled studies are available. In most cases, MMF reduces ocular inflammation if applied with other immunomodulating substances. The recommended dosage is 2 × 1 g/day. The main side effects are gastrointestinal pain, nausea, vomiting, and diarrhea in up to one third, rarely infections, and neoplastic disorders. One should monitor blood cell counts every week for the first month, later at 2-month intervals, and liver enzymes at 3-month intervals [16].

Methotrexate (Mtx) is a folic acid agonist inhibiting dihydrofolate reductase. It inhibits rapidly dividing cells. Oral absorption is reduced by metabolization of the drug by intestinal flora in up to one third, parenteral application is therefore much safer. Addition of 1 mg/day folate reduces nausea. Patients should abstain from alcohol consumption during treatment. The substance is eliminated by the kidneys. The main indications for Mtx are rheumatoid arthritis, juvenile chronic arthritis, psoriasis arthritis, systemic lupus erythematosus, several neoplastic disorders, uveitis, scleritis, orbital pseudotumor. Major side effects are cytopenia, hepatotoxicitiy, interstitial pneumonia, stomatitis, and nausea. Mtx is contraindicated during pregnancy. During treatment one should monitor blood cell counts and liver enzymes at 1- to 2-month intervals [16].

CsA inhibits preferentially immunocompetent T lymphocytes. CsA is metabolized in the liver and excreted in the bile. Bioavailability of CsA shows a broad range. The main indications are solid-organ transplantation, treatment-resistant rheumatoid arthritis, severe plaque psoriasis, uveitis, and Behçet's syndrome. The currently recommended dosage is 2–5 mg/kg/day. Serious side effects include nephrotoxicity, hypertension, less common hepatotoxicity, gingival hyperplasia, myalgia, tremor, paresthesiae, hypomagnesemia, and hirsutism. It is recommended to monitor blood pressure often, at least every month, serum creatinine every 2 weeks for 2 months, then monthly. Detection of CsA blood levels is not necessary [16].

Tacrolimus (FK-506) inhibits activation of T lymphocytes. The absorption of the drug from gastrointestinum varies. Tacrolimus is metabolized by the cytochrome P450 system and shows mainly fecal elimination. Indications for FK-506 are solid-organ transplantations, and uveitis, although only small numbers of patients have been reported. The dosage is usually 0.1–0.15 mg/kg/day for transplantation and 0.05 mg/kg/day for uveitis, respectively. During treatment, monitor drug blood concentration weekly for about 2 months, then monthly; test liver enzymes, bilirubin, blood urea nitrogen, creatinine, electrolytes including calcium, magnesium, phosphate; cholesterol, triglycerides, glucose,

Table 2. Immunosuppression with biologicals

Key molecule	Generic name	Trade name	Company
TNF-α	Infliximab	Remicade®	Centocor
	Etanercept	Enbrel®	Amgen & Wyeth
	Adalimumab	Humira®	Abbott Laboratories
IL-1ra	Anakinra	Kineret®	Amgen
CD20	Rituximab	Mabthera®	Genentech
CD25	Daclizumab	Zenapax®	Hoffmann-La Roche
	Basiliximab	Simulect®	Novartis
EGF rec II	Trastuzumab	Herceptin®	Hoffmann-La Roche
CD11a	Efalizumab	Raptiva®	Genentech
CD2 LFA	3-Alefacept	Amevive®	Biogen
α_4-Integrin	Natalizumab	Antegren®	Biogen
β_3-Integrin	Abciximab	ReoPro®	Centocor

blood cell count; blood pressure. The main known side effects are nephrotoxicity, neurologic symptoms, gastrointestinal symptoms, hyperglycemia, hypomagnesemia, tremor, and hypertension [16].

Immunosuppressive drugs as outlined above have a broad range of effects; they interact with pathologic immune reactions and should block them effectively. However, a lack of specificity or evolving severe side effects sometimes prevents a therapeutic success. In these situations combination therapy with multiple immunosuppressive drugs is sometimes useful. But with regard to a more specific immune regulatory effect, a lot of monoclonal antibodies or sometimes fusion proteins have been developed which specifically block a receptor. This blockade can downregulate an immune reaction if the blocked molecule has a key function in the pathological immune process. An overview of the substances currently used in patients with autoimmune disorders or in studies is given in table 2.

Biological substances with specificity for TNF-α receptors are frequently used in chronic polyarthritis. It has been noted that TNF-α is one key molecule responsible for destruction of cartilage of joints and blocking of this cytokine receptor will stop inflammation and structural tissue disorganization highly effectively [17–19]. But aside from joint inflammation, the blockade of TNF-α receptors is also effective in psoriasis, Bechterew's arthritis and inflammatory bowel diseases [18, 20–23]. Some authors also report beneficial effects of blocking TNF-α receptors in various inflammatory eye disorders [24–33].

TNF-α is a cytokine produced by various cells (i.e. monocytes, macrophages, neutrophils, activated lymphocytes, endothelial cells, fibroblasts, and other

cells) [for review, see 19]. The main function of this proinflammatory cytokine is to induce cachexia and fever. In addition, inflammatory cells will immigrate locally. An increase in synovia cell apoptosis and expression of adhesion molecules takes place. There are two known receptors of TNF-α, one is p55 and the second p75. They are located in the cell membrane and can be cleaved by matrix metalloproteinases. With regard to the eye, we know that TNF-α is expressed in the cornea, especially during inflammation [34]. TNF-α may induce corneal angiogenesis in vivo. There is an interaction between TNF-α and sVCAM-1 [35]. TNF-α may increase NOS2, fibroblast apoptosis, and various MMPs – 1, 3, 10, 11, 13 [36, 37]. TNF-α is elevated in psoriatic skin lesions [38].

Infliximab is a chimeric monoclonal antibody specific for TNF-α with a humanized Fc part and Fab fragment from mouse. In man the usual dosage is 3–5 mg/kg b.w. intravenously. The interval of treatment should be 0, 2 and 6 weeks and then every 8 weeks afterwards. Etanercept is a fusion protein specific for the p75 receptor of TNF-α. The usual dosage is 25 mg subcutaneously applied twice a week. Adalimumab is another monoclonal antibody fully humanized and specific for TNF-α. The usual application dosage is 40 mg given subcutaneously every 2 weeks. These inhibitors of TNF-α show a very rapid anti-inflammatory response and rare side effects. The clinical efficacy of infliximab is superior to adalimumab and etanercept (personal experience). One has to look for possible infections which may cause lethal complications, especially in cases of tuberculosis. Active tuberculosis has to be ruled out before application of these drugs [39]. Skin reactions may sometimes develop in the area of local application. Possibly myocardial insufficiency may become worse, induction of functional autoantibodies and autoimmunity is very rare. The long-term side effects are unclear at present, but an increase in neoplastic disorders is suspected.

Inhibition of the cell surface molecule CD20 is frequently performed in treatment of lymphomas and leukemias. As B cells with CD20 molecules on their cell surface are also involved in a variety of autoimmune disorders, the effect of the monoclonal antibody rituximab, which is able to block the CD20 cell surface antigen, is currently being investigated [40]. At present, favorable clinical results have been reported in the treatment of rheumatoid arthritis [41] or treatment-resistant scleritis due to primary Sjögren's syndrome [42]. However, another study showed no promising effects in Wegener's granulomatosis with complicated longstanding orbital granulomas [43]. At present it is not clear what medical indication is best for rituximab application.

Severe forms of ocular cicatricial pemphigoid are best treated by systemic Cyc [44]. Local treatment with corticosteroids and CsA is not sufficient [44], data for a possible effect of subconjunctivally injected mitomycin have not been reported yet, but the risks of that treatment are known, i.e. reduction of limbal stem cells, necrosis of the sclera and ciliary body. Early cases of ocular pemphigoid

with moderate activity can be successfully managed with dapsone or related sulfapyridine substances [45, 46]. But new treatment options have the potential to reduce side effects and seem to be as effective as Cyc. Promising results show daclizumab (antibody against CD25), intravenous immunoglobulins and methotrexate [44, 47–49]. In addition, surgical treatment may include keratolimbal allografts and amniotic membrane transplantation in combination with penetrating keratoplasty in cases with sufficient immunosuppression [44]. Presumably, similar drugs will be developed for other disorders in the near future.

Although we have a few guidelines and recommendations for the use of immunosuppressive substances in general [16], a lack of controlled studies complicates recommendations, for example for the application of immunosuppressive substances in Sjögren's syndrome. Therefore, it is still a big challenge which substance or combinations should be applied at what dosages and for how long in an individual patient. This matter is still a difficult task for every physician, even for those experienced in that field. Therefore, further work is still needed on evaluation of objective data for optimal adjustment of treatment. Possibly new options will be available in the future, hopefully with a more specific interaction to correct specifically the immunopathology without changing the physiologic conditions elsewhere in the body.

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Dr. med. Bernhard Nölle
Hegewischstrasse 2
DE–24105 Kiel (Germany)
Tel. +49 0431 597 2362, Fax +49 0431 597 2425
E-Mail bnoelle@ophthalmol.uni-kiel.de

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Correction of Entropion and Ectropion

Christoph Hintschich

Augenklinik der Ludwig-Maximilians-Universität München, München, Germany

Abstract

The ocular surface is dependent on the physiological and anatomical integrity of the eyelids and associated adnexal structures. Entropion and ectropion are commonly encountered in clinical practice, and pose a risk to the success of both ocular surface and intraocular surgery. This chapter covers the causes of such lid malpositions, which can be congenital or acquired (e.g. involutional, cicatricial or paralytic) and the clinical examination of the eyelids. Principles underlying corrective surgery are demonstrated and practical aspects of the some more commonly performed and effective operations are described.

The eyelids protect the eye and keep the ocular surface moist. Eyelid malpositions can cause ocular surface disease (OSD) and threaten sight. This is in particular true for any eyelid entropion, which probably is the most common eyelid malposition, but is also true for the different forms of ectropion. This short chapter deals with the various forms of entropion and ectropion and their adequate therapies.

Entropion

Entropion is defined as an eyelid malposition, where the lid margin is inverted and directed towards the globe. The lid margin with or without lashes rubbing against the conjunctiva and the cornea causes foreign body sensation, pain and leads eventually to epithelial defects and finally to corneal scarring. Entropion should be distinguished from trichiasis and distichiasis, which present with similar symptoms, but usually need different therapy. Trichiasis is a common, acquired misdirection of eyelashes arising from their normal site of origin.

Distichiasis is a rare, congenital condition with growth of abnormal lashes from an extra row, usually from the meibomian gland orifices. Under certain conditions, like inflammation in Stevens-Johnson syndrome, metaplastic changes in the meibomian gland orifices can induce 'acquired' distichiasis. In both trichiasis and distichiasis, the position of the lid margin is normal. If there is entropion of the lid margin this must be treated first before treatment of eyelash abnormality.

Different types of entropion can be distinguished, according to the underlying etiology: (1) *congenital entropion:* (a) entropion and (b) epiblepharon, and (2) *acquired entropion:* (a) involutional entropion; (b) cicatricial entropion, and (c) acute spastic entropion.

Congenital Entropion

Congenital entropion is rare and should not be confused with epiblepharon. In congenital entropion the eyelid in its whole horizontal extension is involved and the eyelashes are directed towards the eye, but in epiblepharon the lashes are orientated more vertically. Congenital entropion tends to persist and cause keratopathy, whereas epiblepharon often resolves spontaneously.

Epiblepharon is characterized by an apparent overriding of the pretarsal orbicularis muscle and skin over the eyelid margin, causing the eyelashes to assume a vertical position. It most commonly occurs in Asians and affects the medial part of the lower eyelids. Not every child presenting with an epiblepharon, even when the lashes come into contact with the cornea, has to be operated. Often it resolves spontaneously during the first years of life. If it fails to resolve, or if corneal irritation occurs, surgery is indicated. Recurrent attacks of conjunctivitis and persistent photophobia in children are indicators for symptomatic OSD. Surgical repair consists of circumscribed anterior eyelid lamellar shortening and tarsal fixation. An elliptical strip of skin and underlying orbicularis muscle is excised below and lateral the inferior punctum. The skin edges are sutured to the lower border of the tarsal plate or the eyelid retractors with absorbable sutures to prevent the orbicularis from overriding the lid margin. The cosmetic results are better, when the procedure is performed symmetrically on both sides. The vertical amount of skin excision should be moderate enough to prevent iatrogenic medial lower eyelid retraction causing an eversion of the lacrimal punctum.

Acquired Entropion

Acquired entropion can be either cicatricial or involutional. In addition, a form of acute spastic entropion can be defined in susceptible individuals with

blepharospasm that has been induced by ocular irritation. Cicatricial entropion is due to contraction of the posterior lid lamella, involutional entropion caused by changes in the tissue structures with ageing. It is mandatory to distinguish involutional entropion from cicatricial entropion. Therefore, cicatricial changes in the conjunctiva have to be sought after. When examining a patient with entropion, the everted tarsal conjunctiva of both lower and upper eyelid should be investigated under the slit-lamp. Conjunctival and subconjunctival scar formation with or without shortening of the fornices and symblepharon formation are clinical signs for a cicatricial entropion. Severe posterior lamellar cicatrization causes in addition lid retraction.

Any condition that causes contracture of the conjunctiva can result in a cicatricial entropion. Such conditions include mechanical and chemical trauma, burns, trachoma infection (particularly in the upper eyelid) and cicatrizing conjunctivitis like topical glaucoma medication, herpes infection, Stevens-Johnson syndrome and ocular cicatricial pemphigoid. If cicatricial changes are present their cause should be established before considering surgery.

Involutional Entropion

Involutional entropion is the most common form of all entropia, and it is probably the most common eyelid malformation. Since involutional changes of the eyelid anatomy are responsible for this kind of entropion, it is therefore seen in the elderly patient. A combination of factors has been advocated to account for this kind of eyelid malposition [Jones, 1960; Collin and Rathburn, 1978]. This includes the following features: (1) horizontal eyelid laxity (desinsertion of lateral and medial canthus and/or tarsal plate laxity); (2) laxity and/or desinsertion of lower lid retractor complex, and (3) overriding of the preseptal orbicularis muscle over the pretarsal orbicularis. Enophthalmos due to orbital fat atrophy might aggravate the pathogenesis of involutional lower eyelid entropion, but is no longer considered a significant factor in its etiology. Any surgical treatment should address these factors.

Patient Assessment

In order to select an adequate surgical procedure for lower eyelid entropion repair, the patient has to be assessed carefully. This includes an assessment of the eyelid position and the condition of the lower eyelid. For this purpose, the simple ‘snap-back’ test is very useful. The lower eyelid is gently pulled downwards and away from the globe, which normally should not exceed approximately 3 mm. After releasing it, the eyelid should then spontaneously return in its normal position without an additional blink (fig. 1).

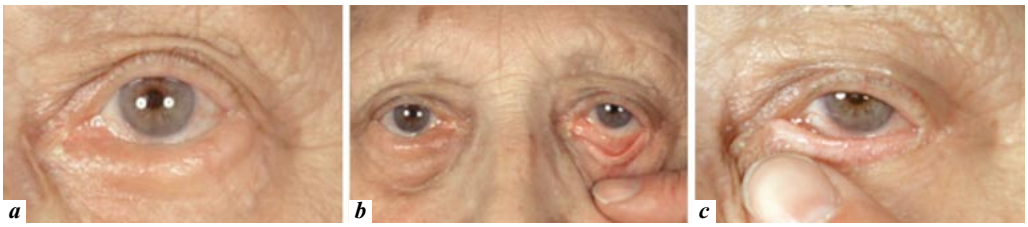


Fig. 1. ***a*** Involutional lower eyelid entropion. Lid margin inverted, positive scleral show. ***b*** 'Snap-back' test, before releasing. Eyelid is easily pulled more than 3 mm away from the globe, indicating lower eyelid horizontal laxity. ***c*** Testing of lateral tendon condition. Lateral canthus stays in place under tension, indicating a normal lateral tendon.

Therapy

The use of tape or therapeutic contact lenses temporarily can help to reduce bulbar irritation. Eventually, surgical intervention is the only effective way to correct this eyelid malposition. To achieve a long-lasting effect, the pathogenic features should be addressed. This includes horizontal lid laxity, vertical lid laxity and eyelid lamella dissociation. In the following a small number of procedures are described, which will allow one to correct the majority of involutional entropia.

Transverse/Everting Sutures

This simple, quick and everywhere (e.g. at the bedside) applicable procedure can correct any involutional entropion, if no marked lower lid laxity is present. A temporary cure for usually about 6 months is available and is particularly helpful in geriatric patients, when more invasive surgery is not indicated [Wright et al., 1999].

Transverse sutures prevent the preseptal orbicularis muscle from overriding the pretarsal part and are placed horizontally through the lid just underneath the tarsal plate [Schöpfer, 1949]. Everting sutures are placed more obliquely through the lid to tighten the lower lid retractors and transfer their pull to the lid margin [Feldstein, 1960].

Three 5-0 Vicryl® sutures are passed through the lid from the conjunctiva to the skin in the lateral two-thirds of the lid, starting from just below the border of the tarsal plate with transverse sutures and emerging through the skin just above that level in a distance of about 2 mm from each other. Everting sutures run more obliquely and start lower in the fornix and emerge nearer to the lashes. The sutures are tied tightly and can be removed, if an overcorrection is present. Usually they are left for spontaneous resorption.

Wies Procedure. The Wies procedure is a transverse lid split combined with everting sutures [Wies, 1954]. By performing a horizontal full-thickness lid split, a fibrous tissue scar is induced, which permanently prevents an overriding of the preseptal orbicularis muscle. This is combined with everting sutures to tighten the lower eyelid retractors and increase their pull to the lid margin. This procedure gives good long-term results, if no horizontal lid laxity is present.

The technique consists of a horizontal full-thickness transsection of the whole of the lower eyelid about 4–5 mm below the lash line. The cut should be as horizontal as possible, and should not reach the lower punctum. Surgery is continued by passing three double-armed 5-0 Vicryl® sutures from the conjunctiva (and with it the lower lid retractors) below the lid transsection through the pretarsal orbicularis muscle to the skin above the transsection. The needles should start 1–2 mm from the conjunctival cut and emerge through the skin 1–2 mm below the lash line and about 2 mm apart. Before tying the everting sutures, the horizontal skin incision can be closed with a running 6-0 silk suture. Skin sutures are removed after 6–7 days. The everting sutures usually are left for spontaneous resorption, unless there is marked overcorrection, which in most cases is due to preexisting horizontal laxity.

Quickert Procedure. In most cases of involutional entropion a horizontal lid laxity is present. In these cases an additional full-thickness shortening is indicated. This is easiest performed by a Quickert procedure [Quickert and Rathburn, 1971], which is a Wies procedure combined with a horizontal lid shortening. The horizontal full-thickness lid split induces a fibrous tissue barrier to prevent the preseptal orbicularis muscle from overriding, the everting sutures tighten the lower eyelid retractors and increase their pull to the lid margin, and the horizontal lid shortening corrects lower lid laxity and stabilizes the lid.

A horizontal skin incision is made 4–5 mm from the lash line in the whole of the lower lid. Then a vertical transsection through the lid is made 5 mm medial to the lateral canthus, down to the horizontal skin incision, followed by the horizontal full-thickness transsection as in a Wies procedure, medially and laterally to the vertical incision. Finally, a full-thickness resection of excess lid margin is performed. The amount of excess tissue is estimated by overlapping the medial and the lateral end of the lid margin under slight tension. Three double-armed 5-0 Vicryl® sutures are positioned in the lower conjunctival wound edge (as in the Wies procedure) before readapting the two ends of the lid margin with tarsal (6-0 Vicryl®) and lid margin (6-0 silk) sutures. Surgery is continued and completed as in the Wies procedure. All silk sutures are removed after 1 week, the everting sutures left for spontaneous resorption.

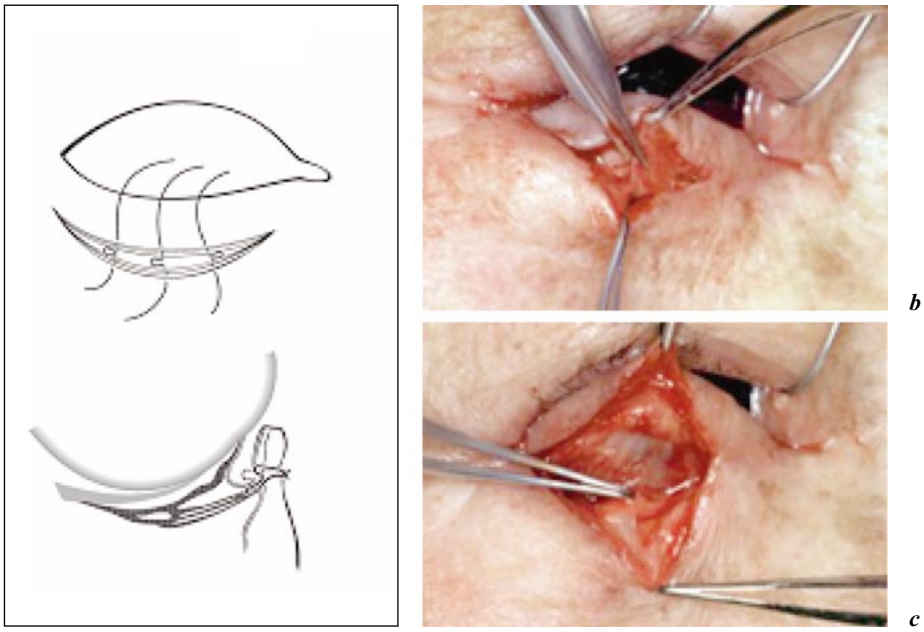
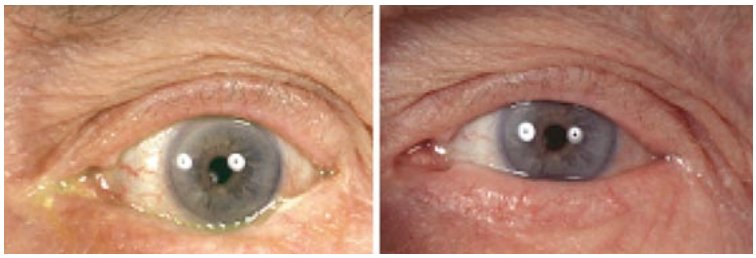


Fig. 2. ***a*** Jones procedure (lower eyelid retractor plication), schematic. ***b*** Jones procedure, intraoperatively. Opening of lower eyelid septum. ***c*** Exposure of lower eyelid retractor complex.

The results after a Quickert procedure are usually good, the recurrence rate is as low as 3.7% [Collin and Rathburn, 1978].

Jones Procedure. Particularly in recurrences of lower eyelid entropion after one or more previous surgeries without horizontal laxity, and in cases where surgical trauma to the conjunctiva should be avoided, plication of the lower lid retractors through an anterior skin approach is indicated. This is in particularly helpful in lower eyelid cicatricial entropion due to ocular mucous membrane pemphigoid, when any surgical trauma to the conjunctiva should be avoided to prevent exacerbation of the disease.

With the Jones procedure the lower eyelid retractors are exposed via a skin approach, shortened, and sutures used to create a barrier to prevent the preseptal orbicularis from overriding the pretarsal part [Jones et al., 1972] (fig. 2). In the presence of additional lower eyelid laxity, particularly in the lateral canthal tendon, this procedure can be combined with a lateral tarsal strip procedure to tighten and shorten the lower eyelid (fig. 3)



a ***b***

Fig. 3. ***a*** Involutional lower eyelid entropion recurrence, after lid shortening procedures. Note combination of entropion and lower eyelid retraction. ***b*** After Jones lower eyelid retractor plication combined with lateral tarsal strip procedure.

Table 1. Compendium of surgical procedures to correct involutional lower eyelid entropion

Procedure	Indication
Transverse/everting sutures	Involutional entropion without horizontal laxity
Wies	Involutional entropion without horizontal laxity
Quickert	Involutional entropion *with* horizontal laxity
Lateral tarsal strip + everting sutures	Involutional entropion *with* horizontal laxity
Jones	Involutional entropion without horizontal laxity Recurrence without horizontal laxity Mild to moderate cicatricial entropion with pemphigoid
Jones + lateral tarsal strip	Recurrence with horizontal laxity

The Jones procedure needs more dissection in the lower lid and more detailed knowledge of the anatomy (table 1).

Cicatricial Entropion

This is due to scarring of the conjunctiva and tarsal plate with shortening of the posterior lamella. Any condition that causes contracture, like chemical burns, mechanical trauma, topical glaucoma medication, ocular cicatricial mucous membrane pemphigoid and others, can induce scarring. It occurs commonly in upper and lower eyelids.

The choice of surgical procedures to correct lower eyelid cicatricial entropion is dictated by the severity of the entropion and the retraction and by the underlying cause. In ocular cicatricial pemphigoid, surgery should be confined to the anterior lamella whenever possible to avoid exacerbating the conjunctival disease. A retractor tightening procedure like the Jones procedure (see above) would be the method of choice.

Circumscribed conjunctival scars can be excised and corrected with a Z-plasty. Moderate degrees of cicatricial entropion with a minor degree of lid retraction can be managed with a 'tarsal fracture' procedure. A horizontal incision is made through the whole length of the tarsus just below its centre down to the orbicularis muscle. Three double-armed 5-0 Vicryl® sutures are passed from the lower fragment just below the incision and out through the skin immediately below the lash line. The sutures are tied to produce a mild overcorrection and removed after 2 weeks.

In severe cicatricial lower lid entropion with more severe degree of lid retraction, a posterior lamellar graft is indicated. The tarsoconjunctiva is lengthened with a graft, which is inserted near the lid margin to allow eversion. A piece of full-thickness buccal mucosa, tarsal plate, hard palate, ear cartilage or donor sclera is sutured with running 6-0 Vicryl® sutures between the superior and inferior fragment of the horizontally divided lower tarsal plate. The lid margin is hold everted and the graft firmly apposed to its bed with everting sutures passed through the graft and tied on the skin just below the lashes. The choice of graft material for fornix reconstruction is discussed in more detail in chapter on page 232.

Acute Spastic Entropion

Topical therapy of the underlying cause of ocular irritation may reverse the eyelid malposition. If this is not the case, a permanent entropion with usually involutional components may ensue, which will require surgical intervention according to the guidelines given before.

Upper Eyelid Entropion

Upper eyelid entropion is an eyelid malposition in which the upper eyelid margin is turned inwards against the globe. It can be responsible for severe OSD and ocular morbidity. It is relatively uncommon in the northern hemisphere in contrast to a number of countries in more arid areas of the world, where trachoma is endemic.

Table 2. Causes of upper eyelid cicatricial entropion

Trachoma
Chronic blepharoconjunctivitis
Erythema multiforme
Chemical/thermic burn
Postoperative (s/p reconstructive surgery)
Pemphigoid
Stevens-Johnson/Lyell syndrome
Postenucleation socket syndrome
Herpes infection
Idiopathic/unknown

The condition can be congenital, which is rather rare, but is mainly caused by cicatricial changes of the posterior upper eyelid lamella. Any trauma, either mechanical or chemical, and infection to the conjunctiva can cause an upper eyelid entropion. Worldwide, trachoma is the most common cause of this upper eyelid malposition, other causes are listed in table 2. In addition to taking a careful history, a complete ocular examination with eversion of the posterior lamella and the superior fornix is essential to determine the etiology.

Upper eyelid trachoma may be further classified according to its severity as mild, moderate or severe. This is essential for choosing the most appropriate surgical procedure (see table 3). However, first it is important to establish the diagnosis of upper eyelid entropion and differentiate this from simple trichiasis. This helps to avoid unnecessary and often useless epilation efforts.

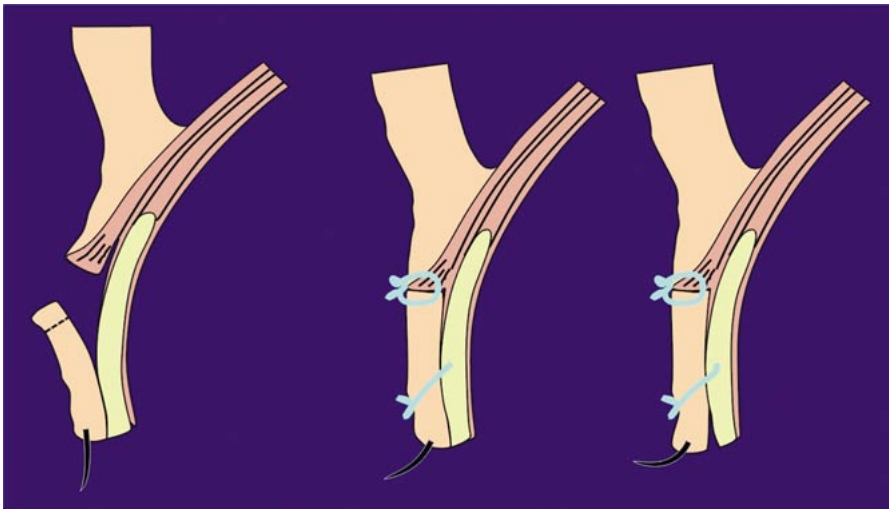
Therapy

Anterior Lamellar Repositioning

This procedure is indicated in mild to moderate forms of upper eyelid entropion. It is easy to perform, safe and corrects the majority of upper lid entropia in the northern hemisphere [Hintschich, 1997]. The surgery divides the anterior from the posterior lamella of the upper eyelid, repositions the anterior lamella superiorly and sutures it to the tarsal plate at a higher level. This is often combined with a lid split at the grey line of the lid margin, which enhances the everting effect to the lid margin (fig. 4). This procedure requires a stable upper tarsal plate.

Table 3. Classification of upper eyelid cicatricial entropion [Kemp and Collin, 1986]

Classification	Clinical criteria
Mild	Apparent posterior migration of meibomian glands Conjunctivalization of lid margin Lash/globe contact on up-gaze
Moderate	Like mild entropion + Thickening of the tarsal plate Lid retraction
Severe	Gross lid distortion Metaplastic lashes Presence of keratin plaques Lid retraction causing lagophthalmos



a

b

c

Fig. 4. ***a*** Anterior lamellar repositioning with lid margin split, schematic. ***b*** Upper eyelid cicatricial entropion, moderate degree. ***c*** After anterior lamellar repositioning. Note mild early post-operative overcorrection.

The superior tarsal plate is completely freed from the overlying orbicularis muscle down to the roots of the lashes through a skin crease incision. The entire length of the lid margin is split in the grey line, just anteriorly to the orifices of the meibomian glands, to a depth of 1–2 mm. Five to six 6-0 double-armed Vicryl® sutures are anchored in the upper third of the anterior tarsal plate and then passed out through orbicularis and skin, just above the lash line. By closing these sutures, the anterior lamella is lifted and the lash-bearing part of the lid margin is everted. The split is allowed to granulate and the sutures can be left for spontaneous resorption.

In more severe forms of upper eyelid entropion a tarsal wedge resection or a rotation of the terminal tarsus can be performed. In cases of post-traumatic upper eyelid entropion, particularly after severe burns, the tarsal plate tends to be thin and unstable. This situation is often combined with upper lid retraction, conjunctival scarring and an upper fornix shortening. Under such conditions, none of the aforementioned techniques are applicable. A posterior lamellar graft is then indicated to stabilize and lengthen the upper eyelid. An autologous graft is put between the upper eyelid margin or the remnant of the tarsal plate and the recessed upper lid retractors. A graft from the hard palate is favorable because it combines some stiffness with mucous membrane lining and is ideal for this kind of upper eyelid correction. Sutures and knots always should be covered by tissue to avoid corneal damage. Any aberrant or misdirected lashes and lid margin malpositions can be corrected at the same time, if necessary, by a full-thickness wedge excision.

It is important to correct cicatricial upper eyelid entropium before starting with any visual rehabilitative procedures, such as keratoplasty. Otherwise the continuing mechanical stress to the ocular surface caused by the lid malposition will jeopardize the result of any of these procedures. In consequence, one might be forced to perform lid surgery earlier than 6 months after the trauma in order to prevent ongoing damage to the ocular surface, although this can be associated with a higher failure rate of the surgery. Usually one waits for at least 6 months until healing and scarring is completed before corrective and reconstructive procedures are performed.

Ectropion

Lower eyelid ectropion is an eyelid malposition in which the lower eyelid margin is turned away from the globe. This condition can be classified into five categories according to the underlying etiology: (1) *congenital ectropion* and (2) *acquired ectropion:* (a) involutional ectropion; (b) cicatricial ectropion; (c) paralytic ectropion, and (d) mechanical ectropion.

Any severe ectropion with secondary lagophthalmos cannot only cause continuing epihora, but also OSD with exposure keratopathy and finally corneal ulceration. For therapy, it is important to be able to classify the actual type of ectropion so that the correct management is chosen based on the underlying cause. However, more than one etiological factor in one individual patient may be present, e.g. ongoing epiphora in a neglected involutional ectropion may lead to secondary cicatricial changes in the skin. This induces a vicious circle, which is increasingly difficult to reverse the longer the surgery is delayed. One should always look for cicatricial changes in the skin – either a general tightness, which is accentuated by asking the patient to look up and open the mouth, or a linear scar. Failure to recognize a cicatricial component is a common cause of surgical failure. Horizontal lid laxity and lateral or medial tendon weakness is assessed as for involutional entropion. Lower eyelid ectropion in facial nerve palsy mostly is associated with other abnormalities of facial nerve function, e.g. inability to lift the forehead or other signs of facial muscular weakness.

Congenital Ectropion

The majority of patients with congenital ectropion suffer from cicatricial ectropion due to a generalized shortage of the periorbital skin. Singular congenital ectropion is rare; it is mainly associated with additional abnormalities as in blepharophimosis syndrome, Down syndrome or ichthyosis. A congenital facial palsy like in a Moebius syndrome causes a paralytic ectropion.

Patients with shortage of skin require full-thickness skin grafting (see below). This surgery is purely functional and the aesthetic results are less favorable in comparison to the results in adults. However, in cases of severe cicatricial ectropion with lagophthalmos causing keratopathy in young children, skin grafting procedures should not be delayed to prevent them from sight-threatening complications. Tarsorrhaphies never work sufficiently in these cases and will only complicate the situation and delay a definite correction.

Acquired Ectropion

Involutional Ectropion

The most common type of ectropion is the involutional ectropion with its variety of involutional tissue changes including horizontal lid laxity, weakness

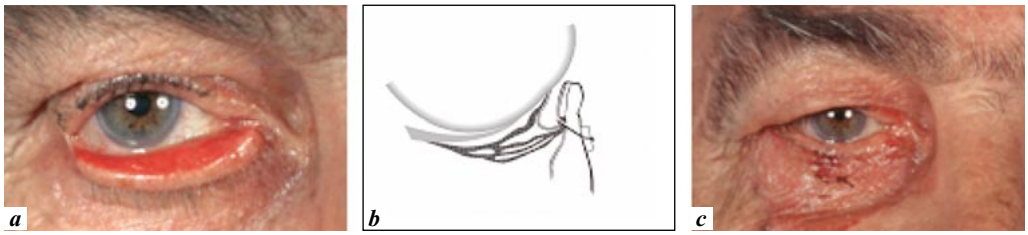


Fig. 5. ***a*** Marked lower eyelid involutional ectropion with disinsertion of the lateral canthal tendon. ***b*** Inverting sutures, tied over bolster, schematic. ***c*** After lateral tarsal strip procedure combined with inverting sutures, same patient.

of the retractors and a dissociation between the lamellae. The surgical procedure should address the underlying etiological factors, as mentioned above. In general, the surgery of an involutional ectropion, particularly of the medial eyelid with punctual eversion, medial tendon laxity, chronic conjunctival exposure and lacrimal pump insufficiency is difficult and the results often are less favorable compared to other lid malformations.

The treatment of involutional lower eyelid ectropion is to correct the lower lid laxity by shortening the lid in the area of maximum laxity. This can be carried out centrally or laterally, under a blepharoplasty flap which allows excess skin and fat to be removed for improved aesthetics, at the lateral canthus or medially just lateral to the punctum. Inverting sutures can support the correction of an everted lid margin (fig. 5). Inversion can be further helped if the posterior lamella of the lid is shortened and the lower lid retractors tightened with the excision of a diamond of tarsoconjunctiva and lower lid retractor plication. If the lid laxity is maximum in the medial canthal tendon this can be tightened with a medial canthal suture or a medial canthal full-thickness resection. Such a medial canthal resection involves cutting the inferior canaliculus that can be marsupialized into the conjunctival sac without necessarily causing epiphora [Collin, 1989].

Full-Thickness Wedge Excision

A full-thickness pentagon of lid is resected from the area of maximum lid laxity. If there is general lid laxity, the excision is performed in the lateral third of the lower eyelid. The amount of excision, which is necessary for correction, is assessed by overlapping the medial and the lateral portion of the lid gently. The lid transsection has to be perpendicular to the lid margin. Once the pentagon is excised, small vessels are cauterized, and the lid defect is repaired.

Lid Margin Repair

Two or three 6-0 Vicryl® sutures on a half circle needle are passed with a horizontal partial-thickness bite into the tarsal plate of one wound edge and then into the tarsal plate of the other wound edge at the corresponding height entering from its conjunctival side. Before closing the sutures, the alignment of the lid margin is checked. Then a silk suture (6-0 or 7-0) is passed through the grey line and in line with it and closed, leaving its ends long. An additional silk suture is passed in the lash line, some more in the skin to close it. The long ends of the grey line suture are caught and knotted with the skin sutures to prevent the grey line suture from rubbing against the globe. The silk sutures can be removed after 1 week.

Lazy-T Procedure

This procedure corrects a medial ectropion with horizontal lid laxity. A medial full-thickness lid resection is combined with an excision of a diamond-shaped part of conjunctiva and subconjunctival tissue, which is closed with an inverting suture (fig. 6). The diamond excision is carried out in the conjunctiva immediately below the lower punctum. One needle of a double-armed 6-0 absorbable suture is passed through the superior apex of the diamond, the other through the conjunctiva below its inferior apex. With this needle, parts of the lower lid retractors are picked up, which are best found lateral to the diamond. Both needles are passed through orbicularis and skin and tied anteriorly. This suture not only closes the diamond excision, but also increases the inversion of the punctum, particularly on down-gaze.

Lateral Tarsal Strip Procedure

This procedure is an excellent method to correct any horizontal lower lid laxity and can be used for both entropion and ectropion repair [Anderson and Gordy, 1979]. It can be combined either with inverting or everting procedures, depending on the underlying pathology. If there is significant medial canthal laxity and the procedure would cause an unacceptable lateral displacement of the punctum, a lateral tarsal strip procedure should not be used (or only in combination with a medial tendon reinforcement).

The principle of this procedure is based on a (re)attachment of the lateral part of the tarsal plate to the periorbital tissue adjacent to the bony orbital rim inside the zygomatic arch. To attain a good result it is mandatory to free the lateral part of the tarsal plate from any epithelial tissues and to suture it as posterior as possible inside the orbital rim. This is necessary to firstly avoid the complication of inclusion cysts and secondly to reach the best alignment of the lid margin to the globe (fig. 7).

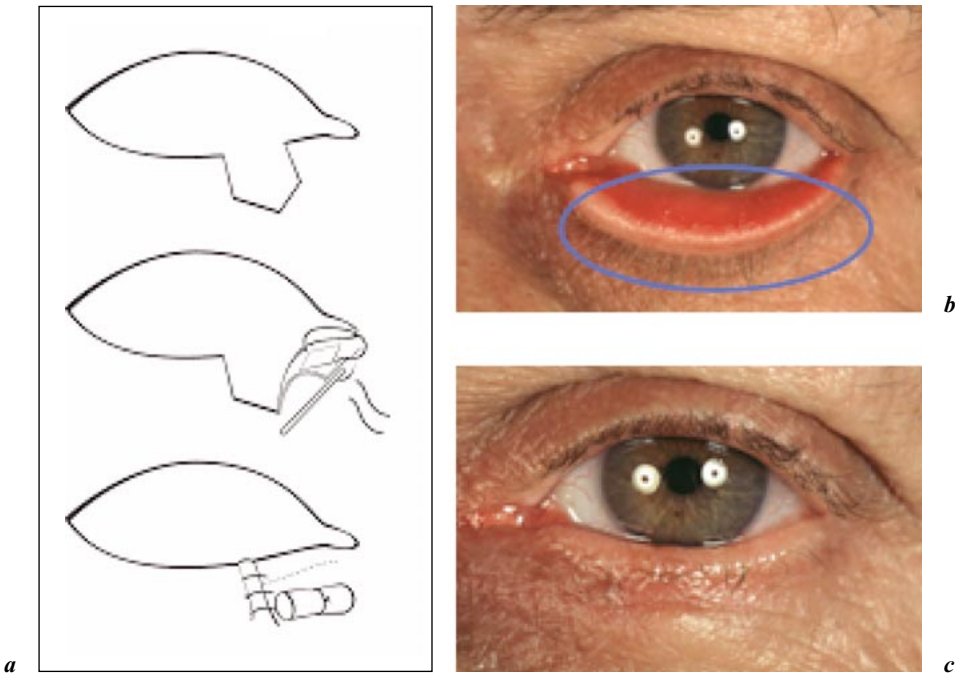


Fig. 6. ***a*** Lazy-T procedure, schematic. ***b*** Marked involutional lower eyelid ectropion with normal lateral canthal tendon. ***c*** After lazy-T procedure.

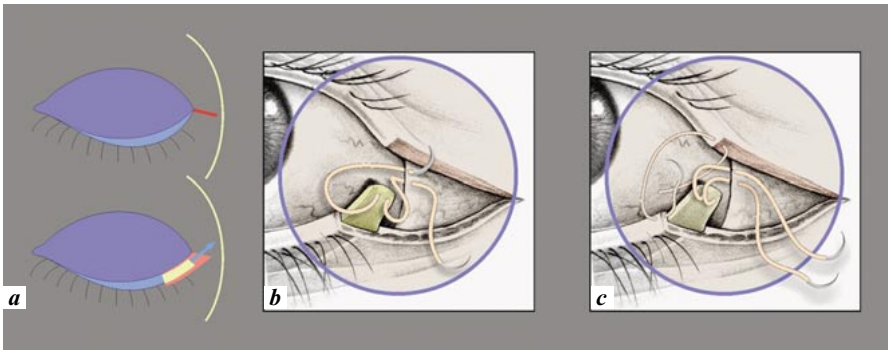


Fig. 7. ***a*** Lateral tarsal strip procedure, principle. ***b*** Lateral tarsal strip procedure, schemtic. Note fixation of double-armed sutures into the periosteum inside the orbital rim. ***c*** Additional suture for lateral canthal restoration.

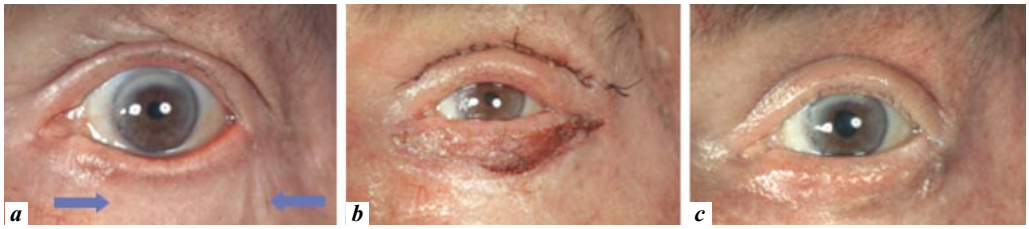


Fig. 8. ***a*** Involutional lower eyelid ectropion with cicatricial component. Note anterior lamellar shortening due to skin cicatrisation (arrow). ***b*** After lateral tarsal strip procedure combined with skin grafting from upper eyelid, early postoperatively. ***c*** Same patient, 6 months postoperatively

Usually monofile non-absorbable sutures, like 6-0 Prolene®, are used, but long-acting absorbable sutures, like 5-0 Vicryl®, also will work. The lateral canthal area and the bone is approached by an approximately 10 mm horizontal skin incision starting from the lateral canthus. The lower limb of the lateral canthal tendon is cut. The lateral part of the lower lid tarsal plate is completely denuded by removing the lid margin with all lash roots, the orbicularis muscle and the conjunctiva. In cases of a stretched tarsal plate causing marked laxity, a piece of tarsus can be resected. If the tarsal plate is too short to form a lateral canthal tendon, which reaches the periorbit, a periosteal flap can be formed. Such a flap can easily be dissected by incising the periosteum at the outer surface of the zygomatic bone, leaving the junction in the inner part of the arch intact. The lateral tarsal strip is sutured with a double-armed suture to either the periorbital tissue or the periosteal flap. The lateral canthus is restored with a hidden simple suture and the skin is closed.

Cicatricial Ectropion

Cicatricial ectropion is due to a shortage of skin. This can be either congenital or acquired. If the skin shortage is local it can be corrected with a Z-plasty and if it is general it should be corrected by the addition of skin either as a flap or a free graft. The treatment of cicatricial ectropion with tarsorrhaphy is useless and a waste of time. However, any additional lid laxity can be corrected with a lid shortening procedure (fig. 8).

Skin Grafting. In the periorbital area, full-thickness grafts are preferable to split-thickness grafts. Suitable donor sites are the upper eyelid (ipsi- or contralateral), the pre-or retroauricular site, and the inner side of the upper arm or the supraclavicular fossa.

The recipient site must be prepared carefully, any subcutaneous scar tissue causing traction be excised and bleeding stopped. Traction sutures help to keep the bed stretched. The graft should be as thin as possible and not oversized, but just fitted into the defect to prevent it from developing a wrinkled surface. The graft should be left undisturbed for at least 2–3 days with a moist pressure dressing applying continuous pressure onto the stretched graft.

Paralytic Ectropion

A paralytic ectropion is caused by a seventh nerve palsy and due to a lack of normal innervation of the orbicularis muscle. Failure of normal lid closure with lower lid laxity and ectropion, upper eyelid retraction and brow ptosis are the clinical signs.

Lagophthalmos can cause severe OSD with corneal epithelial defects. The risk of significant morbidity is higher in patients with peripheral seventh nerve palsy, severe lagophthalmos, missing Bell's phenomenon and reduced corneal sensibility. In these patients, if no early spontaneous restoration of facial nerve function can be observed, an early surgical intervention to improve the lid closure is indicated. This can be either a temporary tarsorrhaphy or a botulinus toxin injection. The lower eyelid primarily requires support to hold the lid up against gravity. Lower eyelid ectropion repair is best performed by a lateral tarsal strip procedure. This can by combined with a medial canthoplasty (Otis-Lee procedure) [Lee, 1951]. With this simple procedure the upper and lower lid margins medial to the lacrimal puncta are sutured together permanently. This reduces the interpalpebral distance at the medial canthus and brings the lacrimal puncta into the tear film. Lid laxity can be corrected medially with medial canthal sutures or in long-standing cases with a medial canthal resection.

Before putting weights into the upper eyelid, it is important to correct any lower lid ectropion and upper eyelid retraction first. Lid loading should be the last and not the first surgical procedure!

Floppy Eyelid Syndrome

Upper eyelid ectropion can be part of the 'floppy eyelid syndrome' [Culbertson and Ostler, 1981] which includes easily everted upper eyelids, chronic papillary conjunctivitis, and non-specific irritation. The typical patient with FES is male and obese with symptoms of foreign body sensation, morning tearing, mattering and redness, photophobia, and awakening with an everted eyelid. 70% of the patients present corneal involvement. The pathophysiology of FES is probably multifactorial with systemic mechanisms (obstructive sleep apnea) and mechanical mechanisms (sleeping preference).

Regardless of the cause, most patients benefit from surgical eyelid tightening after conservative measures such as shields, lubrication, and weight loss have failed to provide relief. To date, the literature on the surgical treatment of FES recommends pentagonal wedge resection beginning at the lateral third of the eyelid or a lateral tarsal strip procedure. These simple approaches are extremely helpful in treating OSD in such patients [Culbertson and Tseng, 1994]. In addition, a number of modifications have been described recently – including medial upper eyelid shortening – for which the reader is directed to the primary literature [Moore et al., 1996; Periman and Sires, 2002; Valenzuela and Sullivan, 2005].

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Prof. Dr. Ch. Hintschich
Augenklinik der Ludwig-Maximilians-Universität München
Mathildenstrasse 8, DE–80336 München (Germany)
Tel. +49 089 51603001, Fax +49 089 51603002
E-Mail Christoph.Hintschich@med.uni-muenchen.de

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Correction of Lid Retraction and Exophthalmos

Lelio Baldeschi

Orbital Center, Department of Ophthalmology, University of Amsterdam, Amsterdam, The Netherlands

Abstract

Exophthalmos and eyelid retraction are typical symptoms of many orbital or systemic diseases, Graves' orbitopathy being the commonest. Independently from the cause, both may increase evaporation with drying of the ocular surfaces resulting in pain, tearing, and photophobia. The structural integrity of the cornea may also be damaged with possible compromise of the visual function. Acute onset of exophthalmos and/or eyelid retraction deserves maximum attention. In order to avoid corneal decompensation and waiting for a more definitive treatment, eye lubricants, moisture chambers, swimming goggles, temporary tarsorrhaphies or blepharorrhaphies represent the measures of choice. Exophthalmos depending on neoplastic, vascular, infectious, inflammatory or malformative causes is, in the majority of cases, amenable of medical or surgical causative treatment while, for endocrine exophthalmos the commonest treatment is surgical and symptomatic and consists of orbital bone decompressions. Eyelid retraction due to active inflammatory processes can be treated medically while for persistent eyelid retraction the treatment is surgical and based on lengthening of the anterior, and/or posterior, and/or mid-eyelid lamellae. Exophthalmos and eyelid retraction due to Graves' orbitopathy, their influence on ocular surface disorders and the treatment of these conditions will be specifically analysed in this chapter.

Pathogenesis of Exophthalmos and Eyelid Retraction

Graves' orbitopathy (GO) is the commonest orbital disease accounting for greater than 85% of bilateral exophthalmos and up to 50% of unilateral exophthalmos as documented in several large series of patients. In addition, 91% of patients with GO presents eyelid retraction at some point in the clinical course of the disease [1].

Exophthalmos and eyelid retraction although typical are not exclusive of GO: many other orbital and systemic disorders can originate these signs

Table 1. Commonest causes of exophthalmos

Endocrine
Graves' orbitopathy
Orbital neoplasms
Primary tumours
Secondary tumours
Metastatic tumours
Vascular disorders of the orbit
Arteriovenous malformations
Arteriovenous fistulae
Haematomas
Orbital infections
Bacterial
Mycotic
Parasitic
Orbital inflammations
Aspecific idiopathic inflammations
Sarcoidosis
Amyloidosis
Wegner's granulomatosis
Polyarteritis nodosa
Sjögren's syndrome
Neurologic
Oculomotor nerve paralysis
Malformative
Craniofacial dysostosis

(tables 1, 2). Because of the fixed volume of the orbit determined by its bony boundary, any orbital space-occupying lesion leads to forward displacement of the eye; however, this condition which is referred to as exophthalmos can also be caused by non-space-occupying lesions such as third nerve palsy.

In the presence of a globe of normal size and position and with the gaze directed in primary position, eyelid retraction exists when white sclera is visible above (upper lid retraction) and/or underneath (lower lid retraction) the sclerocorneal limbus. In GO eyelid retraction and eyelid displacement consecutive to exophthalmos coexist. In addition to GO, eyelid retraction can have a neurologic, myogenic, mechanistic or a miscellaneous number of other aetiologies [2]. Whatever the cause of exophthalmos or eyelid retraction is, both make possible an increased evaporation of tears with drying of the ocular surfaces resulting in pain, reflex tearing and photophobia; the structural integrity of the cornea may also be damaged with possible compromise of the visual function.

Table 2. Commonest causes of eyelid retraction

Congenital	Acquired
Essential infantile bilateral eyelid retraction	Endocrine (Graves' orbitopathy)
Idiopathic unilateral infantile eyelid retraction	Neurogenic (facial nerve paralysis, aberrant regeneration of the oculomotor nerve, trigemino-oculomotor synkinesis, pseudoretraction consecutive to contralateral ptosis, damage to the supranuclear posterior commissure: pretectal syndrome, sympathetic irritation: Claude-Bernard syndrome)
Neurologic (cyclic third cranial nerve paralysis/spasm, aberrant innervation or regeneration of the oculomotorius nerve)	Myogenic (myasthenia gravis, acquired myotonia, iatrogenic: post-botulinum toxin injection)
Myogenic (congenital myotonia)	Traumatic (lacerations, chemical/thermal burns, orbital floor fracture, iatrogenic: after eyelid, orbital, squint, glaucoma or retina surgery)
Endocrine (congenital hyperthyroidism)	Inflammatory (idiopathic orbital inflammation: pseudotumour, allergic or contact dermatitis, psoriasic erythrodermatitis, ichthyosis, bullous pemphigoid)
	Metabolic (hypo-/hyper-kaliemic periodic paralysis, uremia, Cushing's syndrome)
	Pharmacologic (sympathomimetics, phenylephrine, apraclonidine, edrophonium chloride, corticosteroids, prostigmine, succinylcholine)

Independently from the aetiology, acute onset of exophthalmos and/or eyelid retraction deserve maximum attention. In order to avoid corneal decompensation and waiting for a more definitive treatment, eye lubricants, moisture chambers, swimming goggles, temporary tarsorrhaphies or blepharorrhaphies represent the measures of choice.

Depending on neoplastic, vascular, infectious, inflammatory or malformative causes, exophthalmos is, in the majority of cases, amenable of medical or surgical causative treatment while for endocrine exophthalmos the commonest treatment is surgical and symptomatic and consists in orbital bone decompressions.

Eyelid retraction due to active inflammatory processes such as allergic or contact dermatitis, psoriasic erythrodermatitis, ichthyosis, bullous pemphigoid, iatrogenic or posttraumatic scars and other similar conditions can benefit from medical therapy ranging from topical treatments to systemic antimetabolite and immunosuppressive agents. Dermatitis can be treated with topical corticosteroids; ichthyosis, psoriasis and pemphigoid with topical *trans*-retinoic acid or, when not responding to topical measures, with oral 13-*cis*-retinoic acid or systemic metotrexate, cyclophosfamide, or cyclosporine. Massages and steroid

injections can be beneficial in the treatment of recent iatrogenic or posttraumatic scars causing eyelid retraction. The treatment of stable eyelid retraction is basically surgical and mostly consists in lengthening of upper or lower lid retractors complexes. Multiple Z plasty, grafts, or flaps may also be required in order to increase the vertical length of the anterior eyelid lamella.

Owing to their high incidence, and considering that the scarce literature that links exophthalmos and eyelid retraction to ocular surface disorders almost exclusively regards GO, only dysthyroid exophthalmos and dysthyroid eyelid retraction, their influence on alterations of ocular surface and the treatment of these two conditions will be specifically analysed here.

Tear Film Profile in Graves' Orbitopathy

In GO, increased palpebral fissure width, exophthalmos, blink rate, lid lag, lagophthalmos, deficit of elevation and poor Bell's phenomenon can all be potentially connected with drying of the ocular surface. Bartley et al. [1] found a high incidence of various signs and symptoms of ocular surface disease in a cohort of 120 patients with GO during a 10-year follow-up. These included conjunctival hyperaemia (34.5%), pain or discomfort (30%), epiphora (20.9%), chemosis (23.3%), corneal staining (10.1%) and non-optic neuropathy-related loss of vision (7.2%). Although some of these findings may regress when the inflammatory component of the disease is well controlled with medical treatment, those resulting from increased exposure of the ocular surface are likely to persist.

According to the findings of Gilbard and Farris [3], in GO the damage to the ocular surface depends principally on a widened palpebral fissure which leads to increased ocular surface evaporations resulting in an elevated tear film osmolarity similar to that of keratoconjunctivitis sicca. In their series of GO patients, exophthalmos, lid lag and lagophthalmos did not correlate with ocular surface damage, and tear secretion measured by Schirmer test was not abnormal. Increased and not decreased blinking rate was found to be connected with significant ocular surface damage, but this finding was thought to be secondary to damage of the ocular surface. In Gilbard and Farris' series it was not specified whether the included patients were in the inflammatory or in the chronic phase of GO. More recently however, Khurana et al. [4] presented similar results by comparing a population of 30 patients with GO, 15 presenting a short duration and 15 a long duration of their disease, with 30 controls. Although it was not clear if the 15 patients presenting short duration of GO were or were not active, tear film pH, fluorescein staining, marginal tear strips and Schirmer test values were not different in patients and controls, in fact suggesting not abnormal tear secretion GO. Rose bengal and lissamine green staining intensity scores were

significantly higher in patients as compared to controls, indicating the presence of drying epithelial cells in early as well as in late GO patients. Also in this series, an increased blink frequency was noted in patients which was interpreted as a mechanism of incomplete compensation for decreased break-up time, although a significantly low break-up time was found only in late GO patients.

When active GO has been specifically studied, ocular surface damage correlated significantly with a reduced tear secretion, but not with increased exposure of the ocular surface or impaired up-gaze [5]. The lacrimal gland physiologically expresses the TSH receptor which, in active GO, can bind with circulating anti-TSH receptor autoantibodies contributing in fact to lacrimal gland impairment [5]. Other studies, however, have shown that also in long-lasting GO, the orbital inflammatory process has an effect on the lacrimal gland and this ultimately reflects on its function and, in turn, on tear composition [6, 7].

Although the literature concerning the ocular surface alteration occurring in GO is not extensive and far from being conclusive, the multifaceted nature of the problem is not disputed. Lacking a specific medical therapy for GO, the functional alterations of the lacrimal gland, which are subsequent to the autoimmune process affecting the whole orbit, can not be specifically cured and artificial tears remain the only medical means for relieving patients' discomfort. On the other hand, an increased palpebral fissure width, which resulted in being mainly responsible for exposure keratopathy [3] and which depends on eyelid retraction and eyelid displacement secondary to exophthalmos, is amenable of effective surgical correction.

Surgical reduction of exophthalmos and widened palpebral fissure, which are the key steps in the surgical treatment of the 'dry eye' in patients with GO, will be discussed below.

Timing of Exophthalmos and Widened Palpebral Fissure Correction in Graves' Orbitopathy

The natural course of GO is known to consist in an early dynamic inflammatory phase followed by a static postinflammatory phase, by the contrary the aetiopathogenesis of the disease remains obscure. As a consequence, a specific medical therapy does not exist. Systemic glucocorticoids and orbital radiation therapy, although effective on the inflammatory component of the disease, remain of little efficacy on exophthalmos or increased palpebral fissure width. Prompt restoration of stable euthyroidism and immunosuppression, when necessary, may decrease the duration of the dynamic phase and reverse its tendency to progress towards a more severe symptomatology. Nevertheless, a consistent amount of patients need surgery for functional reasons or aesthetic rehabilitation.

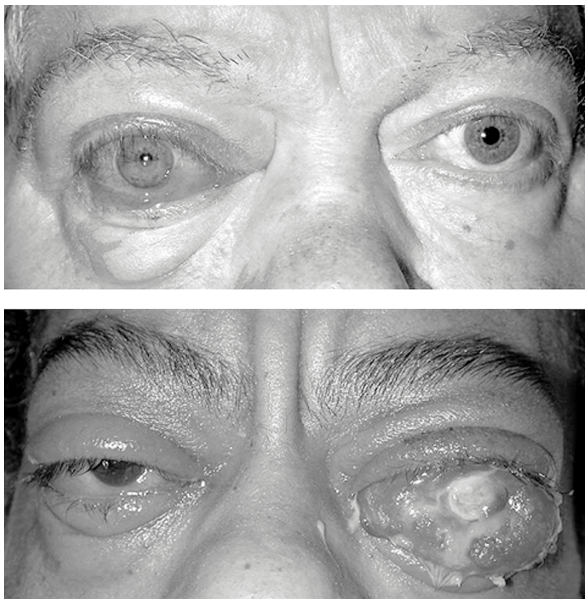


Fig. 1. ***a*** A patient affected by malignant GO presenting with an extensive fluorescein staining corneal epithelial defect involving the two inferior quadrants of the right eye. ***b*** Left eye: extreme consequences of corneal exposure in a patient affected by malignant GO who, for psychosocial reasons, sought medical assistance too late.

During the inflammatory phase, excluding minor procedures, such as temporary tarsorraphies or blepharorrhaphies, surgery consists in decompressions and it is required when systemic steroids or orbital radiotherapy fail to effectively treat two potentially blinding conditions: optic neuropathy or severe exposure keratopathy (fig. 1). During the post inflammatory phase, after a 6- to 8-month period of stable thyroid metabolism and stable orbitopathy, surgery is indicated for aesthetic, psycho-social rehabilitation and for the treatment of symptoms, such as persisting retro ocular tension or exposure keratopathy, even in presence of minimal aesthetic alterations. Depending on the severity of the symptoms, surgical rehabilitation can be more or less extensive, the full treatment consisting in decompression surgery, squint surgery, eyelid-lengthening and aesthetic eyelid and periorbital procedures.

Decompression surgery causes reduction of exophthalmos as well as reduction of upper and lower eyelid displacement [8]. It may positively influence extraocular muscle restriction, but the displacement of the soft orbital tissues caused by decompression surgery may also induce or worsen strabismus. Eventual squint surgery should therefore follow orbital decompressions but considering that vertical tropias may influence eyelid position, squint surgery should

precede any eyelid lengthening procedure. Finally, when necessary, the finishing touch can be given by aesthetic eyelid and/or periorbital surgery.

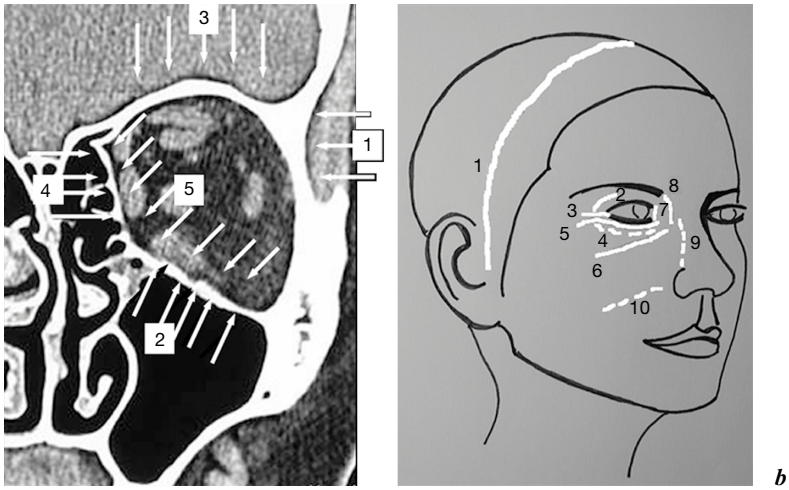
In short, surgical rehabilitation needs to respect the given order since the preceding step may influence the step that follows. In particular circumstances, exceptions are possible and the rehabilitation can be favourably sped up by carrying out more than one procedure at the same time.

Correction of Exophthalmos in Graves' Orbitopathy

The autoimmune process at the basis of GO leads to accumulation of glucosaminoglycans and collagen within extraocular muscles and orbital fat. The consequent oedema and fibrosis lead to marked swelling of the soft tissues confined within the boundary of the bony orbit with increase of intraorbital pressure leading to venous congestion, exophthalmos and other typical signs and symptoms of GO. Any surgical procedure aimed at decreasing the raised intra orbital pressure and its effects, by means of enlargement of the bony orbit and/or removal of the orbital fat is defined orbital decompression.

Orbital fat decompression was first described by Moore [9] in 1920. A mean exophthalmos reduction of 6 mm and an improvement of extraocular eye motility have been reported by Olivari [10] on a large series of patients, but the same results were not confirmed by other authors [11]. Orbital fat decompression has never reached the popularity of bone decompression due to the feared complications that may be connected with this surgical approach and which may encompass damages to oculomotor ciliary and lacrimal nerves, orbital vasculature, extraocular eye muscles, optic nerve and the eyeball itself. Recently, however, bone and fat decompression are no longer considered alternatives but had became complementary approaches concurring in tailoring the most adequate treatment to the specific patient's needs.

The history of orbital bone decompression surgery can be dated back to 1911 when Dollinger [12] first proposed orbital enlargement by removing the lateral wall for the cure of exophthalmos. Since then, various osteotomies performed via different routes and involving one or more of the other orbital walls have been proposed (fig. 2). Also in the case of bone orbital decompression, in spite of theoretical expectations, severe complications are rare in clinical practice. The most common complication of this surgical approach is consecutive strabismus, although infraorbital hypoesthesia, sinusitis, lower lid entropion, eyeball dystopia, or more rarely leakage of cerebro spinal fluid, infections involving the central nervous system, damages to the eye and optic nerve or their vasculature, cerebral vasospasm, ischemia and infarction, can occur [13]. Reactivation of GO after rehabilitative bony orbital decompression is another, recently described, rare complication [14].



a *b*

Fig. 2. ***a*** Removal of different orbital walls as proposed by: (1) Dollinger in 1911, (2) Hirsch in 1930, (3) Naffzinger in 1931, (4) Seval in 1936, and (5) Walsh and Ogura in 1957. ***b*** Common surgical routes for orbital decompression: (1) coronal, (2) upper skin crease, (3) lateral canthus, (4) inferior fornix, (3+4) swinging eyelid, (5) subciliary, (6) direct trans-lower lid, (7) transcaruncular, (8) frontoethmoidal (Lynch), (9) transnasal, and (10) transoral.

In the 1980s, when the number of orbital decompression procedures being performed began to rise, as surgery started to be undertaken not only for functional reasons but also for the aesthetic/psychosocial rehabilitation of Graves' patients [15], the antral-ethmoidal decompression by a transantral approach, as described by Walsh and Ogura [16] in 1957, was the mainstay technique [17]. The major disadvantage reported with transantral surgery was motility imbalance as high as 52% [15] and therefore alternative procedures were sought in an attempt to decrease the risk of decompression-induced diplopia. In cases of mild exophthalmos, trans-lid antral-ethmoidal decompression appeared to be a valid alternative, with a risk of iatrogenic diplopia in only 4.6% of patients [18]. For more severe exophthalmos, inferomedial decompression was used in combination with lateral decompression. Such procedures, whether performed with separate periorbital incisions or via a coronal approach, were also related with a low incidence of consecutive diplopia [16].

In 1989, Leone et al. [19], in an attempt to further reduce the effect of decompression surgery on extraocular muscle motility, proposed balancing the decompression by removing the medial and lateral orbital walls while sparing the floor. This technique, which theoretically should have minimised the risk of iatrogenic diplopia, later appeared to be connected with a higher risk for such a complication

as compared with removal of the lateral orbital wall alone or with studies in which inferomedial and three-wall techniques were described [20, 21].

Recently the lateral wall, and in particular its deeper portion, has been described as an elective zone of possible orbital volume expansion [22, 23], especially if combined with fat decompression [24]. Such a large number of variations illustrates that no single one can be considered the best. An analysis of the current literature on the argument is highly complicated due to the extreme heterogeneity of the patients included in each series, the variation applied to surgical techniques, the use of perioperative glucocorticoids, the difference in timing and modality of assessment of surgical results. Many variables can affect the results of orbital decompression: volume and location of the osteotomy, amplitude of removal or incision of the periorbita, stage of the orbitopathy at the time of surgery, orbital compliance which refers to distensibility and plasticity of the soft orbital tissues, and preoperative Hertel readings, can all play a role.

At present the removal of the orbital roof is no longer used: minimal is in fact its contribution to orbital decompression and its removal establishes a direct communication between the anterior cranial fossa and the orbital content, making possible the transmission of the pulsation of the internal carotids to the latter including the eyeball. The orbital floor, the medial and the lateral orbital walls are currently removed in the course of decompression surgery, the extension of the osteotomy being dependent on the amount of exophthalmos reduction which is to be achieved.

Traditionally the removal of the medial wall and the floor, known as inferomedial decompression, is used to cure mild to moderate degree of exophthalmos and the lateral wall removal is added when more severe degrees of exophthalmos impose a greater decompression effect. Recently, in a further attempt to minimize the risk of iatrogenic strabismus, it was proposed to start decompression surgery by removing the lateral orbital wall and eventually to increase the effect of decompression by removing the orbital fat or the medial orbital wall leaving the removal of the floor as the very last option [22].

A number of different surgical routes can be used for decompression purposes, hidden incisions are to be preferred to visible trans-cutaneous approaches, such as Lynch or the mid-lower lid incisions which produce exposed scars. Typical ophthalmological routes to inferomedial decompression, are the transcaruncular and the transinferior fornix (fig. 3a). The latter also permits lateral decompression, which however is easier if the fornix incision, is coupled with an incision at the lateral canthus. That in fact permits the lower lid to swing outwards and gives a wide access to the lateral wall. This approach first described by McCord [25] in 1981 and known as ‘swinging eyelid’ is at present widely adopted – it gives an excellent exposure of medial inferior and lateral orbital walls and leaves an inconspicuous scar at the lateral canthus. As an alternative the lateral orbital wall can also be approached by means of a separate upper skin crease incision. The coronal

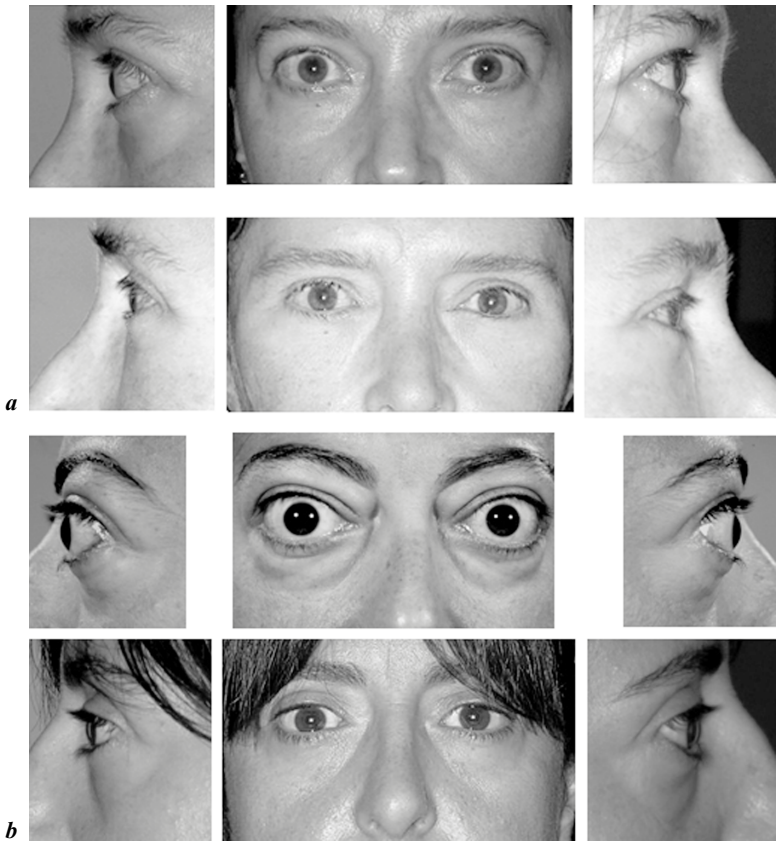


Fig. 3. Preoperative (upper) and postoperative (lower) aspect of patients affected by GO presenting with (***a***) mild exophthalmos treated with inferomedial orbital decompression by inferior fornix approach, and (***b***) severe exophthalmos treated with three-wall orbital decompression by coronal approach.

incision (fig. 3b) implies a more extensive surgical dissection if compared with the swinging eyelid approach or other periorbital incisions but, in turn, provides access to all the orbital walls and the best exposure of the deep lateral orbital wall, which represents an elective zone for orbital expansion. The coronal approach can be performed also in those patients with GO presenting remarkable periorbital swelling or conjunctival chemosis, which may adversely interfere with periorbital incisions. It is the elective approach for minimising the number of periorbital incisions which are necessary to accomplish the full rehabilitation and this can be particularly advantageous in young or black patients. In addition to this, the coronal incision is to be used when the lateral wall including the lateral orbital rim is

completely removed. The coronal approach implies the elevation of a subperiosteal plane which, differently than with direct periorbital incision, does not disrupt the anatomical planes of the periorbital region: depressed disfiguring iatrogenic scars due to adhesions between deep and more superficial layers are consequently infrequent. The swinging eyelid approach is to be preferred to the coronal approach in unilateral cases or in male patients with impairing baldness. The swinging eyelid or the transinferior fornix approach can be associated with transconjunctival lower lid blepharoplasty or with lower lid-lengthening procedures speeding up the surgical rehabilitation of GO.

Orbital Decompression by Coronal Approach: Surgical Technique

A coronal incision is made with a No. 10 blade from ear to ear, 3–4 cm behind the hairline. Bleeding from the wound edges is controlled with Raney scalp clips. In the central portion of the skull a subperiosteal plane is created by blunt dissection and laterally a surgical plane is bluntly developed between the deep and the superficial temporalis fascia. Laterally and inferiorly, where the deep temporalis fascia divides into a deeper and a more superficial layer to enclose Yasargil's superficial temporal fat pad, the surgical dissection is carried out directly against the deeper division of the fascia. The forehead flap thus created is then turned down in order to expose the superior and lateral orbital rims. The supraorbital nerve is set free by chiselling its bony foramen when present and the periorbita, including the trochlea, is dissected off the orbital bones. After this, the temporalis muscle is dissected from its anterior origin with a No. 10 blade and periosteal elevators, leaving sufficient tissue for suturing at the end of surgery. In this way the lateral orbital wall is exposed. A small osteotomy is chiselled behind the lateral orbital rim, then it is extended inferiorly up to the inferior orbital fissure, superiorly and posteriorly up to the dura of the middle cranial fossa by means of bone-nibbling rongeurs and a surgical high-speed drill equipped with a cutting-burr or a diamond-burr tip. During surgical manoeuvres the soft orbital tissues and the temporalis muscle are retracted and protected with malleable orbital retractors.

When small spots of dura are exposed through the thin inner cortical bone of the greater wing of the sphenoid, bone removal is stopped as any further removal may increase the risk of complications without substantially contributing in creating space for orbital expansion. After this a Frazier suction tip is used to fracture the delicate bone of the medial orbital wall and the floor and Blakesly forceps No. 1 and No. 2 are used to remove bony fragments and mucosa of the sinuses. The bulla ethmoidalis beneath the frontoethmoidal suture is opened towards the orbit from the posterior lacrimal crest up to the orbital apex, and then the orbital floor medial to the infraorbital canal is removed from 0.5 cm behind the inferior orbital rim up to the posterior wall of the maxillary sinus. The posterior two thirds of the maxillary ethmoidal strut are removed creating a wide

antrostomy, while the anterior one third of the strut is left intact in order to prevent globe displacement and the possibility of medial entropion or hypoglobus. The removal of the most posterior portion of the maxillary ethmoidal strut together with the orbital process of the palatine bone give access to the sphenoidal sinus increasing the possibility of apex decompression when necessary.

Finally, the periorbita is incised in order to promote maximal prolapse of the soft orbital tissues into the newly created spaces, the temporalis muscle is sutured back into position with 4–5 interrupted 2/0 Mersilene sutures and, after the insertion of a 3.3-mm diameter end-perforated wound drain into each temporalis fossa, the scalp incision is closed with iron staples.

Orbital Decompression by Transinferior Fornix/Trans Caruncular Swinging Eyelid/Upper Skin Crease Approach: Surgical Technique

After the exposure of the inferior fornix by mean of a Desmarres retractor and a malleable orbita retractor, the conjunctiva and lower lid retractor complex are transsected en bloc with a Colorado needle and the inferior orbital rim is exposed. At that level the periorbit is incised and the medial and inferior orbital walls exposed by developing a subperorbital plane and the bony orbit. In order to obtain the best possible exposure of the medial wall, the bony insertion of the inferior oblique muscle may be detached without consequences, and the conjunctival incision extended upwards, laterally to the caruncle. A separate incision lateral to the caruncle (trans caruncular approach) can possibly be used to address the medical orbital wall when the floor is not to be removed. After this the medial orbital wall and the orbital floor are addressed as for orbital decompression through a coronal approach. With the transinferior fornix approach, however the wide exposure of the orbital floor permits an easy removal of the bony infraorbital canal and the floor lateral to it. If more decompression is needed the lateral wall can be removed starting the osteotomy from the anterior portion of the inferior orbital fissure by means of bone-nibbling rongeurs and by means of a surgical high-speed drill equipped with a cutting-burr or a diamond-burr tip. In order to aid the removal of the upper part of the lateral orbital wall and in particular its anterior-superior portion, a lateral canthotomy and lysing of the inferior limb of the lateral canthal tendon can be performed converting, infact, the pure transinferior fornix approach into a swinging eyelid approach. An upper skin crease incision can also be used in combination with the pure inferior fornix or with the swinging eyelid approach if a wider exposure of the lateral orbital wall is to be attained.

The removal of the lateral orbital wall can be carried out up to the dura as described for the coronal approach and as for coronal approach at the end of the procedure the periorbita is incised in order to promote maximal prolapse of the orbital tissues into the newly created spaces. The canthotomy is closed in layers

as for a regular canthopexy procedure, the upper lid crease incision only needs approximation of the skin edges while the inferior fornix incision does not need any suturing. Transinferior fornix, swinging eyelid, trans caruncular, and upper skin crease approaches can all be used to remove orbital fat too.

Correction of Lid Retraction in Graves' Orbitopathy

In GO, upper and lower lid retraction are due to a combination of inflammation, fibrosis, adrenergic stimulation and restriction of vertical recti muscles. Exophthalmos also contributes in increasing the eyelid aperture by displacing either the upper or the lower lid. Recently the influence of decompressive surgery which leaves the lower lid retractors undisturbed has been reported to similarly contribute to the reduction of upper and lower lid displacement [8]. Correction of upper or lower lid retraction implies recession of the lid retractors. Spacers are not essential for upper lid-lengthening procedures or for the treatment of mild degrees of lower lid retraction that can benefit from free recession of lower lid retractors and lateral canthoplasty. The surgical correction of more severe forms of lower lid retraction requires interposition of spacer grafts between the tarsus and the recessed retractors to provide height and the necessary stiffness to support the lower lid against gravity. A number of autologous, homologous, xenogenic and synthetic materials have been used but the optimum spacer remains controversial. Among biological materials, ethanol-preserved donor sclera has been widely used, but it is of limited availability, carries a risk of transmission of infections and it is associated with recurrent retraction due to graft absorption and fibrosis. Upper lid tarsus is an optimal material but its use is limited by the scarce possibility of harvesting at the donor site. The stiffness of cartilage grafts may alter eyelid contour and adversely interfere with eyelid motility and down-gaze, the same applies to porous polyethylene sheets. Other synthetic materials such as polytetrafluoroethylene or polyester mesh carry the risk of extrusion. An autogenous hard palate mucosal graft is relatively easy to obtain, is similar to lower lid tarsus in terms of contour, thickness and stiffness, has a mucosal surface, has no risk of rejection and undergoes minimal shrinkage following grafting. Ophthalmic complications of hard palate mucosal grafting are uncommon and usually limited to transient corneal abrasion; morbidity at the donor site encompasses secondary haemorrhages, retarded healing due to oral infections, pain, and rarely oronasal fistula [26].

Homologous acellular dermal matrix is a processed donor tissue with appropriate consistency for posterior lamella augmentation. One surface is cut through the dermis, the other has an intact basement membrane which provides a structural template that guides conjunctival epithelial migration and repopulation. Homologous acellular dermal matrix represents a valid alternative to hard

palate mucosal graft, its use reduces surgical time and eliminates the problem of donor site morbidity, but currently is not available in Europe.

In short, at present, hard palate mucosal graft providing structural and epithelial elements represents the best choice for posterior lamella augmentation in lower lid lengthening, although it may be associated with the disadvantage of not negligible donor site morbidity. In light of this and considering that donor site morbidity may be minimised by meticulous surgical technique and appropriate postoperative care, harvesting and implantation techniques will be given and commented below.

The treatment of persistent upper eyelid retraction is surgical and by far less predictable than that of lower lid. The medical therapy of upper lid retraction with α-blockers eye drops is scantly effective and topical or systemic therapy with post-ganglial adrenergic blocker drugs such as guanethidine is connected with several undesirable side effects. Botulinum toxin can also be an option, its effect however is limited in time and multiple injections are required. With botulinum toxin temporary under or over correction can occur. Deficit of elevation and paralysis of the orbicularis muscle may also be possible, undesirable complications in GO patients who are at risk for corneal exposure.

Considering that upper eyelid lengthening is one of the last steps of the long-lasting and somewhat exhausting surgical rehabilitation of patients with GO and that, although several surgical techniques for its cure have been proposed, an elective method is lacking, it is strongly advisable to use the quickest and simplest possible technique [27].

In keeping with this, a quick, systematic approach suitable for every degree of upper eyelid retraction with or without alteration of eyelid contour such as lateral or medial peaks is given in table 3 and the related surgical techniques will be described and commented below.

Lower Lid-Lengthening Surgical Procedure

Hard Palate Mucosal Graft Harvesting

Prior to surgery a careful in-office inspection of the donor site is mandatory for a correct selection of candidates, and at surgery the location of the donor site is fundamental in order not to bare the periosteum or being obliged to apply excessive diathermy as this may cause bone necrosis. Prior to surgery, any lesion suspected for malignancy should be biopsied; oral candidiasis in immunocompromised patients should be cured since postoperative granulation at the donor site can be delayed; the presence of exostosis such as torus palatinus or prominent palatal roots of teeth should be considered since the thin overlying mucosa of these areas may lead to unwanted periosteal or root damage at surgery. The

Table 3. A simple, systematic approach to correction of upper eyelid retraction

Degree of upper lid retraction	Surgical technique
Mild (≤3 mm)	Sutureless transconjunctival Müllerectomy
Moderate to severe (>3 mm)	Free en-bloc recession of conjunctiva-levator complex by anterior or sutureless posterior approach

presence of a bifid uvula or a muscular diastasis of the soft palate can be an important clue to an underlying bony palatal cleft that is not otherwise evident and which represents an absolute contraindication for mucosal harvesting. However, the presence of small isolated clefts of the bony palate may escape clinical detection due to the presence of an overlying intact mucosa and to their asymptomatic nature. Besides iatrogenic damage to the bone and periosteum and infectious causes, fistulas may also develop from such a malformation [25]. At surgery the donor site should be placed between the median raphe and the alveolar process and not extended posteriorly behind the first molar. At this level the submucosa is well defined and partial thickness mucosal dissection can be easily carried out anteriorly to the neurovascular bundle emerging from the greater palatine foramen. The latter can in fact be located medially to the third or to the second molar. Areas close to the gingival border or to the median raphe are not suitable as donor sites since the risk of bone necrosis secondary to periosteal damage is much higher here: at these levels the mucosa is in fact directly attached to the periosteum without interposition of the submucosa (fig. 4a).

Although hard palate mucosal grafts can be harvested under local anaesthesia, general anaesthesia is to be preferred for the patient's comfort. The mouth is open with a Jonson mouth spreader. The hard palate is dried and a dermographic pen is used to mark the graft size that should be about twice the degree of lower lid retraction in width. Submucosal infiltration with lidocaine 2% with epinephrine 1:80,000 is then carried out to aid haemostasis and dissection. The harvesting is carried out first using a No. 15 Bard-Parker blade to incise the marked area, then with a disposable angled keratotome and surgical forceps to dissect the submucosal plane and elevate the graft. The use of suction and of a tongue depressor by the surgical assistant will greatly aid in this phase. Excessive diathermy should be avoided at all times, and at the end of surgery, in order to control oozing at the donor site a rolled vaseline or haemostatic gauze can be inserted into the mucosal defect and kept in place with a previously prepared palatal shell, digital pressure on the shell can also be applied for some time and fibrin glue used if necessary. Bleeding from major vessels can be controlled with injections of local anaesthetic within the bleeding area or into the palatine foramen or with ligation if necessary.

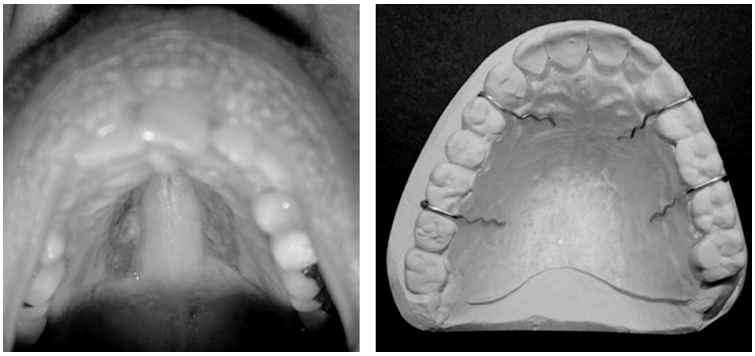


Fig. 4. ***a*** Location of the donor sites of the hard palate mucosal grafts. ***b*** A custom-made acrylic palatal stent.

The mucosa of the graft consisting of epithelium and thick collagenous lamina propria is then prepared for the recipient site by removing the fatty submucosa.

Large spectrum systemic antibiotics and antiseptic mouthwashes are recommended for 1 week after surgery. Soreness at the donor site for a few days after surgery is common especially during eating; custom-made acrylic palatal stents which aids haemostasis and favourite granulation can increase the patient's comfort (fig. 4b).

Lower Lid Lengthening (fig. 5a)

Topical oxybuprocaine HCl 0.4% drops are applied to eye, then 0.5–1 ml of lidocaine 2% with epinephrine 1:80,000 is administered subconjunctivally along the inferior margin of the tarsal plate and 0.25 ml of the same anaesthetic is administrated subcutaneously into the centre of the lower lid. A 5-0 silk traction suture is placed in the centre of the lower lid along the eyelid margin and the eyelid is everted over a Desmarres retractor. An infratarsal incision is done for the whole length of the tarsal plate with a No. 15 Bard-Parker blade and the conjunctiva lower lid retractor complex transsected en bloc. A preseptal plane is then bluntly developed in order to adequately recess the lower lid retractors and conjunctiva. Bleeding is easily controlled with bipolar diathermy (fig. 6a). After this a 6.0 absorbable suture is used to suture the hard palate mucosal graft into place, between the border of the conjunctiva lower lid retractors complex and the inferior border of the tarsal plate, the mucosal surface facing the eyeball (fig. 6b). Multiple steri-strips are applied on the lid skin in order to immobilize lid and graft in a correct position for a few days after surgery. No bandage is applied, but ice compresses are recommended for a few hours after surgery. Artificial tears are also prescribed to implement patient's comfort.

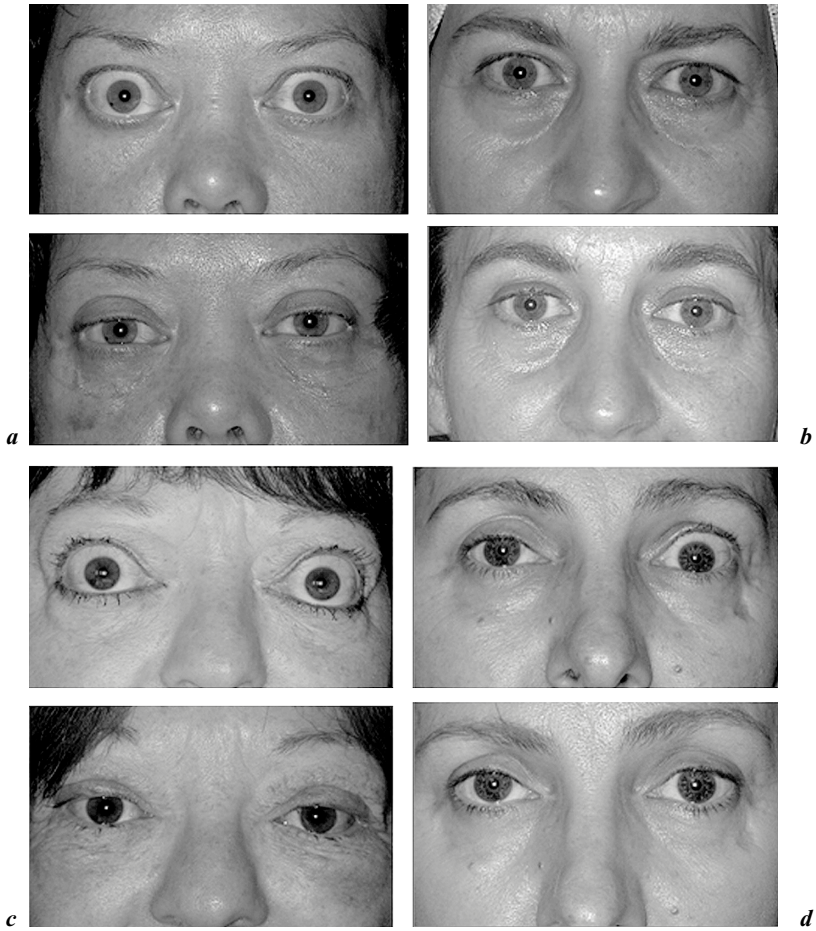


Fig. 5. Preoperative (upper) and postoperative (lower) aspect of patients affected by GO presenting with different degrees of eyelid retraction and treated with: (***a***) bilateral free en-bloc recession of conjunctiva-levator complex by anterior approach and lower lid lengthening by mean of hard palate mucosal graft; (***b***) bilateral sutureless transconjunctival Müllerectomy; (***c***) bilateral free en-bloc recession of conjunctiva-levator complex by sutureless posterior approach, and (***d***) unilateral (left) free en-bloc recession of conjunctiva-levator complex by sutureless posterior approach.

Upper Lid Lengthening

Sutureless Transconjunctival Müllerectomy (fig. 5b)

Topical oxybuprocaine HCl 0.4% drops are applied to the eye, then 0.25 ml of lidocaine 2% with epinephrine 1:80,000 is administered subcutaneously into

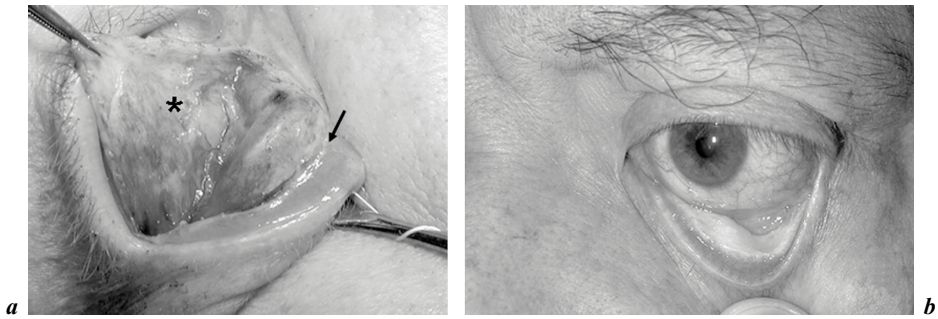


Fig. 6. ***a*** A lower lid everted over a Desmarres retractor in the course of a lower lid-lengthening procedure: the conjunctiva lower lid retractor complex (star) had been recessed from the inferior border of the tarsal plate (arrow). ***b*** Aspect of an hard palate mucosal graft a few months after a lower lid-lengthening procedure: the graft is integrated between the conjunctiva lower lid retractor complex and the inferior border of the tarsal plate.

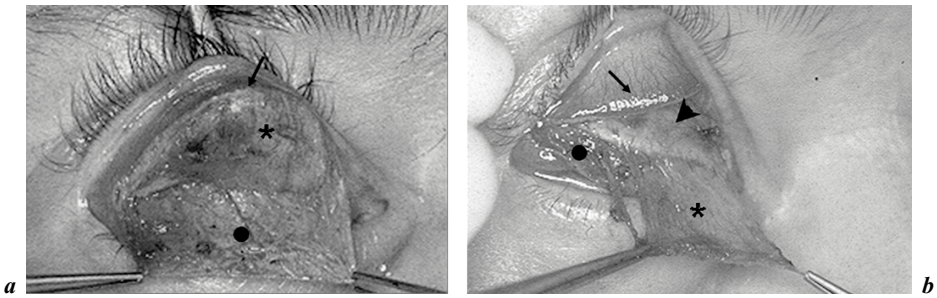


Fig. 7. An upper lid everted over a Desmarres retractor in the course of a sutureless transconjunctival Müllerectomy procedure. ***a*** The conjunctiva (dot) had been incised at the level of the superior border of the tarsal plate (arrow) and separated from the underlying Müller muscle (star) up to the superior fornix. ***b*** Müller's muscle (star) which had been incised at the level of the superior border of the tarsal plate (arrow) and separated from the underlying levator aponeurosis (arrow head) is ready to be removed once its proximal insertion will be severed. At the end of the procedure the conjunctiva (dot) does not need to be sutured back into position.

the centre of the upper eyelid. A 5-0 silk traction suture is placed in the centre of the upper eyelid along the eyelid margin and the eyelid everted over a Desmarres retractor. Then 0.5 ml of lidocaine 2% with epinephrine 1:80,000 is injected close to the superior tarsal border subconjunctivally and between Müller's muscle and the levator aponeurosis over the whole length of the eyelid. A high-temperature battery-powered cautery is used to incise the conjunctiva along and just above the superior tarsal border. After this the conjunctiva is separated from

Müller's muscle first with sharp then with blunt dissection. In this way the superior fornix is approached (fig. 7a). Müller's muscle is then grasped with fine-toothed forceps at the lateral aspect, the tension exerted with the Desmarres retractor is relieved, and a plane can easily be developed between Müller's muscle and the inferior surface of the levator aponeurosis by spreading the blade of blunt pointed straight scissors. The distal insertion of the muscle is gently cauterised, afterwards severed with scissors. The proximal insertion is then similarly addressed. At the end of the procedure the conjunctiva is not sutured (fig. 7b).

Any possible lateral or medial alteration of the eyelid contour is treated by means of weakening the levator aponeurosis at the level of the peak. This is achieved by means of several small horizontal incisions which transform the aponeurosis under consideration in a kind of network increasing in fact its vertical length. At the end of the procedure the traction suture which was placed in the centre of the eyelid is removed. No bandage is applied but ice compresses are recommended for a few hours after surgery. Artificial tears are prescribed to implement the patient's comfort.

Sutureless transconjunctival Müllerectomy is an effective procedure for the cure of mild degree of upper eyelid retractions up to 2–3 mm. It does not interfere with the position of the skin crease since surgical dissection is carried out under the levator aponeurosis. It takes around 10 min/eyelid, reintervention for under- or overcorrection are rare and usually due to surgical mistakes as incomplete excision of Müller's muscle or damage to the aponeurosis of the levator muscle. Tear secretion may be reduced after Müllerectomy by the conjunctival approach. Nevertheless, the clinical risk of dry eye is low, and counterbalanced by the usually good functional and cosmetic results of the procedure [28].

Free En-Bloc Recession of Conjunctiva-Levator Complex by Anterior Approach (Blepharotomy) (fig. 5a)

This technique was developed by Leo Koornneef one of the most bright minded and talented surgeons in the field of orbit and ophthalmic plastic surgery of the 1980s and 1990s. Because of his untimely death he was unable to publish his idea, nevertheless he could present it at meetings and teach it to several of his fellows including myself.

Topical oxybuprocaine HCl 0.4% drops are applied to the eye, the skin crease is lined with a surgical skin marker. Then 0.5–1 ml of lidocaine 2% with epinephrine 1:80,000 is injected close to the superior tarsal border subcutaneously and between the orbicularis muscle and levator aponeurosis over the whole length of the eyelid.

An incision is made along the line previously drawn at the level of the upper skin crease through the skin-orbicularis layer using a No. 15 Bard-Parker blade. Then further dissection is carried out with spring scissors in order to expose the levator aponeurosis and the orbital septum. The orbital septum is

opened along the whole length of the eyelid. After this, an en-bloc, full-thickness levator aponeurosis-Müller's-conjunctiva incision is carried out just above the upper border of the tarsal plate: the levator-conjunctiva complex is grasped with fine-toothed forceps in the central portion of the upper lid, and after a gentle localised cauterisation, spring scissors are used to start the incision as a buttonhole. Then the first incision is extended laterally and medially preceded by gentle cauterisation of the levator-conjunctival complex. If a lateral flare is present the deformity is corrected by means of a graded vertical cut through the levator-conjunctiva complex at the level of the lateral horn of the aponeurosis.

The desired degree of lengthening is checked, against gravity, by closing the skin with a temporary suture positioned in the centre of the lid and bringing the patient to a sitting position. At surgery, a couple of millimetres of overcorrection are advisable at surgery in order to compensate for postoperative retraction. When the desired level is obtained, a careful inspection of the wound is carried out and any bleeding point cauterised. Finally, the blepharotomy is closed by carefully suturing the skin only, with a running interlocked 6–0 Dermalon suture which should stay in place for 1 week. No bandage is applied but ice compresses are recommended for a few hours after surgery (fig. 8).

Free En-Bloc Recession of Conjunctiva-Levator Complex by Sutureless Posterior Approach (figs 5c, d)

Topical oxybuprocaine HCl 0.4% drops are applied to the eye, then 0.25 ml of lidocaine 2% with epinephrine 1:80.000 is administered subcutaneously into the centre of the upper eyelid. A 5-0 silk traction suture is placed in the centre of the upper eyelid along the eyelid margin and the eyelid everted over a Desmarres retractor. Then 0.5 ml of lidocaine 2% with epinephrine 1:80,000 is injected close to the superior tarsal border between levator aponeurosis and orbicularis muscle along the whole length of the eyelid. After a gentle localised cauterisation, spring scissors are used to start a buttonhole incision through the conjunctiva-levator complex in the central portion of the everted eyelid. Through the buttonhole incision, by spreading the blades of blunt spring scissors, a plane is easily developed between the orbicularis muscle and the anterior surface of the levator aponeurosis. Then the buttonhole incision is extended laterally and medially; in order to minimize bleeding, gentle cauterisation of the conjunctiva-levator complex that is to be severed always goes before any extension of the incision. The incision is carried out just above the upper margin of the tarsal plate in bilateral cases or at a higher level in monolateral upper lid retraction. In this way, in monolateral cases, the skin insertion of the levator aponeurosis is left undisturbed, the skin crease does not rise after surgery and symmetry with the contralateral side is preserved (fig. 5d).

The levator aponeurosis and orbital septum are bluntly separated from the orbicularis muscle in order to promote recession of the conjunctiva-levator complex. If

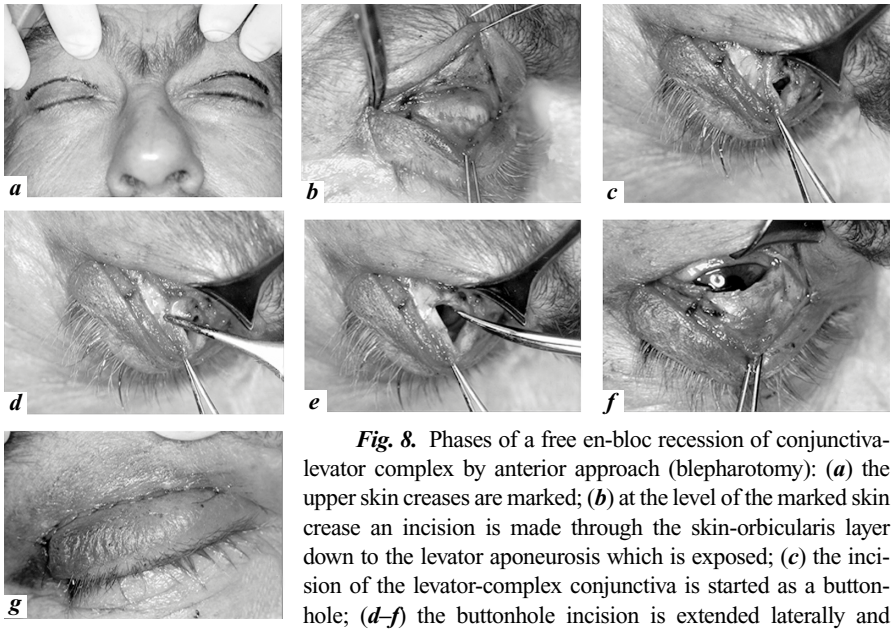


Fig. 8. Phases of a free en-bloc recession of conjunctiva-levator complex by anterior approach (blepharotomy): (***a***) the upper skin creases are marked; (***b***) at the level of the marked skin crease an incision is made through the skin-orbicularis layer down to the levator aponeurosis which is exposed; (***c***) the incision of the levator-complex conjunctiva is started as a buttonhole; (***d–f***) the buttonhole incision is extended laterally and medially preceded by gentle cauterisation of the levator-complex conjunctiva since when the desired degree of upper lid lengthening is achieved; (***g***) at the end of the procedure the skin is carefully sutured in order to avoid fistulas.

a lateral flare is present, the deformity is addressed as for the anterior approach. Also with the posterior approach, eyelid level and contour are repeatedly checked, against gravity, by bringing the patient to a sitting position since when the desired lengthening is achieved. A couple of millimetres of overcorrection at surgery are again advisable in order to compensate for the expected postoperative retraction.

Before the end of the procedure a careful inspection of the wound is carried out and eventual bleeding point cauterised. Finally, the traction suture which was placed in the centre of the eyelid is removed. No bandage is applied but ice compresses are recommended for a few hours after surgery. Artificial tears are prescribed to implement the patient's comfort (fig. 9).

Free en-bloc resection of conjunctiva-levator complex performed via an anterior or a sutureless posterior approach is an effective technique for the treatment of medium to severe degrees of upper lid retraction. The results are however not always predictable and reintervention may be necessary. Several intraoperative factors may affect the setting of the upper eyelid height, their consideration may aid in increasing success. Intravenous sedatives interfere with

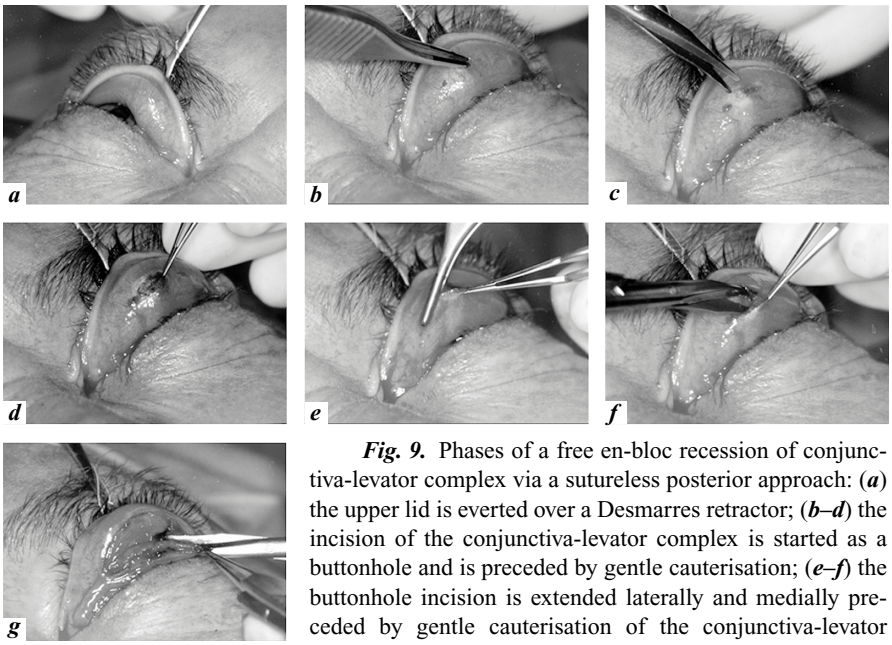


Fig. 9. Phases of a free en-bloc recession of conjunctiva-levator complex via a sutureless posterior approach: (***a***) the upper lid is everted over a Desmarres retractor; (***b–d***) the incision of the conjunctiva-levator complex is started as a buttonhole and is preceded by gentle cauterisation; (***e–f***) the buttonhole incision is extended laterally and medially preceded by gentle cauterisation of the conjunctiva-levator complex, and the latter is recessed since when the desired upper lid lengthening is achieved; (***g***) if a lateral flare is present the deformity is corrected by means of a graded vertical incision through the conjunctiva-levator complex at the level of the lateral horn of the aponeurosis.

the alertness of the patient and with his collaboration in setting eyelid position, thus these drugs should be used only when it is strictly necessary. Povidone-iodine is an adrenergic-blocking agent. Preoperative irrigation of the conjunctival sac with this solution will result in a paralysis of Müller's muscle and should therefore be avoided. Paralysis of levator and orbicularis muscle induced by local anaesthetic and the contraction of Müller's muscle induced by local anaesthetics containing epinephrine are variables that may interfere with the position of the upper eyelid. These variables can be partially controlled if the dose of anaesthetic, its concentration of epinephrine, the sites and the pressure of injection are maintained constant. In order to include the effect of gravity on eyelid height, this should be set by bringing the patient to a sitting position.

The anterior approach may be more desirable to many surgeons since it is the more common technique for ptosis surgery. With this approach, particular attention should be paid to the suture of the skin in order to avoid the risk of postoperative fistulas. The posterior approach cannot be performed in extreme degrees of retraction

in which the tarsus cannot be everted, but it is the elective treatment in dark-skinned patients in which an unpleasant scar may result from an anterior approach.

A full-thickness incision of conjunctiva-levator complex may easily create a flat eyelid contour, if dissection is carried out too far medially. Careful medial dissection also prevents possible nasal droops that are often difficult to be corrected. The graded incision of the lateral horn of the aponeurosis in the case of lateral flare should be vertical or rather parallel to the ductules of the lacrimal gland to avoid any damage to these structures.

In none of the three aforementioned techniques is the conjunctiva sutured at the end of surgery. This prevents possible suture-related corneal erosions and leaves a natural drainage with reduction of postoperative ecchymosis. As previously mentioned, pressure bandages are not applied after surgery and no particular treatments except ice compresses and elevation of the head at sleeping time are required in the immediate postoperative period. In the case that after surgery the operated eyelid or a part of it begins to retract, the patient should be instructed to massage the lid downward while looking upward in order to maintain the eyelid at the physiological position. In the case of posterior approaches, vigorous massages may be started soon after surgery while in the case of anterior approach they must be delayed for at least 2 weeks, in order to avoid dehiscence of the surgical wound and possible fistulas.

Conclusions

GO is the commonest cause of exophthalmos and eyelid retraction. These two aesthetic and functional disabling conditions are amenable to effective surgical treatment. Relatively simple techniques can be used to correct eyelid retraction while more elaborated procedures are required to treat exophthalmos and any possible associated alteration of the ocular surface.

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Lelio Baldeschi, MD
Room D2–436, Orbital Center, Department of Ophthalmology
Academic Medical Center, University of Amsterdam
Meibergdreef 9, NL–1105 AZ Amsterdam (The Netherlands)
Tel. +31 20 566 3680, Fax +31 20 566 9053, E-Mail l.baldeschi@amc.uva.nl

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Lacrimal Drainage Surgery in a Patient with Dry Eyes

Geoffrey E. Rose

Moorfields Eye Hospital, London, UK

Abstract

The dry-eyed patient has both inadequate surface wetting, and a severe inability to clear the ocular surface of extrinsic debris, lid-margin bacteria (and their toxins), and the intrinsic inflammatory mediators secreted from the inflamed conjunctival surface. Tear evaporation compounds the problem of impaired production, this leading to significant concentration of inflammatory mediators on the abnormal ocular surface – this concentration being even greater where tear drainage is impaired. Nasolacrimal duct obstruction is, moreover, associated with a backwash of toxic debris from the lacrimal sac and, in the patient with dry eye, this backwash exacerbates an already compromised ocular surface. Surgery to re-establish tear drainage and eliminate the reservoir within the lacrimal sac may, therefore, improve the ocular status of patients with dry eye: many patients will benefit from external dacryocystorhinostomy, this being combined with retrograde canaliculostomy where there is proximal canalicular blockage. Secondary placement of a canalicular bypass tube may be required where these procedures have failed and tear drainage is needed. Where there is no risk of ocular surface toxicity due to complete stasis of the tear lake, the canaliculi can be ablated with thermal coagulation or canalicular excision. Rarely required as a primary procedure, dacryocystectomy may be used where dacryocystitis occurs in the presence of long-established canalicular occlusion.

Although incorrect, it is a commonly held view that the patient with true dry eye – that is, a lack of aqueous tear production – should never require surgery to the lacrimal drainage pathway, apart from canalicular or punctal occlusion to preserve fluid on the ocular surface.

Ocular surface health – particularly that of the hydrophobic corneal epithelium – is dependent upon two main factors: First, an adequate precorneal tear film that requires not only secretion of the correct proportions of surface water, mucus and oil, but also the regular downward sweep of the upper lid that evenly spreads these various components across the upwardly-moving cornea

during the blink cycle. Secondly, the removal of ocular surface debris that is achieved by the continuous flow of tears from lateral to medial across the ocular surface, by the dilution of the tear lake with new secretion, and by removal of debris through tear drainage.

Failure of lacrimal drainage will prevent this physiological cleansing of the ocular surface and thereby lead to an accumulation of noxious substances within the tear film; this failure of clearance being exacerbated by concentration of retained surface debris by evaporation from the stagnant tear lake. The noxious substances may be extrinsic or intrinsic: Extrinsic factors include external allergens (such as pollens or dust mites) and external physical or chemical irritants, such as irritant fumes or dusts. Intrinsic factors include the antigens from commensal bacteria (especially staphylococci) on the lid margins or in meibomian secretions, and the inflammatory mediators that spill onto the ocular surface from the chronically inflamed conjunctiva of the dry eye. The inflammatory load on the ocular surface is particularly great in a dry eye without tear drainage – not only because of their lack of removal and their concentration by tear-film evaporation, but also because the poor environment is easily exploited by periocular commensal bacteria which, in turn, proliferate and markedly exacerbate the already significant chronic conjunctivitis [1–3]. A much more severe inflammatory and infective load – often with unusual bacterial flora – can arise where nasolacrimal duct occlusion is present, with transcanalicular wash-back of debris from the lacrimal sac into the tear film (a so-called 'volume' sign [4]). Although canalicular occlusion alone will stop wash-back of this infective and inflammatory debris, such occlusion risks a severe dacryocystitis unless occlusion is preceded by dacryocystectomy or dacryocystorhinostomy (DCR).

Rational Management of the Lacrimal Drainage System in Dry-Eyed Patients

Where occlusion of the lacrimal drainage puncta or canaliculi occurs as part of the underlying disease causing dry eye (for example, with mucous membrane pemphigoid or after Stevens-Johnson syndrome; fig. 1), lacrimal surgery is required only rarely. However, despite intensive treatment with preservative-free anti-inflammatory and antibacterial drops, some of these patients develop such a severe toxic response that the ocular surface is improved only by establishing free drainage of the inflammatory mediators. This type of patient typically requires external DCR with retrograde canaliculostomy [5] or with primary or secondary placement of a glass Jones' canalicular bypass tube [6].

Where the patient with a dry eye and patent tear drainage pathways needs preservation of ocular surface fluids, consideration should be given to canalicular

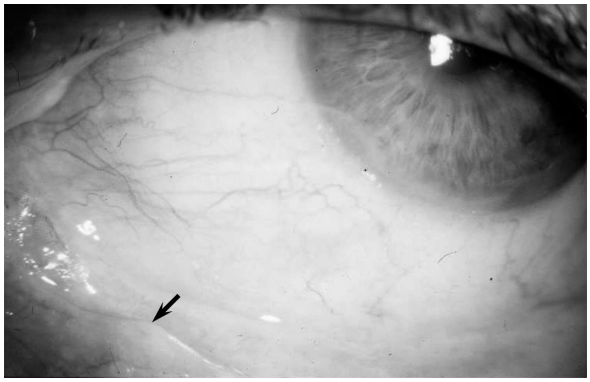

Fig. 1. Occlusion of upper and lower (arrow) lacrimal drainage puncta due to cicatricial conjunctival disease arising from chronic topical ocular medication. Squamous metaplasia and the loss of plica semilunaris and caruncular structure are readily evident.

occlusion. Whilst there are many commercially available plastic plugs for occluding either the puncta or canaliculi, the foreign surface of such devices inevitably gathers a gross biofilm (particularly in the already disadvantaged ocular environment of the dry eye) that can only exacerbate the toxic changes on the diseased ocular surface. If such patients require occlusion of outflow, this should first be tested by a reversible occlusion of both the upper and lower canaliculi – with punctal plugs or self-dissolving (collagen) canalicular plugs – to check that the ocular surface disease is not worsened by the loss of tear-film outflow: where all is well, canalicular occlusion by thermal cautery will succeed in almost all patients, but excision of the canalicular ampulla may be needed where this fails.

To reduce 'wash-back' of toxic debris from the lacrimal sac into the tear lake, patients with nasolacrimal duct occlusion should all undergo DCR; the absolute cure of wash-back being – in practical terms – achievable with external DCR and anterior ethmoidectomy [4]. Although dacryocystectomy would also eliminate wash-back, with the apparent benefit of occluding outflow, a complete absence of fluid drainage from the ocular surface might – as already discussed above – actually worsen the dry eye. Rather than primary dacryocystectomy, it is best to perform external DCR with later canalicular occlusion.

Surgical Techniques

External Dacryocystorhinostomy

DCR is designed to widely open the lacrimal sac into the nasal space, thereby eliminating the lacrimal sac and opening the common canaliculus directly into

the nose [4] and the wide soft-tissue anastomosis required is possible only with an external approach incorporating a limited anterior ethmoidectomy.

The procedure can be performed under either general or local anaesthesia, typically as a day-case procedure [7]: Local anaesthesia with intravenous sedation tends to provide an excellent operative field, although it can be associated with rather more postoperative nasal oozing than that after general anaesthesia. Local anaesthesia is readily achieved by spraying the anterior nasal cavity with lidocaine 4% spray and infiltrating the medial one-third of the lower eyelid and paranasal area with a solution of 0.5% bupivacaine with 1:100,000 to 1:200,000 epinephrine. Anterior ethmoidal nerve block, using 2–3 ml of the same solution, is achieved by passing a 23-gauge needle along the medial orbital wall from just above the medial canthus and angulated about 20° below the axial plane (to avoid injury to the anterior ethmoidal vessels). The anterosuperior nasal cavity is packed with about 80–100 cm of 1-cm packing gauze soaked in 2 ml of cocaine solution (4 or 10%) and the packing left in place until the silicone intubation is passed through the nasal cavity. Topical ocular anaesthesia, such as 0.5% amethocaine, is also required during the surgical procedure. Maximum vasoconstriction is obtained if the local anaesthetic is given at least 10 min before surgery commences and is most conveniently given prior to surgical gowning.

Where general anaesthesia is the preferred choice of the patient or surgeon, controlled hypotensive anaesthesia suitable for day-case admissions is readily achieved with modern techniques – such as either total intravenous anaesthesia (TIVA) using Propofol and Remifentanyl, or the combination of a volatile inhalation anaesthetic (such as isofluorane) with titrated small doses of a β-blocker to prevent the compensatory tachycardia. For patients under general anaesthesia, nasal vasoconstriction is readily achieved, after sterile preparation and draping, by placing 3 cotton-tips – moistened in 1:1,000 epinephrine – as far superiorly and anteriorly as possible within the nasal space. Whether under local or general anaesthesia, the head-end of the operating table should always be raised during surgery, to decrease the cephalic venous pressure.

A 12- to 15-mm straight skin incision should be placed on the flat paranasal area, starting just above and about 1 cm in front of the medial canthal tendon – this type of incision only rarely leaving a noticeable scar, whereas more posterior incisions tend to ‘bowstring’ across the inner canthal concavity. The skin is then undermined posteriorly to the anterior limb of the medial canthal tendon, leaving the orbicularis muscle and angular vessels undisturbed. The pretarsal and preseptal orbicularis fibres are separated by blunt dissection along the line of the fibres, this revealing the anterior lacrimal crest along which the paranasal periosteum is widely divided using a Rollet’s rougine; damage to the vascular preseptal orbicularis muscle and the angular vessels may be avoided by

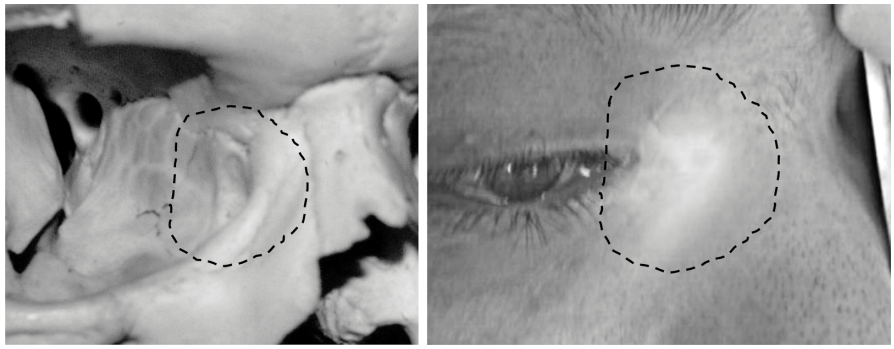

Fig. 2. Landmarks for osteotomy on skull (***a***) and on clinical transillumination (***b***), indicating a size that allows suture of adequate mucosal anastomoses and, thereby, ensuring an absolute cure of 'volume' symptoms and signs of lacrimal disease.

retracting them medially with a squint hook, or (where under general anaesthesia) by placement of 2/0 silk traction sutures through the anterior periosteal edge, encircling the angular vessels and orbicularis, with the sutures clipped under tension to the surgical drapes. The rougine is used to displace the lacrimal sac from its fossa and the maxillolacrimal suture line entered using an angled (e.g. Traquaire's) periosteal elevator, this being worked up and down along the bony suture; should the bone be too thick to breach, at this point, it is possible to enter the ethmoid sinus through the lamina papyracea (behind the posterior lacrimal crest), or the bone of the anterior lacrimal crest may be thinned down using a burr, or hammer and chisel.

A large rhinostomy (fig. 2) is fashioned by first crossing the anterior lacrimal crest as far superiorly as possible (where the crest is thinnest), and the directing bone removal inferiorly and in front of the crest (to give an 'L-shaped' rhinostomy). Every few bites, the periosteal elevator should be swept around the bone edge to separate the underlying nasal mucosa from the bone and, where cotton-tips have been placed within the nose, these should be withdrawn sufficiently to allow the rhinostomy to be fashioned. The remaining spur of thick bone of the frontal process of the maxilla is then removed and the thin bone between the upper duct and nose is removed using a Jensen bone nibbler. Further bone should be removed up to the skull base, to ensure there is none alongside the common canalicular opening, and posteriorly to include a partial ethmoidectomy – removal of the bone fragments and mucosa facilitating the sutured anastomosis of posterior mucosal flaps.

A '00' lacrimal probe is passed, through the lower canaliculus, into the lacrimal sac to tent its medial wall and a No. 11 blade used to enter the lumen of

the lacrimal system at the anteromedial face of the sac-duct junction (thereby avoiding damage to the internal opening of the common canaliculus). Once the lumen has been identified, the medial wall of the sac and upper duct are opened completely with Westcott spring scissors; occasionally it will be found that only the relatively thick lacrimal sac fascia has been opened, and the thin sac mucosa remains intact. Where there is a membranous block of the internal opening of the common canaliculus, this should be carefully excised using a No. 11 blade or fine scissors. With the nasal packing or cotton-tips in place to avoid damaging the septal mucosa, the nasal mucosa is incised vertically with a No. 11 blade to create anterior and posterior flaps; this incision should be about 3–4 mm in front of the 'arch' formed by the anterior end of the middle turbinate attachment – this 'arch' generally being evident after partial ethmoidectomy. Relieving horizontal incisions are made at the superior and inferior bone edges to mobilise both flaps.

The anterior flap is held away from the operative field by passing a 6/0 absorbable suture (on an 8-mm diameter half-circle needle) through the middle of preseptal orbicularis fibres – that is, those that have been retracted medially by the assistant – and then through the middle of the anterior nasal flap, the two ends clipped (with the needle still attached) and hung aside across the nasal bridge. The posterior flaps are sutured – from the fundus of the sac to the entrance to the duct – with a 6/0 absorbable suture placed in a locked continuous suture; to facilitate this suturing in a recess, it is best to use the whole needle length, with it reverse-mounted in a non-locking angled needle holder. The lacrimal probe, kept in place during suture of the posterior flaps, is removed and silicone intubation placed. The preplaced anterior suture is passed through the anterior sac flap, opposite the internal opening – this effectively 'suspending' the mucosal anastomosis from the orbicularis fibres. Two other suspended anterior sutures are passed: the upper one is passed through preseptal orbicularis above the first suture, then through the upper end of the anterior nasal flap, through the upper anterior sac mucosa and finally through the stump of medial canthal tendon; the lower suture is passed through orbicularis, through the lower end of the anterior nasal mucosa, through the anterior sac flap near the nasolacrimal duct, and finally through the subdermal tissues lateral to the lower part of the skin incision. Skin closure is achieved with a 6/0 nylon continuous mattress suture and a firm dressing applied to the operative site for 12 h.

With a sutured primary mucosal anastomosis, nasal packing is not required routinely although ribbon gauze, moistened with 1:1,000 epinephrine, may be placed if major primary haemorrhage occurs and this pack left undisturbed for 5 days. The patient should be nursed semi-erect on bed rest after surgery, to reduce nasal venous congestion and oozing, and hot drinks avoided for 12–24 h. A topical combined antibiotic and anti-inflammatory medication is prescribed for a few weeks and, unless systemic antibiotics have been given during surgery, a short

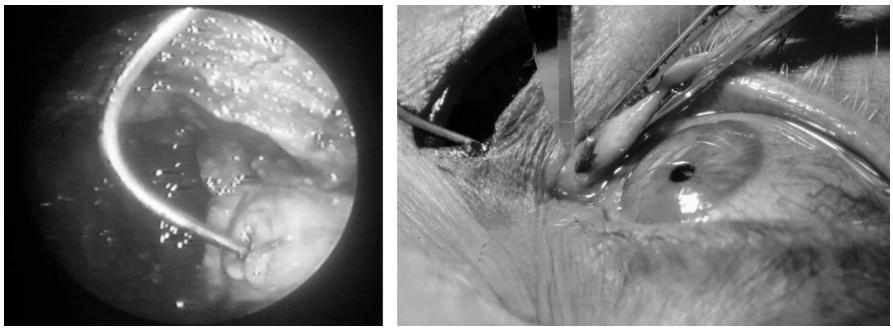

Fig. 3. Retrograde canaliculostomy during DCR. ***a*** Endonasal view of a '1' gauge probe, bent to about 70°, inserted retrogradely into the internal opening of the common canaliculus until it meets the point of canalicular obstruction. ***b*** The eyelid margin is gripped near the probe tip and a marginal incision made into the most lateral point in the canaliculus, prior to silicone intubation.

course of oral antibiotics is recommended to reduce postoperative infection. The dressing is removed on the day after surgery and nose blowing discouraged for the first week, to reduce the risk of epistaxis or subcutaneous emphysema. Skin sutures are removed at about 1 week and the intubation at about 4 weeks after surgery, by which time epithelialisation of the surgical fistula has been completed.

Dacryocystorhinostomy with Retrograde Canaliculostomy

Retrograde canaliculostomy is designed to open – at the lid margin next to the medial tear lake – canaliculi that are blocked within their first 7 mm or so, but have a patent common canaliculus [5]. As the extent of canalicular block can only be established at the time of surgery, the patient should be warned that they might require primary or secondary placement of a Jones' canalicular bypass tube.

External DCR (see above) is completed to the stage of having sutured the posterior mucosal anastomosis and the internal common canalicular opening is entered retrogradely using a '0' gauge lacrimal probe, bent perpendicularly on itself at about 8–9 mm from the end. The probe is passed as far laterally as possible along each canaliculus (if possible), a 1–2 mm cut-down made to expose the probe on the lid margin (fig. 3), the 'pseudo-puncta' intubated and the DCR completed in a standard fashion. If solely the common canaliculus is available, its lateral end should be opened into a carunculectomy site and – in this and other such cases where only a single canaliculus is available – the returning end of the silicone intubation passed through one of the punctal annuli and forced

medially through the lid tissues; this manoeuvre returning the intubation to the nasal space at a site remote from the common canalicular opening. Monocanalicular stenting is unlikely to stay in place because of the absence of a normal annulus at the 'pseudo-punctum'.

The intubation can be removed when the conjunctival and canalicular epithelium have united – typically within 2–3 weeks – and they should not be left for much longer or 'cheese wiring' will cause a cross union between the lids. Closed placement of a canalicular bypass tube is required if the pseudo-puncta fail to control symptoms.

Closed Placement of Jones' Canalicular Bypass Tubes

The canalicular bypass tube (most commonly a Lester Jones' Pyrex tube), is designed to allow free tear flow from the medial tear lake into the nose, by way of a false conduit. Closed placement is indicated where watering continues after canaliculo-DCR, after retrograde canaliculostomy or, exceptionally, after a functioning standard DCR (for example, in patients with facial nerve palsy). Although requiring continued maintenance and associated with various long-term problems, the majority of people with these drainage devices consider them to be of benefit [6].

The nasal end of a bypass tube needs to be free within the nasal space, somewhat in front of the middle turbinate, and intranasal examination is required – best with rigid endoscopy, although a good headlight and nasal speculum are often adequate. As nasal local anaesthesia (with vasoconstriction) creates an inappropriately capacious nasal space, optimum positioning of the tube is achieved under general anaesthesia – when the nasal cavity is closest to normality.

The ocular end of the tube should be positioned hard behind the medial end of the lower limb of the canthal tendon (fig. 4): this is best accomplished by using a Nettleship dilator to pierce the epithelium at the desired position and a track then forced through to the nose using the smallest end of the double-ended ('bull-horn') dilators supplied with the commercial sets; this track should typically run about 30° downhill and in, or slightly forward from, the coronal plane. The position of entry into the nasal space is checked for suitability, an appropriate tube (commonly 11 mm, with a 3.5-mm flange) slipped onto a '1' gauge lacrimal probe that is passed along the dilated track, and the tube forced along the track and into the nose using the end of the thumbnails (fig. 5); the use of any form of instrument on the tube flange tends to shatter it, and this should be avoided at all costs. The position of the ocular and nasal ends of the tube should be checked after withdrawing the '1' probe, and spontaneous flow of saline from the ocular surface verified. Suture of the tube is unnecessary after secondary placement.

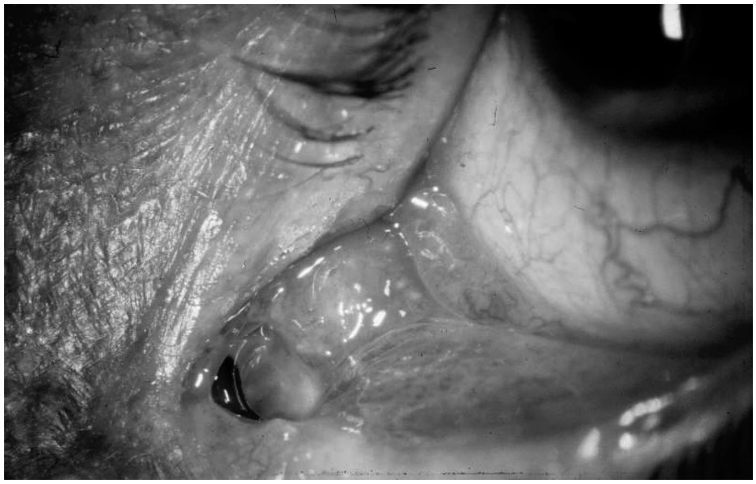

Fig. 4. Jones' canalicular bypass tube positioned at the left inner canthus, just behind the lower lid margin – the lumen of the tube being directed about 30° downwards into the nasal space.

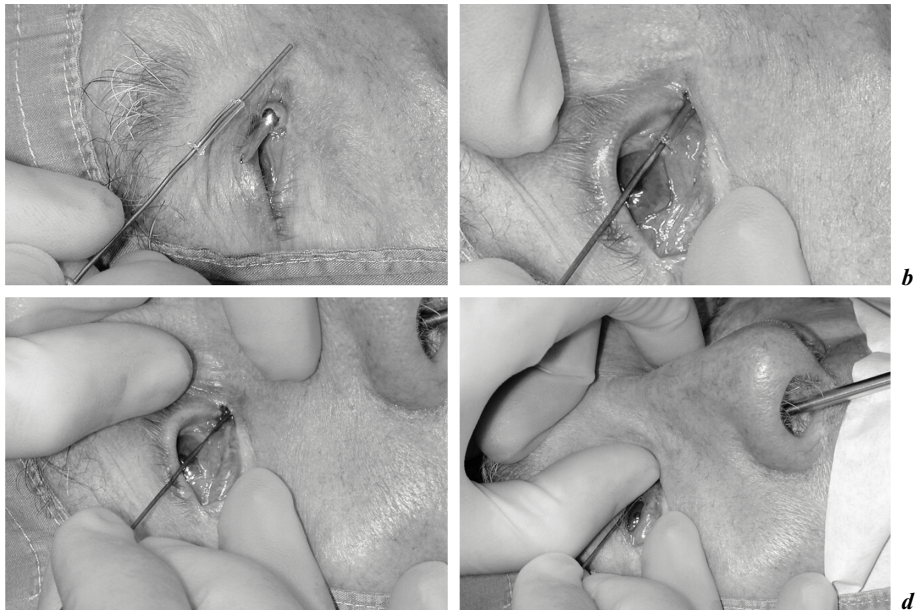

Fig. 5. Secondary insertion of a Jones' tube: After dilating a downwardly directed track from the inner canthus to the nose, the bypass tube – slipped onto a '1' gauge lacrimal probe (***a***) that is passed along the track (***b***) – is forced into the tissues (***c***). The glass flange tends to shatter if instruments are used to drive the tube, and placement should be undertaken using the ends of the thumb-nails (***d***).

Dacryocystectomy

Dacryocystectomy is probably indicated only in patients with well-controlled ocular surface disease in the presence of longstanding canalicular occlusion, in whom there has been an episode of acute dacryocystitis or increasing dilation of the sac due to mucus secretion.

Using the same approach as external DCR, the anterior limb of the medial canthal tendon is detached from the nasal bone and peeled laterally from the underlying tissue before the sac is mobilised from its fossa. Once peeled about 1 cm laterally, the underlying common canaliculus is transected and the sac mobilised medially from the underlying orbital tissues by careful dissection medially across the posterior lacrimal fascia. The tightly bound fundus and medial face of the sac is separated from the lacrimal sac fossa, the isolated sac drawn upwards whilst the superior part of the nasolacrimal duct is freed from its canal, and the duct transected as low as possible. The remaining stump of nasolacrimal duct should be thoroughly cauterised to encourage fibrosis and, after haemostasis, the medial canthal tendon reattached to the neighbouring orbicularis oculi muscle and the skin incision closed.

Permanent Punctal Occlusion

Before performing permanent punctal occlusion, it is imperative to verify the benefit of occlusion by a temporary canalicular plugging: This may be achieved by insertion of collagen plugs, under topical anaesthesia, into the horizontal portion of the upper and lower canaliculi. If the patient develops watering or an exacerbation of ocular surface inflammation, the original diagnosis of 'dry' eye – and advisability of permanent occlusion – should be questioned. Likewise, it is unwise to occlude the canaliculi in the presence of a lacrimal sac mucocoele or pyocoele – conditions in which DCR should be first performed. Techniques for punctal and canalicular occlusion are presented in another chapter.

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Geoffrey E. Rose
Lacrimal and Orbital Clinics, Moorfields Eye Hospital
City Road, London EC1V 2PD (UK)
Tel. +20 7566 2034, Fax +20 7566 2019, E-Mail geoff.rose@moorfields.nhs.uk

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Surgery of the Conjunctiva

Norihiko Yokoi, Tsutomu Inatomi, Shigeru Kinoshita

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Abstract

Background: Dry eye is characterized by aqueous tear deficiency or excessive tear evaporation at the ocular surface, both leading to tear film instability that results in ocular surface epithelial damage. In addition to the lacrimal gland, the meibomian gland, cornea, and conjunctiva also contribute to the formation of the tear film via the production of goblet-cell-derived mucin and the expression of membrane-associated mucin. The conjunctiva can be linked with dry eye through various mechanisms such as inflammation, disturbance of the tear film, and conjunctival fibrosis. Thus, normalization of the conjunctiva is important for the management of dry eye. **Materials and Methods:** Conjunctival diseases associated with dry eye include conjunctivochalasis, superior limbic keratoconjunctivitis, pterygium and pinguecula, and severe ocular surface diseases such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid. The associated pathophysiology and surgical procedures for these disorders are analyzed and described. The major concept of conjunctival surgery for dry eye is to smoothen the surface in order (1) to reduce blink-associated microtrauma, (2) to reconstruct the tear meniscus and conjunctival fornix and their respective functions as reservoirs for tears, and (3) to reduce conjunctival inflammation by the removal of abnormal fibrous tissue combined with the use of mitomycin C and/or amniotic membrane. **Results:** Conjunctivochalasis and pterygium result in signs and symptoms of dry eye by inducing dysfunction of the tear meniscus and/or an ectopic tear meniscus. Therefore, the resection of redundant conjunctiva and abnormal tissue in pterygium is an effective procedure for normalizing the tear film. If cicatrizing conjunctivitis results in tear-film instability due to conjunctival inflammation and squamous metaplasia, reconstruction of ocular surface epithelium is vital for its resolution. **Conclusion:** In order to effectively manage dry eye due to conjunctival disease, it is important to understand not only the surgical procedure but also the pathomechanisms of conjunctival changes leading to signs and symptoms of tear-film deficiencies.

Dry eye is a multifactorial disease [1] characterized by the development of a chronic vicious cycle between the tear film and ocular surface epithelium, resulting in tear-film instability as well as ocular surface epithelial damage that

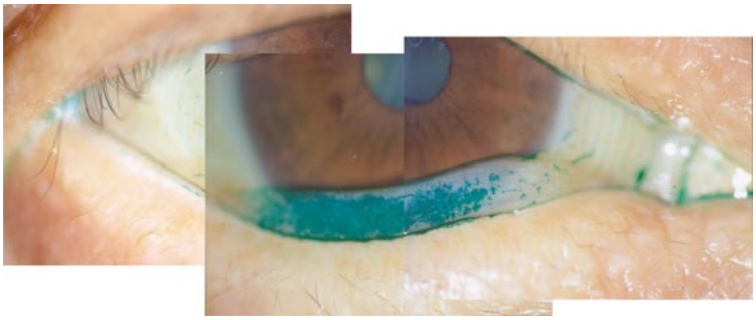

Fig. 1. Representative panoramic picture of CCh. CCh is generally located at and causes dysfunction of the lower tear meniscus.

are respectively observed as shorter fluorescein breakup time and punctate fluorescein staining of the ocular surface epithelium. The vicious cycle may be related to the other dry-eye mechanisms, such as the well-known hyperosmolarity [2] or the more recently emphasized inflammation [3], yet the exact relationship between the three mechanisms (tear-film instability, hyperosmolarity, and inflammation) remains unclear. However, numerous risk factors may be related to the three central mechanisms of dry eye mentioned above, and these risk factors may result in or exacerbate the clinically evident dry eye. The conjunctival abnormalities described in this chapter may all be regarded as risk factors for dry eye, and they include: (1) conjunctivochalasis (CCh); (2) superior limbic keratoconjunctivitis (SLK); (3) pterygium and pinguecula, and (4) cicatricial changes associated with severe ocular surface disease, such as in Stevens-Johnson syndrome and ocular cicatricial pemphigoid.

CCh [4–6], also known as lip-like folds [7], conjunctival pleating [8], and lid-parallel conjunctival folds (LIPCOF) [9], can be both a diagnostic sign and a risk factor for dry eye [4]. From the etiological viewpoint, CCh exacerbates dry eye via the dysfunction of the tear meniscus and mechanical action [6]. CCh is generally located along the lower tear meniscus (fig. 1) where it may interfere with the tear meniscus which is known to serve three important functions including: (1) retention of tears (75–90% of the total tear volume rests in the tear meniscus) [10]; (2) distribution of tears to the ocular surface, and (3) ocular-surface tear-routing due to its connection to the lacrimal drainage system [11].

CCh may result in tear-film instability and the disruption of tear flow leading to delayed tear clearance [5], which then in turn may exacerbate dry eye-associated inflammation [3].

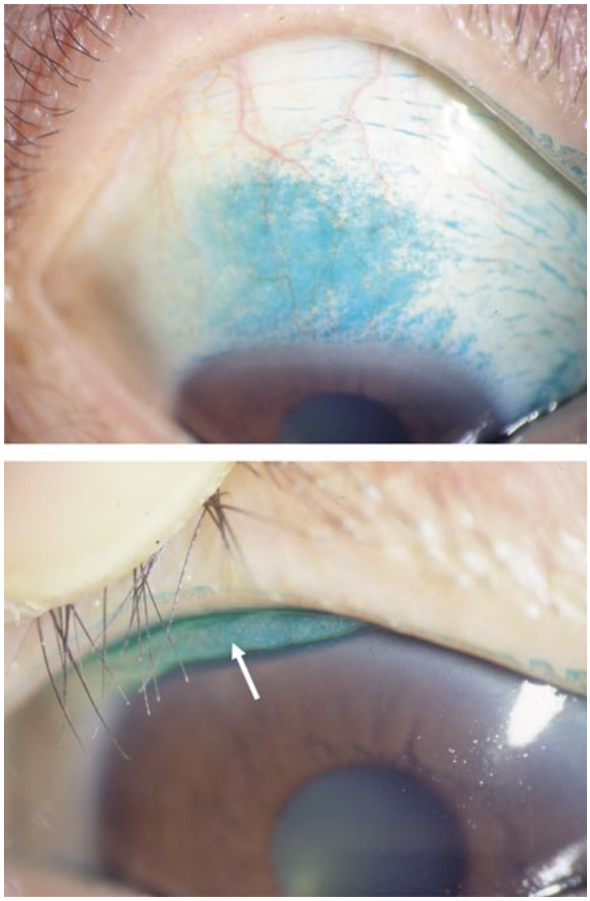

Fig. 2. Lax upper bulbar conjunctiva in SLK which appears at the upper meniscus (arrow) when the upper lid is squeezed downward. This redundant conjunctiva may cause friction with the upper palpebral conjunctiva.

A paradoxical consequence of CCh-associated tear meniscus dysfunction in mild cases of dry eye is pseudo-epiphora. In more severe cases, CCh will not only reduce the retention and distribution of tears but also of tear substitutes applied. Another mechanism exacerbating dry eye or dry eye-associated symptoms is CCh-related mechanical friction. This occurs between the lax conjunctiva and the lid margin and/or cornea. Ocular surface epithelial damage and conjunctival hyperemia are frequently seen in cases with CCh combined with aqueous tear-deficient (ATD) dry eye, and may be attributed to this friction-associated mechanical trauma to the ocular surface. This mechanism is also involved in SLK, where there is friction between the lax upper bulbar (fig. 2)

and palpebral conjunctiva, limbus, and upper part of the cornea. Interestingly, the characteristic changes of advanced SLK include inflammation and inflammation-related focal dry eye, and these can be successfully treated surgically.

Next, when investigating the mechanism that prompts the pinguecula or pterygium to cause or exacerbate dry eye, ectopic menisci formed around pinguecula or pterygium head which invade the cornea should be considered. These ectopic menisci are known to cause thinning of the adjacent tear film [12] resulting in local tear-film instability and focal evaporative dry eye. This mechanism may help explain the superficial punctate keratopathy (SPK) or Dellen [13] found adjacent to the pinguecula or a pterygium head which are often medically uncontrollable; this is especially true in cases with a background of ATD.

Finally, the cicatricial change in conjunctiva seen in severe ocular surface diseases such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid is associated with chronic subconjunctival immunological inflammation. This inflammation involves lacrimal gland ducts and conjunctival epithelium, resulting in ATD and inhibition of the normal differentiation of conjunctival epithelium. This leads to the pathological keratinization1 [4, 15] which transforms hydrophilic surfaces into hydrophobic ones. These mechanisms are found in the severe form of dry eye that is often accompanied by severe ocular surface diseases and is a result of a combination of ATD and evaporative dry eye.

Based on the conjunctiva-associated mechanisms in dry eye described above, several surgical strategies can be considered. For the treatment of CCh, conjunctival resection should be designed to reconstruct the normal tear meniscus to the greatest possible length along the lower lid margin [6]. Ideally, this resection would extend from the lateral canthus to the punctum in order to restore normal tear meniscus function, rather than just a simple resection of the lax conjunctiva. In contrast, in cases of pinguecula or pterygium, resection of the protruding conjunctival lesion, which is thought to induce SPK, should be designed to remove the ectopic meniscus which is the causative factor of focal dry eye. This is usually indicated in cases with ATD.

In cases with severe ocular surface disorders with conjunctival cicatrization associated with dry eye, mitomycin C and/or amniotic membrane can be used at the time of resection of subconjunctival fibrovascular tissues to reduce conjunctival inflammation when anti-inflammatory medical treatment was unsuccessful. However, those cases are sometimes accompanied by corneal stem cell disorders which often necessitate additional reconstruction of ocular surface epithelium.

The previously described treatment modalities are sometimes applied simultaneously, and at other times in a more stepwise approach. The following sections will describe the practical aspects of conjunctival surgery for dry eye, including indications, surgical techniques, and complications.

Surgery of Conjunctivochalasis

Background of the Disease

CCh is a very common ocular disorder that is characterized by a redundancy of bulbar conjunctiva. Although there are two etiological theories associated with this disease (age-related [16] and subconjunctival inflammation-related [17, 18]), our research has demonstrated the breakdown of elastic fibers in the redundant conjunctiva without any inflammatory cell infiltrates [6, 16], thus supporting the age-related theory. However, it is often clinically experienced that CCh may cause non-specific inflammation, possibly via the redundant CCh-induced mechanical action during blinking and/or eye movement, or an exacerbation of dry eye-related inflammation via the CCh-induced delayed tear clearance [5].

CCh is unique in that it may induce tear meniscus dysfunction which is a risk factor for both watering eyes and dry eyes. Symptoms of dry-eye discomfort and/or corneal epithelial damage may be exacerbated not only as a result of tear meniscus dysfunction, but also because of the mechanical friction created between the redundant conjunctiva and the ocular surface. It has also been reported that LIPCOF can potentially be used as a diagnostic marker for dry eye [9]. Historically, surgery of CCh has been little practiced, yet numerous recent reports support the efficacy of a surgical approach for improving ocular symptoms and ocular surface epithelial damage in cases with or without dry eye [5, 6].

Concept of Surgery

Although numerous surgical methods for CC have been reported [5], such as a crescent resection [4], resection combined with inferior peritomy and radial relaxing incision [19], and excision with amniotic membrane transplantation (AMT) [5] and scleral fixation [20], all previous methods involved no firm strategy for tear meniscus reconstruction and most procedures only targeted the redundant conjunctiva inferior to the cornea while redundant conjunctiva in the nasal and temporal areas were ignored. Therefore, the ideal surgical method must be applicable to all variations of CCh and should achieve reconstruction of the entire lower tear meniscus and eliminate ocular surface undulations.

Indication for Surgery

First, surgery for CCh is only indicated when the disorder is symptomatic. Asymptomatic CCh, even if there is excess tissue, is not an indication for surgery. Second, surgery should only be performed if the reported symptoms can be explained by clinically established signs of tear meniscus dysfunction and/or the mechanical action of redundant conjunctiva.

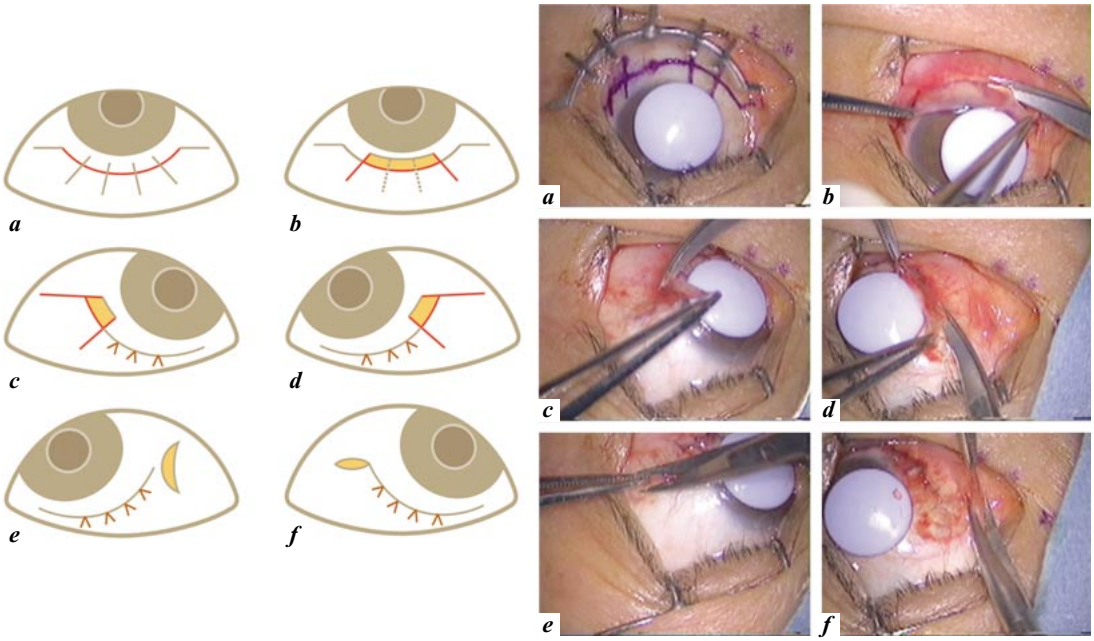

Fig. 3. Surgical steps for CCh: left series (scheme of the steps: (***a***) marking; (***b***) resection at the lower section; (***c & d***) resection at the temporal and nasal sections; (***e***) excision of the plica semilunaris; (***f***) temporal adjustment for the treatment of upper CCh); right series: surgeon's view.

In cases of dry eye combined with CCh, surgery should be performed when medical treatment is found to be ineffective. However, in cases of CCh with unstable tear film and no SPK (often diagnosed as dry eye and ineffectively treated with eyedrops alone), surgery can be expected to produce positive results. Traditionally, punctal occlusion with plugs has been the initial method for treating patients with moderate dry eye and prominent CCh (fig. 1). However, recent results [6] now indicate that CCh surgery should be considered prior to punctal occlusion.

Surgical Procedure

The operation includes the following steps (fig. 3): (1) topical anesthetic eyedrops with epinephrine are applied; (2) planned incision lines are marked using a newly developed marker (Chalasis marker, M-1405; Inami Co., Ltd, Tokyo, Japan). Small eyes require forced bilateral eye movement for correct marking; (3) subconjunctival anesthesia is performed, and an arc-shaped incision is made to the anesthesia-ballooned conjunctiva using scissors (Chalasis scissors, M-1406; Inami Co., Ltd) along the line created by the marker on the

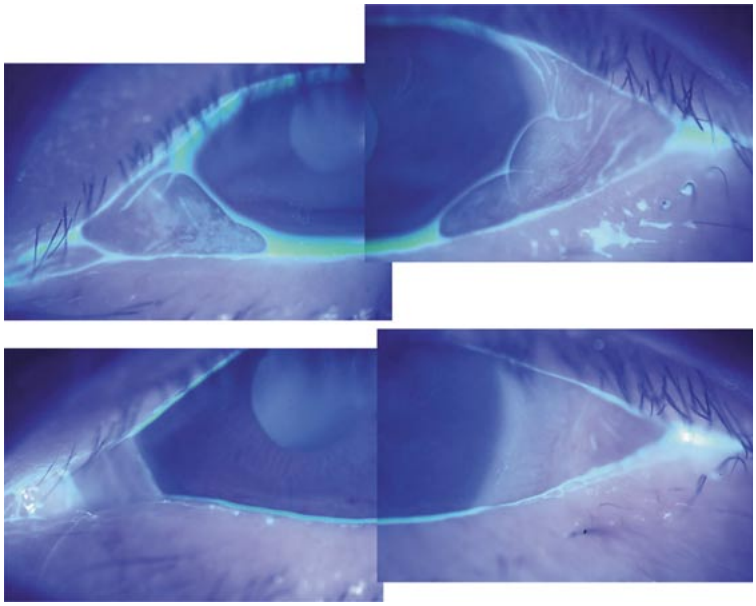

Fig. 4. Pre- (upper) and postoperative (lower) picture of CCh.

lower half of the bulbar conjunctiva; (4) subconjunctival tissues are dissected distal to this arc incision in order to easily stretch the redundant conjunctiva and to obtain firm attachment of the conjunctiva directly to the sclera; (5) radial incisions are then made with the Chalasis scissors in the redundant conjunctiva in order to create three conjunctival sections distal to the arc incision. The conjunctiva in the lower section is then pulled upwards, and any tissue that can be overlaid on the limbal conjunctiva resected and fixed using approximately five 9-0 silk stitches. For the treatment of the lateral sections, forced bilateral eye movement, henceforth referred to as the 'eye rotation step', are performed when judging the amount of excess tissue [6] to avoid suture breaks due to postoperative eye movement. It is important to resect all redundant conjunctiva of the temporal conjunctiva while less resection is required of the nasal side due to the subsequent resection of the plica semilunaris; (6) the temporal and nasal conjunctival flaps are then sutured with interrupted 9-0 silk; (7) excision of the plica semilunaris and minor temporal adjustment is then performed. The plica semilunaris should be excised at the base and no sutures are necessary. Using these procedures, complete reconstruction of the lower tear meniscus and elimination of conjunctival surface-related undulations associated with CCh can be obtained (fig. 4).

Postoperative Follow-Up, Complications, and Management

Postoperatively, patients are advised to wear an eyepatch for 1 week at bedtime to prevent any possible wound dehiscence. Sutures are removed 2 weeks after surgery. During the 2-week postoperative period, 0.1% betamethasone and antibiotic eyedrops should be instilled 4 times daily. Following removal of the sutures, betamethasone should be replaced by 0.1% fluorometholone instilled 4 times daily together with antibiotic eyedrops. Instillation times of the 0.1% fluorometholone should be reduced according to the extent of postoperative inflammation, and fully discontinued within 2 months postoperatively. Dry-eye patients should additionally receive artificial tears (ideally preservative-free) in combination with the above-mentioned postoperative eyedrops. That combination is then substituted with the eyedrops that the patients were using for dry-eye treatment prior to surgery once postoperative inflammation subsides.

Without the 'eye rotation' step, early postoperative complications in our previous study of 168 eyes included secondary lymphangiectasia in 6 eyes (3.5%), dehiscence in 11 eyes (6.5%), and pyogenic granuloma due to a reaction to the 9-0 silk suture in 2 eyes (1.1%) [6]. Lymphangiectasia can be managed by needling or excision, and pyogenic granuloma can be managed with topical steroids or surgical removal.

Surgery for Superior Limbic Keratoconjunctivitis

Background of the Disease

SLK [21, 22] is a unique inflammatory disease, first reported by Theodore in 1963, of the superior bulbar conjunctiva, limbus, and upper part of the cornea. The condition may be associated with corneal filaments, SPK, edema hyperemia and papillary hypertrophy of the superior bulbar and palpebral conjunctiva and limbus (fig. 2). The etiology of SLK is not clearly understood, however, there is a mechanical theory [23, 24] which suggests that in SLK the superior bulbar conjunctiva is lax due to congenital or age-related factors. In addition, blink-associated mechanical friction could lead to chronic inflammation of the lax conjunctiva. SLK is reportedly associated with ATD dry eye [23] and thyroid disease [25], and is accompanied by severe symptoms of irritation. Many non-surgical treatments have been attempted, such as the application of silver nitrate, vitamin A eyedrops, *N*-acetylcysteine and autologous serum, bandage soft contact lenses, and punctal plugs [26]. Effective surgical treatments include simple resection [21], thermocauterization [27], and recession of the abnormal conjunctiva [28].

Indications for Surgery

Artificial teardrops or low-concentration topical steroids, such as 0.1% fluorometholone, should be tried. However, for SLK combined with moderate to severe dry eye, punctal occlusion with punctal plugs is the best method of treatment. SLK cases with myopia are most effectively treated with soft contact lenses in combination with frequent instillation of preservative-free artificial tears. Surgery should only be considered for cases that are unresponsive to medical treatment.

Concept of Surgery

Based on the concept that SLK-associated abnormal findings, such as conjunctival hyperemia, limbal thickening, and SPK, are the result of the friction between the redundant upper bulbar conjunctiva at and around the SLK lesion and the upper palpebral conjunctiva, surgery should aim to eliminate lax conjunctiva without leaving any redundant tissue at the SLK lesion by a crescent excision of the conjunctiva superior to the SLK lesion [12]. Conjunctival redundancy is located mainly at – but not limited to – the SLK lesion. Therefore, we resect the perilesional conjunctiva but not the SLK lesion itself, and leaving intact conjunctiva close to the cornea may be helpful for future cataract or glaucoma surgery. As a result of this procedure, diseased conjunctiva within the SLK lesion is successfully stretched, conjunctival inflammation and positive rose bengal (RB) improve in as late as 1 month, and the amount of goblet cells within the SLK lesion is restored to the normal level [12].

Surgical Procedure

Our surgical method involves four steps (fig. 5): (1) Prior to surgery, a topical anesthetic with epinephrine and RB staining are applied to determine the localization of the abnormal conjunctival area in SLK. (2) After the administration of subconjunctival local anesthesia, an arc-shaped conjunctival incision is placed from the 2 o'clock to the 10 o'clock position adjacent and distal to the RB-stained lesion. (3) After excision of the subconjunctival connective tissue from the superior conjunctiva to the arc incision, the extent of resection is determined by the amount of redundant conjunctiva with the distal conjunctiva overlaid onto the RB-stained proximal conjunctiva. In accordance with the determined extent of resection, the conjunctiva is resected to form a crescent using the arc incision as the base. (4) The crescent incision of the conjunctiva is closed with interrupted stitches using 9-0 silk suture. Throughout the procedure, it is important that the patient is asked to look down as far as possible. This procedure usually results in complete resolution of SLK-associated hyperemia (fig. 6).

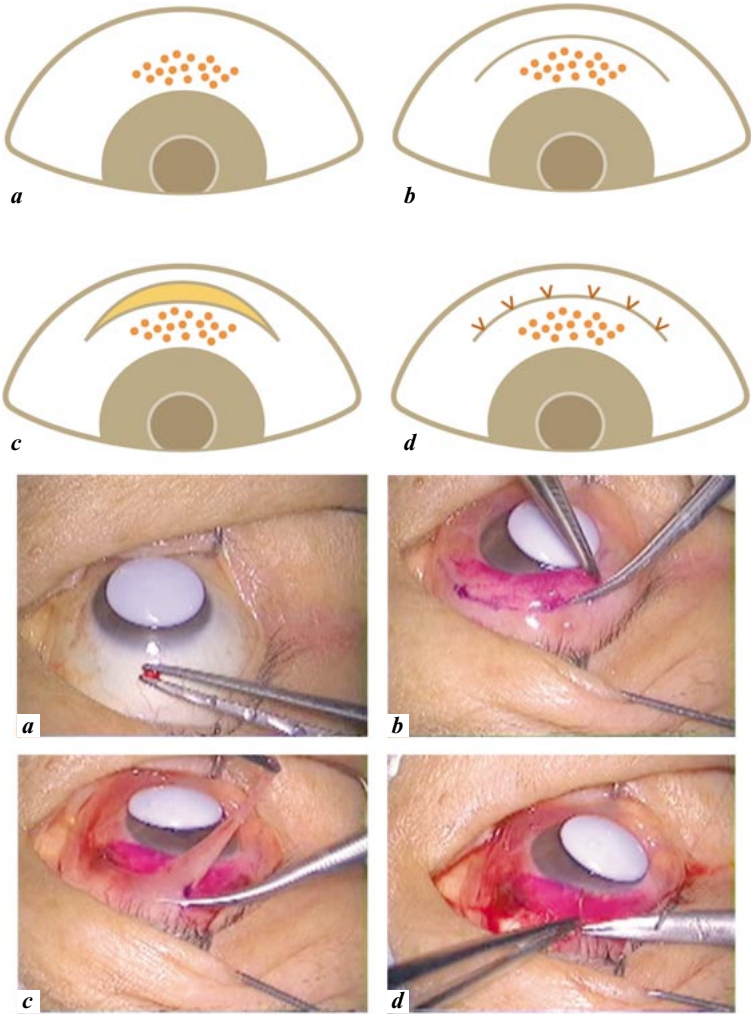

Fig. 5. Surgical steps for SLK: upper series (scheme of the steps: (***a***) rose bengal staining; (***b***) marking and arc incision; (***c***) crescent excision of conjunctiva; (***d***) suture); lower series: surgeon's view.

Postoperative Follow-Up, Complications, and Management

Postoperative treatment consists of antibiotic eyedrops and 0.1% fluorometholone eyedrops, both instilled 4 times daily for 2 weeks and twice daily over the following 2–6 weeks. In cases involving a more invasive removal of subconjunctival tissue, the 0.1% fluorometholone should be replaced with 0.1% betamethasone. The sutures should be removed 1–2 weeks postoperatively. To

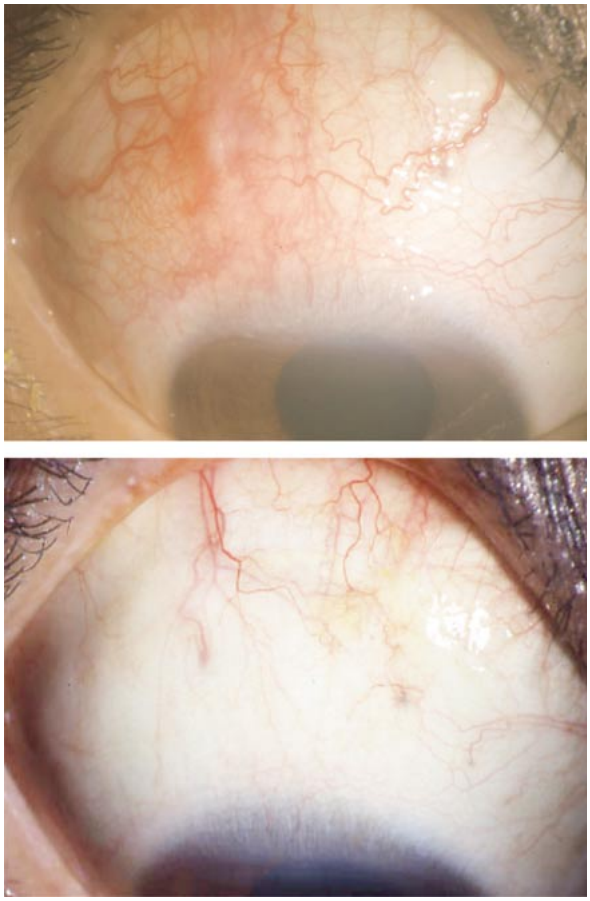

Fig. 6. Pre- (upper) and postoperative (lower: 1.5 years postoperation) picture of SLK.

date, no early or late postoperative complications have been observed. Our success rate was 100% in 6 eyes of 5 patients [12].

Surgery for Pterygium

Background of the Disease

Severe progression or recurrence of pterygium sometimes leads to clinical problems such as corneal scarring and irregular astigmatism. Advanced scarring may extend close to the optical zone and extraocular muscles, resulting in

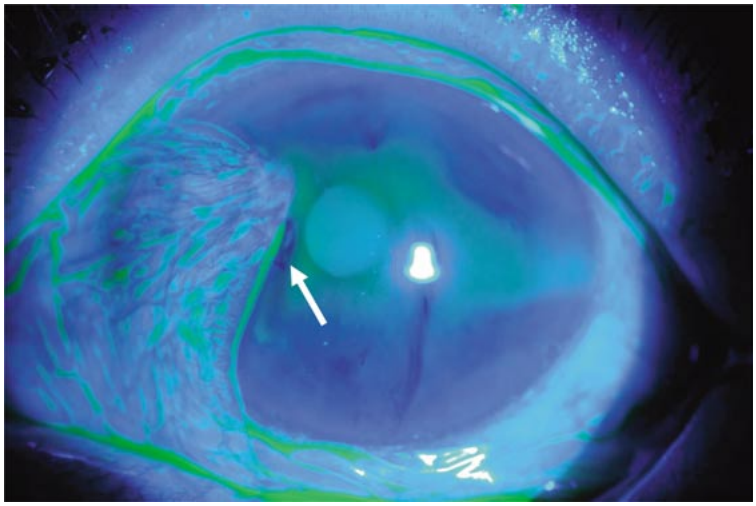

Fig. 7. Focal tear meniscus and abnormal tear distribution bordering pterygium. Arrow indicates the tear-film thinning adjacent to the ectopic tear meniscus at the edge of pterygium in which epithelial damage may be involved in advanced pterygium cases with dry eye.

visual loss and restriction of ocular mobility, respectively. Rarely does pterygium relate to or coexist with the condition of dry eye, but when thick and irregular pterygium tissue invades the corneal surface it can lead to uneven tear distribution which is responsible for the focal evaporative form of dry eye. Early pterygium and pinguecula are commonly not problematic in normal eyes and should not be considered for surgery. However, both have the potential to induce epithelial damage in cases of dry eye and during contact lens wear, because the irregular protrusion of these surfaces is insufficiently covered with tear film under the low tear volume. It is common to observe chronic inflammation in pinguecula of hard contact lens wearers because of physical stimulation and unstable tear-film coverage. When an ectopic tear meniscus is formed along the pterygium head, tear-film thinning will result next to it. This can cause tear-film instability which may lead to SPK around the pterygium head (fig. 7). Tear-film thinning is also notable over the prominent parts of the pterygium, and this may result in symptoms of irritation and dry-eye sensation as well as conjunctival hyperemia. Coincidental dry eye magnifies these symptoms, and the chronic epithelial damage caused by the tear evaporation results in chronic non-specific inflammation and may promote the progression of pterygium and pseudo-pterygium.

Indications

There are numerous reports that explore the surgical treatment of pterygium, yet medical treatment should be tried before resorting to surgery [29]. Frequent use of artificial teardrops and hyaluronic acid instillation can improve apical surface damage in pterygium and focal inflammation should be treated with a low dose of fluorometholone unless steroid-induced complications are observed. The indication for surgery is not clearly defined, and sometimes includes the cosmetic and social requirements of the patient. The most important point of pterygium surgery is to inhibit recurrence of the disease, because the need for reoperation substantially reduces the prognosis and increases the risk of complications due to cicatrization. Indication, selection, and timing of the surgical procedure based on the clinical picture (e.g. chronic injection, bilateral pterygium, and thickening of the Tenon's tissue) determine the success of surgery. In dry eyes, corneal epithelial damage resistant to conventional management with artificial teardrops and punctal plugs is a clear indication for surgery.

Concept of Surgery

The purpose of surgery in primary pterygium is to remove hyperproliferating subconjunctival tissue and the abnormal pterygium head and to minimize the risk of recurrence. Attention should focus on the: (1) area of excision; (2) use of intraoperative chemicals; (3) technique of wound closure, and (4) transplantation of tissue to the area of excision to inhibit recurrence.

For advanced and recurrent pterygium, in order to prevent further recurrences and/or to reconstruct surgically induced conjunctival cicatrization, additional concepts have been proposed. These include: (1) reconstruction of the limbal barrier to block pterygium re-invasion, and (2) reconstruction of conjunctival area lost by excessive surgical resection and scarring.

The concept of an autologous limboconjunctival graft taken from the patient's healthy eye has been reported [30], however this procedure carries the risk of inducing partial limbal deficiency at the donor site. Therefore, keratoepithelioplasty using a preserved corneal graft is an alternative procedure that eliminates the risk of damage for the other eye.

Surgical Procedures (Table 1)

Previously, simple resection with bare scleral closure has been used in early or small pterygia. However, a variety of studies have shown a high rate of recurrence for that technique when not accompanied by adjunctive therapy. Slow epithelial wound healing and prolonged postoperative inflammation may

Table 1. Pterygium surgery

1. Simple resection with bare scleral closure
2. Simple resection with conjunctival closure
3. Conjunctival rotational flap
4. Free conjunctival transplantation
5. Lamellar keratoplasty
6. Keratoepithelioplasty
7. Limbal transplantation
8. Amniotic membrane transplantation
9. Cultivated mucosal epithelial transplantation

activate fibroblasts, resulting in recurrence. It is now widely accepted that adjunctive therapy and creation of a physical barrier dramatically reduces the risk of pterygium recurrence. The adjunctive intraoperative application of mitomycin C (MMC) has been commonly used and is found to improve the clinical outcome even in mild cases [31–34]. MMC is an alkaloid agent capable of suppressing the proliferation of fibroblasts which are thought to be responsible for the etiology of pterygium. The commonly used concentration of MMC ranges between 0.02 and 0.04%, and the duration of application between 1 and 3 min (compared to postoperative topical use). The intraoperative application of MMC is relatively safe, however postoperative complications such as scleromalacia and persistent epithelial defects can result from an excessive MMC effect [35, 36]. Therefore, it is important that MMC is not applied to surgically damaged or thin sclera, and that the ocular surface is thoroughly rinsed with 0.9% saline afterwards.

Conjunctival rotational flaps and conjunctival transplantation are commonly used surgical methods to prevent recurrence [37]. Technically, both approaches are relatively simple and do not require the use of any special materials. However, folding of the conjunctiva after rotation can sometimes cause cosmetic problems. Transplantation of a free conjunctival graft is more complicated and time-consuming, yet superior to conjunctival flap rotation in achieving a smooth conjunctival surface. The technique is especially useful in recurrent pterygia, where a large epithelial defect may result from resection. Free conjunctival autografts not only promote epithelial healing, but also act as an epithelial barrier to inhibit recurrence and were found to be superior to AMT in a comparative randomized trial [38]. On the downside, it results in additional scarring of normal conjunctiva.

Amniotic membrane (AM) is now widely accepted as an effective biological tool to inhibit pterygium recurrence (fig. 8). AM promotes epithelial wound

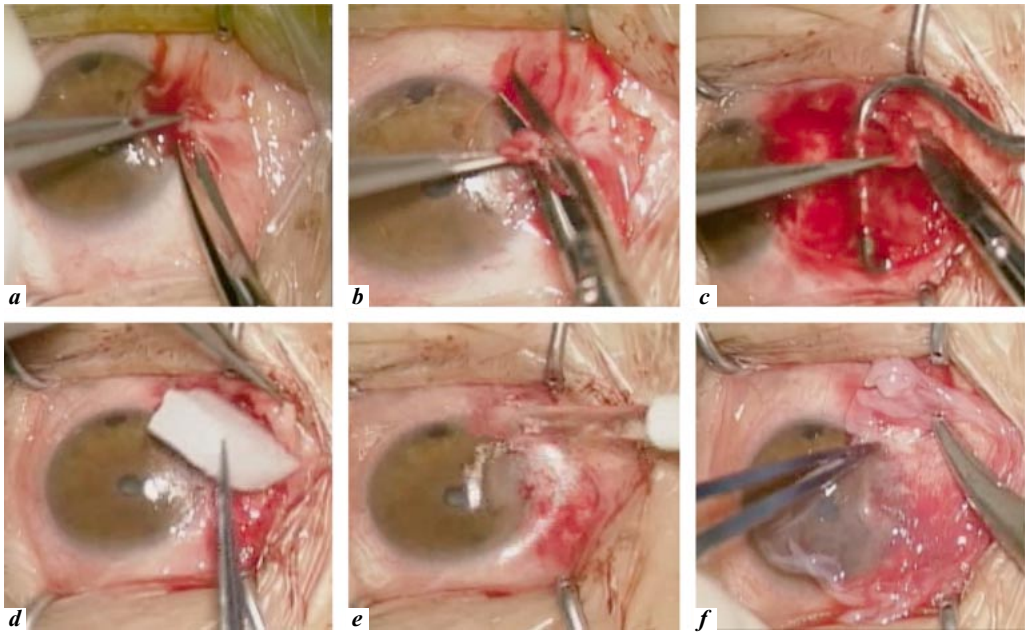

Fig. 8. Pterygium surgery with MMC and AMT. (***a* & *b***) Head part of pterygium is removed from the cornea; (***c***) fibrovascular tissue in subconjunctival space is removed; (***d***) 0.04% MMC absorbed in microsponges is applied under the conjunctival space for 1–5 min; (***e***) MMC is rinsed by the excess sodium saline solution; (***f***) amniotic membrane is sutured onto the bare sclera.

healing and prevents inflammation. AMT was first introduced in pterygium surgery in 1997 by Tseng et al. [39], and several reviews have summarized the proposed basic mechanisms of AM [40]. Although the precise biological effects of AM are still unclear, clinical results have indicated that fibroblast growth under the AM is suppressed and that postoperative complications such as persistent epithelial defect and scleromalacia, even after a large-sized resection, are reduced. AMT appears to successfully improve the prognosis of severely recurrent pterygium.

Postoperative Follow-Up, Complications, and Management

Complications are subdivided into two categories: intraoperative and postoperative. Intraoperative complications are rare. The most serious complication is damage to the medial rectus. Sufficient caution should therefore be paid during the removal of subconjunctival tissue, especially in recurrent pterygia with severe scarring and excessive bleeding, and squint hooks or silk threads should

be used to simplify the separation. Corneal perforation is a very rare complication, but excessive thinning of the cornea during excision should be avoided. Intraoperative surgical slit-lamp examination is a useful tool for examining the corneal thickness at the time of pterygium removal.

Major postoperative complications of pterygium surgery include infection, corneal ulcers, and scleromalacia. Infection is rare, yet it should be noted that wearing bandage contact lenses after large-area resections dramatically increases the risk of infection. Appropriate antibiotic instillations should be used until the wound is fully healed. Persistent epithelial defects and Dellen formation are not common, but they may progress to corneal melting. Frequent instillation of artificial tears and ointments are usually sufficient for treatment. Severe cases occasionally require additional treatment using punctal plugs or bandage contact lenses to increase the stability of tear film and promote epithelial healing. Scleromalacia is the most undesirable complication, because it may appear even after years of intra- or postoperative MMC and β-irradiation. Since scleromalacia is difficult to stop and may require surgical treatment such as scleral patching or lamellar keratoplasty, MMC should always be applied with great care. Although topical instillation of MMC or 5-fluorouracil in the postoperative period have been reported to be efficient, it is wise to remember that these treatments are associated with an increased risk of severe complications such as persistent epithelial damage and scleromalacia.

Surgery for Cicatricial Ocular Surface Disease

Background of the Disease

The majority of cicatrizing diseases of the ocular surface are associated with dry eye. Obstruction of lacrimal ducts opening onto the conjunctival surface due to progressed cicatrization, as well as conjunctival sac shortening and symblepharon formation, all lead to reduced secretion, pooling, and abnormal distribution of tears and tear meniscus. Extensive scar formation and symblepharon also interfere with normal eye-blinking and cause trachiasis and entropion which further degrade the ocular surface environment.

Dry-eye patients in need of conjunctival reconstruction can be divided into two groups: (1) cicatrization caused by exogenous reasons such as thermal or chemical injury, or (2) cicatrization caused by endogenous disease such as Stevens-Johnson syndrome and ocular pemphigoid. Although the pathogenesis of cicatrization varies, excessive proliferation of fibroblasts and conjunctival epithelium and the loss of goblet cells are commonly observed in these disorders. Active autoimmune-related inflammation is thought to be the primary reason for the pathogenesis [41]. Therefore, removal of inflamed tissue and

activated fibroblasts helps to inhibit the progression of these diseases and stabilizes the ocular surface. Medical treatment using steroids and other immunosuppressive medications is essential for controlling chronic inflammation and stabilizes the ocular surface. Intensive medical treatment is first considered to reduce inflammation and to inhibit the progression of cicatrization [42]. Although the surgical indication is controversial, the recent advance of ocular surface reconstruction utilizing the intraoperative application of MMC and AMT notably improves the prognosis of severe cases in both the acute and chronic phases [43].

Concept of Surgery

Reconstruction of the conjunctival sac and removal of scar tissue is the primary rationale for conjunctival surgery when attempting to reestablish a healthy ocular surface. In addition, reduction of chronic inflammation in the subconjunctival tissue also helps to prevent progression of cicatrization and dry eye and subsequent corneal complications such as persistent epithelial defect and stem cell deficiency. Thus, concepts of surgery include not only reconstruction of conjunctival tissue, but also removal of activated fibrotic tissue and immunoantigens.

Indications and Surgical Procedures

The surgical procedures, including intraoperative use of MMC and AMT, are identical for upper and lower conjunctival fornix reconstruction. First, conjunctival dissection is performed 2–3 mm from the limbus. After removal of fibrovascular tissue in the subconjunctival area and symblepharolysis, 0.04% intraoperative MMC is applied using a surgical microsponge for 5 min. The MMC is then carefully washed out using 200–300 ml of 0.9% saline. It is important to coagulate any bleeders to prevent dilution of the MMC and detachment of the AMT. Preserved AM is applied with the epithelial side up to cover the bare scleral area. The AM is then tightly sutured to the scleral surface using 10-0 nylon. If a case requires full coverage with AM, the edge of the AM should be sutured to the lid margin and the fornix should be reconstructed with anchoring nylon sutures (fig. 9). Additional keratoepithelioplasty and transplantation of free conjunctiva should be considered for severe cases.

Recently, cultivated oral mucosal epithelial transplantation (COMET) has been applied as an alternative method. This ex vivo expanded epithelial sheet provides rapid epithelialization and prevents cicatrization without converting to the original oral buccal mucosal tissue structure. Although no comparative studies have yet been performed, our preliminary clinical results indicate that the viable oral mucosal epithelial lining was able to maintain the reconstructed conjunctival space even in cases with recurrent severe cicatrizing ocular surface diseases after conventional AMT [44–46] (fig. 10). COMET is a newly developed

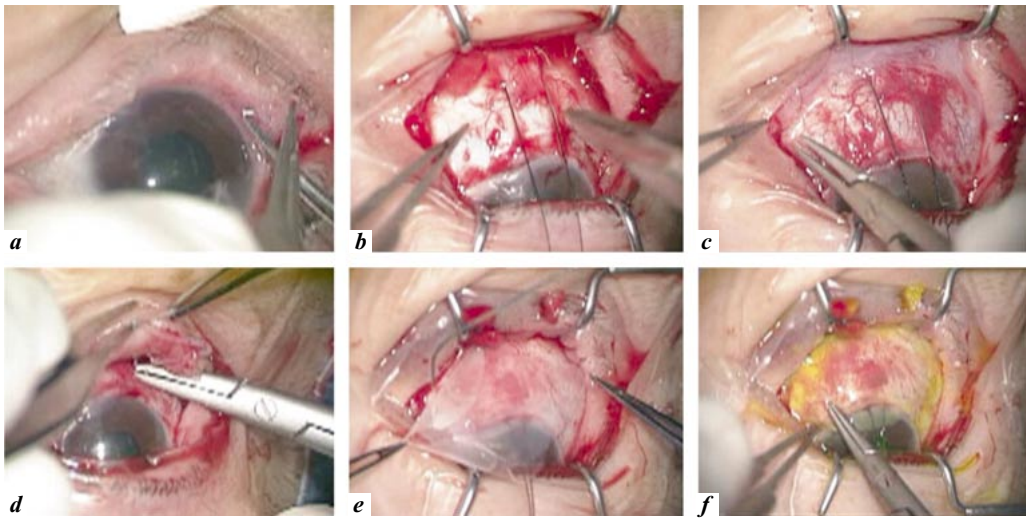

Fig. 9. Surgical procedure of cultivated autologous oral mucosal epithelial transplantation for conjunctival reconstruction in severe cicatricial ocular surface diseases. (***a***) Cicatrized conjunctival sac is released with scissors; (***b***) subconjunctival fibrovascular tissue is treated with 0.04% MMC for 5 min, and then rinsed with saline solution; (***c***) amniotic membrane is placed over the bare sclera; (***d***) transpalpebral anchoring sutures are placed to form the conjunctival fornix; (***e***) cultivated oral mucosal epithelial sheet is transferred with a carrier; integrity of epithelial sheet is confirmed by fluorescein staining; (***f***) cultivated oral mucosal epithelial sheet is sutured on top of a regular amniotic membrane.

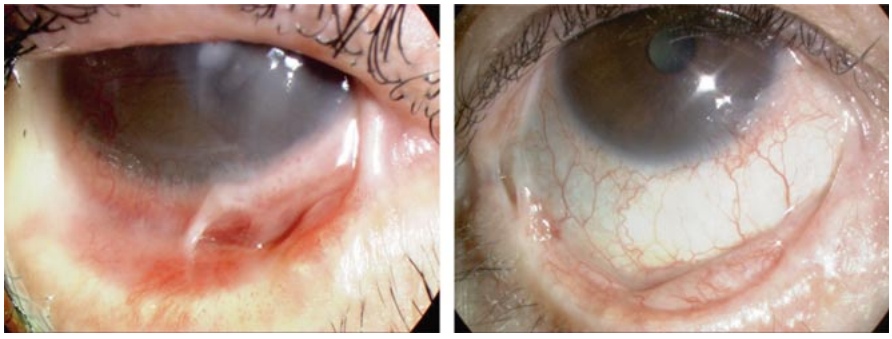

Fig. 10. Severe case of cicatrizing ocular surface disease shows shortening of conjunctival sac due to symblepharon formation (left). Reconstructed conjunctival sac following AMT and COMET (right).

cell-sheet transplantation procedure which uses cultivation technology and AM as a substrate. A small amount of oral mucosa is excised, and from this epithelial cells are isolated by EDTA and enzymatic treatment. The cell suspension obtained is cultured on AM using a co-culture system with 3T3 fibroblasts to generate a stratified epithelial sheet suitable for transplantation. The advantage of this procedure is that it uses autologous epithelium and is independent of the presence of ocular donor tissue, which may be unavailable in severe bilateral disease. Compared to simple tissue transplantation of full-thickness oral buccal mucosa, the oral mucosal epithelium cultivated on AM is composed of 5–7 stratified epithelial layers, similar to corneal and conjunctival epithelium. This epithelial structure is also maintained after transplantation onto the ocular surface without converting to the original tissue structure.

Concepts for Conjunctival Fornix Reconstruction

The concepts include: (1) reconstruction of conjunctival area; (2) prevention of cicatrization through inactivation of conjunctival fibroblasts and inflammatory cells using intraoperative MMC; (3) AMT; and (4) epithelial transplantation, i.e. (a) limbal transplantation, (b) conjunctival transplantation, and (c) cultivated mucosal epithelial transplantation.

Postoperative Follow-Up, Complications, and Management

The appropriate use of postoperative medication is mandatory to achieve and maintain a successful surgical result. Since the primary pathogenesis is frequently exacerbated by the surgical procedure, it is important to limit any inflammatory response during the early phase. Systemic steroids and topical cyclosporin are effective for most cases. Epithelial healing should be promoted for rapid stabilization of the ocular surface using artificial tears and punctal plugs. Effective long-term immunosuppression is required to maintain the reconstructed conjunctival fornix, and this is most important in ocular cicatricial pemphigoid [47].

In summary, management of cicatrizing ocular surface disorders is extremely challenging. Recent advances in ocular surface reconstruction techniques have dramatically changed the indication and strategy of surgical treatment. The application of intraoperative MMC and AMT are especially effective for reducing recurrent fibrosis and chronic inflammation. The introduction of new techniques based on regenerative medicine may potentially bring a future shift in paradigm. However, severe tear volume deficiency resulting from cicatrization has yet to be overcome. Since a minimum of tear secretion is essential for the survival of surface epithelia, every case should be considered carefully to decide whether the indication and time are right for surgical intervention. Appropriate medical management and surgery are required to improve the prognosis in the long term.

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Norihiko Yokoi, MD, PhD
Department of Ophthalmology, Kyoto Prefectural University of Medicine
Kajii-cho 465, Hirokoji-agaru, Kawaramachi-dori
Kamigyo-ku, Kyoto 602-0841 (Japan)
Tel. +81 75 251 5578, Fax +81 75 251 5663, E-Mail nyokoi@ophth.kpu-m.ac.jp

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Surgery of the Cornea: Corneal, Limbal Stem Cell and Amniotic Membrane Transplantation

F. E. Kruse, C. Cursiefen

Department of Ophthalmology, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany

Abstract

Purpose: To demonstrate surgical treatment options for complications of severe forms of dry eye at the cornea, limbus and conjunctiva. **Methods:** Corneal, limbal and conjunctival surgical treatment strategies are outlined. **Results:** Amniotic membrane transplantation, different forms of corneal transplantation and limbal stem cell surgery all are treatment options for complications of dry eye disease. **Conclusions:** Nowadays a broad spectrum of surgical treatment options exists to treat corneal complications of severe forms of dry eye at the ocular surface. Currently available conservative therapy for patients with 'dry eye' is primarily focused on augmenting or stabilizing the tear film and reducing primary or secondary causative factors such as inflammation of the ocular surface. While most patients with 'mild' and 'moderate' forms of dry eye (accounting for more than 95% of all patients with dry eye) can be treated sufficiently with drug treatment as well as environmental measures, some patients with very severe forms of dry eye need surgical intervention. Corneal surgery in the context of dry eye has primarily the objective to correct surface pathologies of the cornea caused by severe dysfunctions of the precorneal tear film. This primarily means persistent epithelial defects of the ocular surface, corneal ulcerations and consecutive corneal scarring. Besides conservative approaches, the first can be treated by amniotic membrane transplantation. Lamellar or perforating corneal transplantations are used to treat stromal scarring or perforated ulcerations as a sequel of persistent epithelial defects and associated apoptotic degeneration of stromal keratocytes. Finally, limbal stem cell transplantation can correct limbal stem cell deficiency states associated with or caused by diseases leading to severe forms of dry eye (e.g. chemical burns leading to destruction of conjunctival mucus-producing cells). All three surgical approaches will be discussed below.

Corneal Surgery in the Treatment of Dry Eye

Severe forms of dry eye can lead to scarring of the cornea. Persistent defects in the precorneal tear film and associated degenerations of the corneal epithelium can cause apoptosis of stromal keratocytes. There is now ample evidence for an intensive 'cross-talk' between epithelial and stromal cells in the cornea [1]. A good example is neurotrophic keratopathy early after penetrating keratoplasty where loss of sensory innervation leads to a reduced autonomous stimulation of tear secretion [2, 3]. If these eyes are not lubricated sufficiently after keratoplasty, superficial stromal scarring can be observed. Luckily, these opacifications often resolve if intensive topical lubrication is initiated early enough. In case of permanent scarring, surgical treatment options come into play.

For persistent superficial stromal scarring, lamellar corneal transplantation offers a relatively safer treatment option compared to full-thickness grafting. In this situation we prefer the deep anterior lamellar keratoplasty (DALK) technique initially described by Melles et al. [4] (fig. 1). After preparation of a scleral tunnel at the 12-o'clock position (fig. 1b) and injection of air into the anterior chamber via a paracentesis (fig. 1a), a custom-made knife is used to dissect into a deep stromal plane immediately anterior to Descemet's membrane (fig. 1c). The depth of incision is judged by the shadow surrounding the tip of the knife [4, 5]. A second (fig. 1d) and then a third specialized instrument is used to dissect within that deep stromal plane all around the cornea up to the limbal border (fig. 1e). Thereafter, air is removed from the anterior chamber and a viscoelastic material is injected into the deep stromal pocket (fig. 1f). A conventional trephine (e.g. Barron) is then used to trephine with a diameter of e.g. 7 mm until viscoelastic material evades from the deep stromal pocket (fig. 1g). After a circular excision of the anterior stromal tissue (fig. 1h), special care has to be taken to thoroughly rinse the stromal bed and remove all remaining viscoelastic material since this later can cause interface haze. Thereafter, the lamellar donor tissue is placed into the stromal bed and immediately fixed with two continuous double-running 10–0 nylon sutures. The donor tissue has to be prepared prior to this step by placing a donor corneoscleral tissue upside down (epithelial side down) and punching out an equally sized circle from the corneal center. Endothelial cells are then removed using fine dry sponges. Thereafter, trypan blue is gently placed onto remaining Descemet's membrane for better visualization and Descemet's membrane is then gently removed from the underlying stroma using fine forceps [4, 5]. Alternatively, for very superficial stromal scars, excimer laser phototherapeutic keratectomy can be used.

In case of deep stromal scarring, conventional full-thickness penetrating keratoplasty is performed. We prefer the non-mechanical trephination of donor and host tissue to reduce postoperative astigmatism and improve visual

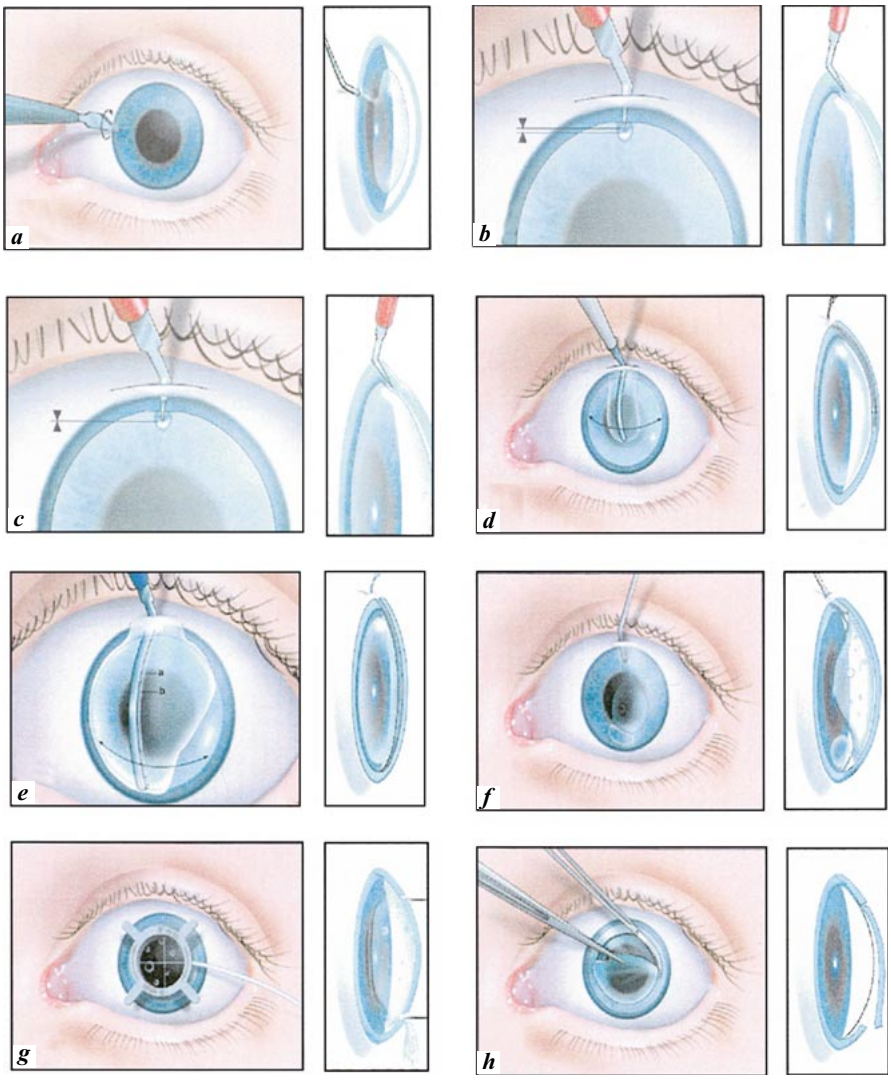

Fig. 1. The DALK technique. Modified from Melles et al. [4, 5], The Netherlands Institute for Innovative Ocular Surgery, DALK course handout; with friendly permission. See text for a detailed description.

results [6]. Trephination of donor tissue is performed in an artificial anterior chamber with a defined pressure of 22 mm Hg. After placing a metallic protection mask onto the center of the cornea, the donor tissue is excised using the 193-nm excimer laser. The recipient is prepared by marking the center of the

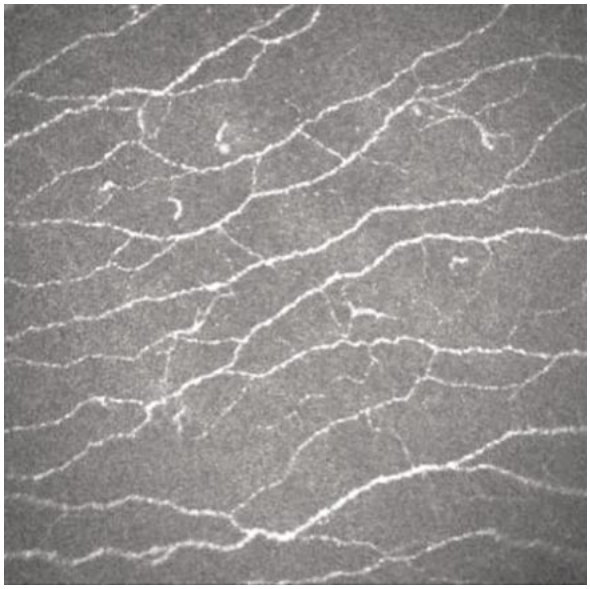

Fig. 2. Normal subepithelial innervation in the central cornea imaged using confocal microscopy technology in vivo (HRT II with cornea module). This technology can be used to assess loss of and regrowth of corneal nerves after keratoplasty.

cornea using a radial keratometry marker. Then again, a metallic protection mask is placed onto the recipient and the center of the cornea is excised along the metallic mask using the excimer laser. After removal of the central host tissue, a small iridotomy is performed in the peripheral iris at 12 o'clock. Then the donor tissue is fixed in the recipient using eight interrupted 10–0 nylon cardinal sutures. Finally, a double-running diagonal continuous suturing technique according to Hoffmann is used to fix the donor tissue permanently into the recipient rim. The cardinal sutures are removed and a placido ring is used to detect potential corneal astigmatism. The latter is then corrected as far as possible by manipulating the suture material [6].

In case of spontaneous perforation of ulcerations associated with severe forms of dry eye, e.g. in the context of chronic graft-versus-host disease, a penetrating keratoplasty à chaud has to be performed. To reduce corneal inflammation, we combine an amniotic membrane patch graft.

Special care has to be taken to provide sufficient lubrication of the graft after transplantation in eyes with reduced tear film. The surgical procedure itself exacerbates tear film deficiency by interrupting the sensory innervation and thereby autonomic stimulation of tear production (fig. 2). Sufficient

Table 1. Surgery for limbal stem cell disease in the context of dry eye

Limbal autograft/allograft transplantation
Transplantation of ex vivo expanded limbal epithelium
Sequential keratectomy

lubrication of the graft after transplantation also seems to reduce the risk of corneal graft rejection [Cursiefen et al., in preparation]. This may be due to the fact that dry eye causes ocular surface inflammation, which in turn activates antigen-presenting cells and promotes graft rejection. In cases of severe dry eye, we perform a simultaneous amniotic membrane patch graft. Surgery for persistent epithelial defects itself using amniotic membrane transplantation is discussed below.

Limbal Stem Cell Surgery in the Treatment of Dry Eye (table 1)

If severe forms of dry eye lead to limbal stem cell deficiency or if limbal stem cells are affected, e.g. in chemical burns causing dry eye due to meibomian gland deficiency together with stem cell deficiency, limbal stem cell surgery comes into play. There are several options when stem cells are deficient, unilateral and incomplete: (a) limbal autograft (from the ipsilateral or the contralateral eye) and (b) sequential keratectomy when the deficiency is localized. The latter can be combined with amniotic membrane transplantation. When unilateral stem cell deficiency is complete, tissue has to be obtained from the other healthy eye either by limbal autograft or by transplantation of ex-vivo cultivated limbal stem cells. These can be grafted on amniotic membrane or e.g. on fibrin gels (fig. 3). Transplantation of ex-vivo cultivated limbal stem cells has the advantage that only a small amount of healthy limbal tissue from the contralateral eye needs to be excised. In cases where bilateral stem cell deficiency occurs, stem cells have to be obtained from donor tissue, again either for ex-vivo amplification or direct surgical transplantation. In these cases, long-term immunosuppression is mandatory to enable survival of grafted tissue.

Amniotic Membrane Transplantation in the Treatment of Dry Eye

Persistent epithelial defects and stromal ulcerations are a common problem in patients with severe dry eye, most commonly associated with neurotrophic

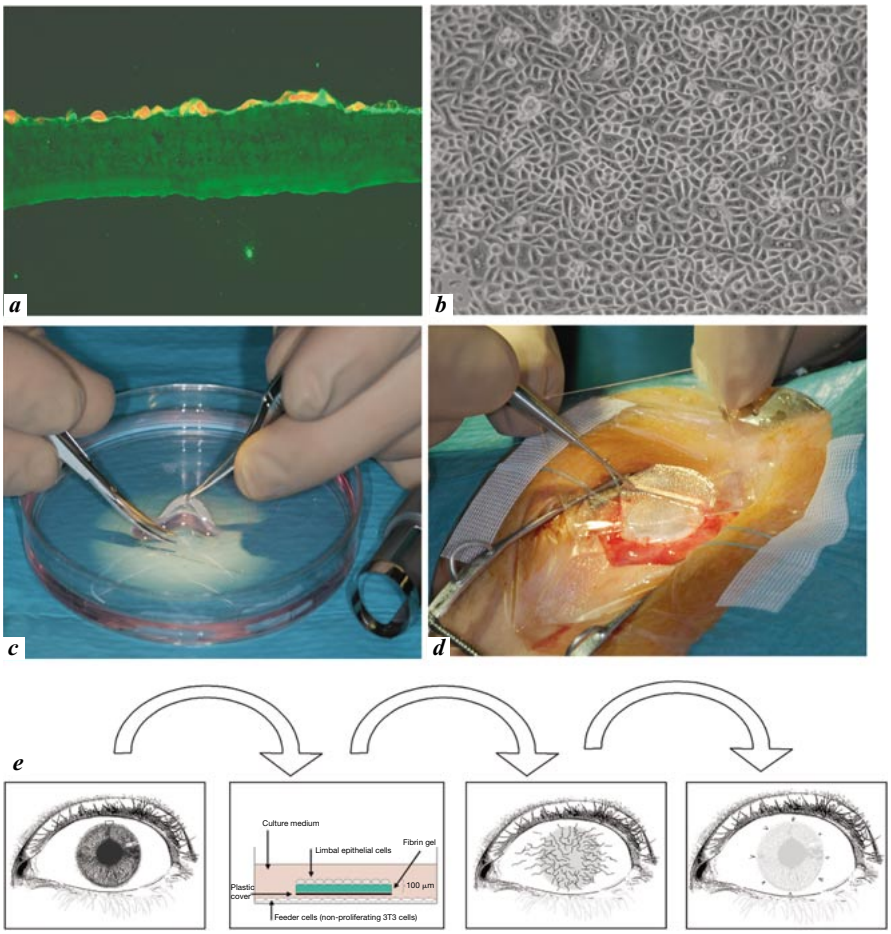

Fig. 3. Technique of surgical correction of limbal deficiency by transplantation of ex-vivo cultivated limbal stem cells on fibrin gels as carriers. ***a*** Cross-section through a fibrin gel with limbal stem cells on top (cell nuclei are stained in red). ***b*** View onto a confluent cell culture on a fibrin gel. ***c*** Excision of a piece from the fibrin gel immediately prior to transplantation. ***d*** The transplanted fibrin gel carrying limbal epithelial cells is sutured onto the recipient cornea. ***e*** Schematic drawing of the procedure: after excision of a small segment of healthy limbal tissue from the contralateral eye (1 × 1 mm), the stem cells are cultured ex vivo and then transplanted onto the diseased eye [with friendly permission from 13].

keratopathy, rheumatoid diseases or chronic forms of graft-versus-host disease. Conservative measures include lubrication of the ocular surface, occlusion of the draining canaliculi, serum eyedrops and bandage contact lenses [7–9]. If these measures fail, transplantation of amniotic membrane usually as a patch

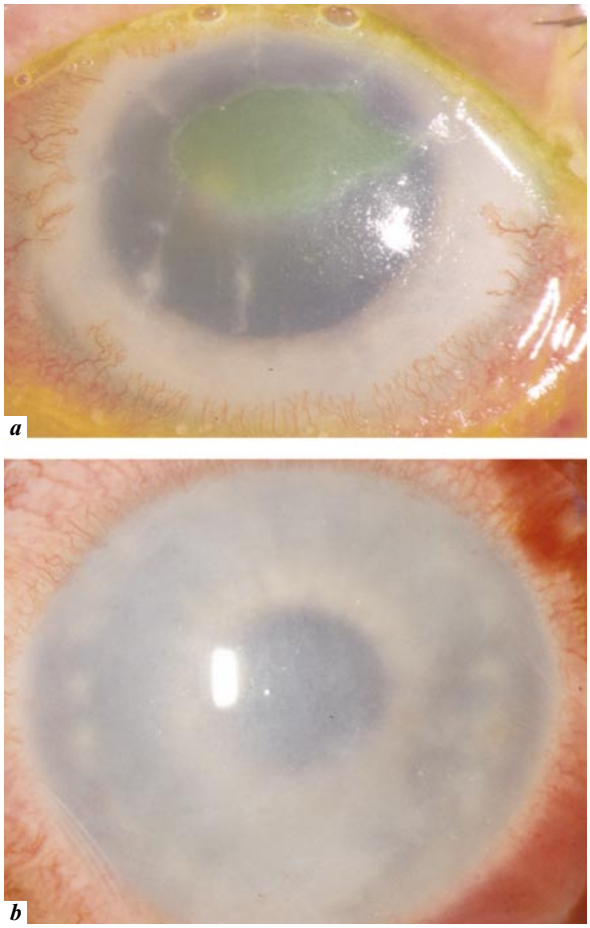

Fig. 4. Amniotic membrane transplantation in the treatment of severe dry eye and persistent epithelial defects in a 42-year-old male patient with chronic graft-versus-host disease after bone marrow transplantation [with friendly permission from 8].

graft is a simple, reliable, fast and cost-effective measure to promote surface healing despite tear film deficiencies [10–12] (fig. 4). Amniotic membrane acts in several ways to promote repair of the ocular surface. First, amniotic membrane can act as a new basement membrane for epithelial cells to grow on. Second, amniotic membrane exerts an anti-inflammatory milieu, e.g. by releasing IL-1 receptor antagonist. Thereby, inflammation of the ocular surface, which in itself causes dry eye, can be inhibited. Third, amniotic membrane contains growth factors (such as neurotropic growth factor (NGF)) which

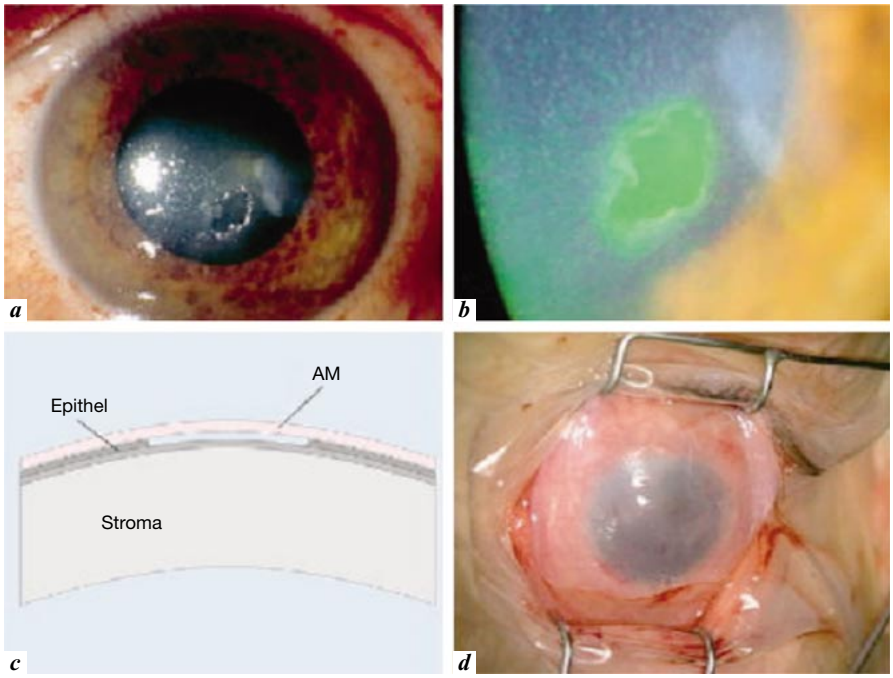

Fig. 5. 'Patch' surgery of amniotic membrane transplantation to promote healing of corneal epithelial defects in severe dry eye [with friendly permission from 3].

directly address the pathophysiology of dry eye in neurotrophic keratopathy. Finally, amniotic membrane integrates into the cornea, either subepithelially, intraepithelially or intrastromally, and thereby smoothes surface defects in case of corneal ulceration. Amniotic membrane can be used in three different forms in the context of erosions and ulcerations of the cornea in severe dry eye: in case of pure epithelial defects, a 'patch' of amniotic membrane is placed over the cornea and acts as a biologic contact lens (fig. 5). The size of the tissue can either be defined using conventional trephines or excised manually. The amniotic membrane is usually fixed using 10–0 nylon sutures with a bandage contact lens on top of it. In case of corneal ulcerations, one up to several layers of amniotic membrane can be placed in the ulcer. The most superficial layer is then sutured to the cornea ('graft' style; fig. 6). Both approaches can be combined in severe surface defect ('sandwich' approach [2, 3]).

Dry Eye Associated with Neurotrophic Keratopathy

Neurotrophic keratopathy is characterized by a combination of severe to moderate dry eye with a reduced healing capacity of the corneal epithelium

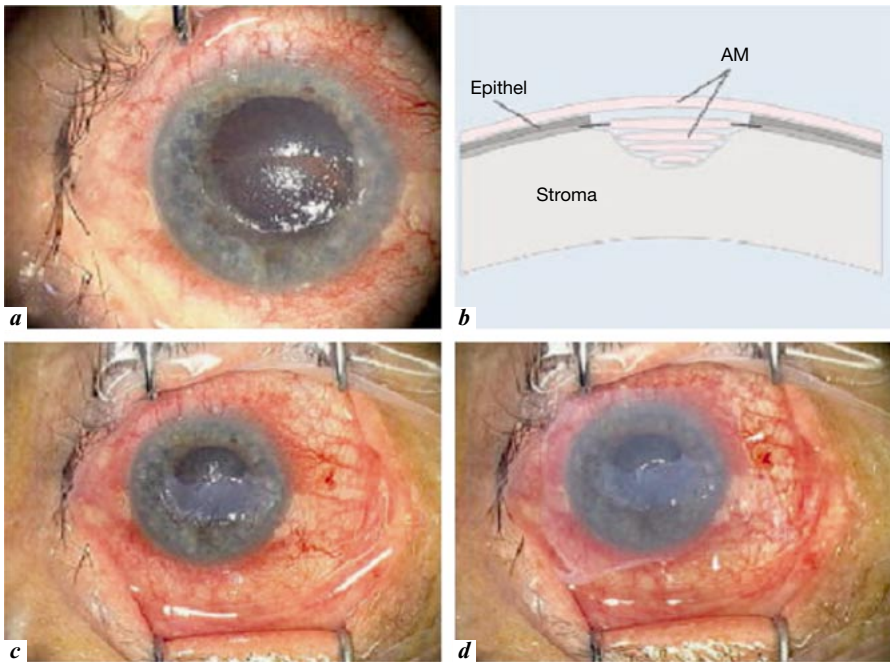

Fig. 6. 'Graft' surgery to seal corneal ulcerations in severe dry eye in neurotrophic keratopathy [with friendly permission from 3].

[2, 3]. Causative for a neurotrophic keratopathy is a defect in the sensory innervation of the cornea, i.e. the first branch of the trigeminal nerve. The reduced sensory information from the cornea leads to a reduced stimulation of the autonomic innervation of the basal and reflex tear production [2]. Clinically, neurotrophic dry eye in the first stage (Mackie stage I [2, 14]) appears as a normal 'keratoconjunctivitis sicca', i.e. epithelial surface irregularities, dot-like fluorescein and rose bengal staining. Especially in the first stage of neurotrophic keratopathy it is very easy to miss the diagnosis and confuse a stage I neurotrophic keratopathy with a dry eye of other origin. Therefore, it is imperative to perform aesthesiometry of the corneal surface in all patients with unilateral or asymmetric or abnormal dry eye disease. Neurotrophic keratopathy then progresses to stage II, which is characterized by a persisting epithelial defect and may eventually lead to stage III disease, which is a corneal ulcer with the danger of progressive corneal melting and perforation. In all three stages, corneal aesthesiometry is a decisive step in making the correct diagnosis. Treatment of stage I–III primarily consists of topical unpreserved lubricants. Additional lid malpositions and other exacerbating factors should be minimized. Other treatment

options in stage I and II include punctum plugs, bandage contact lenses and a temporary tarsorrhaphy. Causal treatment options include the topical administration of NGFs [for details, see 15] or pro-NGF (currently in preclinical evaluation) which are essential for maintenance of normal epithelial wound healing, topical application of serum eyedrops (which also contain NGFs), and amniotic membrane transplantation (which also contains NGF). Amniotic membrane transplantation in neurotrophic keratopathy has two different indications with respect to the stage of neurotrophic keratopathy. In stage I (keratopathia punctate superficialis) and stage II (persisting epithelial defect), the purpose of amniotic membrane transplantation is to provide a natural bandage lens in addition to providing NGFs. This means that in stage I and stage II disease a 'patch' of amniotic membrane will be sutured onto the cornea (diameter up to 10 mm), usually with eight 10-0 nylon sutures, to keep the patch in place. Alternatively a larger patch, e.g. 16 mm, can be fixed onto the cornea and adjacent conjunctiva using eight 8-0 absorbable vicryl sutures. To provide a longer 'survival' of the amniotic membrane on the corneal surface, we usually add a 17-mm bandage contact lens with prophylactic antibiotic topical drops on the amniotic membrane (fig. 5). The strategy shifts in stage III neurotrophic keratopathy with ulceration where amniotic membrane grafts are placed in the ulcer and the most superficial layer sutured to the adjacent corneal stroma, again with usually eight 10-0 nylon sutures (fig. 6) [2, 3]. In addition, one can place a patch on top of the cornea and the conjunctiva again sutured with eight single stitches with a 10-0 nylon sutures ('sandwich'). Again, a 17-mm bandage lens is added on top of this. The sutures and the bandage contact lens are left in place for 4 weeks with prophylactic topical antibiotic eyedrops and tear replacement. After 4 weeks the sutures are carefully removed without damaging the amniotic membrane. In summary, amniotic membrane transplantation either as a patch in stage I or II or as a graft (or sandwich) in stage III is a very reliable, easy to perform and helpful strategy to treat epithelial surface disorders or ulcers associated with the dry eye in neurotrophic keratopathy [2, 3].

Treatment for Dry Eye Associated with Chronic Polyarthritis

Chronic polyarthritis leads to several pathologies of the ocular surface. These include severe dry eye along with corneal melting and immune mediated inflammatory diseases of the sclera and the posterior pole of the eye. Amniotic membrane transplantation presents a useful adjunct treatment option for persistent epithelial defects associated with severe dry eye disease associated with chronic polyarthritis, which is resistant to topical treatment with tear replacement drops and punctum plugs, temporal tarsorrhaphy and serum eyedrops. In case of persisting epithelial defects, amniotic membrane transplantation is usually performed as patch graft as described above and prophylactic topical

antibiotic applied. An additional bandage contact lens and the sutures are only carefully removed after 4 weeks. Amniotic membrane transplantation provides a useful and reliable strategy to relieve symptoms associated with epithelial defects associated with severe dry eye in patients with chronic polyarthritis.

Conclusions

To conclude: (1) severe forms of dry eye can cause persistent corneal epithelial defects, corneal ulcerations and consequently corneal scarring; (2) a very useful instrument in the surgical management of persistent epithelial defects is the transplantation of amniotic membrane (either as patch, graft or sandwich); (3) persistent corneal scars secondary to dry eye can be treated either by lamellar or – if deep in the stroma – by penetrating keratoplasty; (4) limbal stem cell transplantation offers a new opportunity to restore limbal barrier function and corneal surface integrity in diseases associated with severe dry eye and limbal stem cell deficiency (such as chemical burns), and finally (5) the possibility to transplant ex-vivo cultivated limbal stem cells on fibrin gels as carriers greatly improves the management of patients with unilateral limbal stem cell deficiency.

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Prof. Dr. F. E. Kruse
Department of Ophthalmology, Friedrich-Alexander-University Erlangen-Nürnberg
Schwabachanlage 6, DE–91054 Erlangen (Germany)
Tel. +49 9131 853 4478, Fax +49 9131 853 6401
E-Mail kruse@augen.imed.uni-erlangen.de

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Keratoprosthesis Surgery

Christopher Liu[a], *Konrad Hille*[b], *Donald Tan*[c], *Celia Hicks*[d], *Jim Herold*[e]

[a]Sussex Eye Hospital, Brighton, UK; [b]Augenklinik, Klinikum Offenburg, Offenburg, Germany; [c]Singapore National Eye Centre, Singapore Eye Research Institute, and National University of Singapore, Singapore; [d]Lions Eye Institute and Centre for Ophthalmology and Visual Science, Nedlands and Royal Perth Hospital, Perth, Australia; [e]Department of Maxillofacial Surgery, Royal Sussex County Hospital, Brighton, UK

Abstract

Purpose: To survey current knowledge of use of keratoprostheses for visual rehabilitation in the dry eye. **Methods:** Sections deal with: (1) when a keratoprosthesis is indicated; (2) classification of keratoprostheses; (3) the osteo-odonto-keratoprosthesis (OOKP), its history, indications and contraindications, patient assessment, surgical technique, results and complications, and (4) the AlphaCor, its design, indications, results and complications. **Results:** The choice of keratoprosthesis in the severely dry eye is straightforward, as only one device – the OOKP – will work. With careful assessment, adequate technique, regular follow-up, and early recognition and management of complications, most patients can look forward to many years of sight with an OOKP. In the appropriately managed marginally dry eye, an AlphaCor keratoprosthesis may be considered, although the device should be seen as an alternative to high-risk keratoplasty in multiple graft rejection and vascularised corneae. **Conclusions:** KPro surgery is a complex and growing field. Those interested are invited to join the KPro Study Group (www.kpro.org), to add their contribution to the ongoing research and device evaluation.

When Is There a Need for Keratoprostheses?

A keratoprosthesis (artificial cornea) needs to be considered when there is little or no prospect of success with conventional cadaveric corneal transplantation

Commercial interest: C. Hicks has financial interests with the manufacturer of the AlphaCor, CooperVision Surgical, through support of departmental funding, travel and research.

or limbal stem cell transplantation. This may be due to a hostile environment such as a dry keratinised ocular surface, lid deficiency, a highly vascularised cornea, or multiple previous corneal graft failure.

Classification of Keratoprostheses

There are a number of ways to classify keratoprostheses, based on the type of fixation (nut and bolt, intrastromal, epicorneal with tissue covering, supra-Descemetic) or the material of the haptic {PMMA e.g. Choyce [1] and Boston (previously known as Dohlman-Doane [2]) devices, Dacron (Pintucci [3]), titanium [4], ceramics [5, 6], hydrogel (AlphaCor [7]), silicone, expanded PTFE (Legeais [8]), biological materials and analogue such as tooth and bone (Strampelli [9], Falcinelli [10]), tibial bone (Temprano [11]), hydroxyapatite and coral (Leon Barraquer [12])}.

To our knowledge, at present only the Boston keratoprosthesis [2], the Pintucci device [3], the Worst-Singh device [13] and the AlphaCor artificial cornea [7] are commercially available, while the haptics of the osteo-odonto-keratoprosthesis (OOKP) and the tibia bone prosthesis are made usually from the patients' own tissue by the surgeon himself. This article focuses on the use of two distinctly different devices, the OOKP and AlphaCor™ artificial cornea.

The Osteo-Odonto-Keratoprosthesis

OOKP was first described by Strampelli [9] in the early 1960s. Basically, a single-rooted tooth root and surrounding jaw bone is fashioned into a plate measuring some 12–15 mm long and 3 mm thick, through which a PMMA optical cylinder is cemented into a hole previously drilled through this plate. The anterior surface of the plate is entirely bony, and the posterior surface mostly dentine. The osteo-odonto-acrylic plate is buried in a submuscular pocket to acquire soft tissue investment. At the same time as fashioning the plate or lamina, the ocular surface is cleared down to Bowman's membrane and exposed to the level of insertion of the recti muscles. The bare area is covered with buccal mucous membrane harvested from the inside of the cheek. Two to four months later, at stage 2 surgery, the lamina is retrieved and placed on the surface of the cornea, having trephined a corneal opening for the posterior part of the optical cylinder to protrude intraocularly. The iris, lens and anterior vitreous will also have been removed (figs 1, 2).

There was an initial international enthusiasm, but it was mostly forgotten after poor results were reported by some authors [14]. The current technique is

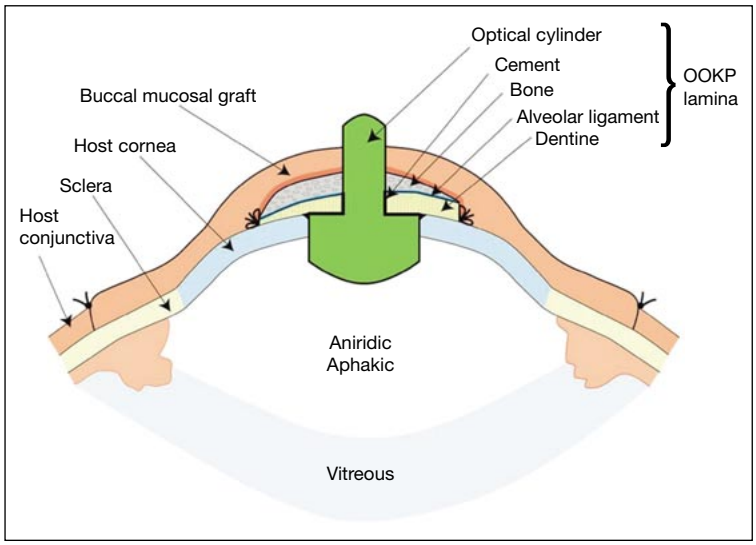

Fig. 1. Cross-sectional anatomy of an OOKP eye.

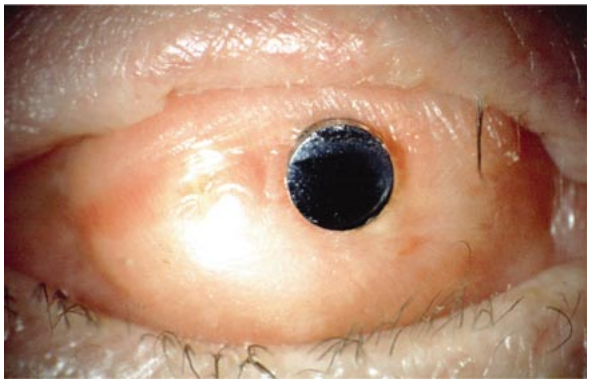

Fig. 2. Appearance of an OOKP eye 7 years following surgery.

that of Falcinelli, who made stepwise improvement of the original technique from the 1970s to the 1990s [15]. Falcinelli's excellent long-term visual and retention results were independently surveyed [16] and his modified technique began to spread after he took on three initial international students in the mid-1990s. The initial spread to Austria [17], Germany [18] and England [19] has

propagated further to Egypt, Japan, Singapore, India and Hong Kong through the efforts of the OOKP teaching group [15].

The strength of the OOKP lies in its ability to be retained even in the dry eye situation. It is not entirely understood as to why the retention rate should be so good, but there are at least three factors. Firstly, there is gradation of materials from non-living rigid PMMA to previously-living rigid dentine, which in turn is interfaced with living porous jaw bone through living flexible alveolar ligament. Secondly, the jaw bone is interfaced with buccal mucous membrane which not only provides a blood supply to the bone, but also a biological seal against infection. Finally, the buccal mucous membrane is mechanically strong and biologically resilient, thus restraining (shrink-wrapping) the OOKP complex even in a hostile ocular environment such as the dry eye.

Indications

The OOKP can be used to rehabilitate all cases of corneal blindness, but because of the gravity of the surgical programme, should be limited to end-stage ocular surface diseases such as severe Stevens-Johnson syndrome, ocular cicatricial pemphigoid, trachoma, other forms of cicatrising conjunctivitides, chemical injury, uncorrectable loss of eyelid, and absolute/severe dry eye states [15]. It is not to be used in unilateral corneal blindness because of the severity of the surgical programme, the possibility of severe complications, the requirement for lifelong follow-up, and because of the difference of image size the OOKP optics would cause, compared to a phakic or pseudophakic eye. In cases of bilateral corneal blindness, only one eye should be rehabilitated although attention should be given to the fellow eye for any glaucoma present. The fellow eye is kept as a spare eye.

Contraindications

The lower age limit is 18 or 19 years of age. Obviously, in eyes with no light perception, there is no hope for visual amelioration. Eyes with severe damage to the posterior segment, i.e. persistent retinal detachment, advanced glaucoma or damage to the optic nerve, should not be operated on either.

Patient Assessment

The patient and their family need to be assessed as a unit, to determine if they are committed to a severe surgical programme and lifelong follow-up at

the OOKP centre. The patient's psychological state and wish for regaining sight needs to be assessed. Prolonged blindness and onset of blindness can lead to depression and various states of dependence on spouse and family. Some patients are happily blind. Some can lead an independent life despite becoming blind, especially if the onset of blindness was at a young age. Some carers cherish the dependence of the blind relative they are caring for, and may subconsciously resent to their regaining independence. Others may push the patient towards surgery when the patient is not seeking surgery. All in all, it is important that it is the patient who wants to have surgery to restore sight, but both the patient and relatives must understand the severity of the surgery, the possibility of serious complications and thus the possibility of further surgery, and the requirement of lifelong follow-up.

Ocular assessment consists of full history and examination, concentrating on ascertaining retinal and optic nerve integrity. Previous surgery (especially lid, cornea, lens) and ocular perforation should be noted. Attention should be paid to the possibility of glaucoma [20, 21], which may be worsened following OOKP surgery due to unintended additional surgical alterations of the anterior chamber angle and the inefficacy of topically applied glaucoma drugs, which will not be absorbed into the anterior chamber through the buccal mucosa covering the haptic. The axial length needs to be measured to determine the optical power of the optical cylinder to be used. Typically, ocular examination includes assessment of relative afferent pupil defect, projection of light in quadrants (patients usually have PL, HM or at best CF vision by the time they come for OOKP surgery), slit-lamp examination, digital palpation of intraocular pressure (the corneae are usually too dry and scarred for applanation tonometry), B-scan to exclude and assess retinal detachment, peripheral anterior synechiae, lens status, and pre-phthisis presenting as a short eye, and A-scan for biometry. Very few cases require electrodiagnostic tests which also cannot be entirely relied upon.

Oral assessment is best done by an oral surgeon, who will also be working on harvesting the tooth together with root and surrounding jaw bone, and buccal mucous membrane. Oral hygiene is assessed. The presence of canine teeth as well as gum and bone recession is assessed, followed by imaging of relevant teeth and their juxtaposition to adjacent teeth with orthopantomography (a form of dental panoramic radiography), individual canine teeth x-rays, and even a spiral CT scan. A single-rooted tooth, usually a canine, with a straight long root of good girth, good bone quality as close to the base of the crown, and good separation from its two adjacent teeth is selected. Buccal mucous membrane is also assessed for area available, quality and whether previous harvesting has taken place and if so on which side. Sometimes, it is necessary to harvest lower labial mucous membrane for lining the upper and lower eyelids.

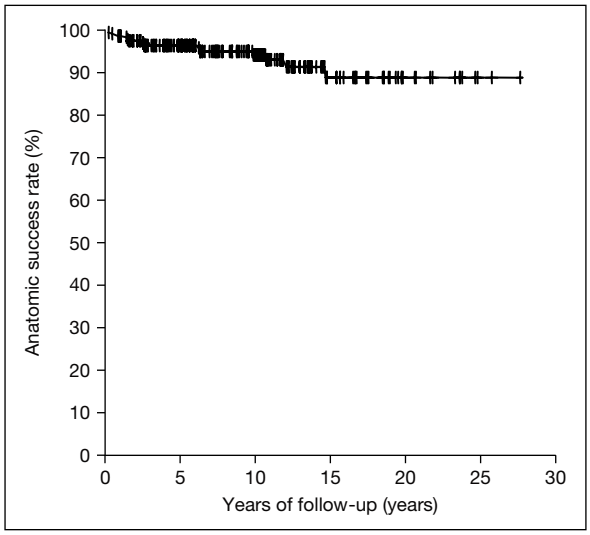

Fig. 3. Kaplan-Meier survival analysis of the anatomic results of osteo-odonto-keratoprosthesis (data of Falcinelli et al. [15], n = 236).

Results of OOKP

The performance of any keratoprosthesis can be measured in terms of a number of parameters including retention (long-term anatomical success), vision (visual acuity, visual field, quality of vision include glare, etc.), patient satisfaction including cosmesis, and sight-threatening complications such as glaucoma, retinal detachment, etc. The size of the visual field depends on the geometry of the optical cylinder and therefore on the size of the available tooth. But often it is much less than its theoretically calculated value [22, 23]. With a classical PMMA cylinder it varies between 30 and 50° and can be enlarged by a larger or conical posterior part of the optic. The visual acuity may be as good as 1.5 (20/12 = 6/4) depending only on retinal status.

Falcinelli et al. [15] reported an anatomic success rate of 96.5% after a follow-up of approximately 5 years, 94.1% in 10 years and 88.8% in about 20 years with a maximum of follow-up of 27 years (fig. 3) In patients with dry eyes, which represent 41.5% of all of Falcinelli et al.'s patients, an improvement of visual acuity at long-term follow-up was found in over 90% of cases [24].

In a smaller German series of 25 patients, one-third had excellent visual acuity of 0.9 or better, two-thirds 'reading vision' (≥0.5 or 6/12) and 80% ambulatory vision (≥0.05 or 1/20). To compare the results of OOKP with other

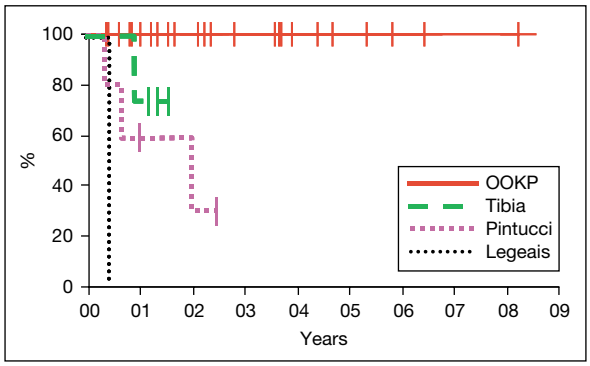

Fig. 4. Kaplan-Meier survival analysis of the anatomic result of a small series of different keratoprostheses (OOKP n = 25, tibial bone keratoprosthesis n = 4, Pintucci keratoprosthesis n = 5, and Legeais keratoprosthesis n = 1) by one surgeon (K.H.).

keratoprostheses, figure 4 shows the Kaplan-Meier anatomic survival analysis of K.H.'s series (Homburg) of different keratoprostheses (25 patients with an OOKP, 4 with a tibial-bone KPro, 5 with a Pintucci KPro, and 1 with Legeais keratoprosthesis). Figure 4 underlines the superiority of OOKP (and the biologic support tibial bone) over other alloplastic haptics.

At the Sussex Eye Hospital in Brighton, we have operated on 35 cases since 1996 (21 male, 14 female, with a mean age of 50.6 years at stage 2). Presenting diagnoses were: 15 Stevens-Johnson syndrome, 5 chemical injury, 6 ocular cicatricial pemphigoid, 4 miscellaneous dry eye diseases, 1 trachoma, 1 linear IgA disease, 1 ectodermal dysplasia, 1 post-bomb blast, and 1 congenital trigeminal nerve hyoplasia. 34/35 proceeded through stage 1 and stage 2 (1 developed a total retinal detachment between stage 1 and stage 2). Mean time interval between stages 1 and 2 was 19.8 weeks (range 9–84). Preoperative visual acuity was: PL (15), HM (15), CF (5). Postoperative visual acuity at last follow-up was: 6/5 (4), 6/6 (2), 6/9 (5), 6/18 (3), 6/24 (1), 6/36 (2), <6/60 (2), HM (4), CF (1), PL (3), and NPL (6) (2 patients required subsequent evisceration). Mean follow-up was: 34.7 months (range 1–96). There were 3 allografts. 7 exhibited clinical resorption of OOKP lamina. 2 subsequently required repeat OOKP surgery. Postoperative complications (episodes, not eyes) were: 5 retroprosthetic membranes, 4 retinal detachments (including the 2 secondary to laminar resorption and endophthalmitis: see below), 3 vitreous haemorrhages, 3 extrusions of lamina, 2 infections of buccal membrane graft, 2 endophthalmitis, 1 expulsive haemorrhage and 1 epiretinal membrane.

OOKP Surgical Technique

Stage 1

OOKP surgery is usually carried out in two stages. In the first stage a monoradicular tooth is harvested to prepare an osteo-odonto-lamina. The root and surrounding jaw bone is sliced sagittally, whilst the crown is grasped with extraction forceps, to expose pulp which is removed. A hole is drilled through dentine through which the anterior part of a PMMA optical cylinder is cemented in place (there are various designs and sources of OOKP optical cylinder, the Brighton school uses cylinders from Lamda Polytech Ltd, Brackley, Northants., UK, the cylinders implanted in Germany had been fabricated by Morcher GmbH, Stuttgart, Germany). The crown is removed prior to drying with filtered oxygen and cementing of the optical cylinder. The saw, flywheel and drill and burr tips are constantly irrigated with balanced salt solution to provide cooling. Where periosteum has been detached, it is glued back with fibrin glue. The KPro is then implanted into a submuscular pouch (often the lower eyelid of the fellow eye) for a period of 2–4 months. A tooth allograft can be considered in edentulous patients, but HLA-matching, screening for blood-borne infections, and long-term immunosuppression with cyclosporin will be required. An allograft may be more rapidly resorbed compared with an autograft. One of us (K.H.) prefers using tibial bone in edentulous patients, but it is known that a tibial bone haptic is resorbed three times as fast as the osteo-odonto-lamina [de la Paz, pers. commun.].

A buccal mucous membrane graft of about 3 cm diameter is used to cover the OOKP lamina, as there are stem cells present, it has proliferating capability and is adapted to high bacterial load. It will be vascularised by the time of stage 2 surgery and will provide the blood supply to the bone part of the OOKP lamina. Once harvested the fat from the buccal mucous membrane graft is removed with curved scissors and the graft soaked in an antibiotic solution until required. The eye is prepared by isolating the recti with stay sutures, a 360° peritomy performed and the conjunctiva and tenons separated from underlying sclera. Corneal epithelium and Bowman's membrane are removed. The buccal mucosa is then trimmed to obtain an oval piece of adequate size to fit snugly on the front of the eye. The mucous membrane graft is sutured onto the side of the insertion of the four recti muscles and to the sclera with interrupted 6-0 vicryl. If possible, the cut edge of the graft should also be sutured to the conjunctiva.

When Not to Do Ocular Surface Reconstruction and Tooth Harvesting Together

If the eye is very dry or there is a risk of the mucous membrane graft not taking, it may be better to perform stage 1 surgery in two steps. The mucous membrane graft to the eye is done first, and it is only when the graft has been shown to be well established before the patient is readmitted for tooth harvesting and preparing an OOKP lamina. Otherwise if there is a significant delay in mucous membrane healing, or if further partial or full repeat mucosal grafting proves necessary, the lamina may be resorbed whilst buried in the lid for an excessively long time.

Stage 2

Stage 2 surgery is carried out 2–4 months after stage 1 in order for soft tissue to become integrated into the bone pores of the lamina. The interval also allows the lamina to recover from thermal damage, and any infection introduced from the oral cavity can be treated whilst the lamina is in the submuscular rather than on the eye. If the lamina is implanted submuscularly for a longer period of time, there may be significant resorption of the lamina. The first step in stage 2 surgery is to retrieve the buried lamina for inspection. It is only if this is of adequate size that the surgeon proceeds to prepare the eye for receiving the device. After the OOKP lamina is retrieved from its submuscular pocket, soft tissue is excised from the posterior surface and the pseudocapsule that has grown around the OOKP is opened in the corners to form four pentagonal-shaped flaps of fibrovascular tissue which are used to fix it to the recipient sclera. Excess tissue is also trimmed from the anterior surface of the implant. A template is made of the lamina in order to plan placement of a Flieringa ring, and preplaced sutures for securing the lamina. The lamina is temporarily returned to its submuscular pocket until the cornea is about to be trephined.

Traction sutures are applied to the lids for access to the eye. A superior rectus stay suture is placed and a buccal graft flap is fashioned by making an arcuate incision from 3 to 9 o'clock under constant irrigation with BSS and adrenaline. The flap is reflected and the cornea exposed. The buccal mucous flap is then reflected and a Flieringa ring sutured in place with sutures left long at 3 and 9 o'clock for traction. The centre of the cornea is marked and the template placed on the cornea and cardinal sutures are preplaced. Intravenous mannitol has by then been administered to reduce the intraocular pressure before trephination. The cornea is partially trephined, the size depending on the diameter of the posterior part of the optical cylinder. This is completed with scissors or a blade. The iris is then completely removed using forceps. If the patient is phakic the lens is removed either by ICCE or ECCE (Falcinelli advocates an ICCE as he fears a capsular rim may occlude the trabecular meshwork. The Brighton school favours ECCE to avoid traction on the vitreous base). A posterior capsulotomy is made (if an ECCE has been used) and an anterior vitrectomy performed, with adequate traction provided by the surgical assistant on the two Flieringa ring sutures. The lamina is then sutured to the cornea with the posterior part of the optical cylinder traversing the corneal opening. Sterile air is then injected to reinflate the eye and indirect fundoscopy performed to ascertain adequate centration, to take note of the appearance of the posterior pole of the eye, and any presence of blood in the vitreous. Further interrupted sutures are applied to secure the lamina onto the sclera. The Flieringa ring is then removed, the buccal mucous membrane is repositioned and sutured in place, with a hole cut through the membrane to allow the anterior part of the optical cylinder to protrude (figs 1, 2).

Complications – Diagnosis and Management

Complications can be divided into operative and postoperative complications. Significant damage to adjacent teeth is uncommon. Very occasionally, the maxillary sinus space may be breached. Facial and jaw fractures are also possible. Overheating of the OOKP lamina can take place without adequate irrigation. Buttonholing the buccal mucous membrane can also take place and requires suture repair. Vitreous haemorrhage can take place, especially if the surgeon does not wait long enough for the iris root bleeding to stop following

total iridodialysis. Expulsive choroidal haemorrhage is possible. Mannitol infusion before opening the eye, and hypotensive anaesthesia help to prevent this catastrophic complication. The optical cylinder may become tilted if suture tensioning of the OOKP lamina is not done correctly.

Among the most common postoperative complications is ulceration or necrosis of the mucous membrane graft. This is less common with a vascularised cornea, otherwise tenons tissue should be mobilised to lie over the cornea and to help supply the central part of the buccal mucous membrane graft with blood. When the mucous membrane should thin or ulcerate, it is important to exclude infection and treat with prophylactic topical and systemic antibiotic. The thinned or ulcerated area, if not healed, will necessitate a bipedicular flap from the peripheral part of the graft, followed by a new graft to the peripheral bare area thus created. The periphery often has a better blood supply. Occasionally it is necessary to repeat the buccal mucous membrane graft altogether. If this has to be done following stage 2, then it will be necessary to remove the device and close the corneal opening with a small corneal graft whilst the device is returned to a submuscular pocket usually under the lower lid of the contralateral eye. It is also possible to use lid skin as cover as a last resort, having removed muscle and fat from the skin first.

Glaucoma may be pre-existent [21, 25] or secondary to OOKP surgery. This needs to be tackled, otherwise continued field loss and finally loss of central vision will ensue despite technical success and retention of the device. Assessment of glaucoma is difficult but it is possible to estimate intraocular pressure with digital palpation through the upper lid, with the patient looking down to avoid the rigid OOKP lamina. Other parameters which can be assessed include optic disc appearance, visual field examination and electrodiagnostic tests [25]. Treatment is limited to systemic carbonic anhydrase inhibitor and surgery (cyclodestruction or drainage tube) which has not yet been worked out fully [26, 27].

It is not known how the OOKP lamina is absorbed, but it is in an ectopic situation, and the fact that it no longer bears a load (it previously did with mastication) may be responsible for increased osteoclastic activity. Bacterial action around the area bound by the mucous membrane graft opening may also play a part. The strategy has been to insert an adequately sized lamina of a minimum thickness of 3 mm throughout to allow for loss. The diameter of the cylindrical opening through the lamina is dictated by the diameter of the anterior part of the optical cylinder. For a thin root, a narrower optical cylinder needs to be used. When there is inadequate bone and dentine, the lamina (or the optical cylinder) can extrude through the overlying buccal mucous membrane. The subsequent entry of microorganisms can lead to the permanent loss of the eye. Thus the laminar dimensions are assessed at each clinic visit, using a cotton bud, the stability of the optical cylinder ascertained, including measuring the refraction, since any change in refraction is most likely to have been caused by an axial shift or tilt of the optical cylinder. Serial photography from the side will also document and demonstrate protrusion of the anterior optical cylinder using the buccal mucous membrane as a reference point. In the absence of a change of refraction, such a protrusion may be due to thinning of the mucous membrane or the OOKP lamina, or a combination of both. Even though imaging will be at the limits of resolution, spiral CT [28–30] and electron beam tomography [31] have been useful in confirming clinical suspicion, leading to fashioning of a new lamina ready for lamina exchange after 2–3 months, in anticipation of device failure.

Retinal detachment is a distinct possibility, especially in a young person following disturbing vitreous. Patients are warned of symptoms of posterior vitreous detachment, and

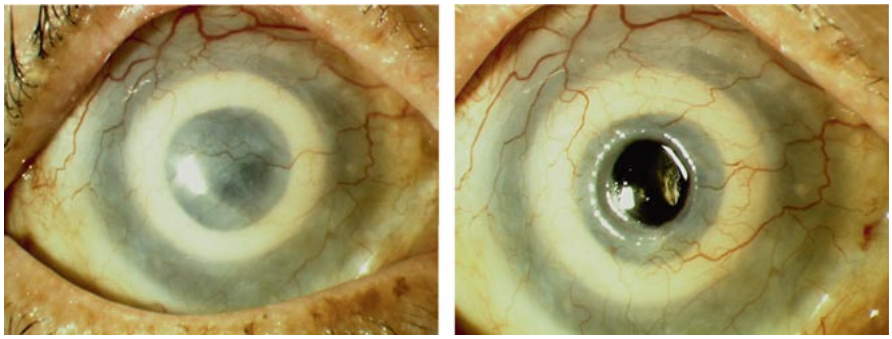

Fig. 5. An image of a patient with AlphaCor in situ before and after stage 2 surgery.

each clinic follow-up is accompanied by a B-scan of the fundal periphery which cannot be viewed through the optical cylinder. Repair is now usually done with the BIOM system, although the endoscopic vitrectomy approach is sometimes called for. Neither technique requires the removal of the OOKP device.

AlphaCor

The Device

An alternative to rigid KPro technology is the AlphaCor™ artificial cornea (Addition Technology Inc., Des Planies, Ill., USA) which has been described previously [32–34] and surgical techniques discussed [35–37]. It is a flexible poly(2-hydroxyethyl methacrylate) (PHEMA) core-and-skirt keratoprosthesis with a peripheral macroporous skirt region that biointegrates through tissue ingrowth surrounding an effectively non-porous transparent optic. It is implanted within a lamellar pocket of which the central 3.5 mm posterior to the optic is removed, with the optic becoming a full-thickness corneal replacement 3 months later at stage 2 of the procedure, when tissue anterior to the optic is removed. A typical postoperative appearance of the device in the eye before and after stage 2 opening is seen in figure 5. A Gunderson flap, as pictured in figure 5, was originally felt a necessary adjunct to AlphaCor implantation, but it is now rarely performed.

The device is designed for use as a corneal replacement in an eye with a reasonable corneal tear film, but may be used in mild-moderate dry eye states (if appropriately managed, for example with artificial tears, lateral tarsorrhaphy, bandage lens and some surgeons believe, with restasis), and in eyes with limbal stem cell abnormality. Although a specially modified earlier prototype was evaluated in animals for a severely dry eye situation [38], this has not been

developed for human application to date. The hydrophilic nature of PHEMA requires it to be positioned in a wet environment such that it retains a tear film to provide a good quality refractive surface. An inadequate or inflammatory tear film could increase the risk of postoperative stromal melting around the device, and of contact-lens type deposition on the optic. AlphaCor's conservative design, which lacks protuberant parts so as to minimise mechanical stresses, does entail the optic being recessed in relation to surround corneal tissue, and this impacts adversely on optic wetting and refractive performance in some cases.

Indications

AlphaCor has gained widespread regulatory clearance for use in adults with corneal opacity unsuited to a corneal graft due to a high risk of failure. Nearly 90% patients to date had previous graft failures (1–13, mean 2.4). Glaucoma affected 56.0% cases preoperatively and 24.9% had a drainage tube in situ. A history of chemical injury was reported in 12.6% of the series, and aniridics represented 6.9%. Detailed data concerning patient profiles and outcomes are voluntarily compiled and updated in the manufacturer's anonymous database, and available to user surgeons.

Outcomes

300 AlphaCors have been implanted to date, with a maximum of just over 7 years' follow-up, mean over 1 year. Protocol cases have a better chance of 1-year retention in situ than a donor graft in similar preoperative conditions, as has been discussed previously, and risk and protective factors for the device have been described elsewhere [39, 40]. Risk factors for graft survival, such as vascularisation, number previous failed grafts, and glaucoma tubes, do not appear to impact adversely on AlphaCor outcomes. (fig. 6) A system for evaluating risk of graft or AlphaCor success preoperatively has been suggested but requires more data to validate [41].

Postoperative best corrected visual acuity outcomes for AlphaCor range between Light Perception and 6/6, with patients demonstrating a mean gain of 2.5 lines visual acuity. The best corrected visual acuity achieved with AlphaCor matches that (paired t-test) of patients achieved from their previous donor tissue graft prior to its failure.

Discussion

The choice of keratoprosthesis in the severely dry eye is straightforward, as only one device – the OOKP – will work. With careful assessment, adequate

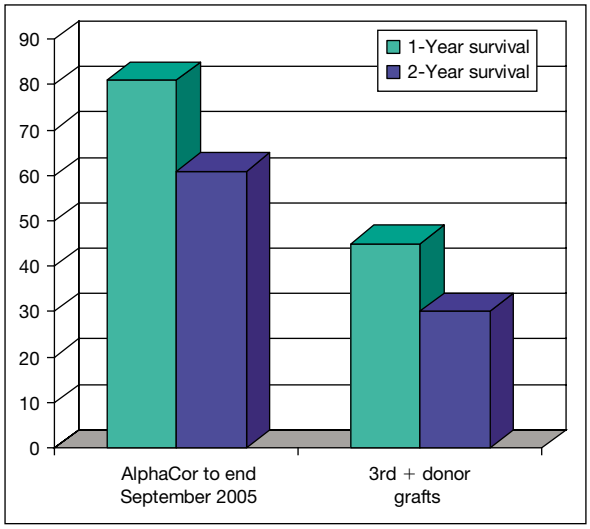

Fig. 6. Chart comparing probability of 1- and 2-year survival in situ for AlphaCor with donor grafts. Graft data from Bersudsky et al. [45]. AlphaCor data current to end September 2005, all on-label cases treated with MPG (n = 180).

technique, regular follow-up and early recognition and management of complications, most patients can look forward to many years of sight with an OOKP. The surgery is complex and requires extensive support including long general anaesthesia, as well as input from oral surgical, oculoplastic, glaucoma, vitreoretinal and radiological colleagues. OOKP surgery should be confined to specialist centres. Shared care with the referring ophthalmologist is only appropriate if the referring ophthalmologist is willing to be rapidly available and is capable of recognising and treating complications of OOKP surgery.

In the appropriately managed marginally dry eye, an AlphaCor keratoprosthesis may be considered, although the device should be seen as an alternative to high-risk keratoplasty in multiple graft rejection and vascularised corneae. Despite encouraging results from AlphaCor in eyes that would be high risk for penetrating keratoplasty [42, 43] and falling incidences of complications as described previously as risk and protective factors have been learned and management improved [44], this is clearly a device still very much on the learning curve and there is room for continued development and improvement of techniques and postoperative management to optimise outcomes. Current data support the concept that patient selection is critical for success and suggest that AlphaCor outcomes result in higher probabilities of success at 1 and 2 years than is achieved by high-risk cases undergoing conventional donor penetrating

keratoplasty. However, ongoing data collection and analysis will be critical in determining definitively which patients should have AlphaCor and which should have a further graft or other procedure in order to achieve the best possible outcome.

KPro surgery is a complex and growing field. Those interested are invited to join the KPro Study Group (www.kpro.org), to add their contribution to the ongoing research and device evaluation.

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Christopher Liu, FRCOphth
Sussex Eye Hospital
Eastern Road, Brighton BN2 5BF (UK)
Tel. +44 1273 606 126, Fax +44 1273 693 674, E-Mail cscliu@aol.com

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Eyelid Botulinum Toxin Injections for the Dry Eye

Sven Sahlin, Rikard Linderoth

Karolinska Institute, St. Erik's Eye Hospital, Stockholm, Sweden

Abstract

The injection of botulinum toxin into the medial lower eyelid causes a local paralysis of the orbicularis oculi muscle. The paralysis leads to a decreased action of the lacrimal pump and an improved lubrication of the ocular surface. The injection reduces the discomfort in eyes of patients with Sjögren's syndrome.

The symptoms of dry eye can be reduced by adding lubricants to the tear film or stimulating tear secretion. Another strategy is to reduce the drainage of tears. A reduced drainage causes the natural tears as well as added lubricants to remain in the eye for a longer period of time. Punctum plugs are a well-established method to block the lacrimal passages but this technique has a significant number of side effects including discomfort, abrasion of the conjunctiva and cornea, epiphora, canaliculitis, dacryocystitis, granuloma formation, extrusion or intrusion of the plug, fragmentation of punctal plugs and canalicular stenosis [1]. The puncti can also be closed surgically with cautery or more sophisticated procedures. However, blocking the lacrimal passages can cause epiphora even in patients with Sjögren's syndrome and with permanent surgical occlusion of the tear drainage system this complication may also become irreversible.

In 1855, Arlt [2] observed that epiphora is a constant phenomenon in facial palsy and further that epiphora may exist in facial palsy without punctal eversion or ectropion. He reported that epiphora was the first symptom making him suspect facial palsy in one patient.

It is also our clinical experience that sometimes epiphora is the only sequel in facial palsy. The observation of Arlt was a strong argument for the hypothesis of a lacrimal pump, an active lacrimal drainage coupled to blinking, an idea

proposed already in the 18th century [3]. The type of coupling between blinking and lacrimal drainage has been widely debated. The conjunctival sac, the canaliculi, the lacrimal sac or the nasolacrimal duct, alone or in combination, have been proposed as the lacrimal pump. However, when dacryocystorhinostomy was introduced [4] to treat dacryocystitis, it became evident that the lacrimal sac and the nasolacrimal duct were not necessary for an adequate lacrimal drainage and that the canaliculi have a major role in lacrimal drainage. The importance of the canaliculi was experimentally confirmed by pressure and flow recordings by Rosengren [5]. The preseptal and pretarsal deep (Horner's muscle) and superficial heads of the orbicularis oculi muscle are thought to be the main muscles acting on the canaliculi [6]. There are also suggestions that the valve mechanism directing the flow of tear fluid towards the nasal cavity is a muscle-dependent mechanism, either by a sphincter mechanism [7] or by apposition of the upper and lower lid during blinking [8]. In addition, lacrimal drainage has a passive component driven by gravity [9].

Blinking not only has a major role in the lacrimal drainage, but also with each blink the tear film is re-established and thus blinking is also responsible for wetting the ocular surface.

Botulinum toxin was introduced in 1980 in the treatment of strabismus [10]. It is one of the most lethal naturally occurring neurotoxins, and is produced by *Clostridium botulinum* bacteria. Different strains produce different types of toxin, but botulinum toxin A is the type used clinically. There are two commercially available botulinum toxin A products, Botox® (Allergan Botox Ltd, Ireland) and Dysport® (Ipsen Biopharm, UK). The nature of effects and side effects of both preparations is similar but the efficacy per unit of toxin differs. In general, the efficacy of Botox® is 2–5 times the efficacy of Dysport®. The toxin acts by rapid and strong binding to presynaptic cholinergic nerve terminals with subsequent internalization of toxin and reduction in the output of acetylcholine. This leads to a down-regulation of post-junctional acetylcholine receptors. The effect is a weakening of the involved muscle, skeletal or smooth. Recovery of muscle function usually requires 2–4 months and occurs through several mechanisms most importantly, neural sprouting and reinnervation [11]. Botulinum toxin, especially type B toxin, also has autonomic effects [12], due to the alterations in peripheral cholinergic parasympathetic nerves. This effect can be used to reduce tear production in lacrimal hypersecretion [13, 14]. In ophthalmology the main use of botulinum toxin is in the treatment of blepharospasm but also to induce ptosis in patients with lagophthalmus or keratitis and in patients with squint problems. In recent years the use of botulinum toxin for cosmetic purposes has become widespread. The side effects are typically reversible and of short duration. In blepharospasm, side effects are caused by toxin effects on adjacent muscles, for example causing ptosis or diplopia or

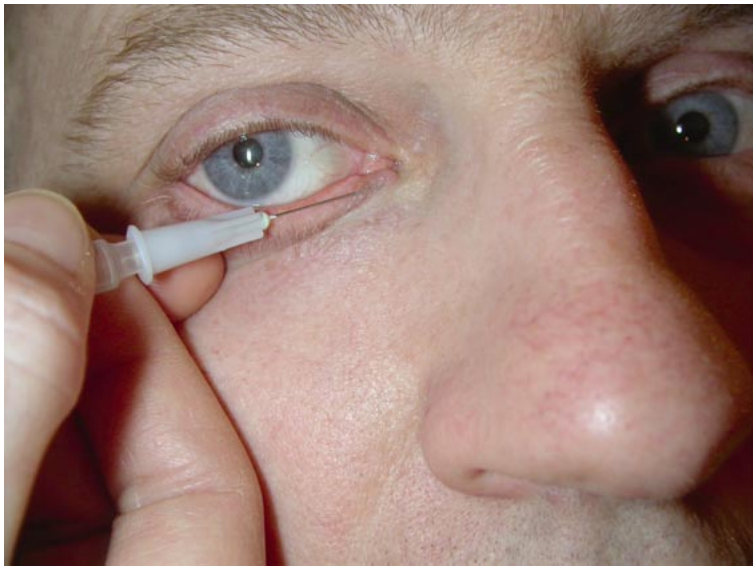

Fig. 1. Subcutaneous injection of botulinum toxin into the lower medial eyelid.

overdosage with impaired blinking causing dry eyes and keratitis. Epiphora is also described as a complication in the treatment of blepharospasm [11].

With this background, we initiated a series of experiments [15] to investigate whether an injection of botulinum toxin could cause a situation similar to facial palsy with a reduction of tear drainage and a beneficial effect to patients with dry eyes.

Method

The anatomical basis for the lacrimal pump is thought to be the deep and superficial heads of the pretarsal and preseptal orbicularis oculi muscle [6]. Therefore, in a previous study [15], a subcutaneous injection of botulinum toxin was given in the area between the punctum and the medial canthus in the lower (fig. 1) and sometimes also the upper lid. The aim was to temporarily denervate the orbicularis fibers adjacent to the canaliculus. Botulinum toxin A (Botox®, Allergan Botox Ltd, Ireland) was used in a concentration of 2.5 IU/0.1 ml. A volume of 0.1 ml to both the upper and lower eyelid or 0.15 ml (3.75 IU) to the lower lid was used.

Injection of botulinum toxin to the medial lower lid reduces the horizontal sliding of the lower lid when blinking and injection to the medial upper lid

causes a discrete retraction and a slightly weaker vertical movement of the upper lid.

In the study it was shown that the blink output (volume expelled with each blink) was reduced to 64–70% of baseline values with lower lid injections and to 38% with both upper and lower lid injections. The lacrimal drainage capacity (drained volume per unit time), including both active drainage by blinking and passive drainage by gravity, was reduced to 52% with one injection and to 42% with injections to both upper and lower lid. The subjective experience of the injections was a more comfortable eye in 6/9 with one injection. With injections to both upper and lower lids, 9/10 patients experienced a wetter eye but 2 of these did not feel more comfortable. We had the impression therefore that injections to both upper and lower lid had a more pronounced effect, however when injections were given to the upper lid some side effects appeared, although they were judged to be tolerable and of short duration. Notably 1 patient complained of increased foreign body sensation for a couple of weeks probably related to a decreased blinking associated with injections to the upper lid. With isolated lower lid injections no side effects were noted. The effect of the injections lasted for approximately 3 months, when blink output and lacrimal drainage values also had returned to baseline.

A small number of patients have had repeated injections over the last 5 years with no side effects and no signs of damage to the eyelid.

Recently, a randomized prospective controlled study (unpublished) was started to further investigate the suggested treatment. The study is still open and includes only well-documented cases of primary or secondary Sjögren's syndrome with dry eyes. Botulinum toxin (3.75 IU) is given subcutaneously in the medial part of the lower eyelid. One eye receives the toxin and the other placebo (saline) in each patient. The patient is unaware of which side is treated with toxin. Three weeks after treatment the patients found the toxin-treated eye 'better' (6/10) or 'similar' (4/10) to the eye treated with placebo. No patient found the placebo-treated eye better. Three months after treatment the patients reported no difference between the toxin-treated and the placebo-treated eye. The most common side effect was epiphora (3/10), no ptosis or lagophthalmus was observed and no diplopia reported. The overall impression was 'positive' in 6/10 patients.

Conclusion

The treatment of dry eyes with botulinum toxin A injections to the lower lid is safe with few and temporary side effects. Our clinical experience is that the botulinum toxin injections have a success rate of 60–70%. The duration of the effect of the injection is about 3 months. The technique is simple.

The orbicularis muscle and the eyelids are responsible both for establishing and removing the tear film, therefore a change in the function of the orbicularis muscle can result in both a dry eye when blinking is impaired and a wet eye when the tear pump is blocked. In facial palsy, sometimes lagophthalmus and corneal drying dominates whereas epiphora in this situation may result from lacrimal pump failure, punctal eversion or paralytic ectropion. Further, the tear production can possibly be impaired by injections of botulinum toxin close to the lacrimal gland. These factors may cause varying results on the tear film of botulinum toxin injections into the eyelids in patients treated for blepharospasm [16–18].

Botulinum toxin injections are not recommended in patients where impaired blinking is a factor causing the dry eye symptoms. In our experience, patients with minor as well as serious dry eye problems have benefited from the treatment. If the effect is unsatisfactory, punctal temporary or permanent punctual occlusion should be considered (see chapter on page 213).

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Sven Sahlin
Ögonplastiksektionen, St. Erik's Ögonsjukhus
SE–112 82 Stockholm (Sweden)
Tel. +46 8 672 3085, Fax +46 8 672 3311, E-Mail sven.sahlin@sankterik.se

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Plugs for Occlusion of the Lacrimal Drainage System

Frank H.W. Tost[a], *Gerd Geerling*[b]

[a]University Eye Hospital, Greifswald, Germany; [b]Department of Ophthalmology, University of Würzburg, Würzburg, Germany

Abstract

Background: Next to medical therapy, blockage of the lacrimal drainage system is the commonest form of treating dry eye. Rather than applying an artificial tear, the latter helps to preserve any remaining natural tear fluid, which by far has the best wetting and nutrient capacity for the ocular surface. A temporary block is usually induced by implants to tamponade on the level of the lacrimal puncta or canaliculi. **Materials and Methods:** A Medline search was performed with the keywords *'lacrimal drainage system*, *punctum*, *canaliculus*, *temporary occlusion*, *plug*, *dry eye*, *keratoconjunctivitis sicca'* for the years 1986–2006. Plugs are a suitable treatment in patients with moderate or more severe disease. The characteristics of the devices used and procedures as well as the complications described were analyzed. **Results:** Criteria such as a lack of Schirmer strip wetting, ocular surface staining and the frequency of artificial tears instillation should be assessed prior to making the decision to occlude the lacrimal drainage. Lacrimal plugs made of silicone or a thermodynamic acrylic polymer, such as hydrogel, appear to be safe and effective, although each patient should be followed on a long-term basis to exclude alterations of the lacrimal system such as chronic inflammatory reactions, extrusion or migration, which may all lead to discomfort. High-frequency ultrasound as a non-invasive, simple diagnostic technique can be used to identify the type or position of plug or inflammatory reaction present. **Conclusion:** Tamponade of the lacrimal drainage system is a simple procedure that is underused. Preserving natural tears by blocking the lacrimal drainage system can successfully maintain the integrity of the ocular surface and corneal transparency and visual acuity. In patients with moderate or severe dry eye, it is capable of improving quality of life and preventing loss of vision.

Background

A stable tear film is a prerequisite to maintain an intact ocular surface and thus corneal transparency. Aqueous tear deficiency can be compensated by

application of artificial tears or by reduction of lacrimal outflow. Next to medical therapy, blockage of the lacrimal drainage system is a commonly used modality to treat dry eye. The residence time of natural tears – the fluid with the best lubricant and nutrient capacity for the ocular surface – can be expanded by partial or complete blockage of the lacrimal drainage system. Implants to tamponade as well as a large number of surgical methods have been described to occlude the lacrimal drainage system [1, 2]. Implants are used in large quantity with an estimated total number of 200,000 plugs per year in the USA (approx. 10,000 plugs in Germany).

Considerations/Examinations Prior to Occlusion

A correct clinical diagnosis is mandatory to choose an adequate treatment from the multitude of modalities available to alleviate dry eye symptoms (fig. 1). It is of particular importance to carefully search for the cause and severity of the tear film disorder (see chapter 4), since symptoms of dry eye are often unspecific. For example, chronic blepharitis should be excluded or treated first since it induces not aqueous deficiency but an evaporative form of dry eye, with oversecretion of tears and the presence of proinflammatory cytokines in the tear film which may determinate if tear drainage is reduced. A success rate (reduction of signs and symptoms) of 83.7% was reported in 80 eyes with isolated aqueous-deficient dry eye, while this was reduced to 76.3% in 38 dry eyes with additional blepharitis [3].

The decision of when and how to occlude the drainage system depends on the severity of the aqueous deficiency. While mild degrees of discomfort resulting from aqueous deficiency can routinely be managed with pharmaceutical tear substitutes alone, moderate to severe disease is more likely to require punctual or canalicular occlusion. Therefore, the patient's medical history should be carefully reviewed and the frequency and type of medication used should be recorded.

Indications for Blocking the Lacrimal Drainage System

Blocking the drainage system can be beneficial for a number of indications, of which aqueous deficiency is certainly the commonest. Clinical studies have established objective and subjective benefit from permanent occlusion in moderate to severe forms of the disease. This approach is therefore well established in the stepwise management of dry eye [4–6] where it has been found to improve tear volume, stability and symptoms in approximately 60%. Elevated tear film osmolarity decreases and rose bengal-positive staining of the ocular

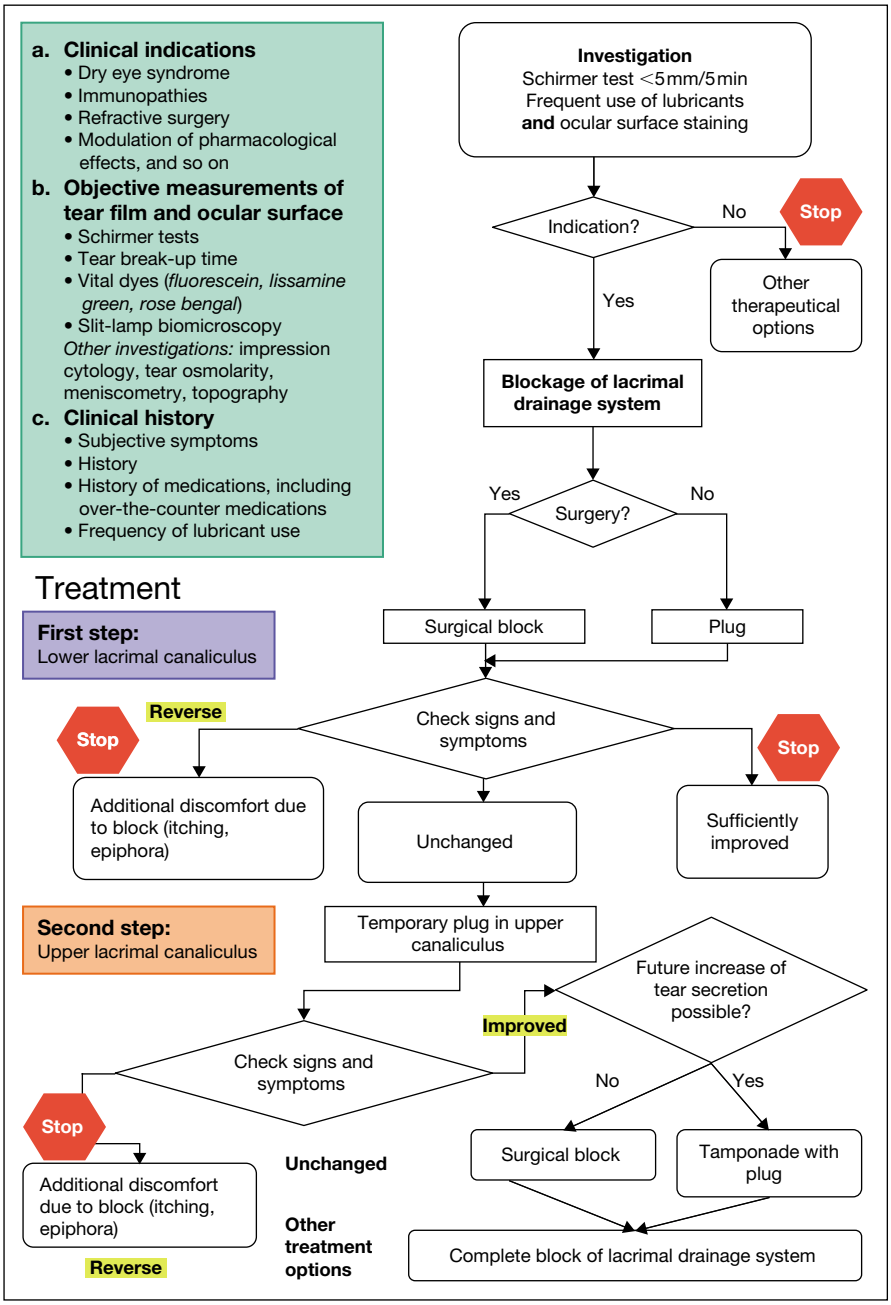


Fig. 1. Indications, objective and subjective parameters and measures involved in the decision-making process of occluding the puncta or canaliculi.

surface improves in 75%, although impression cytologic abnormalities tend to persist for at least 6 weeks [7–9]. Kojima et al. [12] reported that acrylic plug insertion improved the mean corneal fluorescein (pretreatment 4.8 ± 2.3; 3 months 2.1 ± 1.3) and conjunctival rose bengal staining (pretreatment 6.4 ± 2.0; 3 months 3.3 ± 1.6; criteria by van Bijsterveld [10] and Shimmura et al. [11]) significantly in 18 eyes of 10 dry eye patients. While no statistical difference was observed for Schirmer test, tear clearance was significantly reduced by the treatment [12]. As a general guideline, punctal plugs should be considered in patients with symptoms of dry eye, a Schirmer test of ≤5 mm and positive superficial punctate staining.

Punctal occlusion is also effective for contact lens-induced symptoms of dry eye, where punctal plugs were shown to substantially increase the duration of daily contact lens wear [13]. In a group of 9 contact lens wearers with bilateral mild to moderate aqueous tear deficiency (Schirmer test ≤10 mm in 5 min) and specific dry eye signs and symptoms, the lower canaliculus of the eye with the lower Schirmer test was occluded. Virtanen et al. [13] found that at 1 month, (on a scale of 0 to 3) conjunctival hyperemia, rose bengal (treated eyes 0.6 ± 0.2, control eyes 1.1 ± 0.2) and fluorescein staining (treated eyes 0.2 ± 0.2, control eyes 0.9 ± 0.1) and symptoms were significantly lower in the plugged compared to the unplugged eye, although no significant difference in Schirmer test was found (treated eyes 8.8 ± 2.1, control eyes 7.2 ± 1.8). Also, plasmin activity decreased significantly ($p < 0.01$) in the tear film of plugged eyes although however the positive effects were found to be lost again after 3 months. In summary, punctal occlusion of the lower canaliculus seems to induce only a relatively short-lasting subjective and objective benefit for contact lens-associated dry eyes. Becker [14] found that punctal occlusion is also beneficial in aqueous-deficient dry eye patients undergoing lid surgery such as ptosis surgery or blepharoplasty which increases ocular surface exposure.

This is also true for more severe dry eyes, which are often induced by an underlying immune disorder directed against mucous membrane or glandular tissue, such as Stevens-Johnson syndrome, toxic epidermal necrosis or mucous membrane pemphigoid. Inflammation and subsequent scarring of the tissues involved can lead to the aqueous-deficient as well as the evaporative form of dry eye, due to occlusion of the canaliculi, lacrimal or meibomian glands. If the lacrimal drainage system is not already blocked as a consequence of the disease – which may affect puncta or canaliculi – these eyes can benefit from prolonging the residence time of any remaining natural tears or applied substitute medication. The same has been reported for trachoma-induced conjunctival cicatrization and dry eye [17]. On the downside, extensive surgical manipulation as well as retention of proinflammatory cytokines or potentially cytotoxic medication on the ocular surface can also lead to acute exacerbation or chronic

levels of conjunctival inflammation [15, 16, 40]. In this special group of patients, systemic immunosuppression can be mandatory to control inflammation (see chapter 6). This simultaneously avoids preservative-induced toxicity of topically applied medication. It is also important that other contributing factors such as malposition of lid margin and resulting trichiasis are treated adequately.

Refractive Surgery

Refractive corneal surgery, such as PRK, LASIK or LASEK, all permanently alter corneal morphology including corneal innervation. If the sensitive corneal nerve fibers originating from the trigeminal nerve are severed, the afferent part of the lacrimal reflex loop is impaired and this can result in impaired epithelial wound healing. Huang et al. [18] reported that temporary lacrimal drainage occlusion reduced postoperative symptoms and the need for lubricants. It also improved density of conjunctival goblet cells, corneal wound healing and visual acuity.

Topical Modulation of Pharmacological Effects

Lacrimal plugs can be used as an adjunctive modality to modulate the effect or minimize potential side effects of other forms of topical treatment. For example, when tumors of the ocular surface are treated with topical mitomycin C, blocking the lacrimal drainage will not only expand the retention time and efficacy of the drug but also may reduce nasal mucosal irritation [19]. This may also be important in medical glaucoma treatment, but clinical evidence supporting this hypothesis is still lacking.

Types of Plugs

The types of plugs available can be differentiated according to their material as well as their intended location or duration of placement (table 1). Dissolvable plugs are still available for temporary occlusion, but this is more a diagnostic than a therapeutic measure, which can be used to exclude that a patient will develop epiphora following permanent surgical occlusion. Most plugs are made of a polymer and are intended for either punctal or canalicular placement. Absorbable and non-absorbable plugs both have a similar efficacy in reducing tear drainage of dry eye in the short term [20].

Punctal Plugs

Punctal plugs are placed directly in the opening of the lacrimal punctum and extend into the lacrimal ampulla. In this position they prevent the active and

Table 1. Methods for occluding the lacrimal drainage system with plugs

Material	Intended location			Duration of efficacy	Detectable by ultrasonography?
	Punctum	Ampulla	Canaliculus		
Collagen			**X**	Up to 2 weeks (spontaneously absorbed)	*
Catgut 2.0			**X**	Several weeks (spontaneously absorbed)	*
Polydioxanone			**X**	Up to 6 months (spontaneously absorbed)	*
Polysaccharide gum		**X**		Temporary	*
L-lactide/ E-caprolactone		**X**	**X**	Upto 6 months	*
Silicone	**X**			On average 2–6 months (depending on model)	**
			X	Permanent	**
Acrylic polymer		**X**	**X**	Permanent	***
Hydrogel		**X**		Permanent	*
Cyanoacrylate glue		**X**	**X**	Short term, to 3 months	No

passive drainage of tear fluid. Different shapes and materials are available. Their position can easily be controlled and if required the plug can be removed even without the use of a slit-lamp. However, as a consequence of the superficial localization, the devices also more easily cause irritation of the ocular surface (feeling of itchiness or pressure) and may be extruded, e.g. due to patient manipulation. Infection or migration is more rarely encountered.

Shape and Design. A flat cap, a slender cylindrical neck and a notably thicker, usually cone-shaped base are typical. After insertion into the lacrimal punctum, the volume of the base fills the ampulla and prevents extrusion of the plug, while the flat cap adapts to the surface of the lid, projects sideways from the lumen of the lacrimal punctum and thus not only occludes the punctum completely but also prevents dislocation further into the lacrimal drainage system. Sakamato et al. [21] could show that the design has a significant impact on the retention time and the rate of complications of silicone plugs. Devices with a more flexible design can be inserted more easily but are also likely to be lost earlier.

Material for Punctum Plugs. At present, most the punctal plugs dominating the market are made of silicone material [3, 22]. Other materials tested are teflon, HEMA or PMMA, but none of these has shown significant advantages over silicone plugs.

Intracanalicular Plugs

A wider variety of materials and shapes exist for intracanalicular plugs. The available implants can be inserted into the ampulla or in the horizontal portion of the lacrimal canaliculi. Since they do not protrude onto the surface, such plugs avoid mechanical irritation of the ocular surface. Rarely is an initial discomfort reported. The lack of surface contact and the position in the predominantly collapsed canaliculus reduce the risk of contamination. However, due to their position, intracanalicular plugs are more difficult to follow up and – if complications occur (most of all epiphora) – they are more difficult to remove. In principle the diameter of the device is more critical than the length in order to achieve total occlusion of the drainage system.

Temporary Dissolvable Intracanalicular Plugs

Shape and Design. Dissolvable intracanalicular plugs can be used for short- or medium-term closure of the lacrimal drainage system. The duration of the efficacy and residence of such plugs depends on the material. Dissolvable intracanalicular plugs are rod-shaped. Some implants are available in several sizes.

Material for Intracanalicular Plugs. Clinical reports exist for gelatin, catgut (no longer available), and hydroxypropyl cellulose. For short-term closure, collagen implants can be used, which reduce tear drainage – measured as reduced tear clearance – for <48 h [23]. However, all materials from animal sources carry a minute risk of prion transfer and induction of vCJD. Synthetic materials, such as polydioxanone, are recommended for medium-term (of up to 6 months) occlusion of the lacrimal canaliculi.

Permanent, Non-Absorbable Intracanalicular Plugs

Shape and Design. At least three different implants for the permanent occlusion of the lacrimal canaliculi are currently available in Europe. The Herrick® lacrimal silicone plug has the shape of a golf tee. It is compressed and therefore sits firmly in the canaliculus. Modifications with dye (blue) or semi-radiopaque properties are meant to facilitate correct positioning and localization in case of any complications. The SmartPLUG® is made of an acrylic polymer and is rod-shaped (0.4 mm wide and 12 mm long). It can be inserted into the canaliculus without dilating the lacrimal punctum. Upon exposure to body temperature the plug spontaneously shortens to 1.5–2 mm, while the diameter simultaneously increases to well over 1 mm. This is thought to ensure complete occlusion of the canalicular tear drainage. Recently, expandable hydrogel rods (diameter 0.3 mm, length 3 mm) have become available, which are placed in the vertical portion of the canaliculus by means of an inserter. After 20 min, the material fills the ampulla of the lacrimal canaliculus completely.

Material for Intracanalicular Plugs. Extensive experience exists with silicone. With this, occasional infections have been reported. The new materials, such as thermodynamic acrylic polymers and hydrogel, are supposed to reduce bacterial adhesion and biofilm formation and may thus in the long term result in fewer infections.

Insertion

The method of insertion depends on the type of plug selected. Local anesthesia is not normally required, but in certain cases can increase patient comfort. Following a careful documentation of the case history, the following parameters should be defined: (1) intended duration of occlusion, i.e. temporary or permanent; (2) number of puncta/canaliculi to be occluded; (3) position of the plug in relation to the canalicular drainage system – punctum, ampulla or horizontal canaliculus, and (4) plug size, which is only variable (and important) with punctal plugs.

Due to the potential complications, informed consent should be obtained for all implanted devices even for temporary occlusion with punctal plugs. Usually the lower canaliculus is occluded first, since access is easier and extrusion substantially lower than for the upper punctum. Often, closure of the lower lacrimal canaliculus is sufficient to reduce symptoms and artificial tear substitution substantially. In order to ensure complete and lasting occlusion, the punctal diameter can be measured with a specific instrument to select an appropriately sized plug (fig. 2).

Technical Recommendations

Technical recommendations include:

(1) *Choice of anesthesia:* A cotton wool tip soaked in topical anesthetic and directly applied onto the conjunctiva in the caruncular region/medial canthus or a subconjunctival injection of 0.5 ml of a short-acting anesthetic are usually sufficient.

(2) *Preparations to insert to plug:* If required, place the plug on an inserter, which releases the device upon pressure. This is often a double-ended instrument with an additional lacrimal dilator. Evert the lid margin, including the lacrimal punctum and lateralize the punctum in order to stabilize its position. Dilate the punctum while avoiding to overstretch the annulus!

(3) *Insertion of a punctal plug:* Place the plug by means of the inserter and release it with gentle pressure. Minor corrections of the position can still be made. It is important to instruct the patient not to rub or press the medial canthus. To

Fig. 2. Gauging system to measure the lacrimal puncta. The conical tip shows two steps. For the diameter indicated on the instrument the tip has to be fully inserted in the punctum. The first step equals a diameter of 0.1 mm lower than what is written on the instrument's handle.

improve patient compliance, he should be warned that the irritation may persist for several days or weeks!

(4) *Insertion of intracanalicular plug:* Herrick® lacrimal plugs are preloaded to an inserter. The plug is compressed while it is inserted and the carrier can be removed by slowly turning and pulling it. The final position of the plug in the horizontal canaliculus is influenced by the constant blinking and peristaltic motion. Plugs made from acrylic polymer should be inserted either with special forceps provided by the manufacturer or sterile tying forceps covered with silicon sleeves in order to avoid any mechanical damage to the sensitive material. Two-thirds of the plugs are inserted into the lacrimal punctum/canaliculus and the thermodynamic acrylic polymer then contracts upon contact with body heat. The material then becomes gelatinous. To avoid chronic inflammation, contamination of the plug from touching the lid lashes or margin should be avoided. If the local body temperature is reduced due to stress or reduced vascular perfusion, for example in older patients, the rod may not contract rapidly until a warm, sterile cotton wool tip is applied to the medial lid margin.

Follow-Up and Outcome

Tai et al. [3] reported a mean retention time of 85.1 ± 7.3 weeks. Prospective investigations indicate a stabilization of objective functional parameters of the tear film and ocular surface (tear volume, tear film stability, rose bengal staining) [8, 9]. However, it should be remembered that temporary lacrimal plugs made of collagen only effectively occlude the canaliculi for <48 h, reduce the outflow of tears only by 60–80% and may be insufficient to improve symptoms and mimic full occlusion [23]. Among the permanent devices, punctal or intracanalicular plugs show the same degree of objective and subjective improvement, such as reduced artificial tear substitute application or punctate surface staining and increased break-up time as goblet cell density in impression cytology (table 2).

Success of treatment is often difficult to quantify in dry eye, since evaluation of symptoms and signs, such as surface staining, remain predominantly subjective on both the patient's and the doctor's side. In a randomized controlled trial of 44 patients with severe dry eye due to inactive trachoma, patient satisfaction was significantly higher if artificial tear substitution and lacrimal drainage occlusion were combined compared to artificial tears only. Unilateral lacrimal drainage occlusion in severe dry eye due to Sjögren's syndrome was found to significantly improve scores of ocular discomfort, rose bengal staining compared with the non-occluded fellow eye (pretreatment rose bengal staining (mean ± SD) 7.3 ± 1.1, posttreatment 6.2 ± 1.9; control: pretreatment 7.3 ± 1.2, posttreatment 7.00 ± 1.15) [24].

Punctal plugs are easy to follow up. Due to their superficial placement, they can be observed conveniently with a slit-lamp. If the implant is no longer visible, extrusion can be assumed to be the likely cause. Migration into the lacrimal drainage system has been reported, but seems to be a rare event [25]. If in doubt, high-frequency ultrasonography can be helpful to check the lacrimal drainage system for any foreign body. The same modality can also be employed to locate intracanalicular plugs.

The need to inspect the position of an intracanalicular plug only arises if signs or symptoms of dry eye recur or if a chronic inflammatory process in the canaliculi is suspected. Slit-lamp biomicroscopy, assessment of the tear meniscus and spontaneous lacrimal outflow provide some evidence of adequate function or dysfunction of the lacrimal plugs. Herrick® plugs with blue staining can be more easily localized by transillumination of the medial canthal area. Semi-radiopaque lacrimal plugs have not found wide application in clinical practice, due to unnecessary financial and medical burden.

If an acrylic thermodynamic plug is positioned in the vertical ampulla of the canaliculus it can be visualized through the lacrimal punctum. Placing the

in plant in the horizontal part of the canaliculus probably reduces extrusion and impede the formation of biofilm. In this position the implant cannot be visualized directly by slit-lamp microscopy. High-frequency ultrasound can be successfully used for long-term controls and has confirmed a stable placement in the horizontal canaliculus for up to 2 years in 100%. Due to their shape, volume and material characteristics, differentiation of a plug from the tissues of the lid is easier with acrylic than silicone implants (fig. 3).

Removal of Lacrimal Plugs

While absorbable plugs may not require mechanical removal, if they dissolve within days or weeks, slowly-absorbing or even non-absorbable plugs sometimes need to be removed because of symptoms or signs or irritation or epiphora. Given careful patient selection, this is a rare problem and can be done under topical anesthesia. After everting, the plug can simply be grasped with a pair of forceps around its collar, loosened and removed carefully. This may be more difficult where a scar or a hyperplastic tissue reaction has evolved. If the plug's material has become brittle it may break into parts. Since any plug remnants can cause inflammation in the canaliculus, they should be removed. This may require retrograde manipulation via the opposite canaliculus with a pigtail type probe under an operating microscope and local or even general anesthesia. Extensive granuloma formation is rare but may require a canaliculotomy for plug removal and ablation of the hyperplastic mucosa [26].

Due to its form a golf tee-shaped plug can only be removed via the nasolacrimal duct by probing and irrigation of the lacrimal drainage system. Since the plug is very rarely recovered from the nose, reduction of epiphora, improved fluorescein clearance and patency of the system upon irrigation can be used as indicators of successful removal [27]. Ultrasonography may helpful identify plug material in the drainage system, but is not commonly available [28]. Plugs which initially remain in the lacrimal sac may be eliminated spontaneously, as has been reported for fragments of irrigation cannulas or lacrimal probes. However, if signs of impaired flow or even dacryocystitis are observed, retention of plug material in the lacrimal drainage system, usually in the lacrimal sac, should be suspected and surgical removal attempted. Where instruments for endoscopic endocanalicular manipulation (e.g. a microdrill system) are not available, routine dacryocystorhinostomy remains an excellent method to remove the foreign material and to cure any secondary obstruction of tear drainage.

Table 2. Tamponade of the lacrimal system by blocking with punctal and lacrimal plugs (overview of clinical studies). ND = no data, pts. = patients

Author, publication year, journal	Clinical indications	Number of patients, design of study, mean follow-up	Site/material of blocking device (brand)
Jones, CE CLAO 2002;28:206–210	Dry eye, pterygium	228 pts. retrospective, multicentric 9 months	Canliculus, Silicone (Herrick® plugs)
Fayet, B Ophthalmology 2001;108:405–409	Sjögren, Dry eye, Diabetes Bone marrow transplant	424 pts., retrospective 14 months	Punctal plug, Silicone elastomer (FCI)
Willis, RM Ophthalmology 1987;94:514–518	Dry eye Prospective, 1 year	18 pts.	Punctal plug, Silicone (Eagle)
White, WL Ophthalmology 2001;108:1835–1837		41 pts. report of complications	Lacrimal plug, Silicone (Herrick® plugs)
Sakamato, A Cornea 2004;23:249–254	Dry eye, Sjögren	36 pts., prospective 8 months	Punctal plug, Silicone (Eagle®, FCI)
Tai, MC Cornea 2002;21:135–139	Dry eye, epitheliopathy, contact lens intolerance Steven-Johnson-syndrome Pemphigoid, neurotrophic keratopathy	153 pts., retrospective 6 wks	Punctal plug, Silicone (Eagle®, FCI)
Balaram, M Am J Ophthalmol 2001;131:30–36	Dry eye, Sjögren, Ocular graft-versus-host disease	50 pts., prospective 6 months	Punctal Silicone (Oasis®, Eagle®)
Huang, B Am J Ophthalmol 2004;137:52–61	Post-LASIK	11 pts., prospective 1 month	Punctal

Success		Frequency of lubricant use		Side effects
objective	subjective	pre-	post-	
ND	ND	ND	ND	Epiphora 8.8% Displacement 2.2% Ocular irritation and discomfort 2.6%
ND	ND	ND	ND	1.2% (6 pts.) pruritus, extrusion fibrosis
Success rate 83%	Success rate 79%		57% frequency was decreased	Extrusion 22%
				41 pts., epiphora, chronic canaliculitis
Schirmer test fluorescein rose bengal score improved	ND	ND	ND	Extrusion 42% plugs from Eagle 16% plugs from FCI upper plugs were lost more
Success 76.8%	ND	≤3/d: 0% 4–6/d: 39% >6/d: 61%	≤3/d: 18% 4–6/d: 42% >6/d: 40%	Extrusion 60.7% Lower 38% Upper 13% Epiphora 5.4% Hemorrhage 2% Conj. erosion 1.5% Fragmentation 0.5%
94%	86%			Extrusion 40% Discomfort 12%
Reduction of higher aberration				None

Table 2. (continued)

Author, publication year, journal	Clinical indications	Number of patients, design of study, mean follow-up	Site/material of blocking device (brand)
Guzey, M Eye 2001;15: 297–303	Trachomatous dry eye	22 pts. comparative 8 months	Intracanalicular Collagen vs. Silicone (Herrick®)
Virtanen, T Eye 1996;10: 727–731	Contact lens wearer	9 pts. prospective 9 months	Intracanalicular Silicone (Herrick®)

Contraindications, Side Effects and Complications

Contraindications include allergy to plug materials, punctal ectropion and pre-existing canalicular obstruction. As discussed above, obviously severe inflammatory changes of the lids and ocular surface should also be treated to reduce the load of proinflammatory cytokines, since reduced tear clearance may otherwise exacerbate chronic surface disease.

Due to improvements of shape and material of the devices and provided that patient selection is adequate, lacrimal drainage obstruction by means of plugs is a low-risk procedure. If both the upper and lower lacrimal punctum/canaliculus are to be blocked, a trial of complete blockage with absorbable plugs prior to insertion of permanent, i.e. polymeric plugs is mandatory to avoid epiphora or tear meniscus-induced visual impairment [29]. If complications do occur, they relate either to subjective symptoms or objective clinical signs (table 2).

Although plugs are implanted in large quantities, complications have only been reported rarely. However, these can be severe and the use of plugs should therefore always be considered carefully. In particular, multiple insertion of plugs must be avoided. Up to 7 (!) lacrimal plugs in one lacrimal drainage system have been reported [30]. After plug implantation probing, flushing or endoscopic examination of the lacrimal drainage system should not be

Success		Frequency of lubricant use		Side effects
objective	subjective	pre-	post-	
Success rate 17 eyes (77%) Impression cytology	Success rate 22 pts. (82%)		81% pts. frequency was decreased	Epiphora 14%
Success rate 9 pts. (100%)	Success rate 9 pts. (100%)			None

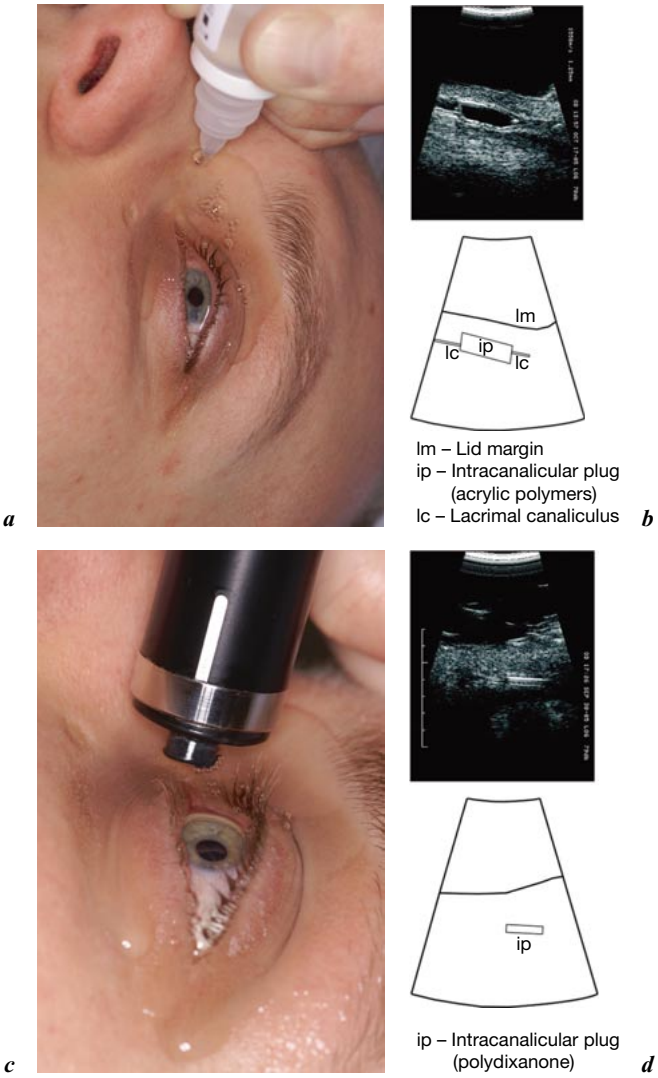
performed, since they are likely to induce displacement of the plug themselves. Careful case history, tear clearance rate as a measure of spontaneous tear outflow, tear meniscus height and, high-frequency ultrasound examination (20-MHz probe) should be sufficient to decide upon diagnosis and further management.

Signs and Symptoms of Irritation

Provided patient selection was adequate and a preliminary trial with temporary plugs was performed, epiphora should be a very rare problem. However, retention of cytotoxic substances and inflammatory mediators at the ocular surface can cause signs and symptoms of irritation, which may require plug removal. In a retrospective study by Tai et al. [3], on 203 eyes lacrimal plugs had to be removed in 6.9% due to severe itching, a sensation of pressure and mechanical irritation. These were more commonly reported for punctum plugs than intracanalicular plugs. The high rate of spontaneously lost punctal plugs may be a consequence of these problems [1, 5, 22, 30].

Loss or Migration of Plugs

Spontaneous loss of punctal plugs has been described by various authors to occur in 29–51% and this is more common in patients with horizontal lid



a ***b*** ***c*** ***d***

Fig. 3. High-frequency ultrasound examination of lacrimal system. The patient is supine, with his head reclined, and looking to the opposite side to retain the methylcellulose that is applied to the medial canthal area (***a***). The ultrasound probe is immersed in the methylcellulose for visualization of the proximal lacrimal system (***b***). Longitudinal cross section of acrylic polymer plug in the proximal lacrimal canaliculus. The intracanalicular plug is easily identifiably by the interface between plug and inferior lacrimal duct (***c***). An intracanalicular plug made from polydioxanone is more difficult to identify in the vertical segment of the lacrimal canaliculus (***d***).

laxity and dilated puncta [7]. In Tai et al.'s [3] study the estimated probability of plug retention was 49% with a mean survival time of 85.1 ± 7.3 weeks. Most of the extruded implants (50%) are lost within 4 weeks. Retention is better in the lower than in the upper punctum [21]. Dislocation into the deeper segments of the lacrimal drainage system is very rare, but can result in more severe consequences [32]. It can occur if too small a plug was chosen, implantation was too deep and or the lacrimal punctum was overstretched. If the plug is still visible through the ostium it can be repositioned using a 27½-gauge cannula [33]. The tip of the cannula is introduced in the central hole of the plug (the former link to the inserter) and the plug lifted, so that its flat top rests again on the lid margin. If canaliculitis or dacryocystitis evolve, canaliculotomy, external dacryocystorhinostomy or endoscopic-microsurgical management are required.

If a plug is lost spontaneously, punctal devices can be anchored by placing a non-absorbable suture through its collar and to the lid margin. Alternatively an intracanalicular plug may be used, since 20-MHz ultrasonography has shown that all of 40 implanted thermodynamic acrylic plugs remained in their original position over a period of 2 years [28, 31]. To reduce patient discomfort and costs due to repeated device insertion and if permanent outflow obstruction is required, we however prefer to block the lacrimal drainage surgically.

Biofilm Formation and Infection

The formation of biofilm and bacterial overgrowth are general problems of artificial materials in medical use. Due to their direct exposure to the surface of the eye and their complex shape, punctum plugs are easily contaminated by microbes. Cultures of punctum plugs removed because of symptoms of irritation showed bacterial colonization by various species of *Staphylococcus*, in more than 50%. The risk of bacterial colonization increased with the retention time. Although the central hole of a punctal plug – required for coupling the device to the inserter – acts as an additional reservoir for bacteria, only few clinical reports of acute or chronic infection or inflammation exist. Bacterial adhesion not only depends on the time but the retention material of the plug and its surface as well as [21]. In-vitro studies have shown that acrylic plugs are much less likely to be colonized by bacteria than silicone devices [34–36].

Chronic Inflammation and Scarring

Chronic inflammation, mucosal hyperplasia and scarring can result from the constant mechanical stress and irritation of the intracanalicular epithelial surface by punctal or intracanalicular plugs. Formation of pyogenic granuloma or papilloma has been reported with the use of both [37]. If this occurs the plug

should be removed, although this may be difficult or even impossible [1, 26, 38]. Sometimes – despite removal of all artificial material – subjective complaints persist. The proximal position in the vertical portion of the canaliculus, i.e. the ampulla, can result in a partial extrusion of acrylic intracanalicular plugs. If the implant cannot be advanced into the drainage system, the part of the protruding implant can be simply removed with Vanna's scissors [39].

Conclusions

- Iatrogenic occlusion of the lacrimal drainage system with plugs is the second most frequent method of treating the dry eye.
- It preserves natural tears or prolongs the retention time of artificial tears on the ocular surface and can substantially improve the quality of life of patients with moderate/severe dry eye.
- Before blocking a lacrimal drainage system a pre-existing blepharitis or other forms of ocular surface inflammation must be treated in order to reduce the load of proinflammatory cytokines on the ocular surface.
- The patient's consent should be obtained.
- The effect of lacrimal canalicular closure can be simulated with absorbable plugs.
- A stepwise approach is recommended, occluding the lower lacrimal canaliculus first.
- Implants differ in terms of material, design, place of application and time of retention.
- Punctal plugs are easy to insert and monitor. Discomfort and a high rate of spontaneous loss due to extrusion are a relevant disadvantage.
- If a punctal plug is sufficient to control signs and symptoms of dry eye and is spontaneously lost, implantation of intracanalicular plugs or surgical measures to reduce tear drainage should be considered.
- Compared with punctal silicone plugs, intracanalicular plugs of acrylic polymer or hydrogel result in less discomfort and are well tolerated, but are more difficult to remove.
- If patients with a history of dry eye and iatrogenic canalicular occlusion present with signs of inflammation of the lacrimal drainage system, the presence of artificial material in the lacrimal canaliculi should be excluded, for example by means of 20-MHz ultrasonography.
- Multiple simultaneous or sequential implantation of polymeric devices increases the risk of inflammation and complication.
- Occlusion of the lacrimal drainage system with plugs is usually easier to reverse than surgical approaches.

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Prof. Dr. Frank Tost
University Eye Hospital, Ernst-Moritz-Arndt University
Ferdinand-Sauerbruch-Strasse, DE–17475 Greifswald (Germany)
Tel. +49 3834 86 5900, Fax +49 3834 86 5950
E-Mail tost@uni-greifswald.de

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Surgical Occlusion of the Lacrimal Drainage System

Gerd Geerling[a], *Frank H.W. Tost*[b]

[a]Department of Ophthalmology, University of Würzburg, Würzburg, Germany;
[b]Department of Ophthalmology, University of Greifswald, Greifswald, Germany

Abstract

Background: If a lacrimal plug that successfully improves dry eye symptoms is spontaneously lost or causes unwanted effects other than epiphora, surgical occlusion of the lacrimal drainage system should be considered. Here we review current irreversible and reversible techniques to occlude the lacrimal drainage and describe a new surgical technique, termed 'punctum switch', which has the advantage of being permanent and yet potentially is reversible. **Material and Methods:** A PubMed search was performed to identify the current literature on surgical occlusion of the puncta and canaliculi for dry eyes. The characteristics of the procedures are described, classifying them as temporary or permanent and their localization being either on the level of the lacrimal puncta or canaliculi. A 'punctum switch' graft involves a superficial excision of a piece of lid margin including the punctum. This graft is then rotated and fixated so that the excised punctum comes to rest lateral to the remaining lacrimal ampulla, which in turn is covered by full-thickness lid margin tissue. **Results:** Established methods include cauterizing or ligating the puncta or canaliculi as well as everting the medial portion of the lid. Both thermal and surgical techniques show a high rate of reopening. If permanent occlusion is achieved, this however often is irreversible and can only be treated by means of lacrimal bypass surgery. The 'punctum switch' procedure can achieve long-term occlusion of the canalicular system while offering potential reversibility. **Conclusion:** A large variety of surgical techniques to occlude the nasolacrimal drainage system exists. These vary significantly in terms of complexity and reversibility. Surgical occlusion should be used more often in patients with moderate or severe dry eye, which previously responded well to temporary occlusion with plugs.

Basic Considerations

Preoperative Evaluation

The decision to permanently occlude the lacrimal drainage system should only be made if symptoms (e.g. foreign body sensation, dryness) and

signs of aqueous deficiency (Schirmer test repeatedly ≤5 mm in 5 min) coincide with signs of ocular surface disease and persist despite frequent application of unpreserved lubricants. Signs of surface disease include conjunctival hyperaemia and superficial punctate keratopathy defined as positive epithelial staining of the cornea or conjunctiva with fluorescein, rose bengal or lissamine green. Ocular surface staining scores, break-up time, conjunctival squamous metaplasia and goblet cell density all improve – even in such severe diseases such as Stevens-Johnson syndrome – following punctal occlusion and deteriorate after recanalization [1, 2]. If surface staining preoperatively is completely negative, other reasons for ocular discomfort should be evaluated, since the reliability and repeatability of the Schirmer test are low and patients with a test result of as little as 1 mm can be free of symptoms and signs of disease.

For several reasons, lacrimal syringing should always be performed prior to opting for permanent iatrogenic outflow occlusion: (1) The canaliculi may be already occluded (e.g. due to cicatrizing conjunctivitis) and epiphora may only be absent due to the reduced tear volume. In this situation, additional occlusion e.g. of the puncta may have little therapeutic value. (2) Symptoms of irritation may have been induced by subclinical dacryocystitis due to the backwash of proinflammatory cytokines from a blocked tear sack. This can be easily treated by a simple dacryocystorhinostomy (DCR). (3) In patients with pre-existing nasolacrimal duct stenosis, additional occlusion of the canaliculi may precipitate serious complications such as acute dacryocystitis [3, 4].

Such complications may occur weeks to years postoperatively and also include suppurative canaliculitis as well as epiphora and granuloma formation. Factors contributing to the development of an acute infection can include the use of systemic immunosuppressives (e.g. systemic corticosteroids in patients with rheumatoid arthritis) or systemic disorders (e.g. diabetes mellitus). A specific history or the presence of a painful swelling in the area of the lacrimal sac or a mucous discharge upon lacrimal irrigation indicates a nasolacrimal duct obstruction. In this situation a prophylactic DCR has been suggested prior to permanently occluding the lacrimal drainage system (see chapter 9).

The question which and how many puncta/canaliculi should be occluded remains controversial. In the normal individual the volume drained via the lower or upper part of the system is approximately the same. Since the lower punctum is more easily accessible it is frequently occluded first. If signs and symptoms of aqueous deficiency persist, the complimentary part of the system is occluded. It has been established that one patent canaliculus is sufficient to prevent epiphora. However, unless reflex tearing evolves, in the dry eye situation the occlusion of both puncta gives better results [5].

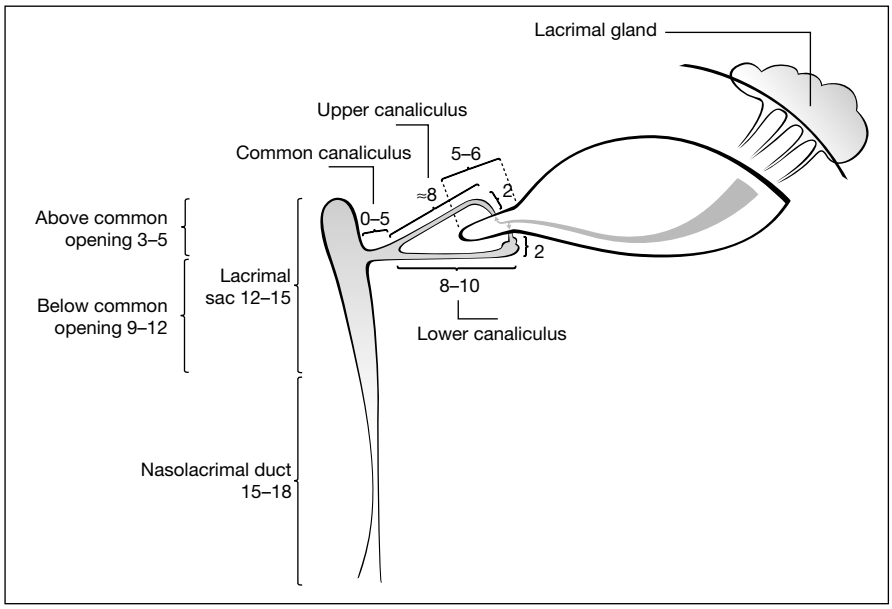

Fig. 1. Diagram of the tear system (all dimensions in millimeters). Modified from D. Oliver, Colour Atlas of Lacrimal Surgery (2002), Butlerworth + Heissemann.

Surgical Anatomy

The canaliculi can be of variable length and in approximately 20% have an individual opening into the lacrimal sack. The vertical portion is approximately 2 mm long and includes the ampulla (fig. 1). The horizontal portion is 8–10 mm long (longer in the lower lid). In approximately 80–90%, both canaliculi meet behind the medial canthal tendon to form the common canaliculus which is 0–5 mm long [6].

Surgical Principles

Even when the indication has been confirmed, permanent punctal or canalicular occlusion can both be difficult to achieve as well as – once successfully established – impossible to reverse [7]. The less destructive the surgical method is, the more frequently recanalization will occur. For example, laser punctal occlusion was reported to have a median time to reopening of 22 weeks versus cautery occluded puncta with 28 weeks [8]. On the other hand, an extensive iatrogenic canalicular block will require bypass surgery in case epiphora becomes a problem. It is therefore advisable to reserve surgical, i.e. potentially permanent occlusion, for severe cases of dry eye and to assess the patient's response to punctal or canalicular plugs as a temporary measure first. However, it should be noted

that undersized plugs, which produce only an incomplete block, may fail to predict epiphora after permanent punctal occlusion [9]. Interventions to block the lacrimal drainage system are not only destructive but also – with the exception of cautery – consume more time and financial resources than the use of plugs. The fundamental surgical principles include: (1) heat-induced damage/shrinkage of tissue; (2) transposition of a punctum/canaliculus, or (3) construction of a mechanical barrier [5].

Irreversible Methods

Heat-Induced Damage/Shrinkage of Tissue

A hot cautery probe, a diathermy or lasers have all been used to occlude the lacrimal outflow by heat-induced damage to the canalicular and pericanalicular tissues. Of these, cauterization is the most frequently practiced and simple method. Variable efficacy, i.e. permanent closure, has been reported and this seems to depend on the technique used. Superficial cauterization of the lacrimal punctum results in 56% in a reopening within 1 month. If the entire vertical portion of the canaliculus is cauterized this rate is reduced to 7% at 1 month [10]. 'Deep cautery' of the vertical plus the horizontal canalicular section of the system is likely to provide an even higher rate of primary and lasting closure.

Alternatively, an argon laser can be used to occlude the punctum. With this technique, 10–50 spots of 100–750 μm diameter and 0.1–2 W are applied in the continuous mode for up to 9 s (most commonly 10 burns of 200 μm at 0.4 W) around the punctum. Although this is associated with less postoperative discomfort and a reduced inflammatory reaction, it also is associated with a higher recanalization rate since the laser light is not capable of inducing sufficiently deep and extensive tissue necrosis which is required for a long-term effect (table 1) [5, 11].

Cautery remains by far the fastest and easiest heat-based method to induce a profound destruction of the canalicular wall. Conventionally, anesthesia is achieved by injection of approximately 0.5 ml of a short-acting local anesthetic into the pericanalicular tissues of the medial eyelid near the tear drainage system. However, pressure topical anesthesia may be equally effective for cautery of the proximal canaliculus. For this a cotton bud soaked in topical benoxinate is placed over the punctum and the patient asked to close the eye voluntarily to keep the cotton bud in place for 5 min. This obviously avoids complications such as pain, bleeding, hematoma formation and unintended ocular penetration all potentially associated with the injection of local anesthetic solutions [12]. Then – following dilation of the punctum – a mono- or bipolar cautery tip is inserted approximately 5 mm into the horizontal part of the canaliculus. Energy

Table 1. Overview of surgical methods to block the lacrimal drainage system. ND = no data

Method of surgery	Reference (first author)	Clinical indication Type of study Mean follow-up	Number of patients (puncta/ canaliculi)	Anatomic success	Symptomatic success	Side effects
Cyanoacrylate adhesive	Diamond 1995 [15]	Dry eye, prospective, 15 months	8	ND	ND	Extrusion 42% Eagle 16 (2) 16% FCI 6(2)
	Köhler 1986 [16]	Dry eye, retrospective, 36 months	4	ND	ND	Inflammation 4 toxic reaction pyogenic granuloma
Thermal cautery	Knapp 1989 [10]	12 months		Deep 82% Superficial 40%	ND	ND
Thermal cauterization vs. argon laser punctal occlusion	Benson 1992 [11]	Dry eye, retrospective, 16 months	(22) puncta	14%	ND	Inefficient in long term
Diathermy, cutting and suturing	Yokoi 2004 [23]	Dry eye, prospective, 8 months	33	100%	ND	ND
Diamond burr and suturing	Liu 2002 [7]	Severe dry eyes, Sjögren, prospective	11 (26)	92%	64% Topical therapy reduced in 36%	ND

Table 1. (continued)

Method of surgery	Reference (first author)	Clinical indication Type of study Mean follow-up	Number of patients (puncta/ canaliculi)	Anatomic success	Symptomatic success	Side effects
Transfer of lacrimal punctum to dry dock	Murube 1993 [21]	Dry eye, prospective, 5 years	7 (12)	12 patients (100%)	10 patients (83%)	Epiphora 2 patients, operation was reversed
Canaliculectomy	Putterman 1991 [19]	Dry eye, prospective, 2 years	3 (10) Other methods unsuccessful	3 patients (100%)	3 patients (100%)	
Punctal patch vs. cauterization	Shalaby 2001 [22]	Dry eye, prospective, comparative 1 year	20 (80) (each group)	Punctal patch 100% Cauterization 80%	Punctal patch 100% Cauterization 80%	Punctal patch: time of intervention longer. Complete occlusion in all patients. More initial discomfort
Punctal switch	Geerling, 2007 (present study)	Dry eye	Switch 10 (18) Patch 2 (4)	Switch 12 (65%) Patch 0 (0%)		

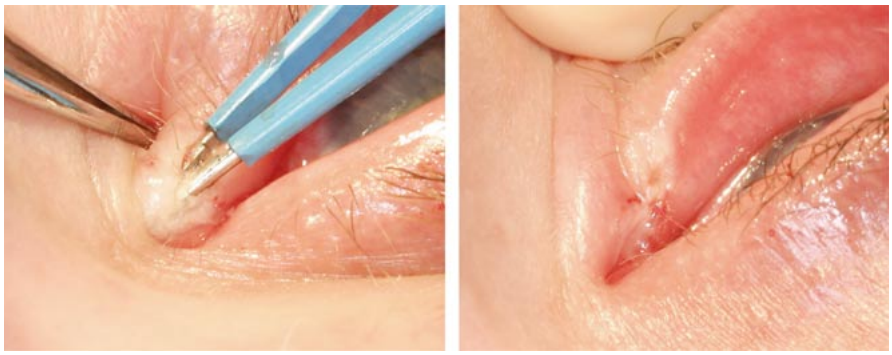

Fig. 2. Canalicular cautery. ***a*** Immediately following cautery with the cantery forceps still inserted. Note the necrotic lid margin tissues overlying the cauterized canaliculus. ***b*** After removing the cantery forceps a 7.0 long-acting absorbable suture is placed in addition to approximate the edges of the cauterized tissue.

is then applied until obvious thermal damage becomes visible on the overlying skin (fig. 2a). The cautery tip will stick to the surrounding tissue and coagulated epithelium will remain attached to the instrument when it is retracted. If felt necessary the applicator can be reinserted to continue the coagulation process until the canaliculus cannot be easily probed anymore. A 7.0 long-acting absorbable suture can be placed to approximate the edges of the cauterized punctum (fig. 2b) and a topical antibiotic is applied for approximately 5 days. Topical steroids should be avoided in order to maximize scar formation in the canalicular area.

If the instrument is advanced >6 mm, cautery of one individual upper or lower canaliculus can in addition block the common canaliculus and damage its ostium into the lacrimal sack. If ever intended, this would be more difficult to reconstruct. An extensive proximal block repair of the canaliculi is best achieved by means of a DCR with retrograde intubation, although this has a substantially lower success rate than a regular DCR [13]. A near total block of the drainage system including the individual canaliculus plus the common canalicular duct will require lacrimal bypass surgery, e.g. by means of a Lester-Jones tube.

Occlusion with Tissue Adhesive (Cyanoacrylate)

An alternative method of occluding the lacrimal outflow on the level of the ampulla or canaliculus uses a tissue adhesive. Patten [14] applied a drop of cyanoacrylate to the punctum which lasted for a mean of 2.5 weeks. Diamond et al. [15] used the glue to permanently occlude the entire lacrimal drainage

system. Following local anesthesia, 100 μl of cyanoacrylate is injected via a lacrimal cannula into the canaliculus, which is approximately the volume required to fill the lacrimal drainage system from the punctum up to the entrance into the lacrimal sac. Pressure is simultaneously applied with the index finger to limit passage of the glue into the lacrimal sac and the medial lid is everted for 30 s to allow the material to fully polymerize without coming into contact with the ocular surface [15]. Any glue material protruding out of the punctum after polymerization can be trimmed with scissors.

Although one would expect that in a biological environment the glue will dissolve in the course of several weeks resulting in recanalization, Diamond et al. [15] could show by means of dacryoscintigraphy that this method was capable of occluding the canaliculi for the full follow-up of a mean of 15 months (11–19 months) in a case series of 8 patients. Patten [14] and Diamond et al. [15] reported only minor complications such as irritation immediately following adhesive application, due to a protrusion of polymer. This was easily managed by trimming the glue. However, with longer follow-up, several cases of canaliculitis or acute dacryocystitis were reported following glue occlusion of the canalicular part of the drainage system. In these cases, histology showed persistent glue as foreign bodies inducing a severe giant-cell reaction [16]. Methods which avoid the use of foreign body material in the nasolacrimal ducts should therefore be preferred for permanent occlusion.

Punctal/Canalicular Ligature

Charleux and Brun [17] described a procedure in which – following local anesthesia – the vertical and horizontal canaliculus is cauterized, the punctum excised and the vertical portion closed with a suture. Liu and Sadhan [7] described the results of a prospective study in which the technique was slightly modified by using a corneal burr (diameter: 0.6 mm) to remove the epithelium from the punctum and the vertical 2 mm of the canaliculus of 26 puncta in 11 patients. A single 6.0 interrupted absorbable suture was placed parallel to the lid margin to approximate and occlude the punctum. This procedure achieved occlusion of punctum or vertical canaliculus in 92% for a follow-up of 14–34 months and was associated with significant subjective improvement in 64% [7]. No complications were observed. Despite the anatomic success and symptomatic relief, the postoperative signs of surface disease (e.g. epitheliopathy after rose bengal or fluorescein staining) did not improve. Since no quantitative Schirmer test data were reported, subjective improvement could have been the result of a placebo effect. DeMartelaere et al. [18] reported about 29 patients in whom 59 canaliculi were ligated following vertical transsection of the horizontal portion of the canaliculus. The procedure resulted in a symptomatic relief in 91%. Due to complaints of epiphora, two canaliculi were later reconstructed

successfully with repeat vertical transsection and routine canalicular repair using a silicone intubation. This procedure may therefore also be considered to be reversible in nature.

Canalicular Excision

This is a more extensive and thus time-consuming method. Following topical anesthesia and dilation of the punctum, a Bowman probe is advanced via the canaliculus into the lacrimal sack. The posterior wall of the canaliculus is incised through the conjunctiva with a D11 surgical blade from the punctum up to the medial canthus just as in an extensive canaliculotomy. The canaliculus is then grasped with a pair of forceps and the desired length of the canalicular wall is excised with the blade, before the wound is closed with interrupted stitches of a long-acting absorbable 7.0 suture. If the intention is to excise only one individual canaliculus the opposite canaliculus together with the common canalicular duct should be probed to avoid accidental damage to these structures [19]. The only complications of canalicular excision reported include a very mild medial entropion or ectropion. The technique was described to have a 100% success rate, but should be considered irreversible, since tear drainage into the nose can only be re-established by means of a conjunctivodacryocysto(rhino)stomy [20].

Dacryocystectomy

This method should be reserved for patients with severe dry eye simultaneously suffering from dacryocystitis. As discussed above, nasolacrimal duct obstruction can be associated with signs of ocular surface disease, such as punctate keratopathy [3]. This is probably due to the backwash of inflammatory cytokines or pus from the occluded nasolacrimal ducts. Dacryocystectomy is then performed transcutaneously. The medial canthal tendon is detached and the lacrimal sac identified, mobilized and severed from the common canaliculus and the nasolacrimal duct. The procedure has a 100% success and irreversibility rate (see chapter 9).

Potentially Reversible Techniques

Most of these techniques involve tissue mobilization/transfer with the potential to reverse all or parts of the induced changes.

Transfer of the Punctum to 'Dry Dock'

This procedure was first described by Murube and Hernandez [21] and involves transferring the lacrimal punctum towards the external lid margin. A circular incision, not more than 2 mm deep, is made around the lacrimal punctum,

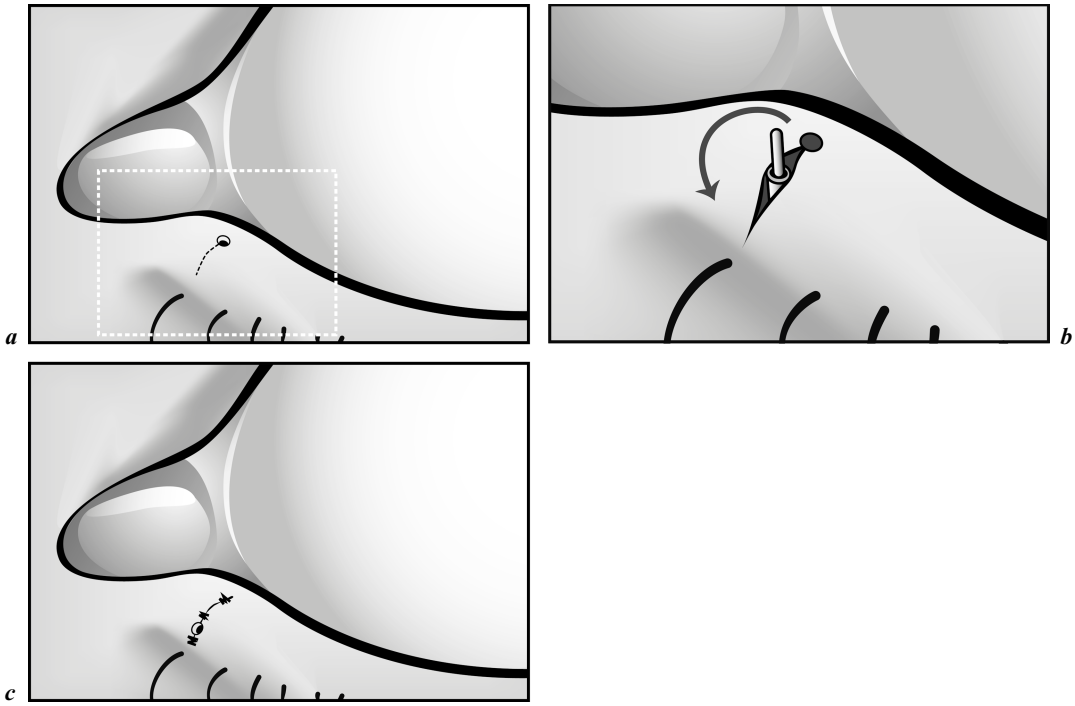

Fig. 3. Diagram of transfer of punctum to dry dock: the punctum is incised anteriorly (***a***). A probe is placed in the punctum and the incision extended around the entire vertical part of the canaliculus which is then moved anteriorly (***b***). Finally the wound is closed posterior to the new position of the punctum (***c***).

which avoids damage to the horizontal canaliculus. The punctum and the vertical portion of the proximal canaliculus (i.e. the ampulla) are rotated outwards to rest between the lid lashes, so that the lacrimal punctum does not enter the tear film meniscus (fig. 3). Of all surgical methods, this procedure is the least invasive one, and has been shown to be reversible. Migration of the punctum to its original position is rare, but may occur. Although frequently primary or secondary atrophy of the lacrimal punctum to a pinpoint size results, this can be dilated and successfully syringed.

Punctal Tarsorrhaphy

This procedure involves the rectangular excision of the superficial 1-mm tissue around the upper and lower punctum (fig. 4). Since the position of the upper punctum is usually more medially, a 3×2 mm large area of lid margin is excised with the upper punctum in the medial half and the lower punctum in its

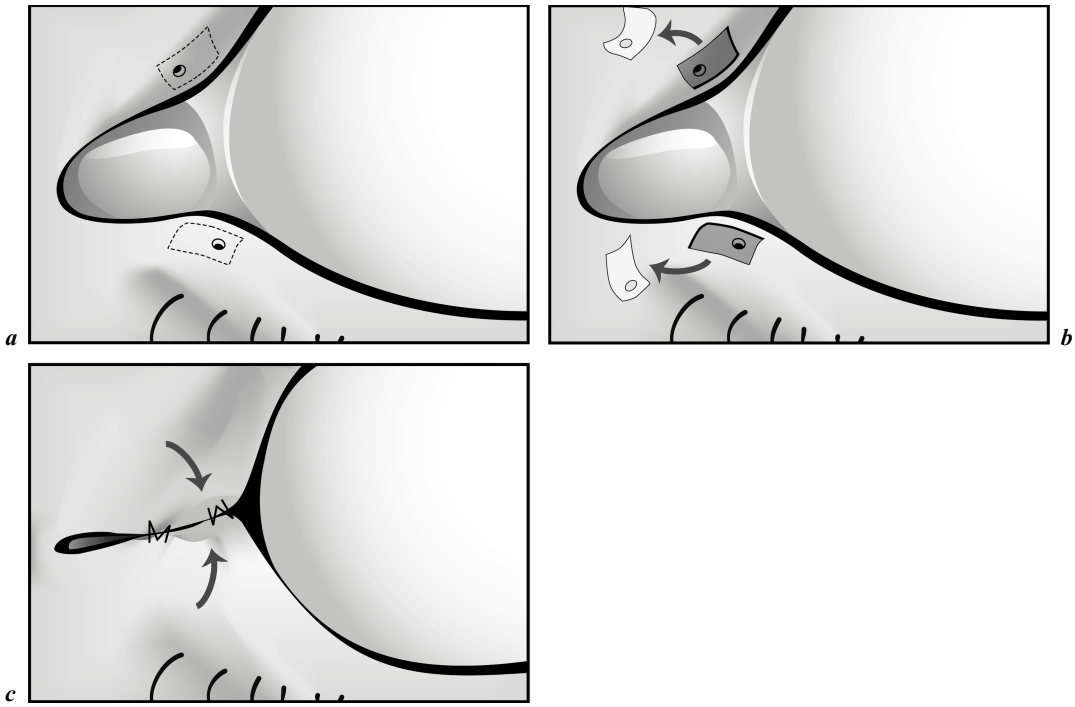

Fig. 4. Diagram of punctal tarsorrhaphy: an eccentric cough of superficial lid margin tissue around the upper and lower punctum is marked (***a***), excised (***b***) and the wound edges of the upper and lower lid approximated (***c***).

lateral half. The denuded areas of lid margin are approximated by means of 8.0 Vicryl interrupted stitches in each corner and pressure is applied to assure close contact of the medial upper and lower lid for 2 weeks by means of a double-armed mattress suture which is then tied over a bolster. No reports on the long-term success of this procedure exist, but conceptually it should be considered equivalent or superior to a regular tarsorrhaphy. Although this shortens the horizontal length of the palpebral fissure by approximately 5–7 mm, cosmesis is usually acceptable [5].

Punctal Patch

This procedure was also introduced by Murube [5]. Under local anesthesia and with the help of an operating microscope, an approximately 2×2 mm large piece of superficial rectangular piece of tissue including the punctum is excised (fig. 5). The obtained piece of tissue is used as a template to mark and prepare a graft from the bulbar conjunctiva, which is fixed with 7.0 interrupted

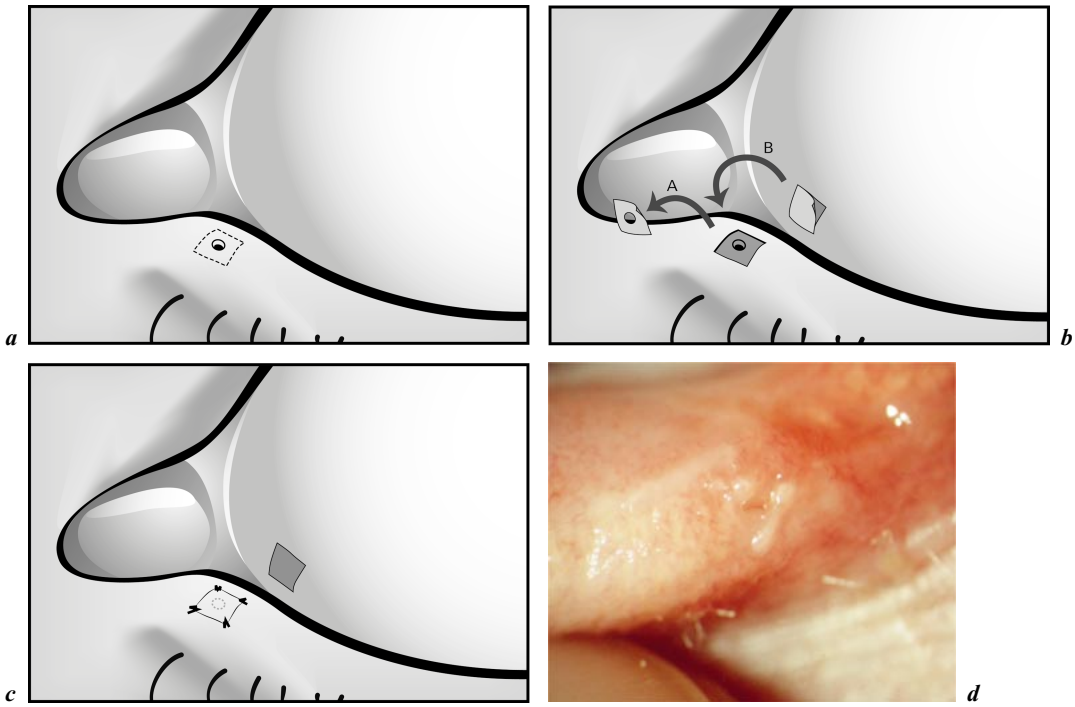

Fig. 5. Punctal patch: a cough of superficial lid margin tissue concentric to the punctum is marked and excised (***a***). An equal size graft of conjunctiva is harvested (***b***) and sutured to the recipient bed (***c***). 3 months post-punctal patch. The occluded punctum has reopened (***d***).

absorbable sutures to cover the ampulla. In a study on 40 patients (160 puncta), Shalaby et al. [22] compared punctal patch and cautery. After 1 year, they reported 100% success with the patch method, while a 20% recanalization rate was observed following cautery. However, despite early anatomic success at 1 week, we have observed recanalization due to necrosis of the graft during further follow-up in 4 out of 4 puncta within 3 months (fig. 5).

This approach has, however, a few conceptual disadvantages: (1) severe ocular surface disease due to dry eye often results from cicatrizing conjunctival disorders, such as mucous membrane pemphigoid or Stevens-Johnson syndrome. In these, loss of even a small amount of conjunctiva may not be acceptable for functional reasons, e.g. where symblephara have formed. (2) Progression of the inflammatory component may also be triggered by any form of conjunctival trauma, which therefore should be avoided. (3) The graft tissue is relatively thin and it is suspended over the lacrimal ampulla without any underlying tissue, hence no mechanical support or blood supply is provided to

the central, i.e. vital part of the graft. We therefore modified the procedure in order to provide a biomechanically stronger graft tissue and to avoid the need for a conjunctival incision, while simultaneously maintaining the conceptual advantages of a complete and permanent occlusion and reversibility. This procedure was termed 'punctum switch graft'.

Punctum Switch Graft

In short, this involves an eccentric autorotational superficial tarsomarginal graft (fig. 6). The procedure is performed under an operating microscope following local anesthesia with approximately 1.0 ml of lignocaine injected into the medial lid margin. A 4.0 Prolene suture is placed to evert the lid margin with traction over a spatula. A large chalazion clamp helps to evert and stabilize the peripunctal tissues. With a D11 blade a 3 × 2 mm superficial area is marked on the lid margin immediately posterior to the lid lashes and including the punctum in the medial half. The marked area is than excised at a depth of approximately 1 mm. Obvious bleeders are cauterized while trying to avoid any excessive thermal damage to the donor/recipient bed. Following this, the graft is rotated 180° and sutured back in place with a continuous 7.0 long-acting absorbable suture. This leaves the excised punctum lateral to the ampulla which itself is covered by full-thickness lid margin tissue. The surgical approach is usually easier in the lower than in the upper lid. Topical antibiotics are applied for 5 days and the sutures removed, if required, at 2 weeks postoperatively.

At 3 months postoperatively, 12 out of 18 canaliculi remained occluded and all puncta remained patent until the last follow-up. Six grafts showed necrosis or partial wound dehiscence (tables 2, 3). This approach largely avoids a surgical trauma to the conjunctiva and covers the drainage system with a biomechanically stronger piece of tissue. Although to date no procedure had to be reversed, the number of patients treated and our follow-up are still limited and more extensive studies required. The technique is also certainly more demanding on time and equipment than simple cautery. However, while the puncta may atrophy with postoperative time, a 'punctum switch' procedure is potentially reversible.

Conclusions

– Before occluding the puncta or canaliculi the lacrimal outflow system should be carefully assessed, since nasolacrimal duct obstruction can also be the cause of symptoms and signs of ocular surface irritation.

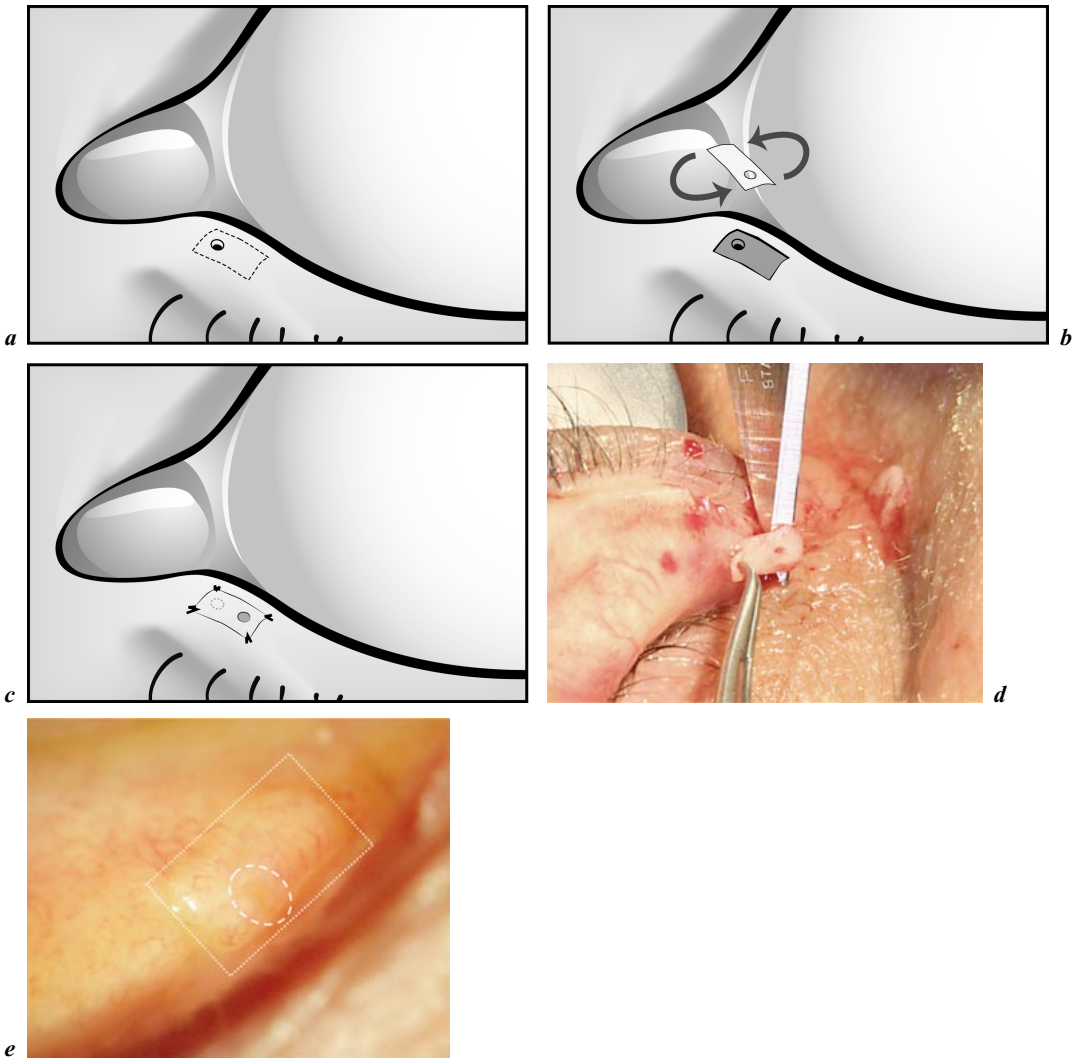

Fig. 6. Punctum switch graft: an eccentric cough of superficial lid margin tissue is excised including the punctum in its medial half (***a***). The graft is rotated (***b***) and fixed to its original bed with the punctum resting temporal to the vertical part of the canaliculus (***c***). Graft after excision (***d***). Viable graft (rectangular box) at 3 months postoperatively with patent punctum (circle; ***e***).

– Prior to permanent surgical occlusion the effect of temporarily blocking the lacrimal drainage system should be tested with silicone or other plugs, since it can be difficult to re-establish transcanalicular lacrimal drainage once the system has been successfully occluded.

Table 2. Clinical studies

Procedure	Localization of block	Rate of spontaneous recanalization	Conceptually reversible?
Thermal			
Cautery	Punctum/ampulla	Very common	No
	Canaliculus	Common	No
Laser	Punctum	Extremely common	No
Surgical			
Punctal patch	Punctum	up to 100%	Yes
Punctum switch	Punctum	33%	Yes
Canalicular ligature	Canaliculus, vertical	10%	Yes
Canalicular excision	Canaliculus, vertical	Very rare	No
	and horizontal		No
Transfer of the punctum to dry dock	Punctum, Ampulla	Not applicable	Yes
Punctal tarsorrhaphy	Punctum	Extremely rare	No
Dacryocystectomy	Canal. comm., saccus lacrimalis	Extremely rare	No

Table 3. Results of punctal patch and punctal switch grafts

	Patch	Switch
Age, years	42 ± 12	46 ± 25
Number of puncta	4	18
Anatomic success at 3 months	0	12
Punctal probing possible	4	18

- The lower lacrimal canaliculus should be blocked first and the common canaliculus should be spared.
- Reversible and irreversible procedures include destruction or transplantation of punctal/canalicular tissues.
- Of all methods, cautery is the most simple one. The primary thermal damage needs to be substantial in order to achieve long-term occlusion. Canalicular ligature can be considered as a simple and successful alternative.
- If symptoms or signs of dryness persist, the puncta should be probed and syringed, since late recanalization is not uncommon.

– Moving the lacrimal punctum to dry dock and punctum switch are new, permanent yet potentially reversible methods.
– Epiphora, granuloma formation, suppurative canaliculitis and acute dacryocystitis have been reported as complications weeks to months after iatrogenic lacrimal outflow occlusion.
– These reported complications following surgical occlusion of the lacrimal drainage system are rare and should not prevent the use of this successful therapeutic strategy in the management of severe aqueous-deficient dry eyes.

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Prof. Dr. Gerd Geerling
Klinik für Augenheilkunde, Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11, DE-97080 Würzburg (Germany)
Tel. +49 931 20120612, Fax +49 931 20120490,
E-Mail g.geerling@augenklinik.uni-wuerzburg.de

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Mucous Membrane Grafting

H.W.A. Henderson[a], *J.R.O. Collin*[b]

[a]The Royal Free Hospital, London, UK; [b]Moorfields Eye Hospital, London, UK

Abstract

Introduction: We review the use of mucous membrane grafting in the clinical management of dry eye-associated ocular surface disease. **Material and Methods:** Literature review of the scientific evidence, presentation of guidelines and surgical details. **Results and Conclusion:** The reformation and maintenance of a conjunctival fornix requires the addition of epithelial tissue, or a basement membrane which can be populated by healthy host epithelial cells. A healthy conjunctival or tarsal autograft, when available, is the ideal material. Oral mucosa does not contain goblet cells and therefore does not supplement the tear film: a full-thickness oral mucous membrane graft is the simplest graft to use if conjunctiva or tarsus is not available. Split-thickness mucosal grafts contract more, but are less bulky and pink than full-thickness grafts, and therefore should be used on the globe. Hard palate grafts are the thickest oral mucosal grafts and contract the least. Nasal mucosal grafts contain goblet cells that may contribute mucous to the tear film. This is maximised in turbinate mucosal grafts, which can relieve discomfort in extreme dry eye situations. Nasal septal cartilage contains fewer goblet cells, but adds rigidity. Amniotic membrane is thin and translucent-like conjunctiva, and possesses antiangiogenic, antiscarring and anti-inflammatory properties. It may become re-epithelialised with normal a conjunctival cell population and prevent postoperative cicatrisation, but requires the presence of healthy conjunctival stem cells to repopulate the graft, adequate lacrimal function to keep the graft moist, and a host site that is free from inflammation, otherwise it rapidly contracts. It can be combined with limbal transplantation and with an adjunctive antimetabolite.

Background

Symblepharon is a sight-threatening condition that may result in abnormalities of the tear film and tear meniscus, a reduction of the goblet cell containing conjunctiva, entropion and trichiasis, limitation of ocular motility, and failure of corneal transplantation and ocular surface reconstruction. Mucous membrane

Table 1. Tissue options for fornix reconstruction

Graft material	Stiffness	Stability	Goblet	Epithelial stem cells	Availability[1] included	Source/ cosmesis
Conjunctiva	−	+	+	+	−	Autologous Excellent
Tarsus	+	++	+	+	−	Autologous Excellent
Buccal mucosa	+	++	−	+	++	Autologous
Full thickness						Poor
Split thickness	+	++	−	+	++	Good
Hard palate	++	++	−	+	+	Autologous Good
Nasal septal cartilage	++	++	+	+	+	Autologous Fair
Nasal turbinate mucosa	+	+	++	+	+	Autologous Fair
Amniotic membrane	−	−	−	−	+++	Heterolgous Excellent

[1]Size available for extensive repairs.

grafts have been used for over a century in the reconstruction of fornices obliterated by symblepharon formation.

Many different materials have been employed to reconstruct the fornices. Conformers and rings used alone result in rapid recurrence of symblepharon after they are removed. Addition of epithelial tissue, or a basement membrane which can be populated by healthy host epithelial cells, is required to maintain the fornix. The ideal epithelial graft tissue would have the same cosmetic appearance as conjunctiva, result in the formation of normal tissue and cell types, including goblet cells, and prevent postoperative cicatrisation. It would also not require a general anaesthetic as many of the patients will be elderly, and would be free from donor site morbidity.

Graft materials available include healthy conjunctival autograft, oral and nasal mucosal autografts, and recently there has been a resurgence of interest in the use of amniotic membrane graft (table 1). Human amniotic membrane has been used since 1910 for three main purposes: to serve as a graft for skin and vaginal reconstruction, to prevent tissue adhesion in surgery of the head, pelvic cavity and otolarynx, and to serve as a dressing for full-thickness skin wounds [1, 2]. Its use in conjunctival symblepharon repair was reported in 1940 by De

Rötth [3] in 8 patients. The results were disappointing with failure in all but 1 patient. He recommended that it be reserved for those patients in whom other options are not available. There was then little in the literature on the medical use of amniotic membrane until the year 1995 when Kim and Tseng [4] reported its use to cover rabbit corneas that had been damaged to produce excessive neovascularisation. Amniotic membrane was used because it has a thick basement membrane thought to encourage epithelialisation. Since then there has been an explosion of interest in its use, including a number of reports of its successful use in fornix reconstruction after the removal of large conjunctival lesions, scarring due to cicatricial disease such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid, after removal of conjunctivochalasis, and (used in combination with skin flaps) in construction of an upper lid in cryptophthalmos [5–11].

Amniotic membrane has been demonstrated to reduce inflammation and fibrosis [12], and is thought to promote re-epithelialisation [13, 14], and elicit goblet cell repopulation [15], however the exact mechanisms of these actions are unknown. It is recognized that damage to the epithelium not involving the basement membrane will result in total epithelial regeneration without scarring. If the injury extends beyond the basement membrane, scarring will inevitably occur. The exact role of the basement membrane in wound healing remains unclear. It may act as a barrier to prevent unnecessary epithelial mesenchymal cytokine interactions. Removing the basement membrane may facilitate cytokine dialogues between the healing epithelial cells and underlying stromal fibroblasts and promote the development of scar tissue in the stroma and cellular hyperplasia in the epithelium, whereas restoring it with amniotic membrane may prevent this.

The stroma of amniotic membrane has been shown to contain cytokines and growth factors [16], but it is not known whether they play a role in the therapeutic effect of the membrane. There have been few clinical comparisons of the effects of fresh and stored amniotic membrane [17], and the extent to which the preparation and storage of the amniotic membrane affects the cytokines and growth factors is not fully understood. It has also been suggested that the therapeutic effects may be in part due to factors such as an increase in oxygenation and hydration, or a reduction in friction to the regenerating epithelium [18].

Guidelines for Choice of Graft Material

A healthy conjunctival or tarsal autograft is the ideal material, however there is limited availability especially in bilateral disease. A full-thickness oral

mucous membrane graft is the simplest graft to use if conjunctiva or tarsus is not available. Split-thickness mucosal grafts contract more than full-thickness grafts, and are therefore less suitable for fornix reconstruction, but are less bulky and pink than full-thickness grafts, and therefore should be used on the globe.

Hard palate grafts are the thickest oral mucosal grafts and contract the least. They are more difficult to harvest than other oral mucosal grafts, but are useful where sufficient buccal or labial mucosa is not available or when it is particularly desirable to avoid contracture. Oral mucosa does not contain goblet cells and therefore does not supplement the tear film.

Nasal mucosal grafts contain goblet cells that may contribute mucous to the tear film [19]. This is maximised in turbinate mucosal grafts, which can relieve discomfort in extreme dry eye situations. Nasal septal cartilage contains fewer goblet cells, but is useful in the reconstruction of the posterior lamella when the tarsus is lacking; the graft replaces the rigidity of the tarsus, and its attached mucoperichondrium provides a mucosal binding which does not shrink and can be wrapped around the skin of the reconstructed eyelid to form a stable eyelid margin.

Amniotic membrane is thin and translucent-like conjunctiva. It may become re-epithelialised with normal a conjunctival cell population, and may prevent postoperative cicatrisation. Additionally, it is not associated with donor site morbidity, and a general anaesthetic is not required for lid surgery using amniotic membrane. However, successful surgery with amniotic membrane requires the presence of adequate healthy conjunctiva to repopulate the graft, adequate lacrimal function to keep the graft moist, and a conjunctiva that is free from inflammation. Rapid contraction occurs if any of these factors are not present.

Our own experience suggests that fornix reconstruction with AMT is a useful tool in reconstructive surgery in the presence of adequate healthy conjunctiva to repopulate the graft, adequate lacrimal function and a quiet conjunctiva. The results appear to be poor in the presence of an ongoing inflammatory condition, or where there is an absence of healthy conjunctiva, and where there is a poor lacrimal function, such as in advanced ocular cicatricial pemphigoid, and severe burns. In cases of difficult to control inflammation, poor lacrimal function, or near total lack of healthy conjunctiva, a buccal mucous membrane graft may be more appropriate than an amniotic membrane transplant.

There is a lack of prospective randomised controlled studies in this area, but recent reports in the literature of the effectiveness of AMT for fornix reconstruction have also produced mixed results. Where it has been used to treat symblepharon caused by non-inflammatory disease, such as after removal of tumours, pterygia, and the treatment of cryptophthalmos, the results have been encouraging

[7–9]. The results of AMT in the treatment of acute ocular burns have been encouraging in the treatment of less severe cases with some healthy peripheral conjunctival tissue, but poor for the treatment of severe burns [20, 21].

AMT for fornix reconstruction in the presence of inflammatory disease has produced more varied results. Solomon et al. [8] report a series of AMT for fornix reconstruction in a variety of ocular surface disorders in which all eyes that developed symblepharon secondary to chemical or mechanical injury resulted in a successful outcome, but patients who experienced a failure or partial success had symblepharon associated with autoimmune disorders or previous surgery. Tsubota and Shimazaki [11] noted that healthy conjunctiva and good lacrimal gland function are required for successful treatment of children blinded by Stevens-Johnson syndrome with allograft limbal transplantation and amniotic membrane transplantation (AMT).

On the other hand, Honavar et al. [6] report successful AMT for ocular surface reconstruction with improved ocular surface and deep fornices in 9 of 10 eyes with Stevens-Johnson syndrome, and recommend it as a first step in multistaged ocular surface reconstruction, prior to allograft limbal transplantation and penetrating keratoplasty where appropriate.

Barbarino et al. [5] report a significant increase in fornix depth after AMT in ocular cicatricial pemphigoid, and likewise recommend it as a first step procedure for ocular surface reconstruction in the treatment of ocular cicatricial pemphigoid.

The results of adjunctive treatments such as the intraoperative application of mitomycin C to reduce postoperative scarring graft shrinkage [22], conjunctival limbal autograft and transplantation of cultivated limbal stem cell sheets to supply healthy epithelial cells have been encouraging and hold promise for the future [23–28]. Further research into this area is required to determine the indications for the use of amniotic membrane and adjunctive treatments.

Surgical Details (figs 1–3)

Fornix Reconstruction

In the perioperative period, any inflammatory lid disease has to be controlled medically in conjunction with an immunologist. The fornix is reformed and scar tissue dissected (fig. 1). The graft material is placed over the defect with the shiny epithelial side up. The graft is trimmed and the edge secured under the conjunctival margins with 8/0 Vicryl. To maintain a deep fornix the graft is also secured to the underlying rectus muscles with 6/0 Vicryl, and either a fornix gutter or ring conformer is used in addition. Postoperatively the

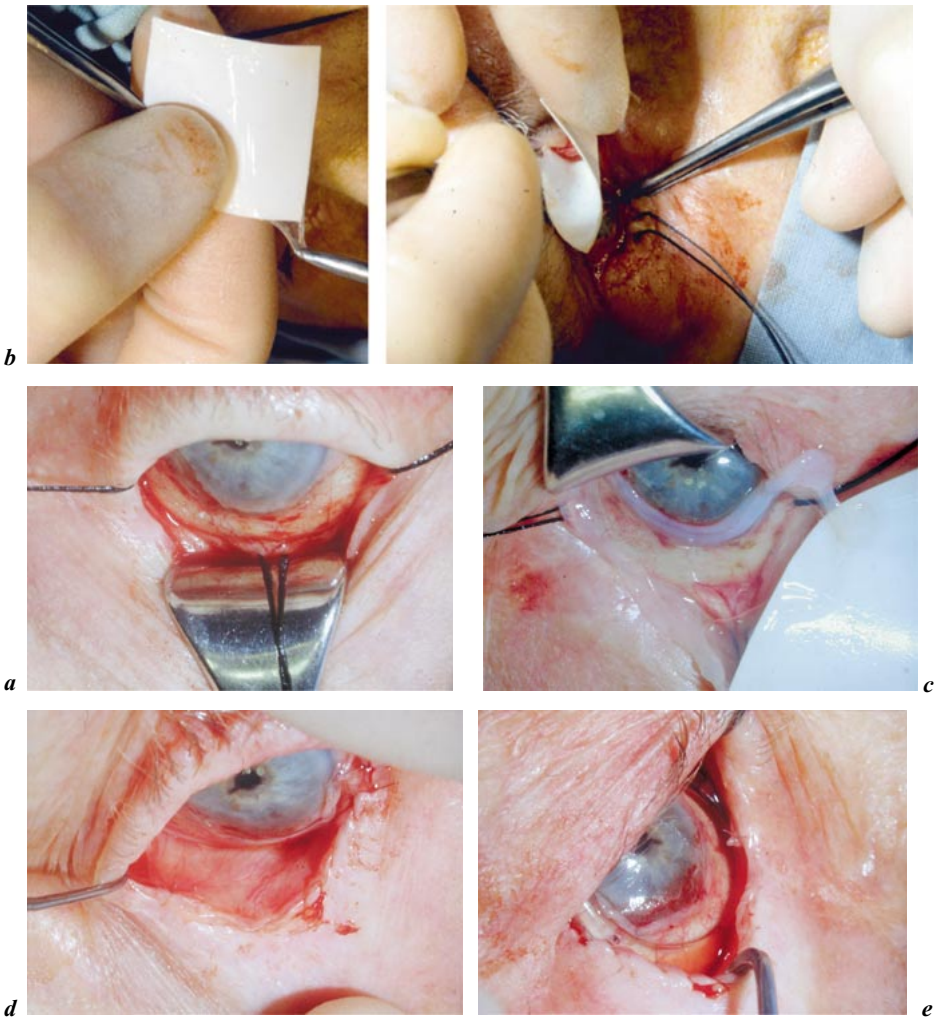

Fig. 1. ***a*** Dissection of scar tissue. Recti isolated with muscle sling. ***b*** Graft material prepared (amniotic membrane is used here) and positioned over defect. ***c*** Graft placed over defect basement membrane side up (epithelial side up if mucosal/conjunctival graft used). ***d*** Graft edge trimmed, secured at margins and to the recti muscles. ***e*** Fornix maintenance with a conformer.

patients are treated with guttae prednisolone acetate 1% six times a day tapering over 6 weeks, guttae chloramphenicol 1% four times a day until complete epithelialisation, and guttae hypromellose 0.3% 2 hourly for 6 weeks. The sutures are removed at 2–3 weeks and the conformer removed at 1 month. *Note*:

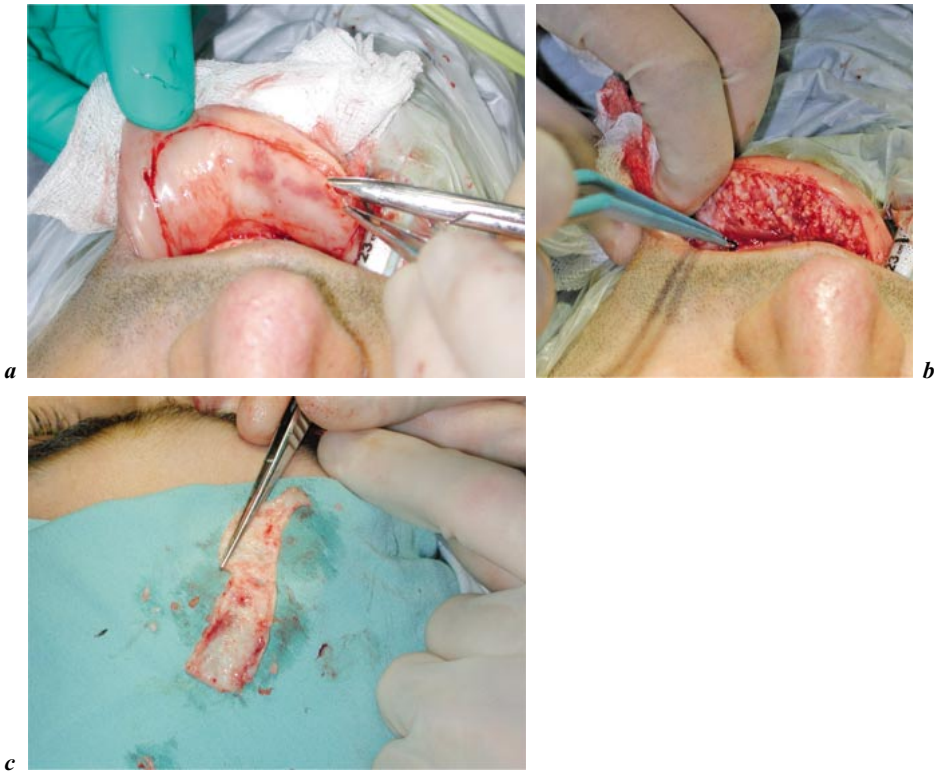

Fig. 2. ***a*** Excision of labial mucous membrane graft after injection of saline to elevate graft from submucosal tissues. ***b*** Diathermy to donor site. ***c*** The fat is trimmed from the underside of the graft.

a fornix gutter can be fashioned from a retinal band and secured with 4/0 prolene sutures passed through the full lid thickness and tied over bolsters on the skin.

Graft Material Harvest

Conjunctiva

Inject local anaesthetic with adrenaline under the conjunctiva. Cut around the proposed graft with a blade while the tissue is elevated with the local anaesthetic fluid. Cut the subconjunctival tissue with spring scissors and slide the graft onto a spatula to keep it orientated correctly. The superior bulbar surface

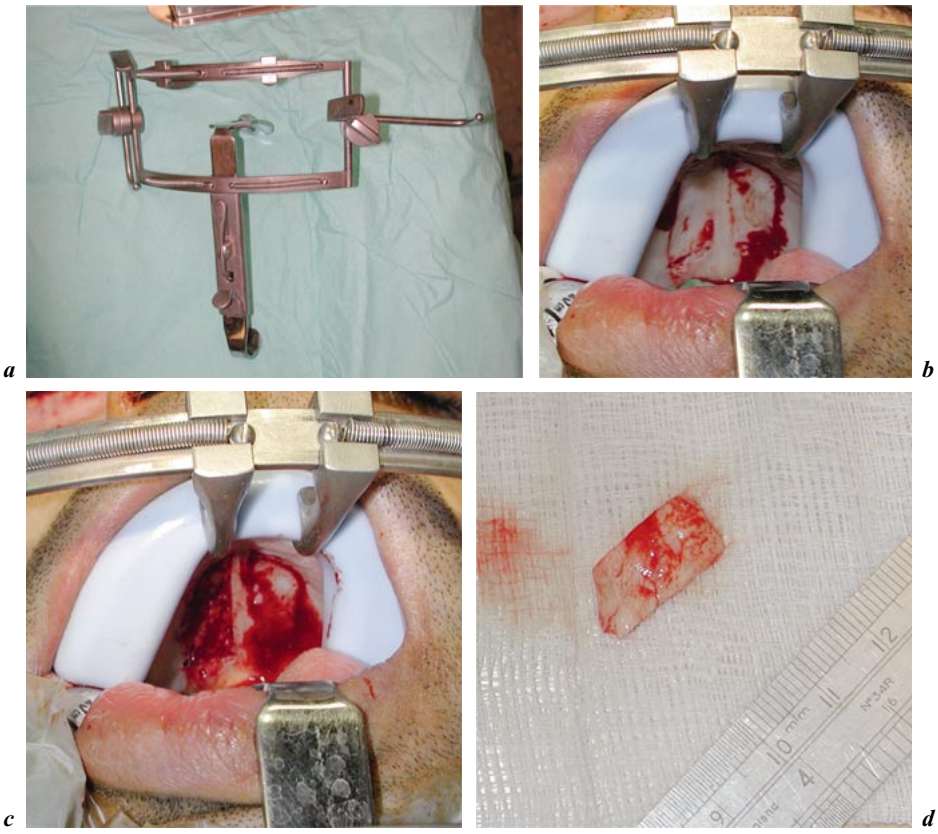

Fig. 3. ***a*** Dingman clamp. ***b*** Incise around the template and inject local anaesthetic with adrenaline under the graft. ***c*** Resection of the graft is as superficial as possible. The right graft has been excised. ***d*** The graft can now be trimmed of excess fat.

can be allowed to granulate and heal by secondary intention. A 7 '0' absorbable suture can be used to close an inferonasal conjunctival defect.

Tarsus

Place a traction suture in the upper lid and evert it over a Desmarres' retractor. Mark the desired graft size on the tarsus extending down from the attached upper border but leaving not less than 4 mm of intact tarsus to maintain the stability of the upper lid margin. When satisfied with the extent of the graft and position of the donor site, make scratch incisions in the tarsus first and then cautiously deepen them to extend through the tarsus. If the lid is being forcibly

everted the tarsal wound springs open when the tarsus is first cut through. The incision can then be completed with scissors along the scratch incisions. If the tarsal graft is being used to reconstruct a lid margin leave a frill of conjunctiva attached to the tarsal graft. Leave the donor site to granulate and heal by secondary intention. If the graft is small the donor eyelid level is not usually affected but if the graft is very extensive the lid level may rise unless the lid retractors are cautiously recessed via the posterior approach.

Oral Mucosal Grafts

Full-Thickness Oral Mucous Membrane Graft (fig. 2). Measure the defect and cut an approximate template e.g. out of paper. Place it on the chosen donor site. The donor sites available are the lower or upper lip (labial), and cheek (buccal). For the lip do not extend too close to the lip margin or gum. For the cheek, adjust its position to avoid the opening of the parotid duct, usually opposite the second upper molar. Make an incision peripheral to the template. Inject saline under pressure to elevate the graft from the submucosal tissues and to reduce haemorrhage by tamponade. Weak adrenaline can be added to the saline but should not be necessary. Excise the graft as thinly as possible using a blade and scissors. Remove all the submucosal fat from the graft. This is easy if the graft is spread over the index finger, held by the thumb, and the fat excised with curved Westcott scissors. The graft bed can be left to granulate or sutured with a few interrupted 4/0 Vicryl sutures if the wound edges can be closed with ease and without deforming the lip in the case of a labial mucosal graft. Postoperatively cover the patient with systemic antibiotics. Mouthwashes, fluids and a soft diet may be required initially, but the wound heals rapidly.

Split-Thickness Mucous Membrane Graft. Evert the lower lip and inject as much saline as possible under the mucosa to separate it from the submucosal tissues. Use a mucotome, a small split-skin knife (e.g. Silver), or disposable dermatome, and excise approximately a 0.3-mm thickness of mucosa, taking care to avoid the vermilion border of the lip. Leave the terminal part of the graft attached and remove the instrument. Slide a flat spatula under the graft and then cut off the terminal attachment. This ensures that the cut surface is clearly identified. If in doubt it is in theory possible to see which of the two surfaces stains with fluorescein which stains the cut surface, but this test is usually not very convincing. Cauterise major bleeding points. Postoperatively the wound heals rapidly but the patient should be covered with systemic antibiotics and mouthwashes should be given for the first few days.

Hard Palate Mucosal Graft (fig. 3). Protect the teeth and hold the mouth wide open with a specially designed clamp, e.g. Dingman, or with dental or maxillofacial wedges or oral clamps. Make a template of the defect and position this on the hard palate on one or other side of the midline raphe. Avoid the most

anterior mucosa above the incisors and the mucosa over the roots of the molar teeth. Do not extend posteriorly onto the soft palate. Incise around the edge of the template. Inject local anaesthetic with adrenaline under the graft preferably using a dental syringe with a fine needle and a cartridge with 1 in 80,000 adrenaline. Raise the corner of a posterior edge of the graft with a long-handled toothed forceps and gently undermine the graft using a combination of a long-handled blade alternating with a scleral pocket knife, angle keratome or beaver blade. Try to keep the resection as superficial as possible. Remove any fat from the graft as with a full-thickness mucous membrane graft. Ensure haemostasis by cauterising the bed of the donor site. Postoperatively cover the patient with systemic antibiotics. Mouthwashes, fluids and a soft diet may be required initially. Postoperative pain can be a problem and can be relieved by sucking anaesthetic lozenges but these may also delay healing. A dental plate can be made to protect the site and allow healing to occur more quickly and comfortably. Postoperative haemorrhage is a risk during the first 2–3 weeks. As a short-term measure the patient should be instructed to stick their thumb in their mouth over the donor site and apply pressure until it stops. Further cautery and systemic antibiotics may be required. Presumed minor salivary gland secretion has been reported after hard palate mucosal grafts, characterised by a stringy mucous discharge over the graft and along the eyelids causing visual blurring [29].

Nasal Mucosal Grafts

Nasal Turbinate Mucosa. Decongest the nasal mucosa with a nasal pack containing a vasoconstrictor such as adrenaline. Identify the middle turbinate using a nasal speculum and an endoscope or head light. The turbinate is resected in its vertical portion using turbinectomy scissors. Spread out the turbinate mucosa on a moist gauze swab and remove the pieces of turbinate bone. The graft can then be sutured onto a suitable recipient site preferably hidden from view, e.g. onto the bulbar surface above the superior limbus under the upper eyelid. Occasionally troublesome bleeding may occur at the posterior insertion of the turbinate from a branch of the sphenopalatine artery; this is easily stopped with endoscopic diathermy.

The inferior turbinate may initially seem more attractive as it offers a larger amount of mucosal and is easier to access than the middle turbinate. It may also be resected in a similar fashion. It is common practice to crush the horizontal attachment of the inferior turbinate with a straight haemostat prior to resection in an attempt to prevent heavy bleeding. Epistaxis following this procedure is however not uncommon, and is occasionally torrential. Resection of the inferior turbinate may also cause long-term crusting and feelings of blockage (paradoxical nasal blockage) and hence the medical nasal turbinate is preferred.

Nasal Septal Cartilage and Mucoperichondrium. The patient's nasal cartilage with the mucoperichondrium attached to one side is harvested. The other mucoperichondrium is left in situ (add figure of donor site after taking graft).

Reduce the vascularity of the septal mucosa preoperatively. In the anaesthetic room paint the nasal septum or pack the nose with a ribbon gauze soaked in a vasoconstrictor solution. Use an operating headlight. Give an extensive submucosal injection of a weak adrenaline solution on one side of the nose to help strip the mucosa from the cartilage. On the other side of the nose, inject locally in the region of the planned incision only. If adequate exposure cannot be obtained with a nasal speculum, cut around the alar base and lift the nostril. Palpate the distal edge of the septum and incise through the mucosa proximal to and in line with it. Clean the surface of the cartilage and partially cut through it with a blade, leaving a strut of septum to support the tip of the nose. Penetrate the septal cartilage carefully with a blunter instrument such as a Rolletts rougine and push the mucoperichondrium away from the far side of the incision. Complete the stripping of the mucoperichondrium with a periosteal elevator, e.g. a MacDonald. Cut the cartilage and its attached mucosa with a specially designed 'swivel knife' if one is available. Alternatively, cut it from the roof and floor of the nose with scissors. Protect the stripped intact mucoperichondrium with a periosteal elevator. If a swivel knife is not available, cut the proximal part of the septum and mucosa with an angled beaver blade, ground down keratome scleral pocket knife or angled scissors. The septal cartilage usually requires thinning before it is used. Cut two fingers from a surgical rubber glove, pack them lightly with ribbon gauze, dip the fingers in glycerine and pack one finger on either side of the remaining mucoperichondrium. Remove the pack the following morning and treat the nose with antibiotic and vasoconstrictive drops four times a day for about a month.

Amniotic Membrane Graft

Amniotic membrane is available as fresh, frozen or lyophilised material. It is obtained at caesarean section from a donor who has given consent and has been tested for syphilis, hepatitis B and C and HIV during pregnancy, and (except in the case of fresh material) at 6 months' postpartum. The amniotic membrane is separated by blunt dissection, bathed in antibiotics, cut and packaged stromal side down on 2 or 3 cm square nitrocellulose cards. It is stored in a mixture of 50% Dulbecco's modified Eagle's medium, and 50% glycerol at –80°C while awaiting the results of the tests for donor infectious disease taken at 6 months postpartum. It can continue to be stored for 6–48 months in this way, or can be stored for longer as a dried preparation.

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Dr. H.W.A. Henderson
The Royal Free Hospital
Pond Street, London NW3 2Q6 (UK)
Tel. +44 20 7830 2208, Fax +44 20 7806 4081
E-Mail hugo.henderson@royalfree.nhs.uk

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Minor Salivary Gland Transplantation

Gerd Geerling[a], *Peter Raus*[b], *Juan Murube*[c]

[a]Department of Ophthalmology, University of Würzburg, Würzburg, Germany; [b]MIRO Centrum voor Ooglidchirurgie en Esthetiek, Mol, Belgium; [c]Department of Ophthalmology, University of Alcala, Madrid, Spain

Abstract

Introduction: Minor oral salivary glands exist in large numbers in the labial, buccal and palatal mucosa, and account for approximately half of the baseline secretion of saliva. They can be transplanted together with the overlying mucosa as a complex graft to the posterior lamella of the eyelids to increase ocular surface lubrication and reduce discomfort in dry eyes. **Material and Methods:** The surgical methods and the results of this technique in 17 patients are described. All patients had been retractive to medical treatment. The recipient bed over the lower or upper lid retractors and a donor tissue of lower labial mucosa with its submucosal minor salivary glands of approximately 2.5 × 2 cm were prepared by means of a surgical knife or Ellman Surgitron high-frequency/low-temperature radiosurgical device. The graft was cut in two strips of approximately 2.5 × 1 cm size and sutured to the recipient site with interrupted or running sutures. The labial wound was left open for second intention healing. **Results:** All grafts remained viable and vascularised within 1 week. Vascularisation of the graft was associated with an improvement of symptoms and increased ocular surface lubrication. Complications included temporary labial hypaesthesia, partial necrosis of the graft (n = 1), herpes simplex virus keratitis (n = 1) and epiphora (n = 1). Viable glandular tissue was found in specimens taken 18 and 36 months postoperatively. Other reported complications include lid malpositioning such as ptosis and entropium. **Conclusion:** Transplantation of minor salivary glands is a promising new treatment option for severe dry eyes. The procedure is simple with minimal surgical risks. These grafts remain viable in over 90% and seem to be capable of sustaining a basal secretion for up to 36 months. Since experience with this technique is still very limited, prospective controlled studies have to be performed to establish the long-term survival of the glands and to characterise the salivary tear film and its impact on the ocular surface.

General Considerations

With absolute tear deficiency, defined by ourselves as a Schirmer test (without prior application of a topical anaesthetic) of <2 mm, ocular surface

disease may progress despite frequent application of unpreserved tear substitutes and occluded lacrimal puncta [1]. Such patients frequently suffer from permanent and sometimes excruciating symptoms of discomfort, but also experience severe loss of vision. In this situation, mucous membrane grafting (see chapter 16) alone may not provide sufficient lubrication to alleviate symptoms or to successfully enable ocular surface reconstruction with e.g. a corneal graft.

Apart from artificial devices termed 'dacryoreservoirs' (see chapter 19), transplantation of significant amounts of actively fluid secreting tissue is the only option available to provide a sufficient volume of substitute lubrication. Various forms of mucous membrane grafts (oral, nasal, ileac) have been used, but failed to provide sufficient amounts of lubrication. Several studies have shown that oral and nasal mucosa could successfully be used to reconstruct the fornices and to provide mucin for lubrication. However, neither after oral nor nasal mucosal transplantation did lubrication increase to a level sufficient to sustain a healthy corneal graft [2–5].

The composition of saliva and tears is fairly similar in its complexity as well as in several specific parameters (table 1 [6–14] and table 2 [15–35]). It contains large amounts of albumin, immunoglobulins, growth factors, mucins and lipids, all of which are also present in tears. In addition, saliva is also characterised by the presence of enzymes such as amylase. However, due to their substrate specificity the latter have not been found to be deleterious for the ocular surface [10, 36]. It is thus not surprising that whole or compounds of saliva have been used to treat dry eye since biblical times (Mark 8:23) [37].

A number of salivary glands have been reported repeatedly as a source of substitute lubrication for the ocular surface [37–40]. These include minor as well as major salivary glands from the oral cavity and neck. Major salivary glands are the paired (right/left) parotid, sublingual and submandibular glands. Minor oral salivary glands exist in large numbers in the labial, buccal and palatal mucosa. Major and minor salivary glands account for approximately half of the baseline secretion of saliva (i.e. without gustatory stimulus) [40]. Other tissues, such as gastrointestinal mucosa, have also been tried but harvesting the graft as well as donor site morbidity and insufficient success have limited further use.

The idea of transplanting minor salivary glands was first conceived by Juan Murube [40], who in 1998 described the use of various complex grafts of mucosa with attached salivary glands. Of these he found the combination of labial minor salivary glands with their covering mucosal sheath most promising in experimental and clinical use (fig. 1). In a group of 6 patients he observed increased surface lubrication and moderate to significant reduction of dry eye symptoms in 4 cases [40].

Table 1. Flow rate and general type of secretion of unstimulated tears, whole and specific parts of saliva. NDA = No Data Available.

	Tears	Whole saliva	Sublingual gland saliva	Parotid gland saliva	Submandibular gland saliva normal	Submandibular gland saliva transplanted (salivary tears)	Labial gland saliva
Flow rate, μl/min (stimulated)	0.6–1.4 (4.4)	~400 ± 200 (~2,000 ± 1,000)	~20	60–80 (260–330 ± 13)	108–134 (450 ± 0.4)	0.12 (0.74)	~300 0.4–5 μl/cm^2 (2.7–3.0 ± 1.3)
Type of secretion	Seromucinous + lipids	Mixed	Mucoserous	Serous	Seromucinous	Mucoserous	Seromucinous
Surface tension, dyn/cm	62 ± 6	15–26		50–70	70 ± 5	66 ± 1	NDA

Table 2. Composition of unstimulated tears, whole and specific parts of saliva. NDA = No Data Available.

	Tears	Whole saliva	Parotid gland saliva	Submandibular grand saliva normal	Submandibular grand saliva transplanted (salivary tears)	Labial grand saliva
Osmolality mosm/l	298 ± 10	200–310	NDA	108 ± 4	165 ± 74	NDA
Potassium mosm/l	18.7 ± 5.5	20 ± 6	30 ± 21	20 ± 6	NDA	NDA
pH	7.47	6.5–7.25	NDA	NDA	NDA	NDA
Glucose mmol/l	0.16 ± 0.03	1.3 ± 0.3		NDA	NDA	NDA
Total protein, g/l (stimulated)	6–23.3 ± 3.4	1.8 ± 0.4	~800 (247 ± 15/min)	0.38 ± 0.16 (0.54 ± 0.34)	1.8 ± 2.5 (1.2 ± 0.56)	NDA
Albumin, g/l (stimulated)	4 ± 0.5	0.04 ± 0.02	(0.0025 ± 0.24)	(2.7 ± 0.26)	NDA	0.23 ± 0.13
EGF, ng/) (stimulated)	5,090–8,466 ± 3,740 (2,763)	864 ± 135	NDA	357 ± 60	NDA	NDA
Vitamin A, ng/ml	16	NDA	NDA	NDA	NDA	NDA
Fibronectin, ng/ml	19 ± 24 (open) 4,127 ± 3,222 (closed eyes)	149 ± 46.2	2.5 ± 1.4	NDA	NDA	NDA
sIgA, μg/ml (stimulated)	1,189 ± 904	89 ± 55	(131 ± 7)	127 ± 178 (42 ± 45)	643 ± 1,183 (828 ± 1041)	69 ± 56
Lactoferrin, μg/ml	3,080 ± 930	10 ± 7	(1.81 ± 0.31)	(1.63 ± 0.21)	NDA	8.5 ± 6.1
Lysozyme, μg/ml (stimulated)	1.4 ± 0.2	1.39 ± 1.37	(1.82 ± 0.16)	6.6 ± 2.7 (8 ± 2.9)	87.7 ± 144.1 (39.8 ± 25.6)	NDA
Amylase, kU/l (stimulated)	NDA	494 ± 44	590	45 ± 182 139 ± 212	41 ± 57 (112 ± 69)	NDA

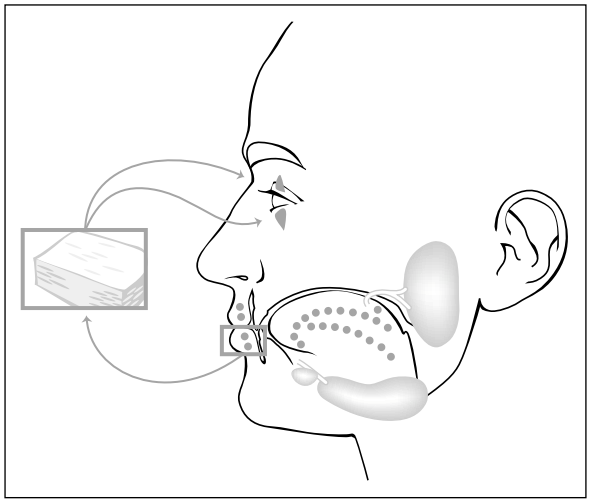

Fig. 1. Diagram showing general distribution of minor salivary glands (grey dots), donor and recipient site of fabial mucosa with minor salivary gland transplant.

The minor salivary glands of the lip are present in such large numbers that they form an almost compact layer of single lobules between the quadratus labii muscle and the oral mucosa. Each lobule measures approximately $2 \times 2 \times 3$ mm and has a short excretory duct exiting onto the surface of the oral mucosa. The secretion of these glands is seromucinous and has a viscosity higher than tears. It contains large amounts of antimicrobial peptides such as IgA and growth factors such as epidermal growth factor [41, 42] as well as a lipid level 4–5 times higher than in other salivary gland secretions.

Surgical Techniques

The complex graft of labial mucosa with attached minor salivary glands is usually taken from the lower lip, since access is easier here than in the upper lip. Also the glandular density per surface area is higher in the lower lip [40, 43]. We have also observed that more salivary glands are found in the lateral compared to the central part of the lip. However, if severe aqueous tear deficiency is bilateral – as is often the case in such disorders as graft-versus-host disease or Stevens-Johnson syndrome – additional graft material has to be harvested and the upper lip or buccal mucosa can be considered.

Preferably surgery is performed under general anaesthesia. First the recipient bed, either in the upper, lower or usually both lids is prepared. The lid is

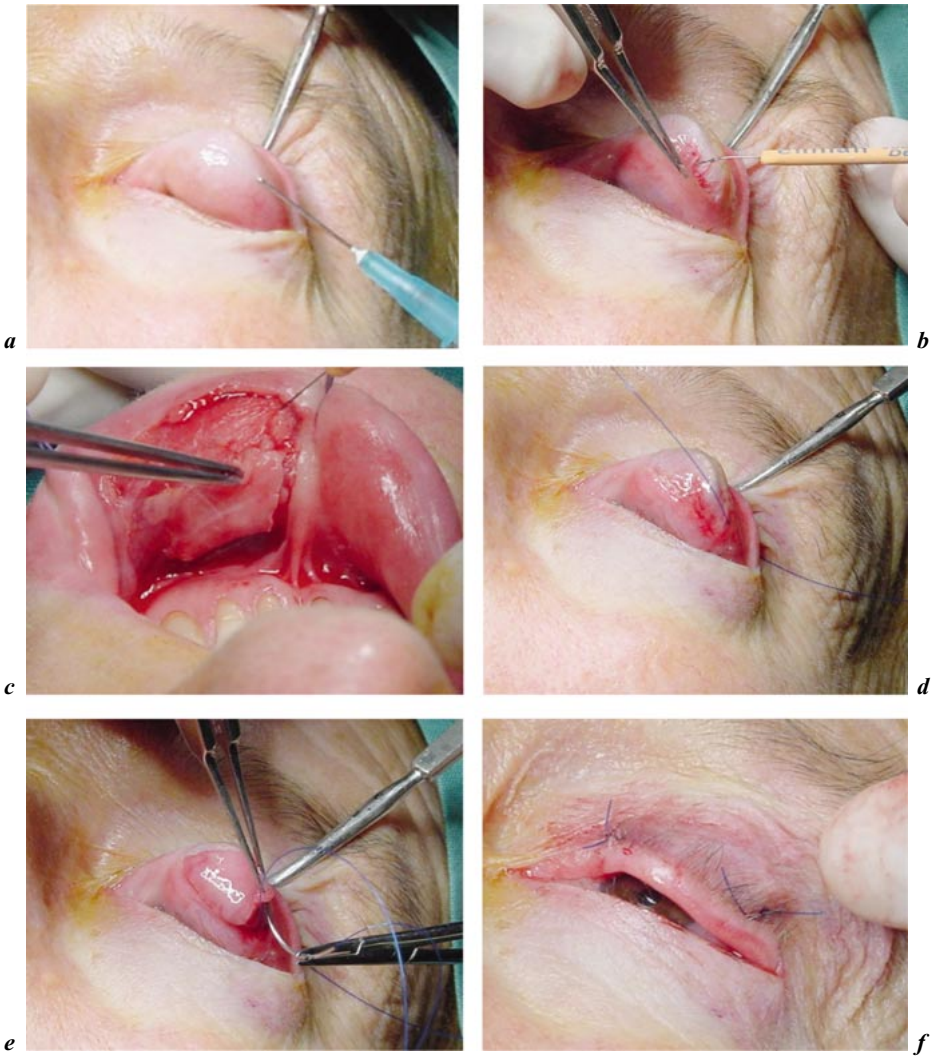

Fig. 2. (***a***) Injection of fluid into the subconjunctival space to ease surgical dissection performed with (***b***) Ellman® radiosurgical device. (***c***) The graft is harvested from the lower lip and fixed with a (***d–f)*** transpalpebral running 4.0 prolene suture in the upper and lower lid.

everted using a Desmarres lid retractor. Isotonic saline or xylocaine 1% solution with epinephrine is injected under the conjunctiva to separate it from the underlying Müller's muscle in the upper lid or the retractor muscle in the lower lid (fig. 2a). The epinephrine causes a local vasoconstriction to (further) limit

bleeding, but on the down side it potentially may reduce oxygen supply to the graft in the early postoperative phase. Next, an incision of approximately 2.5 cm is made along the rim of the tarsal plate using either a surgical blade or a fine wire electrode in the cut/coagulation mode of a radiosurgical unit (fig. 2b). The conjunctiva is dissected posteriorly for approximately 1.5 cm and any major bleeding vessel coagulated without cauterising large areas of the recipient site.

To harvest the donor tissue, the inferior lip is everted either with a large chalazion-style clamp or with two 4-0 silk traction sutures, which are placed at the inner aspect of and parallel to the labial rim. The labial mucosa is exposed with gentle traction. A first horizontal full-thickness incision is made in the mucosa, not closer than 1 cm from the mucocutaneous junction, starting 0.5 cm lateral of the midline of the lip and extending 2–2.5 cm laterally. The first salivary lobules will become visible in the incision, which is then extended at both ends backwards over approximately 1.5–2 cm towards the gingivolabial sulcus. By means of blunt or radiofrequency-assisted dissection, the graft is then lifted from the quadratus labii muscle (fig. 2c). The high-frequency radiosurgery device (4 MHz) has a fine wire electrode, a low power setting to cut, coagulate or remove soft tissues, while minimising collateral tissue damage. For this particular intervention we use the 50:50 cut-coagulate mode, which is helpful in limiting bleeding from the highly vascularised mucosa. Great care is taken to include as many salivary gland lobules as possible, while at the same time avoiding damage to the underlying muscle. The graft is finally severed completely by a fourth incision parallel to the gingivolabial sulcus and placed in a polyvidone solution (1–10%) for several minutes. All obvious bleeders are carefully coagulated. The labial wound is left unsutured. It usually rapidly granulates and is closed by secondary intention healing within 2–4 weeks.

The donor tissue obtained is carefully cleaned and cut into two strips of approximately 2.5 × 1 cm size. All glandular structures are carefully preserved. The upper lid is again double everted with the Desmarres retractor, and the donor piece is sutured to the recipient site. Care is taken to establish good contact between the graft and the underlying lid retractors to support rapid oxygen supply and revascularisation of the mucosa. The procedure is then repeated in the lower lid with the second strip of the donor tissue.

Suturing can be done with 7.0 or 8.0 long-acting absorbable sutures such as polyglactin. To avoid damage to the corneal epithelium, especially from the graft in the upper lid, a bandage contact lens should be applied until complete resorption of the sutures. During the first postoperative month the upper lid is usually fairly edematous and should not be everted to avoid damage to the graft. Alternatively, each graft can be held in place with two horizontal submucosal

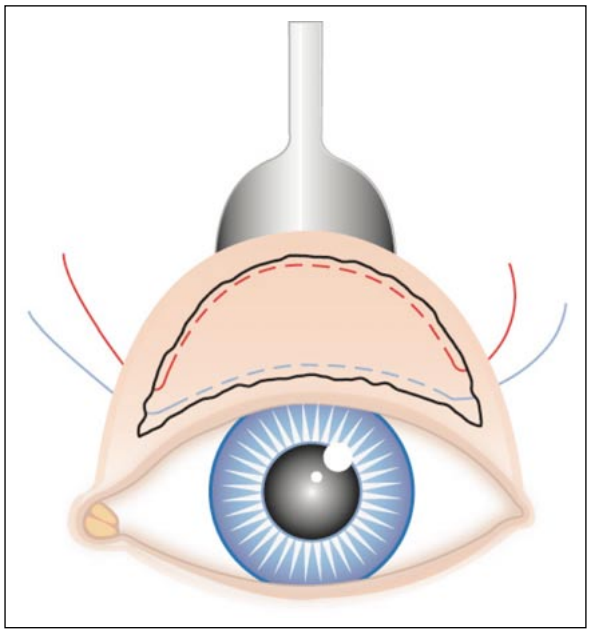

Fig. 3. Position of graft and sutures in the upper lid.

running prolene 4–0 sutures along their upper and lower horizontal border. Both sutures are passed transpalpebral out to the skin, where both externalised ends are tied together (figs 2d–f, 3). This technique avoids the use of a bandage contact lens and reduces the amount and duration of the postoperative palpebral oedema.

Antibiotic eyedrops are instilled and a light pressure bandage is applied for 24 h up to 1 week. A temporary tarsorrhaphy suture can be equally placed to reduce palpebral motility and prevent any bleeding that could reduce the chances of the graft taking. Postoperative treatment includes continued application of topical antibiotics and lubricants 4–8 times daily for usually 2 weeks. At the end of this period the prolene sutures can be removed by simply cutting the ends and pulling the sutures out from the skin.

Results

So far we have performed this procedure in 17 patients with severe dry eyes using the Ellman Surgitron® high-frequency/low-temperature radiosurgical

device. All patients had suffered from severe to absolute aqueous-deficient dry eye, e.g. due to alkali burn, congenital alacrimia and other severe disorders. All patients had previously used various types of artificial tears, gels and/or ointments in most of the cases with insufficient results.

Initially the graft was pale and became chemotic, but showed signs of vascularisation within 1 week, which was when patients began to report relief from dry eye symptoms. After 2 weeks, secretion of saliva often became apparent. This was initially fairly viscous, but became more serous by 1 month. Schirmer test and fluorescein break-up increased in all cases, the latter being potentially a result of the lipid component of the labial gland saliva (table 1).

Complications included almost obligatory temporal local hypaesthesia of the lip, which can persist for a few months. Recipient site complications included 1 case of a partial necrosis (<10% of the graft) which had no effect on the final result as well as 1 case of herpes simplex virus keratitis on the fourth day postoperatively which rapidly resolved with topical acyclovir ointment 5 times a day. One patient also complained of 'watery' eyes, which 18 months postoperatively required partial resection of the graft in both lower lids under local anaesthesia. Histology showed normal glandular acinar tissue in both specimens. In 1 patient a part of the graft became externally visible presenting with a papillomatous appearance. For cosmetic reasons this portion was resected after 36 months. Again, histology revealed normal glandular structures with only minimal local inflammation. Other complications observed include a bulkiness of the lids, which in association with lower lid laxity can lead to entropium and a reduced labial volume.

Murube et al. [40] reported about 6 patients with a mean follow-up of 11 months (6–24 months) who received a labial salivary gland transplant for Sjögrens syndrome (n = 3), ocular cicatricial pemphigoid (1), Stevens-Johnson syndrome (1) or seventh nerve palsy (1). One graft became atrophic, but five grafts remained viable and led to increased lubrication and a reduction of symptoms in four. Mean preoperative Schirmer test improved from 5.7 ± 3.8 to 11.7 ± 9.5 mm. Güerrissi and Belmonte [44] reported a patient with a 2-year history of dry eye secondary to Sjögren's syndrome and severe dry eye symptoms retractive to any medical treatment, who showed significant relief after minor salivary gland transplantation. A biopsy taken 3 months after surgery confirmed the presence of viable salivary gland acini and ducts with mucin content [44]. Soares and Franca [45] reported a graft survival rate of 97% in 37 transplants and a maximum follow-up of 4.5 years. Graft viability was associated with improvement of signs and symptoms including improved vision in 92% of the cases. Complications included infection (n = 1) and ptosis (n = 3) [45].

Conclusion

Transplantation of minor salivary glands seems to be a promising new treatment option for severe cases of dry eye. The procedure is simple to perform with only minimal surgical risks. These grafts remain viable in over 90% and seem to be capable of sustaining a basal secretion for up to 36 months. Since experience with this technique is still very limited, prospective controlled studies have to be performed to establish the long-term survival of the glands and to characterise the salivary tear film and its impact on the ocular surface.

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Prof. Dr. Gerd Geerling
Klinik für Augenheilkunde, Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11, DE-97080 Würzburg (Germany)
Tel. +49 931 201 20 610, Fax +49 931 20 120 490
E-Mail g.geerling@augenklinik.uni-wuerzburg.de

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Transplantation of the Major Salivary Glands

Gerd Geerling[a], *Peter Sieg*[b]

[a]Department of Ophthalmology, University of Würzburg, Würzburg, and
[b]Department of Maxillofacial Surgery, University Hospital of Lübeck, Lübeck, Germany

Abstract

Background: In absolute aqueous-deficient dry eye, severe signs and symptoms may persist despite punctal occlusion and frequent application of artificial tear substitutes. In this group of patients the three major salivary glands, the parotid, the submandibular and the sublingual gland, have been used to lubricate the ocular surface. **Material and Methods:** A PubMed search was performed using the keywords 'dry eye, major salivary glands, parotid gland, parotid duct, sublingual gland, submandibular gland (SMG), transposition, transplantation' to identify the current literature on major salivary gland transplantation. The surgical procedures are described, their principle advantages and disadvantages and the published results are analyzed. **Results:** To use the parotid gland as a source of substitute lubrication its secretory duct is transposed to the lower conjunctival fornix. The procedure results in a purely serous secretion and severe gustatory reflex epiphora. Parts of the sublingual gland, which produces a mucoserous secretion, have been transplanted into the subconjunctival space. Since the graft is left without a direct vascularisation, it frequently becomes non-functional. The SMG finally produces a more tear-like, seromucinous secretion. It is transferred as a free, denervated graft to the temporal fossa, where a microvascular anastomosis with the temporal artery and vein is established. Graft survival in the long term is 72%. Graft viability is associated with a significant improvement of Schirmer's test, break-up time, rose bengal staining and symptoms. In 38% of eyes with a viable graft, salivary epiphora results, which is independent of gustatory stimuli. Since the salivary tear film is substantially hypoosmolar, microcystic epithelial oedema can result and subsequent corneal transplantation remains unsuccessful. **Conclusion:** Of the three major salivary glands, the parotid and the SMG have been used successfully to provide substitute lubrication in severely dry eyes. The surgical technique varies significantly in terms of complexity and reversibility. While the procedures are capable of improving comfort, due to the salivary character of the new tear film subsequent ocular surface reconstruction remains unsuccessful.

In addition to the minor labial salivary glands (see chapter 17), all three major salivary glands, the parotid, sublingual and submandibular gland (SMG), have been tried and tested as alternative sources of lubrication in severe dry eye [1–4]. The glands were always of autologous origin, since donor tissue is easily available from this source and avoids the need for postoperative prolonged systemic immunosuppression, with all its potential complications (see chapter 6). With autologous donor tissue, potential drawbacks are localised and limited to donor side morbidity (e.g. damage of branches of the facial nerve) which is rare and usually neither lasting nor severe, and wound-healing problems of the graft itself, of which the most serious is necrosis of the glandular tissue. Ocular complications are generally limited to excessive secretion and surface irritation due to the salivary character, which are both reversible.

Prior to transplantation, salivary gland disease has to be ruled out, since – if found to be existing, e.g. in Sjögren's syndrome – the tissue to be grafted may have become atrophic due to chronic inflammation. Preoperative evaluation should include a careful medical history to elucidate the aetiology, course and previous treatment of the ocular and any potential systemic disease. Serological tests for anti-SSA/Ro and a biopsy of the minor labial salivary glands of the lower lip with subsequent histology can be used to screen for signs of subclinical inflammation, e.g. Sjögren's disease [5]. Any form of active inflammatory disease in the major salivary glands should be treated medically before proceeding with a gland transplantation. The best option to assure that a viable and actively secreting gland is transplanted is to perform a ^{99m}Tc scintigraphy, which also allows to quantify salivary flow pre- and postoperatively by means of computer-assisted analysis of time-activity curves. For this, 50 MBq ^{99m}Tc-pertechnetate are applied intravenously and dynamic scintigraphies of the head in lateral views are taken. Regions of interest over the transplant can be analysed as time-activity curves to calculate the salivary excretion rate of ^{99m}Tc-pertechnetate without and with stimulus (e.g. i.v. carbachol). Since the results of this method not only correlate strongly with clinicopathologic features of the salivary but also the lacrimal gland, this method can be used to exclude Sjögren's syndrome preoperatively as well as to document the gland's viability postoperatively [6, 7].

Surgical principles include either transposition of a part (i.e. the excretory duct) or free transplantation of the entire gland. Free transplantation requires to sever the gland's nerve and blood supply, of which – if at all – only the latter is surgically re-established. The three procedures reported include (fig. 1): (1) transposition of the excretory duct (Stensen's duct) of the parotid gland to the *inferior* fornix; (2) free transplantation of the sublingual gland to the upper conjunctival fornix *without* microvascular anastomosis, and (3) free transplantation of the SMG *with* microvascular anastomosis and implantation of its excretory duct into the upper temporal fornix.

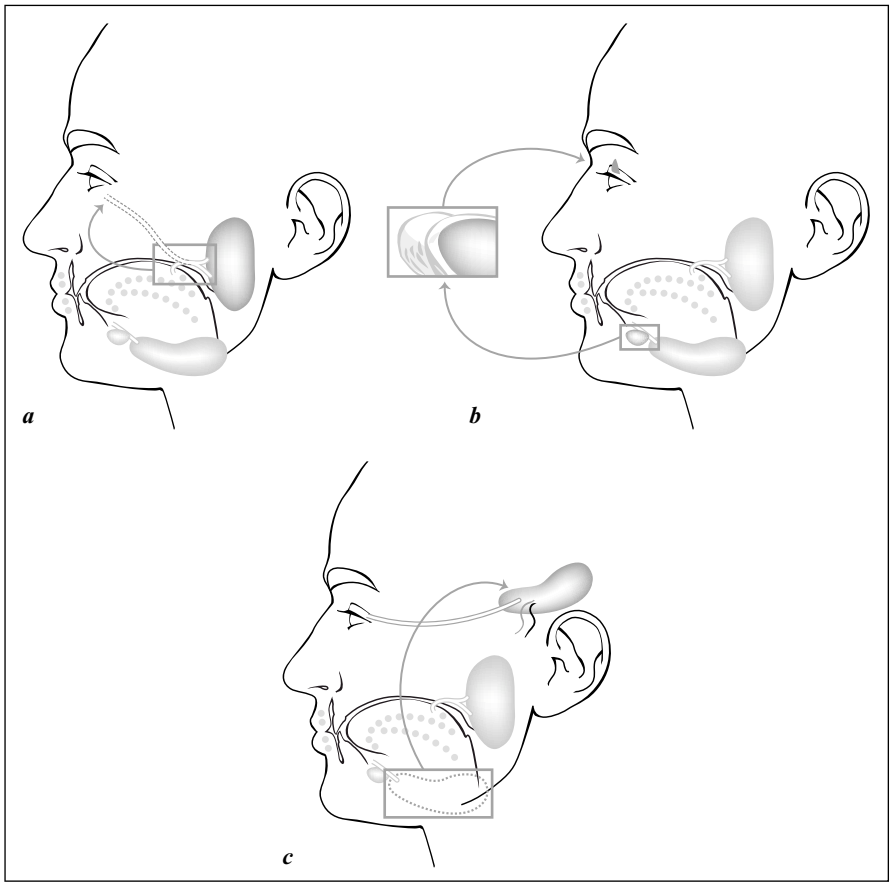

Fig. 1. Diagrammatic illustration of the three different techniques using major salivary glands as source of substitute lubrication. ***a*** Transposition of the parotid duct. ***b*** Sublingual gland transplantation. ***c*** SMG transplantation.

These approaches result in substantially different volumes and quality of lubrication.

Differences between the Various Salivary Glands, Their Secretions and Normal Tears

The daily volume of saliva secreted is 1–2 litres/day, which is approximately 1,000-fold higher than the normal tear secretion (see also chapter 17) (table 1). The major salivary glands account for most of the stimulated secretion. Without

Table 1. Advantages and disadvantages of the three different techniques, which use major salivary glands as source of substitute lubrication [data from 27]

	Parotid duct transposition	Sublingual gland transplantation	Submandibular gland transplantation
Character of saliva	Serous	Mucoserous	Seromucinous
Volume of baseline secretion	++	+	+++
Volume of stimulated secretion	+++	+	++
Vascularisation	Regular	None	Microanastomosis
Innervation	Regular	None	– Survival of parasympathetic ganglia – Sympathetic reinnervation
Complexity of procedure	++	+	+++
Postoperative viability of gland	100%	10%?	76%
Salivary epiphora	Gustatory epiphora in 100%	None	By physical activity/heat in 24–40%
Management options for salivary epiphora	Systemic anticholinergics	Not applicable	Surgical reduction, systemic anticholinergics, Botulinum toxin injection

gustatory stimulus, approximately 50% of the secretion is provided by the minor salivary glands in the oral mucosal lining, 30% by the submandibular, 15% by the parotid and 5% by the sublingual gland [8, 9].

The parotid gland's major purpose is to provide rapid secretion upon gustatory stimulation. Its secretion has the most aqueous nature. The sublingual gland produces a mucoserous secretion. The secretion of the normal SMG is by nature seromucinous with a 90% aqueous component [8, 9]. Of all major salivary glands the SMG has therefore the most tear-like character [10]. Although not identical with tears, saliva often is conceived as being very tear-like. This is certainly true in terms of complexity (especially when compared with pharmaceutical tear substitutes, such as hypromellose, carbomers or hyaluronate) and may also be true to some extent for specific parameters (see chapter 17) (table 1). However, some distinct differences between saliva and tears exist, of which the most striking are found in the content of enzymes and salts (i.e. osmolality). Saliva for example contains high amounts of ptyalin and amylase. Despite this,

saliva has no lytic effects on healthy human corneal epithelium [2, 11, 12]. More important is the lower concentration of salts and hence the hypo-osmolality of saliva compared with tears, which are isotonic to serum [10]. The different osmolality can easily be sensed when tears come into contact with the oral mucosa.

Parotid Duct Transposition

Surgical Technique

The concept of parotid duct transposition from its original premolar position in the mouth to the lower conjunctival fornix was conceived by Filatov and Chevaljev [1] in 1951 and was subsequently modified by others. Filatov and Chevaljev initially used a cutaneous direct approach to the parotid duct, until later Pierce et al. [13] described an entirely oral technique. The direct approach uses a preauricular skin incision to visualise and mobilise the entire parotid duct. Following probing, the ostium of the duct in the buccal mucosa is excised with a small cuff of mucosa. From the lower anterior end of the incision a subcutaneous tunnel is created by blunt dissection to the inferotemporal conjunctival fornix [14] (fig. 1a).

The indirect or oral approach consists of the intraoral dissection of a ca. 2×7 cm long, anterior-posterior directed strip of full-thickness mucosa centred around and including the ostium of Wharton's or Stensen's duct. The duct itself is probed and freed over 2–3 cm from the muscle of the cheek (up to the anterior border of the masseter muscle). The mucosal strip is folded onto itself and sutured over a tube to achieve a total length of 7–8 cm of mobilised 'ductal tube'. This is then passed through a tunnel on the periosteum of the zygoma deep to all muscles, vessels and nerves. Its end enters in and is sutured to the conjunctiva of the inferotemporal conjunctival sac [13, 15].

Early surgical complications include desinsertion/obstruction at the level of the fornix or fistulation of the duct at any position. Contraction or lack of length of the ductal tube frequently resulted in a mechanical lower lid entropium or ectropium and this was more common with the transcutaneous approach [15].

Results

Parotid duct transposition provides copious wetting, but due to a maintained innervation of the parotid gland is associated with a gustatory reflex epiphora. A number of case reports and descriptive studies exist but none of the entirely historic studies were prospective or provide detailed, (semi)quantitative

follow-up data [2, 13, 15]. Until recently the technique has been popular with veterinary ophthalmologists who have performed it in beagles, which frequently suffer from severe dry eye. From this we know that in addition to gustatory reflex tearing the postoperative course can be complicated by blepharitis, corneal calcifications and an increased load of colony-forming bacterial units in the conjunctival sac. Although the conjunctival flora was found to be altered from a predominantly Gram-positive towards a more mixed bacterial type, this was not found to induce overt ocular surface pathology [16, 17].

Excessive secretion may be bothersome but was also described to lead to traumatic keratitis due to the patient frequently wiping his eye. Systemic anticholinergics and implantation of a lacrimal bypass tube were used to manage this, but were either associated with systemic side effects or were found to be insufficient to drain the excessive volume of ocular surface lubrication [2]. Alternatively, parasympathetic denervation of the gland was considered but impracticable since surgical access is difficult and collateral damage to the facial nerve during such manoeuvres are likely. Therefore, the technique seems to have been completely abandoned.

Sublingual Gland Transplantation

Surgical Technique and Results

Murube was the first to transplant autologous sublingual gland tissue to the conjunctival fornix in rabbits and humans. This involves excision of a block of approximately $25 \times 10 \times 6$ mm of sublingual gland together with overlying mucosa which is transplanted to a conjunctival recipient bed in the temporal upper fornix. The graft is fixed to the fornix and lacrimal gland with transpalpebral sutures. The conjunctiva and mucosa are sutured with interrupted absorbable sutures. The concept of surgery was based on the idea that the grafted tissue would become vascularised from the contact area in the recipient bed over the course of days and weeks (fig. 1b).

According to Sieg et al. [18] however, salivary glands tolerate a maximum ischemia of up to 1.5 h at physiological temperatures only. Since sublingual gland transplantation did not involve a vascular anastomosis, such grafts should become completely necrotic within 6 h. From histological studies in rabbits, Murube et al. [9] found that the grafts first underwent partial atrophy before some acinar tissue was regenerated. However, when used in 5 patients with severe aqueous-deficient dry eyes, due to the absence of any vascularization, the grafted tissue became apparently necrotic in 2, and of the remaining 3 patients only 1 showed a minimal increase in Schirmer's test from 0 to 2 mm.

Since this initial publication, the use of sublingual gland transplantation has not been reported again.

Submandibular Gland Transposition

Free autotransplantation of the SMG with microvascular anastomosis has several conceptual advantages: (1) the seromucinous secretion of the SMG is capable of replacing the mucous and the serous component of the tear film, (2) blood supply to the graft – mandatory for long-term survival of the acinar tissue – is re-established, and (3) intraoperative denervation of the graft avoids gustatory reflex salivation (although the total volume of the secretion of the transplanted SMG after exceeds normal tear production).

Surgical Technique

Surgery should be performed by a collaborative team of maxillofacial and ophthalmoplastic surgeons with the patient under general anaesthesia. Since the procedure requires 5–6 h surgical time, appropriate measures e.g. to prevent pressure sores should be arranged. First the SMG and its vascular supply from the facial vessels are prepared via a conventional surgical access to the submandibular triangle in a skin crease in the neck (fig. 2a). The secretory duct of the SMG is cannulated and excised at the sublingual caruncle together with a small cuff of mucosa. In patients with a shortened conjunctival fornix this may be specifically chosen to be larger to facilitate the implantation of the duct and to simultaneously achieve partial fornix reconstruction. The parasympathetic innervation – nerve fibres branching from the lingual nerve – are severed. Now the recipient bed is prepared in the temporal fossa posterior to the frontal branch of the facial nerve. A branch of the superficial temporal artery and vein is prepared for later anastomosation. Preoperative identification of the superficial temporal vessels will reassure the surgeon but is not mandatory since this is usually relatively simple to achieve intraoperatively once the skin is incised over the temple due to active bleeding. Alternatively vessels from the preauricular area can be used if temporal artery or vein are too small for anastomosation. Then the temporalis muscle is fenestrated down to the underlying skull bone in order to create a pocket of a sufficient size for the graft and a subcutaneous tunnel to the superotemporal conjunctival fornix is created (figs 2b, c)

Now the arterial and venous supply of the SMG are ligated, cut close to the facial vessels, before transferring and fixing the graft in recipient bed in the temporalis fossa (fig. 2d). First the arterial, then the venous branch of the transplant are microsurgically anastomosed to the temporalis vessels with inter-

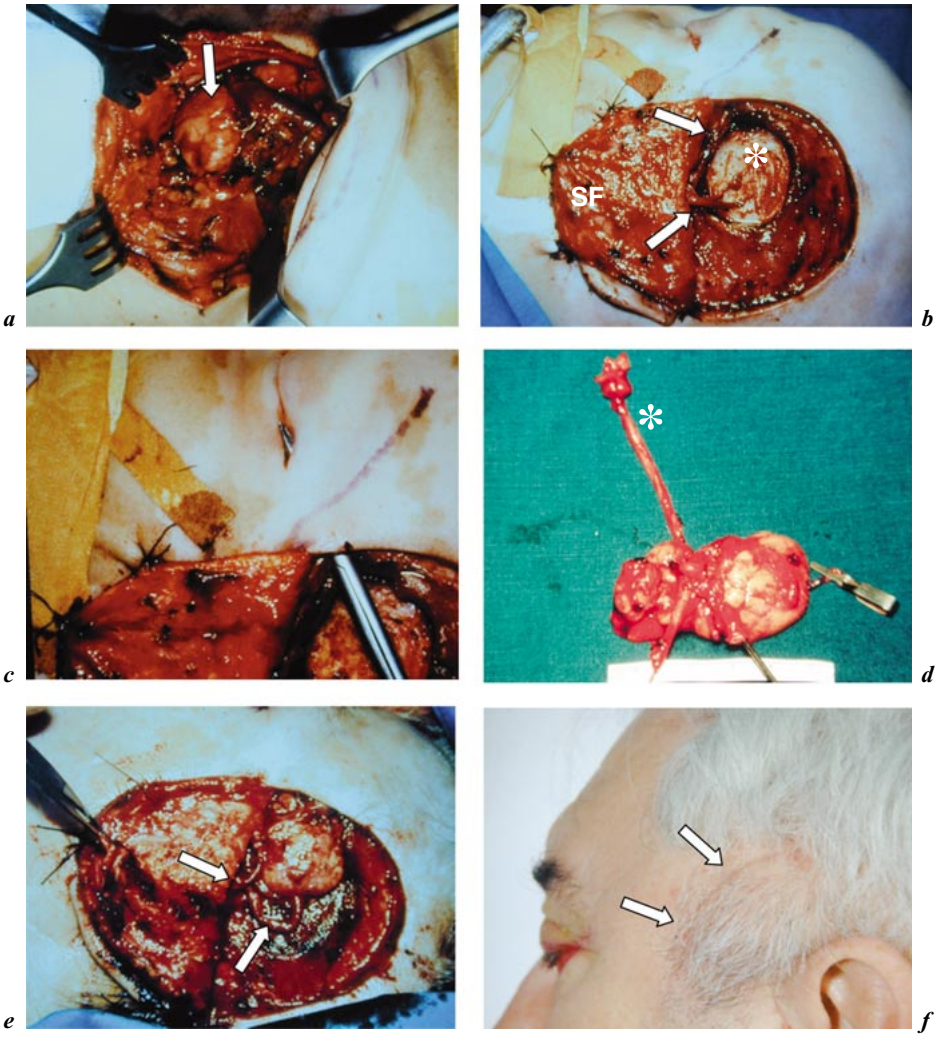

Fig. 2. SMG transplantation: ***a*** Surgical access in the submandibular triangle. Arrows mark the gland in it's natural position prior to transplantation. ***b*** Recipient bed in the left temple with the skin flap (SF) flipped down onto the cheek. Arrows mark the temporal artery and veine. Part of the temporalis muscle has been removed to create a recipient bed (asterisk). ***c*** Subcutaneous tunnel marked by artery clamp for the excretory duct of the graft prepared to the temporal conjunctival fornix of the left eye. ***d*** Free graft with vascular pedicle and excretory duct (asterisk). ***e*** Graft fixed in the recipient bed with completed microvascular anastomosis (arrow). ***f*** Temporal area 6 weeks postoperatively. Arrows indicate the previous incision.

rupted 10.0 nylon sutures. The secretory duct is passed through the previously prepared subcutaneous tunnel and its distal end implanted at the temporal upper edge of the upper lid tarsus where it is fixed with interrupted 6.0 absorbable sutures (fig. 2e). Insertion of a vacuum drain is followed by wound closure at the temple. During the operation and for 3 days postsurgery, all patients receive a systemic and topical antibiotic and low-dose subcutaneous heparin (fig. 2f) [4,18–20].

Results

In rats and rabbits the transplanted SMG remained viable during a follow-up of 6 months and maintained a basal salivary secretion for the maximum follow-up of 6 months [21–23].

Four independent groups of authors have published clinical results with this procedure in patients with severe aqueous-deficient dry eyes. Murube et al. [3, 24] reported that 5 out of 7 of such grafts remained viable for up to 3 months. However, they found that the secretory activity was not clinically obvious in all cases and that they had to use amylase detection in the tear film rather than Schirmer's test to establish whether the graft was viable. Later, MacLeod and Robbins [25] reported about 12 successful gland transfers in 8 patients who all showed improvement of Schirmer's test and an increased fluid meniscus but no detailed ophthalmic long-term follow-up was presented.

We have transplanted 42 SMG in 34 patients and collected complete ophthalmologic follow-up examinations for up to 7 years [4, 20, 26–28]. Based on Schirmer's test, improvement of clinical symptoms and ^{99m}Tc-pertechnetate scintigraphy, 32 of the 42 (72%) SMG grafts remained viable until the last follow-up [7]. Seven graft failures were observed due to complications associated with the vascular anastomosis, 2 due to obstruction of the secretory duct, and 1 due to newly induced autoantibodies to salivary gland tissue [27].

In 2004, Yu et al. [29] reported a group of 38 patients in whom SMG transplantation – although with undefined duration of follow-up – had been performed successfully in 87%. Five grafts had to be removed within 1 week after surgery due to early thrombosis of the venous drainage. Yu et al. confirmed that from the fourth postoperative month onward, patients with viable SMG grafts had a substantially improved volume of lubrication. Although they presented only limited ophthalmic data, they stated that the patients could discontinue the use of artificial tear substitutes and that the vision improved in six eyes.

Yu et al. [29] and our group have observed a specific pattern of postoperative salivary tear flow. Initially a phase of hypersecretion of several days results which appears to be due to 'degeneration activity', caused by release of neurotransmitters from degenerating sympathetic and any sectioned post-ganglionic

Table 2. Schirmer's test, fluorescein break-up time, number of artificial tear substitute instillations (in 14 h), score of dry eye symptoms, fluorescein and rose bengal staining (on a scale from 0 = absent to 4 = very severe) in 14 eyes with (1) aqueous tear deficiency, (2) due to cicatrising conjunctivitis and a (3) viable submandibular gland transplant.

	Preop.	3 months	1 year	3 years (mean)
Schirmer's test, (mm)	1 ± 1	16 ± 8	33 ± 21	31 ± 13
Fluorescein break-up time, (s)	2 ± 3	10 ± 6	14 ± 6	23 ± 3
Frequency of artificial tears	57 ± 25	17 ± 22	5 ± 4	4 ± 3
Symptom score	2.6 ± 0.4	1 ± 0.4	1.5 ± 0.6	1.95 ± 0.4
Fluorescein staining (cornea)	2.6 ± 1.5	1.8 ± 1.2	1.2 ± 1.1	1.1 ± 1.2
Rose bengal (conjunctiva)	2.1 ± 0.4	1.4 ± 0.4	1.0 ± 0.4	1.2 ± 0.4

parasympathetic terminal axons. This is followed by a period of minimal secretion during which time supersensitivity of acinar cells develops. Over the subsequent months the amount of secretion increases. Contrary to short-term reports by others, after 1 year this can result in excessive salivary epiphora [4, 20, 26, 30]. Although the secretory flow does not depend on gustatory stimuli, it is stimulated by physical activity, local hyperthermia or caffeine ingestion. Systemic application of carbachol results in a rapid increase of secretion from the graft as documented by scintigraphy.

Histological specimens of the SMG taken prior to and more than 1 year after transplantation show some parenchymal atrophy. However, cholinesterase-positive nerves are abundant and in a similar distribution to normal with scattered positive ganglion cells. Adrenergic axons are also present in the glands but are less numerous than normal and more irregularly distributed. The latter are thought to have originated from sectioned sympathetic nerves around reconnecting arteries and to have grown by sprouting down mainly formerly parasympathetic glandular nerves [30].

In a prospective, controlled clinical cohort study, we evaluated the long-term follow-up after autologous SMG transplantation in the most demanding group of patients, i.e. with absolute dry eyes due to cicatricial keratoconjunctivitis (e.g. due to Stevens-Johnson syndrome or ocular cicatricial pemphigoid). We recorded Schirmer's test, fluorescein break-up time, degree of discomfort, use of pharmaceutical tear substitutes, visual acuity, conjunctival rose bengal staining and hyperaemia in 14 eyes with a successful SMG transplant and 11 dry eyes without salivary lubrication [27, 28]. Over a mean postoperative period of 3.3 years, the successful transplantation group showed significant improvement of Schirmer's test, fluorescein break-up time, use of pharmaceuti-

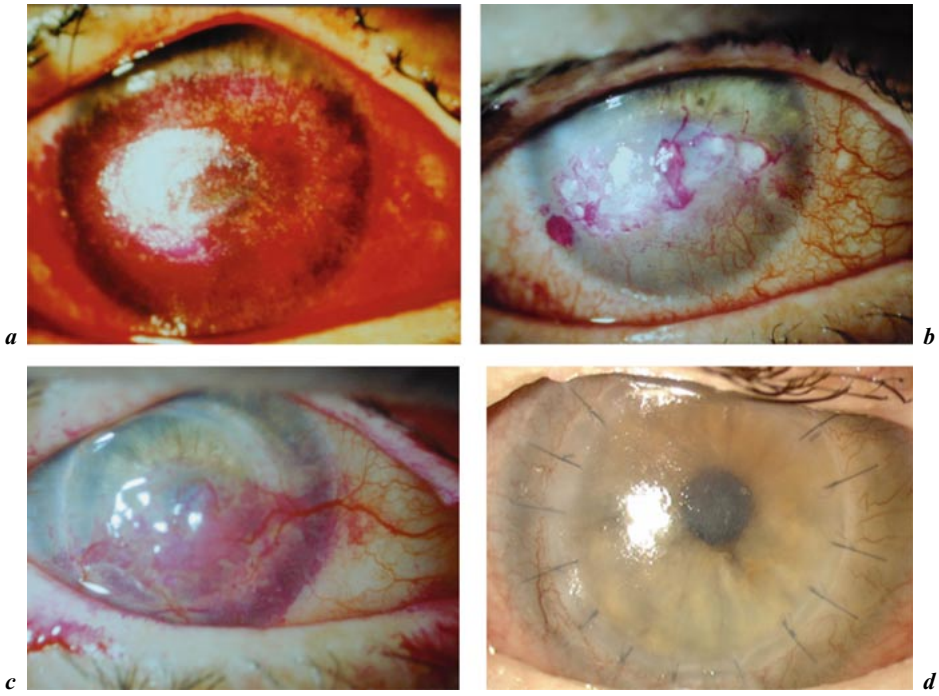

Fig. 3. ***a–c*** Rose bengal staining before (***a***), 1 year (***b***) and 6 years (***c***) after SMG transplantation in an eye with absolute tear deficiency due to damage to the major petrosal nerve following resection of an acoustic neuroma. Note the obviously improving mucin coating of the ocular surface as demonstrated by a reduction of Rose Bengal staining that is maintained for the entire follow-up. A penetrating keratoplasty was performed 3 years after the SMG transplantation for visual rehabilitation of a dense corneal scar. Due to recurrent vascularisation and scarring in the corneal graft, vision remained reduced. ***d*** Microcystic epithelial corneal oedema following penetrating keratoplasty for a perforated corneal ulcer in an eye with good surface lubrication following successful SMG transplantation.

cal tear substitutes and discomfort up to the last follow-up when compared with the control group (table 2). While rose bengal staining showed improved surface coating with salivary mucins, conjunctival hyperaemia and corneal epithelial barrier function remained largely unaltered (fig. 3). These signs of persistent surface irritation are likely to be due to preoperatively existing morphological alterations, e.g. conjunctival scars and stem cell failure, as well as the salivary, i.e. hypoosmolar character of the new tear film which leads to microcystic epithelial oedema in cases with oversecreting transplants. As a consequence, mean visual acuity did not improve in this cohort [27, 28].

Complications

Although the secretion does not depend on gustatory stimuli, in 24–40% of eyes with a viable graft, excessive salivary epiphora is observed and can be associated with some increase in discomfort (i.e. a 'burning sensation', but not 'dryness') [28, 29] (table 2). This can successfully be managed either by application of a parasympatholytic, such as oral benzhexol or periglandular injections of botulinum toxin [31]. While systemic parasympatholytics are associated with systemic unwanted side effects such as tremor and dry mouth, the effect of botulinum toxin injections is limited to a maximum of 3 months. Therefore, approximately one third of all viable grafts have to surgically be reduced in size [31].

We also frequently observed a microcystic epithelial oedema in eyes with excessive salivary epiphora, which was temporary and resolved when the salivary epiphora was controlled. Analysis of the preocular fluid (termed 'salivary tears') after SMG transplantation revealed that the secretion maintains a salivary character. Salivary tears show high concentrations of secretory immunoglobulin A and amylase as signs of an actively secreting graft and – relative to tears – the typical low osmolality of saliva [4, 20]. Not salivary enzymes such as amylase but this hypoosmolality leads to epithelial cell toxicity and is likely to be responsible for the epithelial oedema observed clinically [12]. Two eyes with microcystic oedema developed a persistent epithelial defect, which healed in one eye after amniotic membrane transplantation but went on to perforation in a second eye later requiring repeated penetrating keratoplasty (fig. 3d). Five keratoplasties (4 penetrating and 1 lamellar) were performed in eyes with a viable SMG graft. However, due to rejection, infection, calcification or epiphora-associated epithelial oedema with subsequent corneal perforation none of these was successful (figs 3c, d) [28]. Surgeons (especially if they are not ophthalmologists), must understand these ocular limitations and potential complications of the procedure.

Recommended Current Indication

Of all procedures involving the transplantation of major salivary glands for severely dry eyes – due to some principle advantages – autologous SMG transplantation is the only one of the three procedures described above that currently can be recommended for the use in humans. It is only indicated in patients with absolute aqueous tear deficiency (Schirmer's test ≤ 1 mm) with persistent severe pain despite punctal occlusion, a trial of scleral or limbal fit rigid contact lenses, at least half-hourly application of unpreserved tear substitutes and a conjunctivalised corneal surface. For these patients the demand on time and financial resources is however justified not only by significant relief of severe symptoms and some signs of dry eye, but also by substantial gains for society

[32, 33]. Visual rehabilitation by means of keratoplasty nevertheless remains unsuccessful even after successful SMG transplantation. When salivary tear flow becomes excessive (usually after 1 year) this may lead to a temporary microcystic corneal epithelial oedema. Salivary epiphora can successfully be managed by systemic parasympatholytic, periglandular injections of botulinum toxin or surgical reduction of the gland. If a simple method to control secretory flow from transplanted SMGs would exist, the indication for this procedure – although by nature demanding on expertise and resources – could be much expanded.

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Prof. Dr. Gerd Geerling
Klinik für Augenheilkunde, Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11, DE-97080 Würzburg (Germany)
Tel. +49 931 2012 0610, Fax +49 931 2012 0490
E-Mail g.geerling@augenklinik.uni-wuerzburg.de

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Mechanical Pump Dacryoreservoirs

Juan Murube[a], *Gerd Geerling*[b]

[a]Clinica Murube, Madrid, Spain; [b]Department of Ophthalmology, University of Würzburg, Würzburg, Germany

Abstract

Background: The two most important characteristics of the natural tear are its chemo-physical properties and the continuity of its delivery. The chemical characteristics of tears are very difficult to reproduce since they contain more than 200 different components. In severe dry eyes – due to their relative short residence – manual application of artificial tears from small bottles to the eye has to be performed every 5–10 min, while at night no lubrication at all is provided. Previously, for continuous lubrication of the ocular surface, dacryoreservoirs attached to spectacles or placed in pockets of the patient's clothes were used, but were often complicated by infection. A new option is the implantable pump dacryoreservoir. **Material and Methods:** In 21 patients with a Schirmer test without anaesthesia of <2 mm in 5 min, a Medtronic 60-ml reservoir was implanted into a pocket under the subcutaneous tissues of the anterior abdominal wall and connected to a silicone catheter that ascended subcutaneously along the chest, neck and temple to the upper conjunctival fornix. The results of this procedure and complications associated with the implantation of reservoirs in general – as evaluated on the basis of a Medline search – are presented. **Results:** Postoperatively all patients reported a dramatic improvement of dry eye symptoms. Slit-lamp microscopy revealed a substantially prolonged break-up time and a reduction of signs of ocular surface disease such as superficial punctuate keratopathy and conjunctival hyperaemia. A penetrating keratoplasty was successfully performed in 2 eyes with an implanted dacryoreservoir and remained clear throughout the follow-up of up to 3.5 years. No infections of the catheter reservoir were observed. Prominent parts of the catheter induced skin ulceration, but no infection, in 2 patients which was managed successfully by removal of the catheter, systemic antibiotics and subsequent re-implantation of a new catheter. A literature review showed that infection is not a frequent problem with implantable and external reservoirs. **Conclusion:** At present, this is the only safe and effective method able to maintain a continuous lubrication of the ocular surface with artificial tears, and the only one that allows corneal, conjunctival or limbal transplantations in severe dry eyes.

The two most important characteristics of the natural tear are its chemo-physical properties and the continuity of its delivery. The chemical

characteristics of tears are very difficult to reproduce as most of their approximately 200 components found so far (β-lysin, lactoferrin, lysozyme, interleukins, complement fractions, enzymes, etc.) are unstable and degrade rapidly. Therefore, artificial tears mainly reproduce only some of the physical properties of natural tear, such as surface tension, viscosity, lubricity, and for this purpose non-natural tear components such as cellulose, dextrans, polyvinyls, etc. are used. With respect to the continuity of the delivery, we are no more advanced than almost a century ago, as application of artificial tears from small bottles to the eye is manually by the patient or another person. The mean half-life on the eye of routinely used lubricants such as 1.4% polyvinyl alcohol, 0.3% hydroxypropylmethylcellulose or 0.2% sodium hyaluronate solution was measured to be 39, 44 and 321 s respectively. The ocular surface residence time of artificial tears applied in the form of drops is limited to a few minutes [1]. In absolute aqueous tear deficiency – defined by us as a Schirmer test result of ≤1 mm – continuous lubrication therefore requires the patient to apply drops every 5–10 min, which may seriously conflict with daytime activities and is completely impossible during sleep [2]. While it is known that the secretion of natural tears in normal individuals is almost completely downregulated during sleep, patients with absolute aqueous deficiency report severe symptoms of dryness and the need to apply tear substitutes at night.

As continuous lubrication of the ocular surface is important, several potential solutions have been investigated but none have been successful. Among these are so-called dacryoreservoirs attached to spectacles or placed in pockets of the patient's clothes [3, 4]. A mechanical device delivers the content of the reservoir through a catheter to the ocular surface, either via the interpalpebral fissure [5], or a subcutaneous tunnel in the temple [6]. These devices frequently had to be removed after some weeks or months. It remains unclear why, but it seems likely that infection of the site where the delivering tube penetrated the skin or discomfort due to movements of the tube during physical activities were the likely reasons for this.

A new way with a sustainable result is the abdominal pump dacryoreservoir described in this chapter. This form of reservoir is implanted under the subcutaneous tissue of the anterior wall of the abdomen [7], and delivers artificial tears through a silicone catheter that ascends subcutaneously along the chest, neck and temple. It exteriorizes into the lacrimal basin in the upper conjunctival cul-de-sac (fig. 1) and avoids penetration of the skin. At present, this is the only method able to maintain a continuous lubrication of the ocular surface with artificial tears and other topical medication, and the only one that allows corneal, conjunctival or limbal transplantations in severe dry eyes [7].

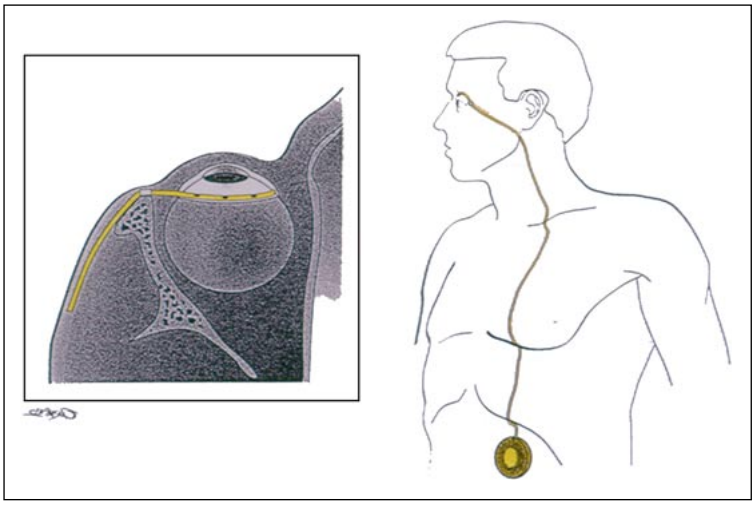

Fig. 1. Subcutaneous abdominal artificial tear pump reservoir. The reservoir is sutured to the aponeurosis of the abdominal muscles. The artificial tear pump reservoir delivers its fluid content via a subcutaneous catheter from the abdomen to the upper conjunctival fornix.

Material and Methods

Implantable Dacryoreservoir – Device Characteristics

The pump reservoir currently used is a Medtronic unit manufactured by Anschütz & Co. GmbH, model IP 20.1 (fig. 2). Other companies produce alternative models, though the differences are negligible. The maximum volume that can be stored in the devices is 60–70 ml. The average costs for one device are approximately EUR 5,000. The Medtronic model is a rigid one-piece titanium box of discoidal shape, 30 mm high and 77 mm in diameter, and with a weight of 120 g when empty. Inside (fig. 3), there are two chambers: a sealed peripheral chamber permanently filled with a chemically inert fluid, Frigen R-114 (which changes from liquid to gaseous at 3.6°C), and a central and superficial expandable and compressible chamber with a capacity of 0–70 ml, that can be filled with a fluid via a port. The expansion of one chamber leads to reduction of the other and vice versa. The gas chamber is hermetically closed. The artificial tear chamber is not hermetic because it has two external connections: one is an inlet hole in the centre of the superficial wall of the titanium box, plugged with a permanent, thick and prominent self-sealing silicone rubber septum, which can be punctured with an injection needle to refill it with artificial tears. The other external connection is a glass capillary, the length and diameter of which determines the rate of flow from the fluid reservoir to a connecting tube. For tear substitution this should be in the dimension of the normal tear flow (1 μl/min) with a total of approximately 1.5 ml/day (see chapter 1). The glass capillary is inside a metal tube that protrudes from the box by 10 mm. On the exterior of the box there are also four metallic loops at a 90° angle, which are used to fix it to the aponeurosis of the

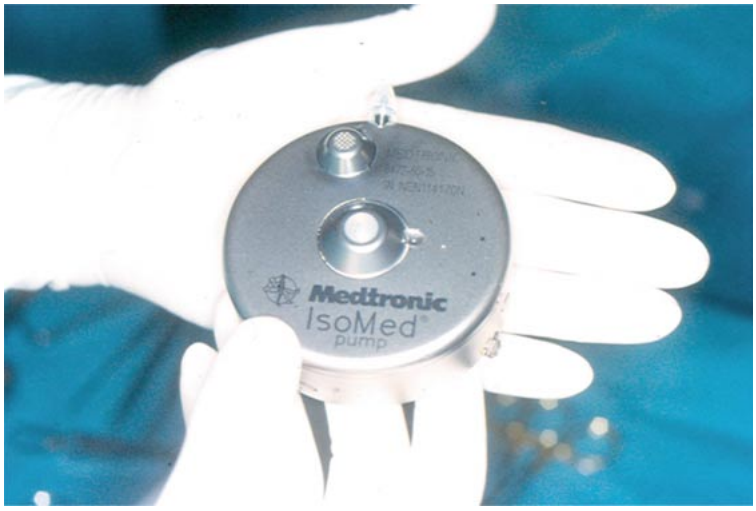

Fig. 2. Pump reservoir. Titanium box with two compartments – one for the artificial tear and the other is permanently filled with gas.

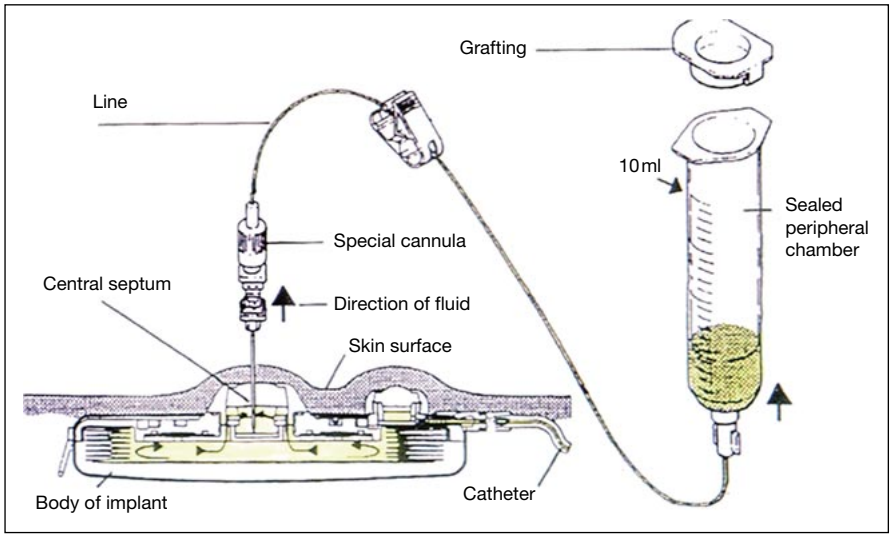

Fig. 3. Refilling of the subcutaneous reservoir.

oblique and straight abdominal muscles with sutures. When placed in the abdominal wall of the patient, the reservoir is connected with the conjunctival upper fornix via a silicone rubber catheter (figs 4, 5) with an external diameter of 1.4 mm. The catheter has two stretches. The first (in reference to the reservoir) is connected to the metallic outlet. At its upper end it is

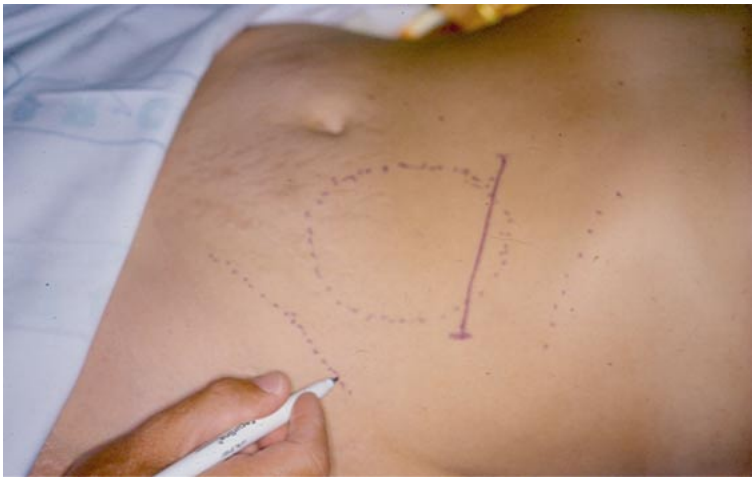

Fig. 4. Location of the abdominal incision (straight continuous line) lateral to the umbilicus. The final position of the pump reservoir is painted with a dotted circle. In the photo the surgeon is painting the location of the anterior iliac crest.

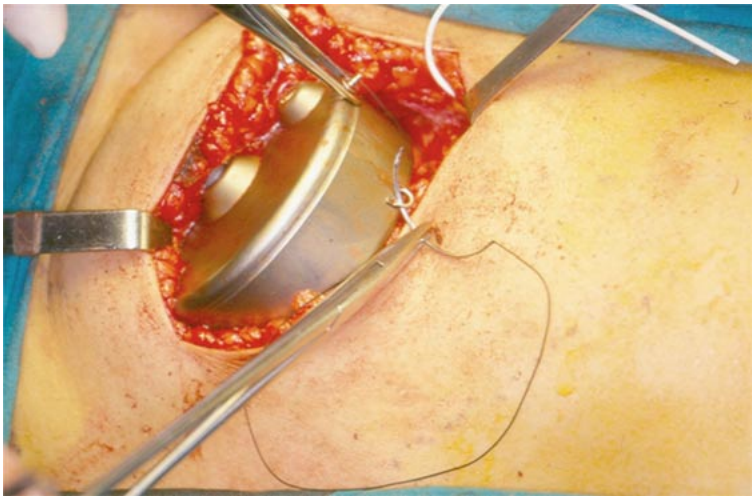

Fig. 5. The pump reservoir is being introduced in the abdominal subcutaneous pocket. One of its fixation loops is being sutured to the abdominal aponeurosis.

connected to the second stretch, which again at its upper end terminates with six lateral foramina. This end protrudes out into the upper conjunctival cul-de-sac.

The reasons for dividing the catheter in two stretches are (a) to allow shortening of the tubes at the connecting ends to adjust the total length of the catheter to the distance between

the dacryoreservoir and the upper cul-de-sac, as well as (b) to be able to remove only the upper stretch of the catheter in case of an infection. The distal end of the second stretch is passed through the plastic sleeve of a butterfly cannula, which is fixed to the periosteum and aponeurosis of the lateral orbital rim.

Surgical Technique of Implantation

Surgery is performed under general anaesthesia with the patient lying on his back. Normal asepsis and antisepsis are applied to the abdominal wall, the thorax, neck and face. The skin is incised about 3–4 cm below the lower ribs of the right or left rib cage, and parallel to it over a length of 7–8 cm (fig. 4). Either abdominal side can be used, but the left side may be occasionally better, as there is a larger chance for independent pathology (hepatitis, cholecystitis, duodenitis, appendicitis, etc.) on the right side. The wound is deepened through the subcutaneous tissue until the aponeurosis of the external oblique and straight abdominal muscles becomes visible. A pocket is prepared by blunt dissection between the subcutis and the aponeurosis, about 1–2 cm upward and 7 cm downward. Any haemorrhage is stopped by electrocautery. The pump reservoir is inserted in this pocket with its external metallic outlet tube pointing upward or upwards and medially. The box is fixed to the aponeurosis by suturing its metallic loops to the aponeurosis with 1-0 or 2-0 non-absorbable sutures.

An incision about 30 mm in length is made under the clavicle of the side of the eye to be reached. Then, a trocar – with cannula and inner guiding punch – is passed subcutaneously upwards from the abdominal wound over the chest to the subclavicular station where the connection of both halves of the catheter will be placed. The punch is withdrawn, the lower stretch of the catheter introduced through the trocar's cannula and cannula removed leaving only the catheter in place, the lower end of which is now connected to the metallic outlet tube of the reservoir.

Two more approximately 10-mm incisions are now made in the skin and subcutaneous tissue in the supraclavicular region lateral to the sternocleidomastoid muscle (fig. 6) and in a crow line over the lateral orbital rim and again connected by subcutaneous tunnel. The upper or second stretch of the silicone catheter (diameter: 1.4 mm) is passed through this and a butterfly plastic cannula which has an approximate diameter of 1.5 mm (fig. 7). The trocar is then passed from the conjunctiva in the superolateral fornix downward and laterally passing in front or behind the lateral canthal tendon at the orbital rim and out through the skin incision at the temple (fig. 8). The upper end of the silicone catheter is now passed to the upper cul-de-sac, where 10–20 mm of its fenestrated end are placed freely (fig. 9). The butterfly cannula is then sutured to the periosteum of the orbital rim and the aponeurosis of the temporal muscle, so that it directs the end of the catheter upward and medially. This helps to prevent contact of the catheter with the cornea. The anchored butterfly also avoids that the end of the catheter is irreversibly pulled backwards and into to the temple when moving the head. Any excess length of the silicone tubes is removed to avoid tension on the catheter when moving the head and trunk, the two parts connected and the wounds closed.

The implantation of the dacryoreservoir in the abdomen is always performed together with a surgeon, usually from the Pain Clinic, with experience in abdominal implantations for injection of fluids in the intrathecal or epidural spaces. The implantation procedure of the dacryoreservoir and the catheter takes about 2 h.

The anterolateral wall of the abdomen has been found to be the best position for placing the reservoir, since the intestines are protected here by a thick muscular wall. Any accidental

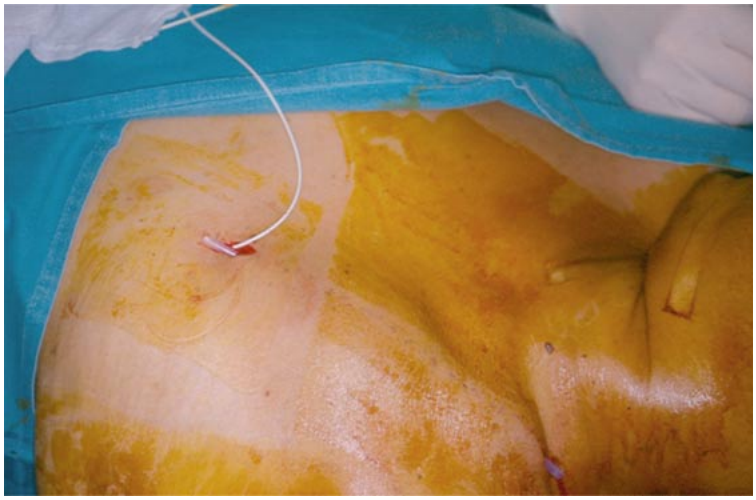

Fig. 6. The silicone catheter has been passed subcutaneously from the abdominal pocket of the pump reservoir to the subclavicular area. In the figure, the catheter is being passed from the subclavicular to the supraclavicular station through the trocar, whose ends are protruding.

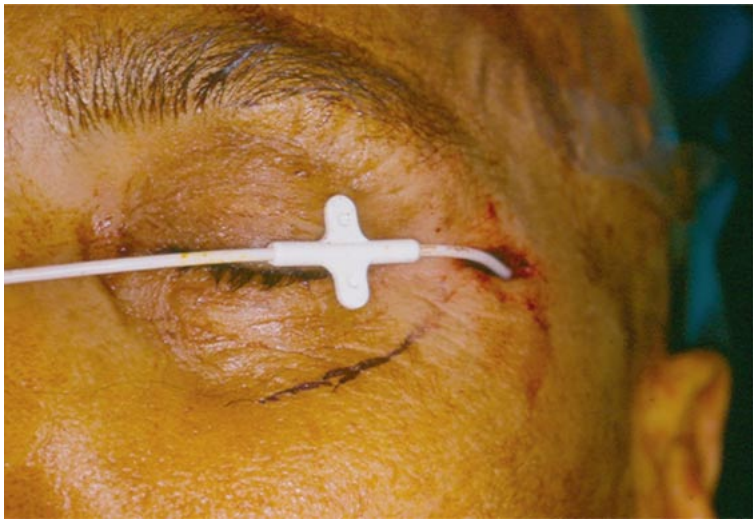

Fig. 7. The upper stretch of the catheter has been passed through a subcutaneous tunnel from the supraclavicular area to the temporal orbital station. A fixation butterfly has also been placed around the catheter and will be sutured to the aponeurosis of the musculus temporalis and the periosteum of the temporal orbital rim.

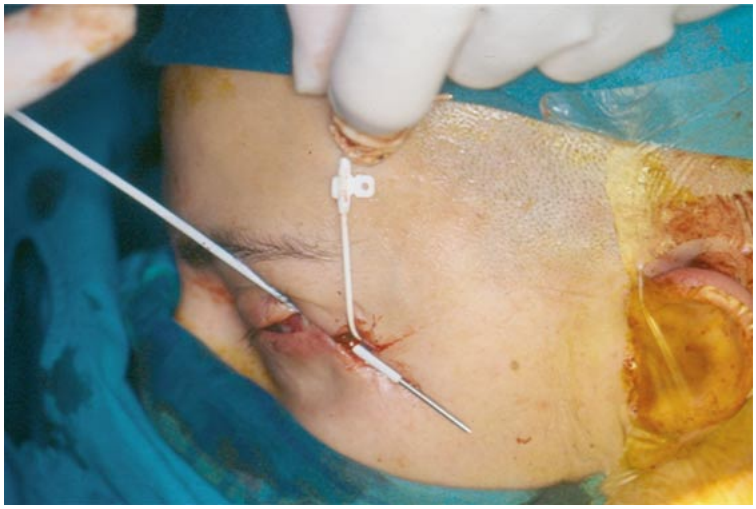

Fig. 8. The trocar and guiding punch perforate the lateral conjunctival fornix to the temporal station from where the catheter will be placed into the conjunctival fornix.

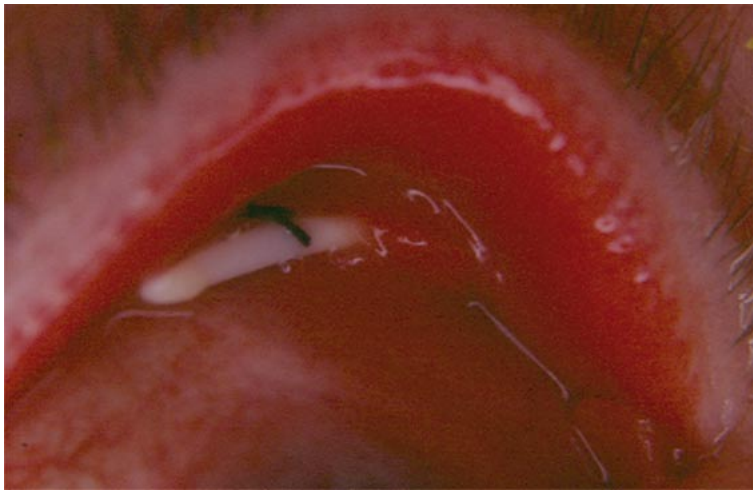

Fig. 9. Final position of the upper end of the silicone catheter. After calculating the length required for the externalized end of the catheter, the fixation butterfly has been sutured to the aponeurosis and periosteum in order to stabilise the position of the catheter in the superior conjunctival fornix.

compression of the reservoir is well absorbed by the surrounding soft tissues. Any initially discomfort induced by the dacryoreservoir disappears within days or weeks. For brusque or heavy work or sports, a belt or girdle can be used to support the dacryoreservoir backwards and to prevent displacement. The idea of placing the perforated end of the catheter in the upper conjunctival fornix was triggered by the personal observation that the accidental displacement of a soft contact lens to the upper conjunctival cul-de-sac may remain unnoticed by the patient for months or years without causing any discomfort, until the lens was finally discovered by chance.

Chemical Content of the Reservoir

So far, only isotonic electrolyte solutions (BSS, Alcon Laboratories: NaCl, KCl, $CaCl_2 \cdot 2H_2O$, $MgCl_2 \cdot 6H_2O$, $C_2H_3NaO_2 \cdot 3H_2O$, $C_6H_5Na_3O_7 \cdot 2H_2O$, and AQSIA, Bausch & Lomb Inc.: NaCl, KCl, $CaCl_2 \cdot 2H_2O$, $MgCl_2 \cdot 6H_2O$, $C_2H_3NaO_2 \cdot 3H_2O$, $C_6H_5Na_3O_7 \cdot 2H_2O$) for lubrication of the ocular surface with this device, but a mixture of BSS with ethylenediaminetetraacetate (EDTA), autologous serum or cyclosporin A have been used occasionally and at least the latter found to reduce signs of inflammation [8]. It is unknown so far whether cellulose, polyvinyl alcohol or other commercial artificial tears could be used, or whether these compounds would interfere with the permeability or flow rate through the glass capillary of the reservoir. However, other types of drugs such as antibiotics and steroids to treat or prevent microbial infections (Tobradex, Alcon-Cusí Lab.), antiallergics (Levocabastine, Livocab, Jannsen-Cilag Lab.), immunosuppressants (cyclosporine, Modusik-A, Sophia Lab.), growth factors (bFGF, Scios Lab., Inc.), and in a few cases fluorescein to measure the time it takes until the artificial tears reach the ocular surface have been added without altering the flow from the reservoir.

Emptying Process

The Frigen R-114 gas in the expandable chamber has a pressure of 2.1 bar. It is adjusted to ensure that the flow rate from the box remains stable even if the body temperature or ambient air pressure (e.g. during sunbathing, sauna, fever, mountain trips, air travel) vary. The diameter of the outlet quartz capillary foramen ensures a flow rate of 1 μl/min with a total of approximately 1.5 ml/day. This resembles closely the daytime flow rate of normal tears, but much exceeds nocturnal tear flow. The latter offers a substantial advantage, since it may prevent increased friction or even adhesion of tarsal conjunctiva to cornea or bulbar conjunctiva, which can result in deterioration of the superficial keratopathy or even recurrent erosions. Devices which allow programming of different flow rates for day- and night-time or specific daily activities are being used by some xero-dacryology ophthalmologists.

Refilling of the Reservoir

Based on a flow of 1.5 ml/day and a total volume of lubricant of 60 (70) ml, the reservoir must be refilled every 40 (46) days. Exceeding the recommended volume may damage the reservoir. Refilling is performed under sterile conditions with the patient on the operating table using a specific 22-gauge (0.7 mm diameter) 32-mm long refilling cannula. The location of the prominent silicone filling septum is localized by palpation. The hard relief of the filling septum is gripped with the tip of three fingers, pressing it posterior to avoid displacement. With the refilling cannula the skin between the three fingers, the subcutaneous tissue and the silicone septum of the reservoir are perforated to enter into the expandable chamber

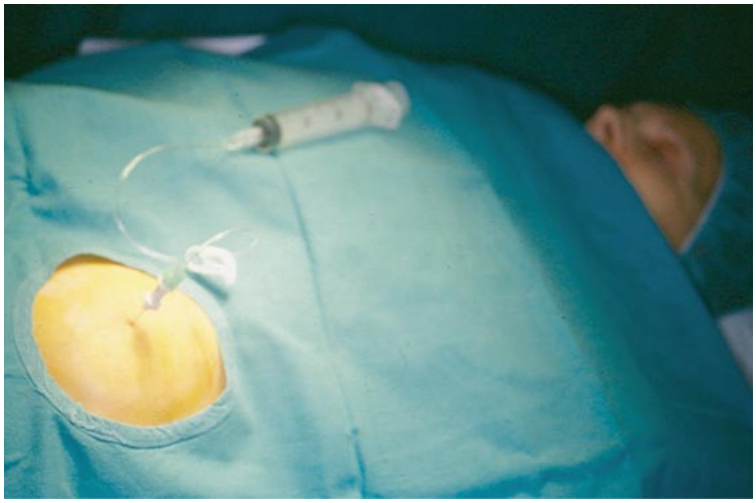

Fig. 10. Refilling of the pump reservoir (required every 40–45 days). The abdominal cutaneous and subcutaneous tissues and the silicone septum of the pump reservoir are perforated with a specific refilling cannula and 60–70 ml of artificial tears injected.

(fig. 10). Any remaining content of the artificial chamber is drained completely and measured to determine whether the real rate of delivery was actually 1.5 ml/day.

There are specific types of refilling cannulas, with a closed tip and lateral opening, to avoid damage to the silicone septum. With these cannulas approximately 500 refills can be done without damaging the hermeticity of the dacryoreservoir. The outline of the reservoir and its prominent filling septum is more evident in slim/slender people, where its localization by palpation is easy. In obese people the reservoir may have been placed deep in relationship to the skin and identification of the position of the rubber septum may be more difficult. When the tissue thickness over the dacryoreservoir exceeds 2.5 cm, refilling is only possible with longer cannulas.

While the need to return to the hospital for refilling the device every 40–45 days is certainly inconvenient for the patient, the procedure itself is not painful because the abdominal cutaneous wall is insensitive to the puncture and the procedure can therefore be performed without any form of anaesthesia. Although the weight of the reservoir after refilling increases by about 1 g/ml to a total of around 180–190 g, the patient is usually unaware of its presence.

A Medline search was also performed using the following keywords: external reservoir, implantable reservoir, pump reservoir, anaesthesia, complication, infection, extrusion.

Results

Severe Dry Eye. After implantation of the dacryoreservoir, it takes about 2.5–3 h until the lumen of the catheter with an approximate volume of 150 μl

is filled and the ocular surface is lubricated. After refilling, the outflow is immediate since the catheter is usually not empty. Symptomatic relief is usually reported immediately or several days later. With a flow rate of 1 μl/min the Schirmer test result increases by approximately 10 mm and break-up time by approximately 5–10 s. Even if the procedure is only performed in one eye, the symptoms often improve in both eyes. It can only be speculated that this may be due to the patient unconsciously keeping the non-operated eye closed. Reversible signs due to the ocular surface dryness, such as vital staining of the ocular surface, disappear in the absence of other confounding factors.

It is obvious that the dacryoreservoir only resolves the problem of aqueous deficiency. Associated problems such as symblepharon, trichiasis, distichiasis, limbal epithelial stem cell failure, or other irreversible manifestations require additional treatment. Furthermore, any progressive autoimmune disorder, such as ocular cicatricial mucous membrane pemphigoid or graft-versus-host disease, requires continued immunosuppression and adjuvant treatment.

Recurrent Erosion Syndrome/Nocturnal Ocular Surface Abrasion. Several patients have reported waking up at night time with an acute pain in one eye and present with a corneal abrasion. This is thought to result from nocturnal reduction of tear secretion with subsequent adhesion of the ocular to the palpebral surface, leading to abrasion of the corneal epithelium upon eye opening. Three of these patients, who also suffered from a very severe aqueous tear deficiency, received a dacryoreservoir, and have not reported any recurrences during a follow-up of 3 years. This clearly stresses the importance of lubricating the ocular surface day and night rather than to use a programmable pump reservoir that decreases or stops the flow of artificial tears at night.

Corneal Calcification. Calcified corneal plaques are frequent in severe dry eyes, therefore in some cases we added EDTA to the BSS in the reservoir and found that such deposits disappear months or even years after implantation of a dacryoreservoir [9].

Blepharospasm. Tonic or clonic blepharospasm due to severe aqueous tear deficiency also improves in most cases after implantation of a dacryoreservoir [7].

Tissue Transplantation. Severe aqueous deficiency – as observed in ocular cicatricial mucous membrane pemphigoid, Stevens–Johnson syndrome, or radiation-induced dacryoadenopathy- has led to corneal ulceration and subsequently a central leucoma. So far, penetrating keratoplasty has only been performed in two eyes that previously had received an abdominal dacryoreservoir, with a follow-up of up 2 years, the grafts have remained clear and showed no signs of ocular surface disease [8].

Complications

Skin Ulceration. This has only be observed in 21 cases three times at the junction of the superior and inferior halves of the catheter in the subclavicular region and twice at the fixation butterfly in the temple, mainly if there was external friction or compression of the overlying tissues. However, neither at the site of the reservoir nor the perforated end of the tube in the upper fornix has tissue damage occurred. Even if the patient rubbed the eyelids in a downward direction causing the free end of the catheter to extrude in the interpalpebral fissure no corneal pathology resulted, and the tube repositioned spontaneously and immediately to the cul-de-sac.

Infection. So far we have never seen an infection of the catheter or the abdominal reservoir itself. This may be due to the continuous flow of artificial tear that may prevent ascending microbial contamination of the tube. The only two infections observed were associated with skin ulcers at the connection between the superior and inferior stretch of the catheter or near the fixation butterfly. Systemic intravenous antibiotics were only effective once the upper stretch of the catheter had been removed. Although the reservoir and the lower stretch were left in situ, no oedema was observed in the subclavicular area as the flow of 1 μl/min BSS obviously was easily absorbed by the surrounding tissues. In all cases a new upper stretch of the catheter was reinserted 2 weeks later. From the more extensive literature on the use of internal and external reservoirs for long-term pain relief, chemotherapy or insulin substitution infection in the pocket where the device is implanted is only considered to be an extremely rare problem. However, as patients with severe dry eyes have an altered conjunctival flora, prophylactic use of a topical antiseptic, such as PHMB, may be considered [10].

Loosening of the Titanium Box or the Fixation Butterfly. When the dacryoreservoir becomes mobile the anterior surface of the titanium box may rotate towards the muscular aponeurosis. This may only be discovered when the prominent inlet septum cannot be localized on occasion of the next attempted refilling. When the butterfly sleeve is not well fixed to the orbital rim, the aponeurosis of the temporalis muscle head movements can result in irreversible retraction of the end of the catheter from the conjunctival fornix to the temporal subcutaneous tunnel where the artificial tears will be absorbed. In this situation, radiography can help to identify the position of the end of the catheter, which will then have to be repositioned surgically.

Discussion – Conclusion

Position of the Reservoir. Several alternative sites for implantation of the reservoir, i.e. the scalp, breast, maxillary sinus, have been considered – but

never tested – by those using it to treat chronic pain. The abdominal wall is still preferred since the surrounding tissues offer a very soft and deep background which can absorb any accidental external pressure.

Rate of Delivery from the Dacryoreservoir. Review of the daily delivery from the old, external dacryoreservoirs (hand-compressed reservoir or a tension spring reservoir) varies significantly with daily volumes of 20–30 ml [11], 10–15 ml [6], 2–5 ml [12], and 1.5–6 ml [4]. The clinical experience with patients using the implantable dacryoreservoirs indicates that a daily rate of continuous delivery of 1.5 ml (i.e., about 1 μl/min) is satisfactory. While this resulted in an increase of Schirmer I test from 0–4 to about 6–8 mm, some patients still requested to increase this flow rate. Although the flow rate of tears has been measured by others to be in the range of 0.1 μl/min and thus much lower than the flow from the reservoir, the patient's wish should always be considered carefully, since he/she is usually the most sensitive judge of the degree of discomfort and disease. In these cases, occlusion of the lacrimal puncta with autologous conjunctiva or palpebral skin may also be considered. None of the patients who received both forms of treatment (i.e. dacryoreservoir plus punctal occlusion) have complained of epiphora since the flow rate chosen (1.5 ml/day) equals the natural flow rate.

Bilateral Reservoirs. Many patients with the severe aqueous deficiency are affected bilaterally. Bilateral implantation lubrication at present is only possible by implanting two independent reservoirs, thus multiplying costs and increasing discomfort, since the patient may be unable to sleep while lying on the side. Alternatively a Y-shaped catheter tube delivering artificial tears to both eyes can be connected to a single reservoir. While this not only increases the frequency of refilling, it may also be insufficient in treating both eyes. Experience with external reservoirs [13] indicates that the fluid frequently chooses the path of least resistance. Since the hydrostatic pressure inside the catheter is low, any small difference of pressure between the right and left catheter, e.g. due to variations in the position of the body or the head, will result in a unilateral flow only.

Currently Recommended Indications

Abdominal dacryoreservoirs are only advisable in cases with severe aqueous tear deficiency leading to severe symptoms of ocular discomfort combined with signs of severe ocular surface disease. They are not suitable for patients with symptoms but without signs [14–17]. They are also indicated when ocular surface reconstruction is attempted in a severely dry eye by means of corneal, limbal or amniotic membrane transplantation as they would fail otherwise. Alternative options for this group of patients are (1) to lubricate the eye with saliva by means of transposition of the Stenson's duct or transplantation of an

autologous submandibular gland, however this will not allow successful visual rehabilitation but merely improve discomfort, and (2) to perform keratoprosthesis surgery. Both options are discussed in separate chapter.

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Prof. Juan Murube, MD
Clinica Murube
San Modesto 44-1, ES–28034 Madrid (Spain)
Tel. +34 91 735 07 60, Fax +34 91 734 09 56, E-Mail murubejuan@terra.es

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Clinical Trials in Dry Eye in Surgery for Dry Eye?

Michael A. Lemp

Georgetown University and George Washington University, Washington, USA

Abstract

Purpose: To provide an overview of considerations in the design and performance of prospective clinical trials in the evaluation of new pharmaceutical and surgical treatments in dry eye disease (DED). **Design:** A compilation and interpretation of experiences in the challenges and pitfalls of clinical trial design based on experiences documented in the peer-reviewed literature over the last 40 years. **Methods:** A review of the literature in the design and performance of clinical trials in DED with an interpretative and prognostic outlook. **Results:** Published results of clinical trials in DED reveal problems in the design of clinical trials which are unique to this disease. These include a discordance between the signs and symptoms of DED, variability in disease course and short-term environmental effects on ocular surface staining. **Conclusions:** The development of better efficacy endpoints will be necessary to improve the outcomes of clinical trials to evaluate new pharmaceutical and surgical approaches to the management of dry eye. The most promising field is that of biomarkers which serve as surrogates for disease severity. As these markers undergo validation with clinical changes, it is likely that they will assume greater significance in future clinical trial designs.

The randomized controlled clinical trial is a relatively new development in the history of medical advances. The father of this scientific genre is considered to have been Sir Austin Bradford Hill. His contribution to medicine was considered by the president of the Royal College of Physicians to have been ‘as important and valuable as the discovery of penicillin’ [1]. It is instructive to consider why the introduction of scientific principles to the design and application of clinical trials is important and how these properties of design and performance can avoid erroneous conclusions.

The history of advances in medicine can be viewed as a series of informed opinions. These opinions are, however, subject to considerable bias and are

Table 1. Characteristics of a clinical trial

Ethical consideration
Protocol and study design
Control groups
Randomization
Masking
Adequate patient numbers
Biostatistical data analysis
Complete patient follow-up

largely based on experiences with individual patients. Ederer [2] has pointed out that medical training emphasizes the uniqueness of patients and the study of their distinctive characteristics. Maitland [3] has stated that 'the training of a doctor as a doctor is in some ways the reverse of an investigator's training'. The clinician-scientist Thomas Lewis [4] noted that 'Self-confidence is by general consent, one of the essentials to the practice of medicine, for it breeds confidence, faith and hope. Diffidence, by equally general consent, is an essential quality in investigation for it breeds inquiry. A natural companion of confidence is an easy and uncritical acceptance of statements of fact and hypothesis. The companion of diffidence is skepticism'.

Clinicians are generally interested in dealing with individuals, have a bias for action and are not detached in that they identify with their patients' desire for good results. These factors lead to overly optimistic judgments on the efficacy of treatments. Recognition of this clinical bias has led to the use of designs which 'detach' the clinician from the interpretation of the results of a trial in an attempt to increase the objectivity of interpretation.

Clinical trials are of use when the difference between a new and old treatment is not clear, the disease follows a chronic, variable and erratic course and a large number of known or unknown factors may influence the course of disease and the outcome of treatment [5]. These are exactly the conditions that obtain in dry eye disease (DED). Table 1 lists the characteristics of a clinical trial; these will be discussed in the following text.

The use of randomized controlled clinical trials did not become common in ophthalmology until the last 25 years. The field of DED presents special challenges in the design of therapeutic clinical trials. These challenges become especially daunting as the output of new surgical strategies and therapeutic agents from laboratory research holds promise for better ways to manage DED but also raises questions about the safety and efficacy, not to mention the relative efficacy of each new approach. The decisions made by regulatory agencies

on the approval of new drugs and by managed care directors on the use of these agents will depend on the evidence accumulated through the application of large randomly controlled clinical trials with rigorous scientific standards.

Considerations in Designing a Clinical Trial

Ethical Considerations

Foremost in the design of a prospective clinical trial to evaluate the efficacy of a new treatment modality is the principle, 'primum non nocere' attributed to Hippocrates in the 4th century BCE. The injunction to 'first do no harm' is embedded in the modern clinical trial in several ways. First clinical trials of a surgical or pharmaceutical intervention are preceded by safety studies to discern risk to the subjects. These studies involve animal or in vitro laboratory studies. Once safety has been established involvement of human subjects is limited to small groups with close monitoring to recognize any untoward effects at an early stage in order to withdraw the subject and manage complications.

Other elements designed to protect human subjects include full disclosure of the known and unknown possible risks to the subject in partaking in the trial along with possible benefit. A full document explaining the purpose of the trial, necessary cooperation of the subject, risks, reporting and 'escape' strategies is an essential component of the trial. Over the last 40 years virtually every academic center has established an institutional review board. This board consisting of academic experts has, in recent years, been expanded to include specialists in bioethics and frequently a lay representative. The board acts on behalf of the study subject by reviewing the study protocol to ensure an unbiased assessment of the risks and possible benefits. Only with board approval can human clinical studies be conducted.

International agencies have become involved to assure humane treatment of study subjects and the Helsinki principles are an example of a widely accepted list of guidelines to protect patients. An even newer development is the prospective registration of clinical trials to assure public access to the results of clinical trials (see below).

Sample Size

Let us consider some of the problems in clinical trial design for DED. Some concerns in attempting to design a clinical trial in DED involve factors that are common to all clinical trials; these include the need for adequate sample size to minimize the effects of unknown variables and the well-known placebo effect, i.e. a seeming effect from a treatment or intervention that is not

due to effect of the treatment but rather the patient's desire to respond to therapy. Estimation of the sample size needed to demonstrate statistically significant differences between controls and treated groups will depend on a number of variables. These include: the estimated degree of effect anticipated, i.e. therapeutic agents with a large anticipated effect will need a smaller sample size to demonstrate a significant effect. In addition, in trials in which uncontrolled variables are likely to be present, larger trial sizes will be necessary to render these factors less determinative in the results. Consultation with a professional biostatistician is essential in design to determine the trial size which is likely to confer sufficient power to the study to reveal real differences between treated and control groups.

Placebo or Control Vehicle Effect

In clinical trials for dry eye the placebo effect is notoriously large and renders demonstration of statistically significant differences between treatment groups difficult [6, 7]. In most clinical trials this placebo effect is limited to subjective criteria but not seen in objective criteria [8]. In dry eye trials, however, both objective and subjective changes attributable to the placebo effect have been reported. This is thought to be due to increased compliance by the patients in using prescribed treatment regimens during the trial.

Another possibility is that prior to the onset of the trial the patient was using a treatment that actually worsened the condition and improvement during the trial is related to cessation of the noxious agent. Avoidance of this problem is usually addressed by the institution of a 'washout' period, i.e. a period of time in which all treatment is discontinued prior to the onset of the trial. Although definitive data on the residual effect of prior treatment on the ocular surface is lacking, most clinical trials in DED assume that a 2-week 'washout' period is sufficient. This is a compromise between a longer period which might be more desirable and the practical concern for patient compliance in eliminating all forms of treatment. A recent presentation (M. Christenson, pers. commun., Alcon Labs Inc.) might shed some light on this issue. In a series of patients who manifested benefit from a regimen using a new artificial tear, patients were asked to stop all treatment and report back at weekly intervals when symptoms of dry eye returned prompting them to resume treatment. At that visit they were examined for objective signs of DED. While some patients returned for the 1-week visit and had evidence of a return of signs, i.e. staining, others did not until 5 weeks. The average interval was 3.5 weeks. This suggests that while the interval is variable probably depending on severity of disease, that 3–4 weeks might be a preferable washout period.

Additional considerations that are more specific to DED include the following:

Length of the Trial

There are no reliable data on the untreated natural history of DED. The expected course of disease with fluctuations in severity and manifestation is, therefore, not precisely known. Variability in disease course over the period of the trial may influence results. The length of time required for a putative therapeutic agent to result in improvement in signs and symptoms will depend on multiple factors, e.g. severity of disease, resolution time for repair of the ocular surface in the case of staining, mechanism of action of the therapeutic agent. Nelson et al. [9] have reported that the corneal surface responds more rapidly to therapy than the conjunctival surface. In a recent trial of topical cyclosporine, both subjective and objective improvements were seen at 4 weeks but further improvement in ocular surface staining and inflammatory markers were seen after 6 months of treatment [10].

Patient Populations

DED consists of a number of subtypes. The NEI/Industry Workshop on Clinical Trials in Dry Eye report identified two major categories of dry eye by pathogenetic mechanism, i.e. aqueous tear deficiency and evaporative dry eye [11]. Figure 1 illustrates this classification scheme with further subtypes. Since there are differing mechanisms operative in different forms of dry eye, results of treatment would be expected to differ in each form. Identification of each major subtype of patient in enrollment into a clinical trial is important in the interpretation of results. Certain types of therapeutic agents would be expected to target a specific mechanism. Therefore, recruitment of patients with a particular subtype of dry eye would be appropriate to test the therapeutic efficacy of that agent. This schema is complicated by the fact that there is considerable overlap of dry eye subtypes in dry eye patients. As an example, roughly two-thirds of patients with Sjögren-associated aqueous tear deficiency also have meibomian gland dysfunction (evaporative dry eye) [12]. Stratification of patients into these subtypes – aqueous, tear-deficient, evaporative dry eye, and mixed – will greatly facilitate interpretation of results.

Inclusion and Exclusion Criteria

A key element in trial design is the selection of appropriate patients who would be most likely to respond to the action of the therapeutic agent being tested. Principal considerations would be the type and severity of DED of the subject.

As we discussed above, the two major types of DED are aqueous tear deficiency and evaporative dry eye. The former is divided into Sjögren-associated and non-Sjögren. The most common form of evaporative dry eye is meibomian gland dysfunction. A drug directed to stimulation of the lacrimal glands would

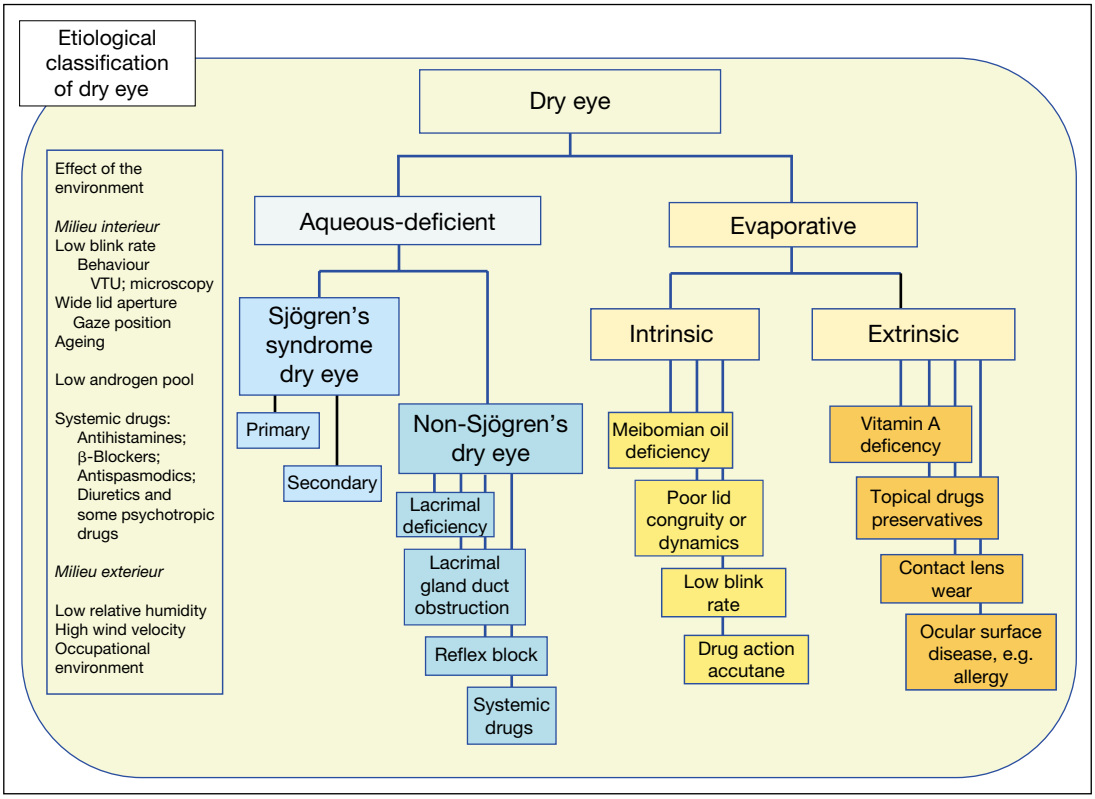

Fig. 1. The figure summarizes the major etiological causes of dry eye. The left-hand box illustrates the influence of environment on the risk of an individual to develop dry eye. The term environment is used broadly, to include bodily states habitually experienced by an individual, whether it reflects their 'milieu interieur' or is the result of exposure to ambient conditions which represent the 'milieu exterior'. This background may influence the onset and type of DED in an individual, which may be aqueous-deficient or evaporative in nature. Aqueous-deficient dry eye has two major groupings, Sjögren's syndrome dry eye and non-Sjögren's syndrome dry eye. Evaporative dry eye may be intrinsic, where it directly affects the regulation of evaporative loss from the tear film by meibomian lipid deficiency, poor lid congruity and lid dynamics, low blink rate and the effects of drug action such as that of systemic retinoids. Extrinsic evaporative dry eye embraces those conditions which increase evaporation by their pathological effect on the ocular surface. Causes include vitamin A deficiency, the action of toxic topical agents such as preservatives, contact lens wear and a range of ocular surface diseases, including allergic eye disease. Further details are given in the text. Reproduced with permission from the International Dry Eye Workshop Report. The Ocular Surface 2007;5:49–199.

not be expected to have a direct effect on evaporative dry eye; conversely an agent directed to normalizing lipid secretion of the meibomian glands would not be thought to have a direct effect on lacrimal gland secretion. Identifying the target subject group based on action of the drug is essential. Since the dry eye subtypes overlap, identification of those subjects with a mixed form of disease is important in interpreting results.

As mentioned earlier, consideration of the primary endpoints may affect inclusion criteria, e.g. if ocular staining is a primary endpoint it is important to select subject with sufficient staining to demonstrate a statistically significant improvement. (The usual requirement by the US FDA is a 25% or a one grade improvement using a four-point scale.) Over the past 15 years the majority of clinical trials in DED have utilized vital dye staining of the ocular surface as an endpoint. Since ocular surface breakdown with staining is characteristic of moderate to severe disease, these trials have been skewed to more severe DED patients. This means that the trial will enroll only patients with moderate to severe DED as these are the only ones with sufficient staining to allow for demonstration of efficacy. A recent example of a different strategy is that of a diquafosol 2% clinical trial in which a lesser grade of staining was chosen but this study failed to demonstrate statistically significant reduction in staining in the treatment group [13].

Another consideration is the exclusion of subjects with other systemic or local conditions which might introduce confounding variables into the study. These are other ocular surface diseases, the use of systemic or topical drugs which could influence outcomes, and non-compliant subjects.

Relationship of Signs and Symptoms

Another challenging aspect of the design of clinical trials in DED is the fact that symptoms and signs frequently do not correlate well. This has been a source of considerable frustration to sponsors of clinical trials in DED in that some regulatory bodies, e.g. the US FDA, have required that for approval of a new therapeutic agent, the sponsor must demonstrate a statistically significant improvement in both a sign and a symptom. The non-concordance of these two manifestations of DED is not completely understood but it is clinically apparent that symptoms usually precede signs. It may be that early or less severe disturbances in the tear film and ocular surface stimulate sensory signals resulting in discomfort prior to more severe objective evidence of DED such as ocular surface breakdown with staining; in moderate to severe DED, reports indicate that with ocular surface inflammation there is a downregulation of sensory receptors which may explain why some patients with objective evidence of severe ocular surface disease experience relative little discomfort. As our knowledge base

enlarges it is likely that we will look to other surrogate markers for severity of disease to assess efficacy, e.g. tear osmolarity, tear inflammatory cytokines, precise measurements of tear film instability and disturbances of vision (see below).

Role of Symptoms in Clinical Trials

Because of the problems with objective signs as inclusion criteria and efficacy endpoints in clinical trials and the recognition that a large percentage of the DED population suffers from a milder form of disease characterized by dry eye symptoms but not traditional objective signs such as ocular surface staining [15], attention has been turned to patient symptoms. The use of questionnaires to elicit and quantify symptomatology is growing. There are a number of instruments which have been developed to assess presence and severity of DED. Some of these have been validated, i.e. shown to correlate with other assessments of DED, e.g. a clinical global impression. Instruments in use include the McMonnies Index, the Ocular Surface Disease Index (OSDI) and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). The later two instruments include an assessment of visual function and a pain subscale. They are reasonably good at identifying patients with moderate to severe dry eye [16]. A recent questionnaire has been shown to correlate with patient assessment of severity and physician assessment of severity was shown to underestimate the severity of disease reported by patients [17]. There is some tautological aspect to these studies in that they measure elements included in the reference assessment. Some of these newer instruments incorporate a quality-of-life component. This element attempts to grade the effect the disease has on functional activities of life and may offer a new avenue for grading severity of disease.

Endpoints in Clinical Trials

In the design of clinical trials it is usual to assign weight to clinical endpoints to demonstrate both efficacy and safety. Safety concerns can be addressed by looking for evidence of worsening of symptoms or signs. The issue of appropriate endpoints for efficacy is more challenging. The choice of a primary efficacy endpoint should relate to the expected effect of the putative therapeutic intervention. Thus a measure of increased tear secretion for a clinical trial of a lacrimal secretagogue would be appropriate. In contrast in a trial with an agent expected to reduce inflammation and improve the ocular surface, surface staining might be chosen. As we have discussed, ocular staining as a primary efficacy endpoint presents a unique set of difficulties.

Other outcome measures can be chosen as secondary endpoints. These can provide additional information as to the action and efficacy of the drug being tested but are not usually central to its action. These secondary endpoints can assume importance, particularly in trials in which the outcome based on

primary endpoints might be equivocal. The data accumulated can provide the basis for a post-hoc analysis of data which may lead to a better demonstration of the action of the drug. An example of this is approval of topical cyclosporine A (Restasis-Allergan) by the US FDA. This approval was reportedly based on an improvement in Schirmer test scores in a subset of patients under treatment. The Schirmer test result was a secondary endpoint in the study design.

This area is one is evolution. A good dialogue with the regulatory agency on the appropriate clinical design prior to the initiation of the trial is essential to avoid unwanted post-trial surprises.

Tests Employed in Clinical Trials in DED

Objective tests employed in clinical trials include those in use for the diagnosis of DED in clinical practice. There are differences, however, in that some tests in common use in practice are insufficiently precise and repeatable and some tests suitable for clinical trials require excessive time, are difficult to perform, and require special instrumentation not widely available. To be appropriate for use in clinical trials the objective test should be: specific, i.e. measure a particular aspect of tear production, loss, or change in structure or composition. The test should be repeatable with an acceptable range of variance and should be validated as reflecting a clinically relevant status of the patient's ocular surface health. Let us consider tests which are in common use in clinical trials and which meet these criteria.

Tests of Tear Production or Volume

The Schirmer test is over 100 years old. It is an indirect measure of tear production. The methods of performing this and other tests is discussed in chapter 3. It is used in three ways: without topical anesthesia, with topical anesthesia, and with nasal mucosal stimulation. These methods reflect different degrees of stimulation of tear production. It is difficult to standardize the exact amount of stimulation employed in the test and the Schirmer test is thought to be quite variable particularly in subjects with only mild to moderate decreases in tear production. As DED progresses, the results become more serially consistent. While it has limitations in mild to moderate disease the test is easy to perform and remains a standard method of assessing tear production. The phenol red test is a variant which is less invasive.

Meniscometry involves measuring the curvature of the tear meniscus over the lower lid margin. This requires a special machine; the curvature can be used to calculate tear volume in the meniscus and total tear volume estimated. This test has not been used very much in clinical trial but has potential.

Interferometry employs an interferometric measurement of the thickness of the lipid layer of the tear film. As such it is a measure of lipid volume. Although requiring a special apparatus it has potential to give good information on lipid structure.

Meibometry is a test in which lipid secretion from the meibomian gland openings is collected with an adhesive strip and then changes in transparency are measured photometrically. It can provide estimates of volume of lipid secretion.

Tests of Ocular Surface Integrity

As DED progresses the earlier events of tear film hyperosmolarity and instability give rise to desiccation and inflammatory changes which lead to disruption of the glycocalyx and the epithelial cell walls. These changes are seen clinically by uptake of vital dyes. Fluorescein is used to outline corneal cell uptake and either rose bengal or, more recently, lissamine green to visualize conjunctival staining (see chapter 3 for details). As mentioned earlier, dye uptake is a relatively late sign in the development of DED. In performing these tests a few cautionary notes are pertinent [14].

Fluorescein 1% dye viewed with a Wratten 12 yellow filter is best visualized within 1–2 min of application as the dye tends to diffuse throughout the epithelial layer and stroma. On the other hand, lissamine green takes time to penetrate and is best viewed after 3 min.

There are several larger issues with staining as a primary efficacy endpoint in dry eye clinical trials. Staining of the ocular surface occurs as both a long- and short-term condition. In the short term the degree of staining is dependent on local events such as changes in environmental challenges; longer-term changes in the tear environment lead to more persistent staining. It has been reported that in normal subjects clinically significant staining was observed in 37% [18]. Most of the stain occurred in the inferior cornea at the 4- and 8-o'clock positions; an additional 21% had some punctate staining of the cornea which was judged to be insignificant. Some of this staining was attributed to incomplete blinking. The difference between clinically significant and insignificant involves a subjective judgment.

While these percentages in normal subjects seem high, the occurrence of some punctate staining of the cornea does occur in subjects with no other evidence of dry eye. Since some of this is due to short-term changes in environmental challenges, attempts to judge serial changes over the course of treatment are subject to 'noise'. This makes the demonstration of statistically significant changes associated with treatment effects more difficult. One approach might be to consider staining of the central cornea where the more transient staining is less likely to confound the measurement. The choice of a grading system such as the Oxford Scale which recognizes and allows for minimal peripheral

corneal staining with a 0 score is a step in the right direction. All grading systems are susceptible to repeatability problems in clinical trials.

Impression Cytology

This test is useful in demonstrating morphological changes in conjunctival cells. Loss of conjunctival goblet cells is characteristic in DED. The use of semiquantitative scoring systems, e.g. Tseng [19] and Nelson et al. [20], can be very useful in moderate to severe DED subjects.

Tests of Tear Film Stability

An unstable tear film is a global characteristic of DED [11]. It is an early sign of disease. The primary initiating factor of tear instability is not known but tear osmolarity is highly suspect. It is known that an increased electrolyte concentration is associated with quantitative and qualitative changes in tear mucins which are thought to play a major role in tear film stability. In addition, hyperosmolarity is associated with changes to lipid-tear interactions and damage to the underlying ocular surface.

The traditional test for tear stability is tear break-up time (TBUT). Noninvasive methods, i.e. those that do not require instillation of fluorescein solution into the tears, have been described (see chapter 3) and used. These methods, however, require instrumentation that is not in general use. More commonly the minimally invasive TBUT method is that employing an unpreserved 1% fluorescein solution. It is important to standardize the amount of dye applied since larger amounts temporarily destabilize the tear film. In clinical trial, 2–5 μl dispensed from a micropipette are used. After several blinks and blotting of any excess fluid from the lid margin, the precorneal tear film is scanned at the slit-lamp using the cobalt blue excitation filter looking for the appearance of the first randomly appearing dry spot. Three readings are taken and averaged. Test results are influenced by ambient conditions so it is important to control for these to the extent possible.

A newer more precise, standardized method for measuring TBUT has been reported [21]. In this method video recordings of the TBUT are taken and analyzed repeatedly; a small timer recording in 0.1-second intervals is projected onto the screen. Minor differences can be determined in this method. Such differences may be important in determining efficacy of tear film stabilizers. It is thought that in DED the tear film breaks up between blinks; small extensions of TBUT may provide clinically significant improvement in corneal tear covering between blinks.

Recently another method of measuring and analyzing TBUT has been developed [22]. It employs videokeratography with serial images captured every second. In these reports, TBUT in DED was significantly reduced.

Tests of Tear Composition

Tear osmolarity has been considered a 'gold standard' for the diagnosis of DED. In disease the electrolyte concentration of tear rises due to increased evaporative water loss, changes in tear secretion or both. This global feature of DED is thought to be not only a marker but a pathogenetic mechanism (see above). While there is substantial literature on the utility of this test in the diagnosis of DED, its use has been limited by the difficulty of performance, lack of repeatability data and expense of the machines. Nonetheless, in experienced hands, tear osmolarity is a highly sensitive and specific test. It is reflective of health of the tear environment bathing the ocular surface. Recently data on a new point-of-care device has been presented which holds the promise of an easier, reproducible methodology which could lead to widespread use [23]. Tear osmolarity is an attractive endpoint for efficacy in DED clinical trials.

In the last several years a number of reports identifying the presence of elevated levels of inflammatory cytokines in the tears of DED patients have appeared. A reduction in these cytokines has been reported in clinical trials employing cyclosporine A. More recently another inflammatory marker, HDL-A, has been shown to be overexpressed in the conjunctiva of DED patients [24]. As mentioned earlier, it is likely that as the literature on these and other biomarkers grows, their incorporation into clinical trials will become more widespread.

Tests of Visual Function

It is a common clinical observation that DED patients complain of vague visual disturbances and ocular fatigue. Despite these complaints, measurement of visual acuity using standard Snellen charts seldom reveals significant abnormalities of vision except in patients with extensive ocular surface damage. Only recently have methods been developed to document earlier visual changes in DED patients. The continuous functional visual acuity system reported by Goto et al. [25, 26] is described as follows. After a small amount of a topical anesthetic has been applied to the eye, the subject is asked not to blink for 30 s. Within that time a series of optotypes requiring different resolving power are presented to the subject at 10, 20, and 30 s and the smallest optotypes recorded. The authors have reported significant declines in visual acuity in DED patients. In the same study, improvement in functional visual acuity has been documented in patients treated with punctal plugs.

Similar decreases in visual function have been reported with glare contrast and wave front aberrometry [27]. These methodologies open the door to include visual function endpoints in clinical trials.

Challenge Models

DED patients are quite susceptible to changes in the environment, e.g. wind, humidity, sun exposure, visual activities. This leads to uncontrollable variables over the course of a clinical trial. In an attempt to better control for these variables, the concept of a 'challenge' model has been developed [28]. This model has proved successful in testing for allergic disease with recruitment of a predisposed cadre of subjects with a known response to specific allergens. Presentation of the inciting allergen in a controlled environment can remove unwanted environmental variables and allow for measurement of effects of therapeutic agents in protecting against the induction of allergic conjunctivitis. DED is thought to provide a conditions that can be studied by challenging predisposed subjects to a 'controlled adverse environment' while measuring various activities and examining for clinical changes. This concept is attractive in that it can study the action of drug in protecting the ocular surface over a short time. Most of the results obtained using this model are in the realm of proprietary information so it is not possible to adequately assess its utility as yet.

Sequencing of Tests in Clinical Trial

It is important to consider the sequence of tests performed in clinical trail in order to minimize interference with subsequent test. The general principle is to employ the least invasive tests first progressing to the more invasive in a stepwise manner. This is outlined in chapter 3.

Emerging Trends and Future Directions

One of the most recent developments affecting clinical trials is the movement to require that clinical trials be registered in a publicly available database prior to their initiation [29]. The impetus for this requirement is the recognition that positive results of a clinical trial in which a statistically significant benefit for a new treatment is reported can change the standard of medical care. Past experience has shown, however, that negative or equivocal results are frequently not published. Sponsors of clinical trials, corporations, institutions or individuals, may not want to publicize negative or harmful results and this could limit the dissemination of important knowledge. A policy proposed by the International Committee of Medical Journal Editors (ICMJE) states that these journals will not publish the results of clinical trial not previously registered [30]. The editors of several leading peer-reviewed ophthalmic journals have endorsed this policy, as have other non-ophthalmic journals [31]. A set of 20 items to be provided in the registration has been developed. The implementation of this policy in the next several years should have the effect of making information more readily accessible to the public.

Major challenges remain in the design, performance and interpretation of clinical trials in DED. The lack of a thorough understanding of the pathogenetic

sequence of events in the development of DED, the influence of short-term environmental factors on objective signs of DED, the newly developed methodologies for measuring visual function which will require further validation and the only gradually emerging correlation between clinical events and biomarkers limit the robustness of clinical trial design in DED. It seems clear, however, that the future will see the development of new primary endpoints for determination of efficacy in the treatment of this widespread yet elusive disease. The principal candidates for new efficacy endpoints include: biomarkers such as tear osmolarity which reflects the health of the tear film, other biomarkers related to the presence of inflammation and new methods of visual function.

The use of the randomized, controlled clinical trial in the testing and development of newer, more effective treatment modalities is essential and unavoidable. The challenges lie not only in the design but in the performance of the trials with a precise, fastidious and demanding observance of all aspects of the trial. This work is tedious and demanding; patience and perseverance are essential virtues. And yet there is no viable alternative to prove the value of new treatment modalities. As Fredrickson [32] observed about clinical trials which he called an 'indispensable ordeal' almost 40 years ago, 'They lack glamour; they strain our resources and our patience and they protract to excruciating limits the moment of truth. Still they are among the most challenging tests of our skills. I have no doubt that when the problem is well chosen, the study appropriately designed and all the populations concerned made aware of the route and the goal, the reward can be commensurate with the effort. If in major medical dilemmas, the alternative is to pay the cost of perpetual uncertainty, have we really any choice?'

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Michael A. Lemp, MD
4000 Cathedral Ave. N.W. #828B
Washington DC 20016 (USA)
E-Mail malemp@lempdc.com

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Animal Models of Dry Eye

Stefan Schrader[a], *Austin K. Mircheff*[b], *Gerd Geerling*[c]

[a]Department of Ophthalmology, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [b]Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, Calif., USA; [c]Department of Ophthalmology, Julius Maximilian University Würzburg, Würzburg, Germany

Abstract

Background: The causes of dry eye include lacrimal gland insufficiency, meibomian gland dysfunction, impairment of the neuronal innervation and environmental stress – all leading to irritation of the ocular surface. Several animal models have been developed to imitate different pathophysiologic mechanisms in the development of dry eye. Understanding the characteristics and limitations of these models will help researchers choose the right models to address specific problems and develop new treatment modalities in dry eye. **Methods:** Medline searches were performed to identify English language articles relating to different animal models of dry eye. Manual cross-referencing was also performed and some historical articles were included. **Results and Conclusion:** A huge variety of animal models exists, mimicking different pathophysiologic mechanisms which can cause dry eye. The mouse is the model most commonly used to study autoimmune mechanisms, because of the diversity of different knockout and transgenic strains and good availability of antibodies. For studying dry eye signs, rabbit or dog models are more suitable, because they present decreased tear secretion and ocular surface changes, have longer lifespans, and offer better accessibility of the ocular surface. For studying special causes of dry eye, such as defects of neuronal reflex loops, environmental changes, or evaporative dry eye, the model of choice should recapitulate the underlying pathophysiologic mechanism.

The causes of dry eye can be divided into quantitative, qualitative, and combined tear film deficiency, and they can be induced by different pathophysiologic mechanisms. Many animal models for studying special forms of dry eye have been developed to mimic these different mechanisms. Ocular and systemic characteristics, and the practicability of the dry eye models varies considerably and depend on the pathomechanism, the type and extent of tear film dysfunction and

other difficult to define parameters. We subsequently describe the models available to study the different forms and pathomechanisms of dry eye as well as their advantages and disadvantages.

Quantitative Tear Film Deficiency (Aqueous Deficient Dry Eye)

Models for Autoimmune Disease

Mouse Models

In the past two decades the mouse has become the major model organism for the study of autoimmune diseases. There are several mouse models, exhibiting different characteristics of sialo- and dacryoadenitis, which can be used to study particular aspects of Sjögren's syndrome (table 1).

The MRL/lpr mouse is primarily used as a model for systemic lupus erythematosus (SLE); it was derived from the MRL/n mouse strain. The *lpr* gene (lymphoproliferation) is a mutated Fas antigen; it causes lymphoproliferation, which seems to accelerate rather than induce autoimmune disease. MRL/lpr mice show some of the serological manifestations characteristic of Sjögren's syndrome (anti-SSA, anti-SSB) and exhibit lacrimal gland infiltration predominantly by CD4– T cells. The onset of dacryoadenitis is discernable at 1 month of age, and it is significantly more severe in the females than in males [38, 40]. The development of sialo- and dacryoadenitis is accompanied by SLE and arthritis, which also exist in patients with secondary Sjögren's syndrome, suggesting that this mouse strain is suitable for comparison with the subgroup of patients with secondary disease.

A mouse model exhibiting characteristics of organ-specific autoimmunity is the non-obese diabetic (NOD) mouse. It was initially established as a model for insulin-dependent diabetes mellitus. It shows a predominantly CD4+ Th1 cell infiltration of the lacrimal gland that is secondary to the appearance of autoimmune diabetes; this model is somewhat atypical in the sense that the onset of dacryoadenitis is earlier in males (8 weeks) than in females (30 weeks). Other organs, including the pancreas, submandibular and thyroid gland, are also affected. It has been shown not only that the incidence of dacryoadenitis is much higher in male than female NOD mice, but also that testosterone increases the incidence and severity of the autoimmune lesions in the lacrimal glands [37]. In contrast to the MRL/lpr model, NOD mice show decreased secretion of tears and saliva. Although tear function is reduced by 33–36%, no signs of ocular surface disease have been reported [16]. Autoantibodies, especially against M3 muscarinic acetylcholine receptors, are proposed to mediate the decrease of secretory function in NOD mice [31]. An important role of

Table 1. Animal models of quantitative aqueous tear film deficiency

Model	Pathomechanism	Reduced tear secretion + to +++(test used)	Ocular surface signs
Mouse models			
Non-obese diabetic (NOD) mouse model	Predominantly CD4+ Th1 cell infiltration of the lacrimal gland, secondary to the appearance of autoimmune diabetes	+ (Cotton thread test)	No signs of ocular surface disease were reported
Id3-deficient mouse model	T-cell-dominant lymphocyte infiltration in the lacrimal gland	+ (Tear volume after pilocarpine stimulation)	Periocular skin lesions due to eye scratching
Neurturin-deficient ($NRTN^{-/-}$) mouse model	Defects in the autonomic, enteric and sensory nervous system	+ (Cotton thread test)	Corneal sensation ↓, mucin production ↓, ocular surface inflammation ↑
Rabbit models			
Sjögren's syndrome model	Autoimmune dacryoadenitis induced by injection of activated autologous peripheral blood lymphocytes	++ (Schirmer test)	Corneal surface staining ↑
Irradiation model	Impairment of lacrimal function by single dose irradiation (15 Gy)	+ (Schirmer test)	Presence of dry eye signs were not examined
Neuronal pathway dysfunction model	Blockage of lacrimal gland innervation by topical atropine (50 µl 3 times/day)	+ (Schirmer test)	Increased corneal fluorescein staining
Canine models			
Spontaneous dry eye model	Growing evidence for autoimmune disease	+++ (Schirmer test)	Signs of moderate to severe dry eye
Model of surgical induction of dry eye	Mechanical removal of the main lacrimal gland and gland of the nictitating membrane	+++ (Schirmer test)	Signs of keratoconjunctivitis sicca
Monkey models			
Squirrel monkey model	Mechanical removal of the main lacrimal gland	+ (Schirmer test)	None

autoantibodies in the loss of secretory function has also been postulated for patients with Sjögren's syndrome [1]. This parallel makes the NOD mouse an attractive model for studying functional aspects of the autoimmune process.

The NOD.B10.H2^b mouse is a NOD mutant with an altered MHC region. This strain does not develop autoimmune diabetes but still shows lacrimal T-cell infiltration. Because of these findings it has been postulated that two different autoimmune mechanisms are responsible for insulitis and dacryoadenitis in NOD mice [32]; thus, the NOD.B10.H2^b is an even more attractive model for studying primary Sjögren's syndrome.

A fourth model for primary Sjögren's syndrome is the Id3-deficient mouse. Id3 is an immediate early-response gene in growth regulation and is involved in TCR-mediated T-cell selection during T-cell development. Id3-deficient mice develop T-cell-dominant lymphocyte infiltration in both lacrimal and salivary glands before 6 months of age. They also show anti-SSA and anti-SSB antibodies after 1 year of age. Tests of lacrimal and salivary gland function demonstrated reduced abilities to secrete tears and saliva. At an older age the mice also develop skin lesions due to excessive periocular scratching, which may be a sign of dry eye [24]. This model also seems to lack other autoimmune symptoms, so it also may serve as a model for primary Sjögren's syndrome.

A spontaneous autosomal recessive mutation in the non-autoimmune NFS/N mouse resulted in the establishment of the NFS/sld model. NFS/sld mutant mice spontaneously develop severe inflammatory changes in the submandibular, parotid and lacrimal glands if a thymectomy is performed 3 days after birth, whereas no significant inflammatory lesions are reported in other organs. No additional immunisation is involved in this model. The incidence of autoimmune lesions is higher in the females than in males. The autoantigen 120-kDa α-fodrin was identified in this model and postulated as a critical antigen in the development of Sjögren's syndrome [13]. No data exist about ocular surface changes in this model, and the changes in the immune system caused by thymectomy make it unattractive for long-term prospective studies.

Lacrimal gland infiltration is seen in other mouse models, such as the NZB/NZW F_1, TGF-β_1 knockout, alymphoplasia (aly) and IQI/Jic mice. However, no data exist concerning altered tear secretion, ocular surface changes, or any other signs related to lacrimal gland insufficiency or dry eye [22, 28, 39, 40].

Rat Models

A report published by Liu et al. [25] in 1987 describes autoimmune dacryoadenitis produced in Lewis rats by a single injection of lacrimal gland extract emulsified in complete Freund's adjuvant. The incidence and severity was markedly enhanced by simultaneous injection of dead *Bordetella pertussis*.

Lymphocytic infiltrations appeared in the lacrimal tissue after 2 weeks and reached a maximum after 4–6 weeks. No data on reduced tear secretion or ocular surface alterations in this model have been published.

Rabbit Models

The only rabbit autoimmune model of Sjögren's syndrome was presented by Guo et al. [11]. In this model, autoimmune dacryoadenitis is induced by coculture of peripheral blood lymphocytes with purified acinar cells obtained from one autologous lacrimal gland and injection of the activated lymphocytes to the contralateral gland. This procedure results in CD4+ T-cell infiltration in the lacrimal gland accompanied by signs of dry eye such as reduced tear production, reduced tear film stability, and abnormal corneal surface staining which are evident by 2 weeks [42] (table 1). Interestingly, not only the eye that received the lymphocyte injection, but also the contralateral eye, develops dry eye signs. These findings may indicate a generalized disease, because in rabbit the removal of the lacrimal gland alone did not lead to dry eye signs in most of the studies (see below: Removal and Irradiation of Lacrimal Gland).

Canine Models

Spontaneous keratoconjunctivitis sicca (KCS) in dogs is a well-known phenomenon affecting approximately 35% of the general canine population. Among these the American Cocker Spaniel has the highest incidence for KCS (20.6%), followed by Lhasa Apso (12.7%), Shih Tzu (11.5%) and mixed breeds (11.5%). Interestingly, beagles which are often used in laboratory studies have a much lower relative incidence of KCS (1.2%) [19] (table 1). The cause of KCS is not entirely clear, but there is growing evidence that canine KCS is an autoimmune disease similar to Sjögren's syndrome [18, 20, 21]. A study by Gao et al. [8] revealed decreased apoptosis of lymphocytes and increased apoptosis in lacrimal acinar cells and conjunctival epithelial cells in KCS dogs, supporting the thesis of an autoimmune origin. KCS dogs show moderate to severe dry eye symptoms, and they provide a large ocular surface, readily amenable for clinical examination. These characteristics make the canine model very useful for pathophysiologic studies as well as development of therapeutic interventions for KCS. However, to identify a source of animals suffering from KCS for experimental purposes may be difficult and costs of maintenance are high.

Removal and Irradiation of Lacrimal Gland

Surgical removal of the main lacrimal gland is an approach that has been used in several studies. The choice of the right animal model plays an important

role because of the varying contributions the accessory lacrimal glands make to total aqueous tear secretion in different animals (table 1). In dogs the removal of the main lacrimal gland caused a slight reduction in tear secretion. The additional removal of the gland of the nictitating membrane caused massive reduction of Schirmer test values and clinical signs of KCS [14]. In mice and rabbits the removal of the main lacrimal gland seems to result in decreased basal tear production, but does not necessarily cause signs of ocular surface disease because the accessory lacrimal glands seem to provide adequate tear supply [2, 17, 27]. Only in one study was corneal ulceration observed in 55% of rabbits after removal of the main lacrimal gland, although no significant decrease in Schirmer test values could be detected in that subgroup [23]. In squirrel monkeys, which have similar anatomical structures to humans, the removal of the main lacrimal gland caused a decrease in aqueous tear secretion but neither biomicroscopical signs of KCS nor any histological changes of the cornea and conjunctiva occurred [26].

Also the effect of irradiation on lacrimal gland function has been investigated. In a study by Hakim et al. [12] a single dose of 15 Gy was used to induce lacrimal gland impairment in a rabbit model. The procedure resulted in immunohistological and ultrastructural changes of the lacrimal gland and reduced tear secretion, still evident but less obvious after 1 month. The presence of dry eye signs was not examined in this study (table 1).

Dysfunction of Neuronal Pathways

Dry eye results from dysfunction of the physiological system that is comprised of the ocular surface tissues and secretory glands. The system's function is integrated by the sensory afferent nerves innervating the ocular surface and the autonomic nerves innervating the tear-secreting glands [36]. Thus, inhibition of lacrimal gland secretion can be achieved by pharmacologic blockage of the parasympathetic autonomic nerves (table 1).

Burgalassi et al. [4] introduced a simple rabbit model of dry eye, where innervation of the lacrimal gland was blocked by the daily application of topical 1% atropine eye drops. This treatment significantly reduced tear production (measured by Schirmer I test) within 2 days. Additionally, corneal erosions were noted after 3 days. This model does not exactly reproduce the human dry eye syndrome, but it may be useful for examination of the effects of artificial tear substitutes on the ocular surface in a desiccating environment.

Another interesting model of dysfunction of the neuronal reflex loops, is the Neurturin-deficient ($NRTN^{-/-}$) mouse model. Neurturin, a member of the transforming growth factor-β family, functions as a neurotrophic factor and is

essential for the development of specific postganglionic parasympathetic neurons [10]. NRTN$^{-/-}$ mice show defects in their autonomic, enteric and sensory nervous systems. Parasympathetic innervation of the lacrimal and submandibular salivary glands is dramatically reduced in NRTN$^{-/-}$ mice, as is corneal sensation [15, 33]. Observations of the ocular surface in this model revealed decreased aqueous tear production and tear fluorescein clearance accompanied by altered corneal epithelial barrier function, reduced mucin production and inflammation of the ocular surface [35]. These properties make the NRTN$^{-/-}$ mouse a suitable model for clinical investigations, especially for diseases affecting the neuronal pathways that integrate the function of the ocular surface system.

Qualitative Tear Film Deficiency (Evaporative Dry Eye)

Meibomian Gland Dysfunction

The lipids produced by the meibomian glands stabilize the tear film. Altered function due to diseases such as ocular rosacea result in evaporative forms of dry eye with reduced break-up time (table 2). A simple rabbit model mimicking meibomian gland disease was developed by Gilbard et al. [9], who closed the meibomian gland ducts by cauterization, which resulted in increased tear film osmolarity in the presence of normal lacrimal gland secretion. A decrease of goblet cell density and corneal epithelial glycogen levels after 12 weeks and an increase of inflammatory cells in the bulbar conjunctiva after 20 weeks was also observed.

The tabby mouse is the mouse counterpart of human x-linked anhidrotic ectodermal dysplasia (EDA), which results in skin abnormalities and absence of some glandular tissues like submandibular, preputial and meibomian glands. Tabby mice show different ocular surface changes like corneal epithelial defects, keratitis, corneal ulceration, neovascularisation, keratinisation, blepharitis, and conjunctivitis. Most of these changes seem to be not due to meibomian gland aplasia but are primary signs of EDA. Nevertheless this is still an interesting model to examine aspects of meibomian gland dysfunction. A transgenic mouse model presenting meibomian gland atrophy is the APOC1 mouse model. Beside altered lipid metabolism, the APOC1 mice show skin abnormalities and atrophic sebaceous and meibomian glands. Extensive crusts around the eyes and pruritus, often causing self-inflicted wounds, were observed in these mice, maybe due to ocular surface inflammation caused by altered meibomian gland function. Together with other new mouse models with meibomian

Table 2. Animal models of qualitative (evaporative dry eye) and combined tear film deficiency

Model	Pathomechanism	Reduced tear secretion + to +++ (test used)	Ocular surface signs
Mouse models			
X-linked anhidrotic ectodermal dysplasia (EDA) mouse model	Absence of meibomian glands	Not measured	Corneal epithelial defects, keratitis, corneal ulceration, neovascularisation, keratinisation, blepharitis, conjunctivitis
APOC1 transgenic mouse model	Meibomian gland atrophy	Not measured	Extensive crusts around the eyes, pruritus, self-inflicted periocular wounds
Controlled environment chamber model	Exposure to low humidity and constant airflow	++ (Phenol red thread test)	Corneal fluorescein staining ↑, goblet cell loss
Combined lacrimal gland insufficiency and evaporative dry eye model	Induction of lacrimal gland insufficiency by scopolamine application + desiccation by airflow	+++ (Cotton thread test)	Corneal epithelial permeability ↑, goblet cell density ↓, apoptosis of ocular surface cells ↑
Rat models			
Environmental stress model	Induction of reduced blink frequency and environmental stress by airflow + jogging board	+ (Phenol red thread test)	Significant increased corneal fluorescein staining
Rabbit models			
Desiccation short-term model	Mechanical prevention from blinking, e.g. by speculum	Not measured	Induction of dry spots and corneal fluorescein staining within hours
Meibomian gland dysfunction model	Closure of the meibomian orifices by cauterization	Tear secretion normal or elevated Tear film osmolarity ↑	Goblet cell density ↓, corneal epithelial glycogen levels ↓, inflammatory cells in the conjunctiva ↑
Tear film instability model	Exposure of the ocular surface with HOCl	Tear break-up time ↑	Slightly punctuate fluorescein staining

gland hypoplasia (Scd1$^{ab\text{-}j}$, Dgat1 mouse) and ductal ectasia (Hr, Odc mouse), these models may be useful for assessing new aspects of the pathophysiology of evaporative dry eye [2].

Environmental Stress

Environmental stresses are important factors in the development of dry eye. Even with normal tear secretion, exposure to a dry environment can result in dry eye symptoms. Several animal models have been developed to study the changes of the ocular surface under desiccating conditions (table 2).

Short-term models include the use of lid specula or sutures in rabbits to prevent blinking. This induces dry spots and fluorescein-positive staining of the corneal epithelium within hours [7]. These extreme conditions may be useful for evaluating the effects of artificial tears, but they are not suitable for studying the development of dry eye as a chronic process of inflammation.

Two model situations of a desiccating environment have been described which are capable of inducing signs of dry eye in animals. In these models animals were kept under conditions in which humidity, airflow and temperature are maintained at a level of choice and one model also uses stress as an additional factor for developing dry eye.

Barabino et al. [3] placed female BALB/c mice in a controlled environment chamber and exposed them to a low-humidity environment (18.5 ± 5.1%) and constant airflow (15 l/min) for up to 28 days. Under these conditions the mice developed a significant decrease of tear secretion within 3 days, increased corneal fluorescein staining and a loss of goblet cells in the superior and inferior conjunctiva as shown by light microscopy.

Nakamura et al. [30] established a long-term model of dry eye in the rat by using a combination of low-humidity airflow and a jogging board. The rats were kept in a low-humidity environment (25 ± 5%) and exposed to a continuous airflow (2–4 m/s). This resulted in a slight increase of blinking frequency but no significant difference of Schirmer score compared with the control group held under standard conditions. In addition, one group of animals was placed on a jogging board which forced them to run continuously for 7.5 h/day. This additional stress was found to be associated with a significant reduction of blinking frequency, Schirmer test and tear clearance, as well as increased punctate corneal epithelial staining compared with desiccating conditions only. This model therefore allows to assess the contribution of fatigue and reduction of blink frequency which is thought to be associated with mental and physical strain and the subsequent development of dry eye signs and symptoms in humans [5, 34].

Pharmaceutically-Induced Tear Film Instability

A rabbit model of tear film instability, mimicking the widespread problem among swimmers in chlorinated pools, was again introduced by Nakamura et al. [29]. In this model, the tear film was compromised by adding a 1 ppm solution of sodium hypochloric acid (HOCl) in tap water. The solution was loaded into a plastic chamber attached to the rabbit eye to immerse the ocular surface for an exposure time of 1 h. The procedure increased the tear break-up area as evaluated by image analysis (table 2). The tear break-up area took 6 h to return to a normal level with no further treatment but recovered dramatically when artificial tears were administered immediately after the bathing procedure.

This is an attractive short-term model, mimicking tear film instability after impairment of the tear film by irritating substances such as HOCl; it may be used to test the ability of artificial tears to stabilize the tear film on the ocular surface.

Combined Lacrimal Gland Insufficiency and Evaporative Dry Eye

In a model of CBA mice, the application of transdermal scopolamine patches to the mid-tail was used to reduce aqueous tear production and thus mimic lacrimal gland insufficiency. The desiccation was amplified by adding environmental stress using an air blower [6]. The treatment caused a significant decrease in cotton thread test wetting and tear clearance accompanied with an increased corneal epithelial permeability to fluorescein, conjunctival squamous metaplasia and a loss of goblet cells (table 2).

A modification of this model was used by Yeh et al. [41] using 129Sv/CD-1 mice to evaluate the effect of experimental dry eye on ocular surface apoptosis. The mice received subcutaneous injections of 1 mg scopolamine three times a day and were exposed to a continuous air draft for 10 h/day for 12 days in an environmentally controlled room (50% humidity, 18°C). This resulted in increased apoptosis of the central and peripheral corneal epithelium, bulbar and tarsal conjunctival epithelia, tarsal conjunctival stroma and lid margin as shown by TUNEL assay, immunostaining for caspase-3 and poly(ADP-ribose) phosphate (PARP), DNA nuclear staining and TEM.

The combination of lacrimal gland dysfunction and environmental stress makes these models attractive for studying the influence of environmental challenges on individuals with relative lacrimal insufficiency, a very common cause of dry eye symptoms. A disadvantage may be that this is a model of a relatively

acute disease due to the parasympathetic block and the additional airflow, which is in contrast to the dry eye situation in humans often caused by chronic inflammation.

Models of Severe Ocular Surface Damage

Surgical approaches are especially indicated in more extensive adnexal or ocular surface disease. Models exist for example for facial nerve palsy, neurotrophic keratopathy, total limbal stem cell failure or symblepharon formation.

Alkali burns are used frequently to induce severe ocular surface damage in combination with a severe inflammatory reaction. Several caustic agents including solid silver nitrate applicators or a sodium hydroxide solution (e.g. 0.2 M NaOH) have been described. While a solid agent induces a localised damage, a liquid results in more extensive damage to the entire surface. A metal cylinder can however be used to confine the damage, e.g. to the cornea or the conjunctiva alone. These agents have been used in severe ocular burns of mice, rats and rabbits in the assessment of pharmacological and surgical treatment modalities [43–45].

The species is usually determined by: (1) the required anatomical or physiological similarities with the human; (2) the kind of therapeutic intervention (e.g. medical or surgical) planed, and (3) the availability of appropriate methodology to assess the functional or histological parameters chosen as outcome measures (e.g. availability of specific immunoreactive agents).

As a new therapeutic modality for the treatment of dry eye after ocular burns, an automated system for the delivery of eyedrops was introduced by Kwon et al. [48]. In a rabbit model, microinfusion pumps were used to deliver eyedrops to the conjunctival fornix after severe alkali burns. Such systems were initially developed for insulin treatment of diabetes mellitus, but can also successfully be used to improve ocular surface lubrication with a flow rate between 0.6 and 1.2 μl/min which is equivalent to unstimulated tear flow in humans.

Ocular surface damage can also be induced by simple excision of corneal, limbal and/or conjunctival tissues [46, 47]. Inflammation is less dominant after this procedure compared to chemical burns, which allows to assess surgical methods of surface reconstruction in a situation similar to burned out clinical end-stage disease. In addition, these models avoid a long posttraumatic ‘induction phase’ required if surgical corrections of conjunctival or adnexal disease (e.g. cicatricial entropion) are to be studied.

Models of nerve palsies (e.g. lagophthalmos secondary to seventh nerve palsy or neurotrophic keratopathy) usually involve a surgical trauma to the

facial nerve or the trigeminal ganglion and rabbits and dogs have been used for this. Large mammal animals, such as dogs, are considered to be preferable to murine models, because in the latter the neural regenerative potential is known to exceed the human [42].

Conclusions

A huge variety of animal models is available to mimic the different pathophysiologic mechanisms of dry eye syndrome. To study autoimmune disease the mouse seems to be the most attractive model because of the diversity of different knockout and transgenic strains and good availability of antibodies. Several mouse models show lacrimal gland infiltration and different characteristics of primary or secondary Sjögren's syndrome, but of these models only the NOD- and the Id3-deficient mouse show decreased tear secretion. However, no obvious clinical signs of dry eye have been demonstrated in these models.

Rabbit or canine models are more suitable to study actually developing signs of dry eye and the progress of disease over time in humans. In these animals different models have been established which provide not only a decrease in tear secretion, but also ocular surface changes. In addition, these animals also have a longer lifespan, which is important if later phases of the disease are to be evaluated. They also provide better access to the ocular surface making clinical evaluation of signs of disease more reliable.

Further models exist to study specific other pathophysiological aspects of dry eye. Since the causes of dry eye are many and various, not one model but many are required to study the full range of mechanisms involved, and this also holds true for the assessment of new treatment modalities, especially if they address specific pathomechanisms.

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Prof. Dr. Gerd Geerling
Klinik für Augenheilkunde, Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11, DE-97080 Würzburg (Germany)
Tel. +49 931 2012 0612, Fax +49 931 2012 0490
E-Mail g.geerling@augenklinik.uni-wuerzburg.de

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Flow Chart on Surgical Approaches to Dry Eye

Gerd Geerling[a], *Horst Brewitt*[b]

[a]Department of Ophthalmology, University of Würzburg, Würzburg, Germany;
[b]Augenklinik der Medizinischen Hochschule Hannover, Hannover, Germany

Abstract

Introduction: Based on the type and severity of dry eye, we propose a structured approach to the surgical management of the disease. **Material and Methods:** The guidelines for assessing the form and grade of dry eye as recently suggested by the 'Dry Eye Workshop (DEWS)'. Flow chart on the surgical and medical management are presented. **Results and Conclusion:** Surgery should only be considered if any significant inflammation and concomitant adnexal disease has been controlled and medical management remains insufficient to control signs and symptoms of dry eye. The presence of signs of surface disease is considered mandatory. Although infrequent pre-existing occlusion of the lacrimal drainage system should be excluded, since this can also induce surface disease. The suggested sequence of treatment options makes use of less invasive procedures first while at the same time maximising efficacy and practicality. Often several measures have to be applied simultaneously to prevent loss of vision. Visual rehabilitation should only be attempted (e.g. by means of stem cell transplantation, keratoplasty). Once all concomittant factors have been addressed and measures to substitute the tear have been applied. In persisting aqueous deficiency osteoodontokeratoprosthesis remains the final option to improve visual function.

The first steps in making a decision about the form of treatment consist of establishing the type as well as the severity of dry eye. The guidelines for both steps have recently been updated by a Dry Eye Workshop [DEWS manuscripts: The Ocular Surface] under the guidance of the Tear Film and Ocular Surface Society (TFOS). Since subjective symptoms and objective signs often differ significantly and since the diagnostic tool kit for dry eye suffers from some limitations of sensitivity and specificity, and hence repeatability, we proceed with surgery only if in addition to discomfort significant objective signs of ocular surface disease, e.g. fluorescein or rose bengal-positive staining or adnexal disorders

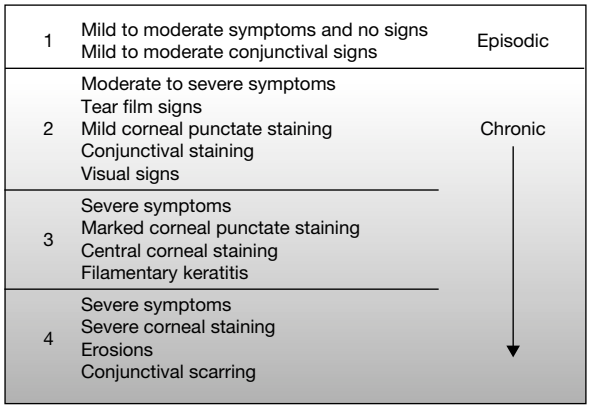

Fig. 1. Management of dry eye as recently suggested by the 'Dry Eye Workshop (DEWS)'.

such as lid margin malposition, lid retraction or exophthalmos are obvious. Although infrequent in this context, pre-existing occlusion of the lacrimal drainage system on the level of the nasolacrimal duct resulting in backwash of toxic cytokines should be excluded, since this can also induce surface disease.

The suggested sequence of treatment options is not obligatory, although it aims to use the less invasive procedures first while at the same time maximising efficacy and practicality (figs 1, 2). For example, punctal occlusion, especially if reversible, is more invasive than wearing scleral or limbal fit rigid contact lenses. However, it is also likely to be more practical for many patients.

Prior to any surgical attempt, inflammation of the ocular surface or adnexae should be controlled medically. Concomitant factors should also be excluded or – if present – treated first. Lid margin malposition (e.g. trichiasis, entropion, ectropion), lid retraction (e.g. due to thyroid disease or fornix shortening) and exophthalmos should be corrected. If the evaporative form of dry eye prevails, medical management including lid hygiene, topical anti-inflammatory and systemic antibiotic treatment is common first-line treatment and tear substitutes should be used only as additive therapy. On the contrary, in aqueous deficiency, tear substitutes and subsequent occlusion of the lacrimal drainage are the obvious methods of first choice. If together with these measures contact lenses fail to relieve symptoms and signs of dry eye disease, then more invasive procedures such as minor salivary gland transplantation should be attempted. Only in the most severe cases, with severe visual impairment and discomfort recalcitrant to any other means should major salivary gland transplantation or implantation of a dacryoreservoir be considered.

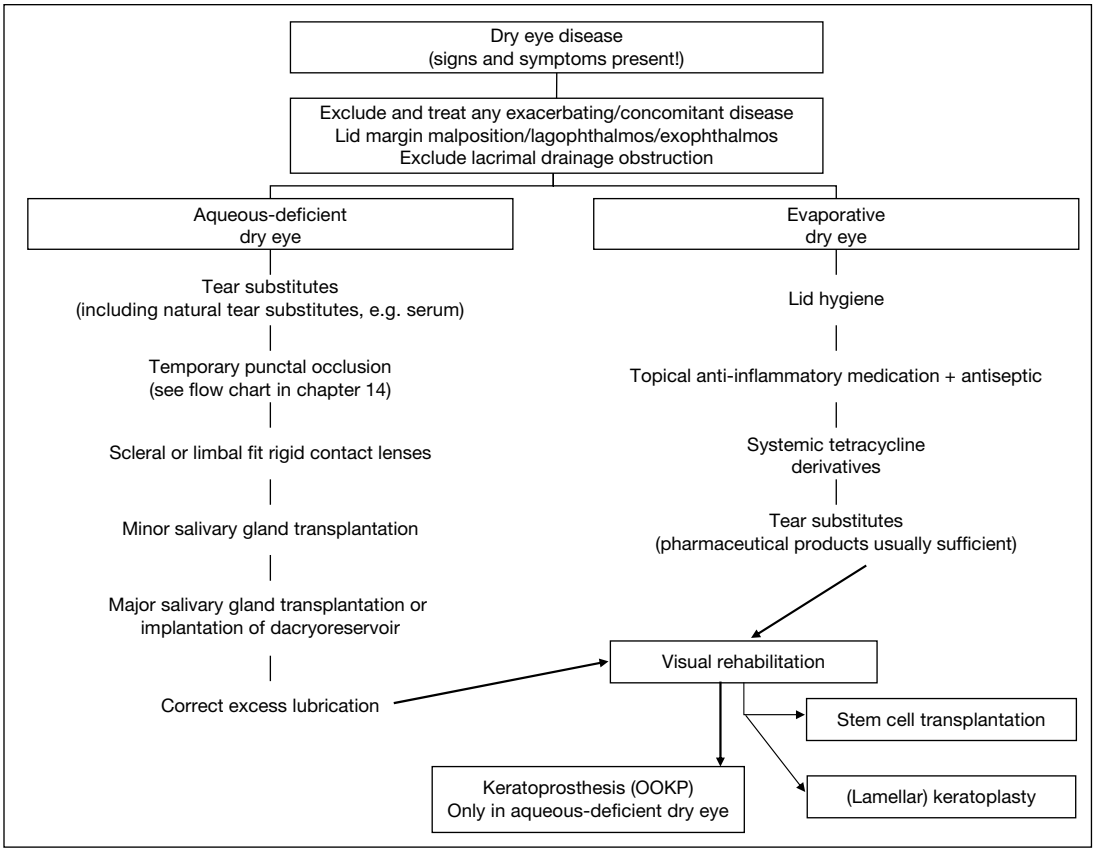

Fig. 2. Flow chart on the surgical management of aqueous-deficient and evaporative dry eye.

Combinations of both forms of dry eye disease exist and if present require combined treatment. If the disease is mild to moderate with no threat of acute visual loss it is appropriate to take a stepwise approach and establish which means are and which are not effective. In more advanced disease with either severe discomfort or danger of loosing vision, several measures should be applied simultaneously.

Visual rehabilitation should only be attempted once all concomitant factors have been addressed appropriately and the above medical and surgical methods for substitution of the tear film have been successfully used. In the evaporative dry eye, limbal stem cell transplantation and/or corneal grafting, preferably as a

lamellar anterior keratoplasty to reduce the risk of endothelial rejection, are options. In persisting aqueous deficiency, osteoodontokeratoprosthesis remains the ultimate ratio to improve visual function.

Prof. Dr. Gerd Geerling
Klinik für Augenheilkunde, Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 11, DE-97080 Würzburg (Germany)
Tel. +49 931 2012 0610, Fax +49 931 2012 0490
E-Mail g.geerling@augenklinik.uni-wuerzburg.de

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