with DED is based on the study of conjunctival impression cytology specimens, which provide information about the epithelium, but not of the full thickness conjunctiva. Therefore, the findings of Stern et al. [488] in conjunctival biopsy specimens from patients with either SSDE or NSDE are of great interest, particularly because there was no qualitative or quantitative difference in infiltrating cells and of activation markers between groups. A summary of inflammatory events in the conjunctiva of patients with both SSDE and NSDE is presented in Table 12.

Stern et al. demonstrated large numbers of infiltrating lymphocytes in both SSDE and NSDE specimens, which were mostly $CD4^+$T cells but included $CD8^+$ cells [488]. T cells were mainly in the anterior substantia propria and subepithelium and rarely in the epithelium. A small number of B cells were also present. Immunoreactivity for major histocompatibility complex (MHC) class II antigens indicated the expression of both HLA-DR (a ligand for the T-cell receptor) and HLA-DQ (an essential accessory molecule for antigen presentation), not only by lymphocytes, but also by conjunctival epithelial cells, indicating a possible role for them as non-professional APCs.

Additionally, ICAM-1 immunoreactivity was detected on vascular endothelial cells, infiltrating lymphocytes in the *substantia propria* and on resident epithelial cells. ICAM-1, as a cell surface adhesion molecule that facilitates lymphocyte homing and entry into target tissues, is of importance during inflammation [464,730]. Increased expression of LFA-1, the T cell ligand for ICAM-1, was also detected. It was noted that expression of ICAM-1 by resident epithelial cells encouraged cell contact between infiltrating lymphocytes and the epithelial cells, facilitating apoptotic epithelial cell damage and that expression of ICAM-1 by infiltrating lymphocytes could provide a signaling molecule for antigen presentation [731,732].

9.1.8. The meibomian glands in Sjögren syndrome

It is not known if the meibomian glands are an autoimmune target in Sjögren syndrome. In a study by Shimazaki et al., patients with Sjögren syndrome were found to have more severe ocular surface changes (as verified by vital staining) even when they had the same tear production (as verified by Schirmer's test) as age-matched NSDE [375]. Sjögren syndrome patients had a higher prevalence of MGD, a higher tear evaporation rate and more severe MGD, (57.9% in the Sjögren group vs. 18.5% in NSDE individuals). The combination of ADDE with MGD-associated EDE is considered to amplify the dry eye state [207].

A greater disturbance of meibomian gland architecture has also been observed by confocal microscopy in SSDE–related MGD than in NSDE, MGD and in healthy controls. Meibomian glands in Sjögren syndrome were reported to show more peri-glandular inflammation and higher acinar cell reflectivity compared to normal controls and MGD patients without Sjögren syndrome [733]. There were no differences between the meibomian glands in pSS and sSS. Signs of obstructive MGD were also similar in both pSS and sSS (SLE and rheumatoid arthritis) [1201].

The question arises as to why the prevalence and degree of MGD is higher in Sjögren syndrome. One explanation could be that the meibomian glands are a primary autoimmune target in this disease, although there is no evidence for this possibility. Alternatively, they could be influenced directly by inflammatory cells or cytokines arising locally in the conjunctiva or delivered to the conjunctival sac in the lacrimal secretion [426,687]. Another proposal is that, in severe disease, the loss of reflex sensory drive seen in the lacrimal gland may similarly affect the maintenance of meibomian gland secretion. A further explanation is the androgen deficiency in Sjögren syndrome (see TFOS DEWS II Sex, Gender and Hormones report [1222]).

9.1.9. The ocular surface in severe SS – squamous metaplasia

In advanced DED, including Sjögren syndrome, a process of squamous metaplasia can occur in which the moist epithelial mucosa is converted to an epidermalised, non-wettable tissue by a process of transdifferentiation. There is a modification of the epithelial glycocalyx, a loss of goblet cells and keratinization of the conjunctival and corneal epithelia, with the aberrant expression of cornified envelope precursor proteins, including the small proline-rich proteins (SPRRs), involucrin, late envelope proteins (LEPs) and filaggrin.

Squamous metaplasia is a response to chronic inflammation, with IL-1 β and IFNγ playing a key role in the process. The expression of the relevant genes precedes the squamous phenotype [478]. Both cytokines have been demonstrated in excess at the ocular surface in DED. IL-1β is a potent inducer of inflammation and stimulates the production of many proinflammatory cytokines at the ocular surface, including IL-6, IL-8, TNF-α, and interferons [453]. The levels of IL-1α, IL-1β and TNF-alpha are increased in the tears and conjunctiva in pSS and in animal models of DED [535,734,735] and there is a significant correlation between IL-1 β expression by human conjunctival epithelial cells and pathological keratinization of the ocular surface, using SPRR1B expression as a measure of squamous metaplasia [589].

The role IFN-γ in the process of squamous metaplasia has been studied. This cytokine is released at the ocular surface by infiltrating Th1 cells and NK cells. It can promote goblet cell loss, epithelial apoptosis and keratinization of the conjunctival epithelium in a DES mouse model of DED [478,530] and is an important contributor to squamous metaplasia in human DED [532]. It has been demonstrated to upregulate the expression of cornified envelope precursors in keratinocytes [736], corneal epithelial cells [737] and in conjunctival epithelial cells from patients with Sjögren syndrome [738,739].

Macrophages and T cells have been studied in mice and humans by McNamara's group. In a series of studies they examined the AIRE KO mouse (a Sjögren syndrome model) and human Sjögren syndrome biopsies of conjunctival tissue [580]. These studies have shown that homing of autoreactive $CD4^+$ T cells to the eyes of AIRE-deficient mice promotes both macrophage infiltration and the local release of IL-1 [453]. In adoptive transfer studies, it was shown that autoreactive $CD4^+$ T cells can initiate local inflammation at the ocular surface by activating IL-1R1 signaling in resident epithelial cells [453,589] which sustains inflammation through the local retention of the infiltrating T cells. Depletion of ocular surface macrophages by the subconjunctival injection of clodronate liposomes [580] decreases the signs of DED, such as lissamine green staining and epithelial SPRR expression, supporting their role in the development of ocular surface metaplasia. Similarly, depletion of APCs during the induction of DES blunted the DED phenotype [479].

IL-1β may also promote squamous metaplasia by inducing the expression of small proline rich proteins (SPRRs) which are minimally expressed in non-keratinized mucosal tissues but become overexpressed in response to stress or inflammation [453,478,740]. Li et al. [453] demonstrated the induction of SPRR by the addition of recombinant IL-1β to cultured human conjunctival epithelial cells, through activation of a p38 MAPK pathway, which appears to be a common intermediate of both the IL-1β and IFN-γ signaling cascades. SPRRs have been shown to trap conjunctival goblet cells during DES and also to be upregulated by IFN-gamma [427].

The importance of IL-1 in this process is supported in additional ways. Ocular surface staining and expression of SPRR1B are markedly reduced in AIRE KO mice lacking the IL-1 receptor (AIRE/IL-1R1 double knockout mice) [589] even though lymphocyte infiltration is not attenuated. Additionally, local inhibition of IL-1 signaling at the ocular surface in AIRE-deficient mice, by the topical application of the IL-1 receptor antagonist, anakinra, improved tear secretion,

Table 12
Inflammatory events in the conjunctiva in patients with aqueous-deficient dry eye disease.

Event	Technique Used				
	Flow cytometry	IHC or IF*	mRNA - impression cytology	Findings compared to controls	Type of dry eye disease
Metaplasia		SPRR1 β	SPRR1 β, SPRR2α, SPRR2γ	Increased	(Li et al., 2008, Kawasaki et al., 2003, Pflugfelder et al., 2015) SSDE [532,737,1175]
Inflammation			IL-1 α and β, IL-6, IL-8 IL-10, TNF-α, and TGF- β 1	Increased	Pisella et al., 2000, Jones et al., 1998, Jones et al., 1994) SSDE [471,1176,1177]
		MUC1		Decreased	
		IL-6		Increased	(Yoon et al., 2007) SSDE [466]
		IL-1β, TNF-α		Increased	(Zhang et al., 2016) NSDE [1178]
			IL-8,, Ephrin	Increased	(Narayanan et al., 2006) Moderate DED [1179]
			IL-1α, IL-6, IL-8, TNF-α and TGF-β1	Increased	(Pflugfelder et al., 1999) SSDE [1180]
Immune Activation			HLA-DR		(Kawasaki et al., 2003, Jones et al., 1994) SSDE [1175,1177]
	HLA-DR + cells	CD11c + HLA-DR+		Increased decreased after treatment	(Epstein et al., 2013, Baudouin et al., 2002, Baudouin et al., 2005, Brignole et al., 2000, Brignole et al., 2001, Sheppard et al., 2013, Pisella et al., 2000, Tsubota et al., 1999a, Tsubota et al., 1999b, Rolando et al., 2005, Kunert et al., 2000) SSDE and NSDE [471,1181–1190]
		HLA-DR		Increased	(Versura et al., 2011) NSDE [1191]
T Cell Response	CD4+CXCR3+ cells	CXCL9, −10, and −11, and CXCR3		Increased	(Yoon et al., 2010) SSDE and NSDE [1192]
	CD4+CCR5+ cells		CCR5	Increased	(Choi et al., 2012, Baudouin et al., 2005) SSDE and NSDE [468,1190]
		IFN-γ, IFN-γR, IL-13, IL-13R, MUC5AC		Increased IFN-γ and IFN-γ R; no change in IL-13 and its receptor, decreased MUC5AC	(Pflugfelder et al., 2015) SSDE [532]
			IL1β, IL-6, IL-23, IL-17, TNF-α, IFN-γ, MMP-9, TGF-β1, TGF-β2	Increased	Chotikavanich et al., 2009, de Paiva et al., 2009)SSDE and NSDE [316,456]
Immune Cell Trafficking	ICAM-1				(Pisella et al., 2000) SSDE [471] (Tsubota et al., 1999b, Tsubota et al., 1999a) DE [1186,1187]
			ICAM-1	Increased	(Jones et al., 1994) SSDE [1177] (Narayanan et al., 2006) NSDE [1179]
MMP Production		MMP-9	MMP-9	Increased	(Uchino et al., 2015, Chotikavanich et al., 2009, de Paiva et al., 2009, Gurdal et al., 2010) SSDE and NSDE [155,316,456,1193]
			MMP-9, Transglutamnase 2	Increased	(Aragona et al., 2015) SSDE [1194]
Oxidative Stress		HEL, 4NE		Increased	(Wakamatsu et al., 2013) SSDE [1195]
		Peroxidation markers		Increased	(Choi et al., 2016) NSDE [1196]
		ROS generation XO		Increased	(Cejkova et al., 2007) SSDE [1197]
		ROS scavenging SOD, Cat, GP		Decreased	(Cejkova et al., 2008) SSDE [1198]
ER stress			GPR78, sXBP1	Increased	(Coursey et al., 2016) SSDE [1199]
Other			hBD2	Increased	(Narayanan et al., 2003) NSDE [1200]
			hBD1, hBD3	No change	(Kawasaki et al., 2003) SSDE [1175]
			KLK7, CXCL9	Increased	(Kawasaki et al., 2003) SSDE [1175]
			Aquaporin 3; IFN-γR	Decreased	

Key: * = biopsy or impression cytology; IHC = Immunohistochemistry; IF = Immunofluorescence; Cat = Catalase; hBD = human defensins; GP = Glutathione Peroxidase; NSDE = non-Sjögren Syndrome dry eye; SSDE = Sjögren Syndrome dry eye; SOD = Superoxide Dismutase; SPRR = small proline-rich proteins; XO = Xanthine oxidoreductase/xanthine oxidase; SOD; KLK7 = Kallikrein 7; GPR78 = 78 kDa glucose-regulated protein; sXBP1 = spliced X-box-binding protein-1. See text for other abbreviations. For a detailed list of biomarkers reported in the tears in dry eye disease, please refer to the TFOS DEWS II Tear Film report [1223].

restored ocular surface integrity and reduced keratinization [741]. However, whether these findings can be translated to the treatment of humans remains to be shown. A recent clinical trial with a topical IL-1 receptor antagonist for the treatment of DED was not successful [1209].

9.2. Non-Sjögren Syndrome dry eye

NSDE includes congenital and acquired forms of DED without the systemic autoimmune features of Sjögren Syndrome. Conditions include age-related NSDE, congenital alacrima and familial dysautonomia [742].

9.2.1. Intrinsic lacrimal deficiency

9.2.1.1. Lacrimal gland ablation. DED may be caused by ablation of the lacrimal gland at any age, or by severance of the ducts during lid surgery. DED is not an inevitable outcome, since the accessory glands and conjunctival secretions may compensate in some cases [743].

9.2.1.2. Congenital alacrima. Congenital alacrima or lacrimal agenesis may occur as an inherited disorder [744] sometimes with agenesis of the salivary glands [745] and is a rare cause of DED in youth or infancy. Additional associations are with blepharophimosis [746], lacrimal-auriculo-dental-digital syndrome (LADD), Pierre-Robin sequence [747] and Allgrove syndrome (see below).

9.2.1.3. Triple A-syndrome. Triple A- or Allgrove syndrome, is a progressive, recessively inherited disorder, in which congenital alacrima is associated with achalasia of the cardia, Addisons disease, central neurodegeneration and autonomic dysfunction. It is caused by mutations in the AAAS gene, encoding the protein ALADIN [748–750].

9.2.2. Age-related Non-Sjögren Syndrome dry eye

The most common form of NSDE is age-related ADDE and corresponds to the term keratoconjunctivitis sicca (KCS) cited in the older literature (Lemp 1995). The clinical features resemble those of SSDE, but, in general, age of onset is later, the degree of lacrimal gland infiltration lower, the rate of progression slower and severe disease less common than in SSDE. Evidence for its increased frequency over the lifespan is presented in the TFOS DEWS II Epidemiology report [1226]. A steady increase in incidence of this form of ADDE is identified from around the age of 50 years.

Aging may be defined as the accumulated changes in structure and function that occur in a tissue or organism over its lifespan. Such changes may contribute to but be distinct from those events that are responsible for age-related disease [751]. According to Rocha et al. [751] theories of aging may be usefully classified as Programmed – involving genetic, hormonal and immunological influences and Damage- or Error–based, involving wear and tear, tissue oxidation and cross-linking, post-translational modification or the consequences of somatic mutation.

Of these factors, the role of hormones is addressed by the TFOS DEWS II Sex, Gender, and Hormone report [1222], while, in contrast to the situation for Sjögren syndrome, genetic susceptibility has received little attention. In a study of monozygotic and dizygotic female twin pairs, Vehof et al. found a hereditability of 29% (95% confidence interval [CI], 18%–40%) for DED symptoms and of 41% (95% CI, 26%–56%) for DED based on a physician's diagnosis and concurrent use of artificial tears. However this result derived from the use of a questionnaire, which did not identify the nature of the DED. Apart from this, there have been some small, candidate gene studies in NSDE patients which have reported a possible role for polymorphisms in proinflammatory cytokine genes [752], and in killer cell Ig-like receptor and human leukocyte antigen-C genes [753]. These results have not yet been replicated and a future search for genetic polymorphisms in age-related NSDE will be important to pursue.

9.2.2.1. Aging of the lacrimal gland. The potential contributions of tissue aging to this disorder have been reviewed by Rocha et al. [751], who point out that the reported fall in reflex Schirmer values over the life span [754–756] could be due to a failure of any of the elements that go to make up the lacrimal functional unit and therefore to any one of a combination of factors such as a loss of sensory drive from the ocular surface, a reduced delivery of secretory neururotransmitters, as well as the loss of functional secretory tissue. The Schirmer test measures the secretory response of the lacrimal gland to increased sensory drive and information about the influence of aging on lacrimal secretion in the absence of a sensory input from the cornea is not available. There would be some value to explore the effect of aging on the anesthetic Schirmer response or on lacrimal secretion as measured by fluorophotometry, in defined environmental conditions. Hamano et al. [757], inferred a loss of tear volume with age, based on results from the phenol red test.

Corneal sensitivity to mechanical [389,758–760] and chemical stimuli [389,760] falls with age, which could reduce the sensory drive to lacrimal secretion, but an age-related fall in thermal sensitivity (cold or hot) was not detected by Bourcier et al. [389], using the gas esthesiometer. On the other hand, numerous papers report that the regulated secretion of the lacrimal-derived proteins, lysozyme, lactoferrin and peroxidase fall with age [755,756,761–763] which would be in keeping with a loss of lacrimal gland function.

T cell lymphocytes are among the normal immune cell population of the human lacrimal gland (Table 1). From about the age of 40 years, the glands are increasingly infiltrated by $CD4^+$ and $CD8^+$ T-cells, which are considered to be the basis of a gradual destruction of lacrimal acinar and ductal tissue. Histopathologically, a low-grade dacryoadenitis occurs, associated with interacinar and periductal fibrosis, paraductal blood vessel loss and acinar cell atrophy [764–766]. A marked leukocytic infiltration of the human lacrimal gland in older individuals was also recorded by Kojima et al. [767] It has been suggested that the acinar atrophy is secondary to duct obstruction, much as has been proposed for MGD. It is reasonable to suppose that infiltrating inflammatory cells, releasing cytokines and other mediators into the gland, contribute to the lacrimal tissue damage and that, at some point, the cumulative effects of this age-related, structural damage determines the onset of lacrimal secretory deficiency. Studies in MRL/lpr mice, a model for Sjögren syndrome, suggest that pro-inflammatory cytokines, such as IL-1β, released by lymphocytes infiltrating the lacrimal gland, can impair the release of neurotransmitters and inhibit agonist-mediated lacrimal gland secretion [768,769]. If this is relevant to SSDE in the human, it may be assumed that a similar mechanism could operate in age-related DED.

The potential role of viral infections in initiating a self-limiting inflammatory response in the human lacrimal gland and of the sex hormones in favouring a pro-inflammatory environment within the gland, are dealt with elsewhere in this and other reports.

One of the proposed mechanisms of glandular damage over the lifespan is oxidative stress, resulting from the production of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide, in the process of aerobic metabolism. Free radical production occurs in the course of mitochondrial electron transfer as part of the process of energy production. These ROS are normally removed by the scavenging machinery of the cell, by enzymes such as superoxide dismutase (SOD) and reducing agents such glutathione. Data from

experimental studies in mice show that increased mitochondrial superoxide production (as seen in the conditional, Tet-mev1 transgenic mouse) [770] or decreased superoxide scavenging, (as seen in the superoxide dismutase knockout mouse - SOD1$^{-/-}$) [767] cause lacrimal gland damage, associated with increased lipid peroxidation, oxidative DNA damage and inflammatory cell infiltration. This is accompanied by reduced tear volume and increased corneal staining, of greater severity in older animals. Intriguingly such changes do not occur in the salivary glands in the Tet-mev1 model [770]. It is not possible to say whether the corneal changes are a consequence of reduced lacrimal secretion, or to the direct effect of oxidative stress at the ocular surface, but such models suggest that oxidative stress could play a role in age-related DED. It is relevant that, in a comparison of human lacrimal tissue from young (17–48 year) versus old (76–87 year) cadavers, evidence of lipid peroxidation and of oxidative DNA damage was found in the older group [767]. Since activated, phagocytosing leukocytes are potent source of ROS [771] inflammatory cells, infiltrating either the lacrimal gland or conjunctiva, cannot be excluded as the source of this oxidative damage [772] or, of the lipid peroxides demonstrated in the tears of patients with age-related NSDE [773].

9.2.2.2. Aging of the conjunctiva. Giebel et al. showed an age-related expression of apoptosis-related genes such as casp-3, Bad, Bax and Bcl-2 in human conjunctival cells obtained by impression cytology [774]. Zhu et al. [775], using confocal microscopy, found an age-related decrease in structures interpreted as dendritic cells but no difference in conjunctival in either epithelial cell or goblet cell density. There was an increase in epithelial microcysts, which have been mooted by some to be the product of goblet cell degeneration [776]. Earlier, Kessing [97], using histology, had reported occlusion of goblet cells with retention of their contents, in older people and Abdel-Khalek et al. [777], observed the presence of hyaline bodies in the conjunctival epithelium in 25% of subjects over the age of 79 years. Overall, such reports suggest that the conjunctiva is relatively resistant to the of age.

9.2.2.3. The ocular surface in age-related NSDE. In age-related NSDE, a reduction in lacrimal secretion dominates the clinical picture and is the basis of tear hyperosmolarity. This results chiefly from loss of secretory lacrimal tissue, but a fall in corneal sensitivity to all sensory modalities, reported in both NSDE and SSDE may contribute to the reduced secretion based on a lack of sensory drive [389]. Conjunctival inflammation is a well-recognised aspect of NSDE, of lesser degree than encountered in SSDE. Its features are illustrated in Table 12. Marked conjunctival infiltration with CD4$^+$ T cells, expressing HLA-DR, has been reported [488] which likely orchestrates inflammatory events by the release of cytokines such as IFN-γ, that can promote goblet cell loss, induce apoptosis and stimulate keratinization of conjunctival epithelium [478] as well as increasing the numbers of IFN-γ secreting NK cells [522]. In addition, there is a decreased number of immunosuppressive T-regs and an increase of IL-17 producing T-cells which are involved in damage to the corneal and conjunctival epithelium. Th-1 and Th17 cells have been shown to infiltrate the ocular surface in a mouse model of DED [529]. Th17 cells secrete IL-17 as their signature cytokine, capable of up-regulating MMP-3 and MMP-9 mRNA in corneal epithelium. As has been indicated this cytokine may disrupt the integrity of the corneal barrier.

In keeping with these events, increased levels of inflammatory cytokines and chemokines are also detected in the tears of ADDE patients and these are discussed in detail in the TFOS DEWS II Tear Film report [1223]. Their likely source is the conjunctiva but an origin from the inflamed lacrimal gland is also a possibility. Massingale et al. [778], found a correlation between the concentration of tear cytokines and severity of DED. Increased concentrations of IL-6, IL-8, and TNF-α could amplify inflammation by recruiting activated immune cells to the ocular surface [458].

9.2.3. Inflammatory and other infiltrations of the lacrimal glands

9.2.3.1. Sarcoidosis. Sarcoidosis is a chronic systemic disorder of unknown origin with an estimated prevalence ranging from 1 to 40 cases per 100,000 population [779]. It is characterized by the presence of non-caseating granulomas in multiple organs with the lungs being involved most frequently. Other organs include the spleen, liver, lymph nodes and skin, and the salivary and lacrimal glands [780,781]. Patients with lacrimal gland involvement (up to 63% of the cases) typically show significant enlargement of the gland [782]. The occurrence of DED secondary to sarcoidosis is very common and is consequent to lacrimal gland inflammation [782,783]. Scattered lymphocytic infiltrates are frequent, but, in contrast to those of Sjögren syndrome, do not form foci [784,785]. Elevated levels of circulating proinflammatory cytokines (TNF-α) are also found [786,787].

9.2.3.2. Lymphoma. Infiltration of the lacrimal gland by lymphomatous cells may cause DED [788].

9.2.3.3. Viral infection

9.2.3.3.1. Hepatitis C. In a study of 321 patients infected with hepatitis C virus (HCV), sicca symptoms (eyes and/or mouth) were noted in 10% of the cases [789]. Several studies showed that patients with chronic HCV infection present extrahepatic manifestations that may mimic the clinical, immunologic and histologic manifestation of primary Sjögren syndrome [790] and in a study of 1020 HCV patients, nearly half the cases (47.5%) had Sjögren syndrome [791].

9.2.3.3.2. HIV – AIDS. DED is also a common finding in patients infected with human immunodeficiency virus (HIV) with its prevalence estimated at 38.8% [34,792,793]. In AIDS-related DED, unlike the situation in SSDE, there is an infiltration of the lacrimal gland with predominantly CD8$^+$ suppressor cells, rather than CD4$^+$, helper cells [794].

9.2.3.4. Radiation injury. DED may be a complication of radiotherapy for benign and malignant conditions of the orbit [795], or of the head and neck, if the periorbital area is included within the treatment field. Several human studies have reported that the development of DED is dose-dependent [345,795–798]. In summary, published data suggest that doses >57 Gy are predictive of certain DED whereas those <30 Gy are less likely to cause it [795]. Onset of DED symptoms is delayed after exposure, from 4 to 11 years at doses <30 Gy, or between 9 and 10 months after treatment at high doses [795].

The most frequent ophthalmic findings in response to radiation exposure in humans are external eye disorders [799]. As shown in studies of children after the Chernobyl disaster, these findings include decreased lacrimation, and acute and chronic blepharoconjunctivitis [799]. Those children who lived closest to the source of radiation had the greatest degree of aqueous tear deficiency.

In animal studies, there are fewer reports of the effects of radiation on the lacrimal gland than on the salivary gland [800–803]. One study reported the effect of a single dose of radiation (15 Gy) on rabbit lacrimal glands, 3 and 30 days post treatment [801]. In three other studies the effects of single doses of radiation, 2.5–20 Gy, on the lacrimal gland and other ocular adnexa, were studied in monkeys [802], 24–48 h [802,803] or up to 112 days [800] post-treatment. A common finding in all these studies was the rapid (24 h) apoptotic loss of acinar and myoepithelial cells. In contrast, ductal cells were either unaffected, at low dose, or were

dilated at higher doses and at later time points. Also, at 24 h following radiation treatment, the tissue was infiltrated with neutrophils, which were gradually replaced by mononuclear cells and macrophages. Other reported changes were secretory retention in acini, vacuole formation, extracellular edema and thickening of the basement membrane. One study showed redistribution of the tenascin-C matrix. The severity of the lacrimal gland lesions was dose-related and diminished with time, but the tissues did not recover completely in the longer term. The authors hypothesized that this is probably due to the death of the acinar progenitor or stem cells.

One finding from the study by Stephens et al. [802], was that radiation treatment (24–48 h) did not affect other ocular adnexae, namely the meibomian glands and conjunctival goblet cells. The authors hypothesized that "acute loss of lacrimal gland serous acini and the resulting reduction of tears is alone sufficient to cause DED and could predispose to the development of secondary changes in the other glands of the eyelids". This hypothesis needs to be tested to establish if this animal model could be a quantifiable model for ADDE.

9.2.4. Lacrimal gland obstruction

9.2.4.1. Cicatricial conjunctivitis. DED can be a serious outcome in those diseases causing extensive conjunctival scarring, such as chronic graft-versus-host disease (GVHD), Syndrome (SJS)/toxic epidermal necrosis (TEN), mucous membrane pemphigoid and trachoma and also after physical and chemical injury. The DED is of mixed phenotype, due to the combined involvement of the lacrimal and meibomian glands and to ocular surface changes affecting its wettability and secretory capacity. Tear distribution may also be affected. As a consequence, clinical severity is often high and ocular surface inflammation due to DED is compounded by inflammatory events that are part of the primary disorder. At their worst, such conditions may lead to corneal opacification, perforation and blindness. In one UK report of cicatrizing conjunctivitis, OcMMP accounted for 61% of new cases in a single year, SJS/TEN for 20% and other causes for 20% [804]. Some causes of cicatricial conjunctivitis are discussed below.

9.2.4.2. Ocular graft-versus-host disease

9.2.4.2.1. Introduction. Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective treatment for hematological malignancies. However, success is hampered by chronic GVHD (cGVHD), which can cause death or significant morbidity with a severely diminished quality of life [805]. DED is a major late complication [806–810] and has attracted worldwide attention [806,811–814]. Ocular cGVHD occurs in 40–80% of recipients and presents several months after the date of HSCT. The associated DED is an immune-mediated, inflammatory disorder [489,815].

Reported risk factors for cGVHD include: the presence of peripheral blood mononuclear cells among stem cell sources [816], female to male transplantion [817,818], Epstein-Barr virus in the donor, and previous, acute skin GVHD [818], repeated allo-HSCTs and diabetes mellitus. The occurrence of cGVHD in multiple organs may amplify the severity of ocular GVHD [819].

Chronic GVHD is considered to be a later phase of the acute GVHD reaction, due to host tissue recognition (allo-recognition) by donor T cells, but there may also be an autoimmune element. Accelerated, immune-mediated fibrosis leads to functional changes in the lacrimal gland, cornea, conjunctiva and lid, as well as in additional organs. The main histologic feature of cGVHD-related DED is widespread tissue atrophy and fibrosis, with lymphocytic infiltration. Immune-mediated fibrosis leads to both lacrimal gland duct obstruction [815,820–824] and obstruction of the meibomian gland ducts [825]. Donor-derived fibroblasts may be involved in this process [815,822] and epithelial mesenchymal transition (EMT) [821].

As mentioned earlier, EMT is a process whereby epithelial cells are converted into multipotent mesenchymal stem cells that can differentitate into a variety of cell types. In cGVHD-related DED, cross-reactions between the donor and recipient immune cells generates a "cytokine storm", which compromises the mucosal barriers on the ocular surface and may trigger EMT at various sites. In the lacrimal gland, under the influence of local T cells, EMT affecting myoepithelial cells is considered to cause severe fibrosis, resulting in gland loss and lacrimal duct obstruction [821]. EMT in the conjunctival epithelium may disturb wettability by affecting microvilli and the expression of glycocalyx mucins [826]. The ocular features of GVHD are complex and involve an interaction between the lacrimal and meibomian glands and the ocular surface. Manifestations observed using OCT, include abnormal meibomian gland orifices, conjunctival keratinization and chemosis, and corneal epithelial opacification, thinning and sloughing [827].

9.2.4.2.2. Involvement of the lacrimal gland. Various events lead to lacrimal gland inflammation and tissue damage in cGVHD. Activated $CD4^+$ and $CD8^+$ T cells, present mainly in periductal areas, colocalise with the full complement of surface molecules necessary for antigen presentation, viz. periductal fibroblasts expressing $CD34^+$ and HLA-DR and adhesion molecules such as $CD54^+$, and costimulatory molecules such as $CD40^+$, $CD80^+$, and $CD86^+$ (Fig. 11) [823,828]. Macrophages within affected glands in cGVHD have been incriminated as a source of cytokines and chemokines and of increased of oxidative stress, contributing to the cicatirizing lacrimal gland disease.

The tissue renin-angiotensin system (RAS) present in the lacrimal gland may contribute to lacrimal gland inflammation in cGVHD [820]. In a murine model, the frequency of $CD45^+$ inflammatory cells and $HSP47^+$ fibroblasts and the expression of fibrogenic molecules, increases in the cGVHD-affected lacrimal gland and is decreased by an AT1R antagonist [829], suggesting that tissue RAS is linked to the inflammatory and fibrotic cascade.

9.2.4.2.3. Involvement of meibomian gland. Periglandular meibomian gland changes have been observed in GVHD using confocal microscopy and infrared meibography. Inflammatory cell infiltration, fibrosis and obstruction of meibomian ducts have been reported which are more diffuse than those reported in MGD [825]. Early detection and monitoring of ocular GVHD changes will be feasible using this technique [830].

9.2.4.2.4. Conjunctival involvement. The conjunctiva is a recognised target in ocular cGVHD [821,831] and inflammatory cell infiltration together with conjunctival keratinization [824] and scarring are significant features [832], accompanied by local elevation of CXCL9 and CXCL10 chemokines and their C-X-C motif receptor 3 in GVHD-related DED [833].

9.2.4.2.5. Corneal involvement. Jabs et al. reported that corneal epithelial thinning and keratinization were the major features of GVHD [824]. Keratinization of the conjunctiva and cornea were attributed either to a primary manifestation of the GVHD or as secondary to the DED state, but it was also suggested that corneal epithelial thinning might be related to chemotherapy preceding transplantation. The GVHD cornea may show severe epithelial damage and the occurrence of early tear film breakup may add to the visual disability. Corneal perforation may occur occasionally and $CD8^+$ T cells [834] and macrophages have been shown to infiltrate the perforation margin. MMPs, such as MMP-2 and MMP-9, have also been detected and are assumed to be responsible for tissue loss [835].

9.2.4.2.6. Findings in the tears. Changes in the tears in GVHD either reflect or contribute to inflammation at the ocular surface. Tear turnover is reduced and the tear film lipid layer, observed by DR-1 interferometry, can be severely disturbed [836]. In one study,

tear osmolarity was raised (314.0 ± 22.1 mOsm/L) and inversely correlated with the TBUT and Schirmer test results [837]. INF-γ is reported to be elevated in the tears in the early phase of ocular GVHD and IL-6 in a later phase [838] while another study showed that IL-6, IL-10, and TNF-α elevation are strongly correlated with ocular findings [839]. In another study, soluble TNF receptor 1 expression was upregulated [840]. Tibrewal et al. [245], reported an increase in eDNA and NET formation in GVHD in common with other forms of DED.

9.2.4.2.7. Preclinical models of ocular GVHD. The pathophysiology of cGVHD has been studied in a number of animal models [489,815,841,842]. Herretes et al. [489] developed a mouse model of ocular GVHD in which donor T cells were recruited to the eyes of the recipients of MHC-matched, allogeneic hematopoietic stem cell transplants. In this model, MHC-matched (H2b) C3H.SW mice were lethally irradiated and several hours later received donor B6 BMCs replete with B6 T cells. Several weeks post HSCT, animals receiving donor T cells lost weight and began to exhibit clinical signs of murine GVHD including ruffled fur, hunching, and diarrhea. Approximately 3–4 weeks following transplantation, increased fluorescein staining was observed in the corneas of recipient mice, which progressed to corneal ulceration by about 6 weeks. There was a difference in the tempo of induction of systemic and ocular GVHD. In another model, using an MHC-matched, minor histocompatibility mismatched, HSCT, donor fibroblasts derived from mesenchymal stem or stromal cells were shown to contribute to the pathogenesis of immune-mediated fibrosis [815]. Such models offer an opportunity to explore the underlying mechanisms of ocular GVHD.

9.2.4.3. Stevens-Johnson syndrome/toxic epidermal necrosis. SJS/TEN is a life-threatening, dermatobullous disease that affects the skin and mucous membranes, including the cornea and conjunctiva [843]. Other targets include respiratory, gastrointestinal, hepatic, oral, otorhinolaryngologic, renal and genitourinary systems [844]. The condition involves widespread keratinocyte death and epidermal necrosis, leading to splitting of sub-epithelial layers and epithelial detachment at skin sites and mucosal surfaces. Diagnostically, SJS is distinguished from TEN by skin detachment affecting less than 10% of the body surface compared to a loss of over 30% in TEN. An overlap SJS/TEN syndrome is defined by a loss of 10–30% of skin [845]. SJS affects children and adolescents whereas TEN may occur at any age. The estimated incidence of SJS is approximately 0.4–7 cases per million.

SJS/TEN must be distinguished from another bullous skin disorder, erythema multiforme, which runs a shorter course with limited mucosal involvement. It is triggered by infection, usually HSV, as opposed to drugs and other chemical and physical factors, which is more characteristic of SJS/TEN [846].

Antibiotics [847] are a common cause of SJS, in addition to analgesics, cough and cold medications, NSAIDS and anti-epileptics [848] and drugs used in the treatment of gout [849–851]. Doxycycline- and acetazolamide-sensitive cases have also been reported [852,853]. The use of antiretroviral treatment for HIV infection has been a cause of SJS in sub-Saharan Africa [854,855]. Other etiologies include physical agents such as sun exposure and radiation therapy [846]. It may also be idiopathic.

The occurrence of SJS/TEN shows a genetic susceptibility, which is related to ethnic group and may show drug specificity. HLA-B*1502 is associated with carbamazepine-induced SJS in people of Han Chinese descent [856] and IKZF1 has been identified as a susceptibility gene for cold medicine-related SJS/TEN with severe mucosal involvement, in Japan, Korea, Brasil and India [850]. HLA-A*02:06 and HLA-B*44:03C appear to increase the risk of severe mucosal involvement in the Japanese.

Kinoshita and colleagues have proposed that susceptibility to the ocular complications of SJS/TEN is related to an imbalance of mechanisms controlling innate immunity at the ocular surface. This may determine colonization of the ocular surface by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Staphylococcus epidermidis* (MRSE) after the onset of disease, or be responsible for severe ocular manifestations in TEN [857,858]. Ueta et al. [857], reported a significant role for interactions of HLA-A and the Toll-like receptor 3 (TLR3) gene in the onset of ocular complications and in addition, an interaction between TLR3 and prostaglandin E receptor 3 (PTGER3) [859]. These authors [859] have also reported gene polymorphisms that influence innate immunity. Sotozono et al. [858], emphasized the importance of NSAIDS and cold medicines in the etiology of SJS/TEN.

Acute SJS/TEN is generally considered to be a T-cell mediated type IV hypersensitivity disorder and there is strong support for the role of cytotoxic T cells in its pathogenesis [846]. In the early stages of TEN, $CD8^+$ lymphocytes predominate in the blister fluid and epidermis, many expressing surface markers normally found on NK cells, while $CD4^+$ lymphocytes are localized to the dermal layers [860]. Later, there is an increase in activated monocytes. Keratinocyte cell death occurs by apoptosis [846,861] either by a FAS/FAS-ligand process or by the delivery of granzyme B to target cells by activated T cells, through perforin-induced channels. Either mechanism activates the intracellular caspase cascade, leading to apoptotic cell death [862].

The acute stage of the ocular disease is characterized by the onset of a membranous keratoconjunctivitis. In the chronic stage of the disease, most patients have conjunctival inflammation, symblepharon, entropion, trichiasis, limbal stem cell deficiency and corneal conunctivalization and neovasculization [863]. There is a close relationship between corneal epithelial stem cell loss and the degree of visual impairment [864].

Various changes have been recorded in the tears of patients with SJS/TEN and IL-17 is elevated, as in other cicatrizing forms of severe DED [865]. A fall in level of two lacrimal-derived proteins, lactoferrin and epidermal growth factor (EGF), is thought to contribute to ocular surface damage [866]. MMP-8, MMP-9 and MPO were elevated in SJS and the MMP to tissue inhibitor of metalloproteinase ratio was high, suggesting a potential contribution to corneal melting [149].

DED is often of extreme severity in SJS/TEN, with a total absence of tear production. In this case the relapsing inflammation induces squamous metaplasia and keratinization of the entire conjunctival epithelium, with decreased goblet cell density [867]. This is associated with epithelial hyperproliferation and expression of transglutaminase I [868–870], and filaggrin [871].

9.2.4.4. Mucous membrane pemphigoid and ocular cicatricial pemphigoid. Mucous membrane pemphigoid is a chronic progressive autoimmune, blistering disease, affecting mucous membranes at multiple sites and occasionally the skin. It affects women more than men (F:M 2:1) [872] and usually presents in the later decades of life (≥60 years) although it may occur as early as the first decade.

Mucous membrane pemphigoid most frequently involves the oral mucosa (85% of patients) and conjunctiva (65%), and less, the nasal mucosa (20–40%), skin (25–30%), anogenital area/or pharynx (20%), larynx (5–15%), and esophagus (5–15%) [873–875]. Conjunctival involvement is referred to as OCP. Episodes of inflammation and epithelial separation are followed by fibrosis, which may cause life-threatening strictures in the larynx or esophagus or, in the case of the eye, may lead to blindness. Severity, and the number of mucosal sites affected, varies, and the oral form may occur in isolation. In a UK survey, ocular mucous membrane pemphigoid (implying OCP) accounted for 61% of newly diagnosed

cases of cictatricial conjunctivitis, with an estimated incidence of 0.8 per million population [804]. An incidence of 1.3–2.0 was reported in France and Germany [876,877].

Genetic susceptibility for OCP is suggested by associations with HLA B12, HLA A3, HLA-DR4, and HLA-DQB1*0301 [878,879]. Also, associations with rheumatoid arthritis [880] and Wegener's granulomatosis [881] have been reported. The disease may be triggered or exacerbated by surgery [882] and MMP is occasionally reported as a reaction to drug exposure.

The pathogenesis of MMP involves a loss of immune tolerance to components of the epithelial basal lamina and an antibody-induced, complement-mediated reaction, leading to epithelial detachment [873]. Epithelial separation may result from the cytotoxic effects of inflammatory mediators or from the release of lysosomal proteases [883]. TGF-β may play a role in the scarring process [884].

Serum autoantibodies have been detected against: bullous pemphigoid antigens (BPAg) 1 and 2. Integrin subunits α6/β4, laminin-5, laminin-6, and collagen type I. BPAg2 and α 6/β 4 integrins are transmembrane proteins linked by laminin 5 to the epithelial anchoring fibrils, composed of type VII collagen. These elements are important to epithelial attachment. Diagnosis of mucous membrane pemphigoid or OCP is based on the clinical picture and the demonstration, by direct immunofluorescence microscopy, of linear deposits of IgG and/or IgA and/or C3 in the basal lamina, in a perilesional biopsy.

The presence of $CD4^+$ T cells and B cells within conjunctival infiltrates suggests the involvement of cellular immunity in OCP [884,885,886], with Th17 lymphocytes playing a prominent role [887]. Langerhans cells expressing costimulatory molecules for T-cell activation ($CD86^+$) have been demonstrated [888,889] and connective tissue mast cells are regarded as key players in the fibrotic process [890]. $CD14^+$ cells among $CD45^+$ cells are also found in OCP conjunctiva [891].

Additionally, increased expression of macrophage-colony stimulating factor, collagen binding heat shock protein 47, TGF-β1and IL-4 are considered to enhance both conjunctival inflammation and scarring in OCP [892–895]. In keeping with other ocular surface inflammatory disorders an increase in levels of MMP-8, MMP-9, MPO has been demonstrated in the tears of OCP patients [149,896], together with IL-8 [896].

The clinical features of OCP include a progressive subepithelial fibrosis, fornix foreshortening, symblepharon, ankyloblepharon, meibomian duct obstruction and DED. Additionally, entropion, trichiasis, and corneal neovascularization and scarring occur. The conjunctival fibrosis resembles that seen in cGVHD and SJS/TEN. It may be staged as: stage I - subepithelial fibrosis, stage II - fornix foreshortening, stage III - symblepharon- and, stage IV - ankyloblepharon and surface keratinization [897].

As in other affected mucosae, the initiating cause of OCP is a separation of the epithelium from the underlying stroma followed by subepithelial fibrosis [898]. Its clinical evolution is slow and diagnosis is delayed compared to that of SJS/TEN, with a median of 225 days elapsing from symptom onset, compared to 7 days for SJS/TEN [804]. Severity may be asymmetrical between the two eyes but the disease usually progresses to involve the palpebral and bulbar conjunctiva bilaterally [899]. The onset of DED is relatively late in the disease. As in other forms of cicatricial conjunctivitis, contributing factors include obstruction of lacrimal gland and meibomian gland ducts, conjunctival goblet cell loss [435], altered expression of epithelial glycocalyx mucins, epithelial keratinization and impaired tear film spreading.

9.2.4.5. Pemphigus. Pemphigus is a potentially fatal autoimmune blistering disease of the skin and mucous membranes, with an incidence of 0.1–0.5 patients per 100,000 population per year. It is rare in childhood [900]. It is due to the formation of pathogenic autoantibodies directed against desmosomal proteins concerned in intercellular adhesion. Pemphigus vulgaris (PV), the most common variant, is characterized by circulating IgG antibodies against desmoglein 3 (Dsg3) and, in about half the patients, Dsg1 [901,902].

The characteristic ocular finding in PV is conjunctivitis with hyperemia and mucoid discharge [900]. Conjunctival blisters, erosions, and symblepharon are rare, although conjunctival biopsies may demonstrate similar histopathologic and direct immunofluorescence findings to skin biopsies [903]. Although the ocular manifestations of pemphigus vulgaris may precede oral or skin lesions by several days to months, eye sequelae are generally milder than in OCP and the symptoms usually improve with the institution of systemic therapy. It may be that the self–limiting nature of the ocular changes in pemphigus, compared to OCP, relates to the absence of involvement of the basal lamina [1210].

9.2.4.6. Trachoma. Trachoma is a chronic, scarring keratoconjunctivitis initiated by recurrent infections with *Chlamydia trachomatis* in childhood. The scarring complications, which are a cause of blindness on a global scale, usually occur in adulthood and include corneal opacity resulting from tarsal and conjunctival scarring, limbal stem cell deficiency, and trichiasis. DED is part of the overall picture, resulting from lacrimal gland duct obstruction, goblet cell loss, a cicatrizing meibomian gland obstruction and lid malapposition [904]. In chronic disease, lid thickening is due to a fibrous subepithelial sheet adherent to the tarsal plate [905] whose quantification by *in vivo* confocal microscopy (IVCM) correlates well with histological findings [906]. A variable degree of meibomian gland atrophy was reported by Al-Rajhi [905]. No systematic study of the evolution of cicatricial lacrimal or meibomian gland changes appears to have been conducted.

9.2.4.7. Chemical injury. Accidental or deliberate chemical injury to the eyes, e.g., by exposure to acids and alkalis, are a major source of chronic, symptomatic, ocular disability including sight loss which may amount to blindness. It is the basis of considerable personal tragedy. When extensive, the effects of inflammation and tissue destruction may be compounded by DED, due to meibomian gland and ocular surface damage and obstruction of lacrimal secretion. Its numerical importance is indicated by a population-based study conducted in the United States, over a 2 year period, which recorded a mean of 15,865 new chemical burn cases per year, resulting in an incidence rate of 51.10 new cases per million per year [907]. Projecting this figure globally, a minimum of 357,710, burn accidents were predicted to occur per year, worldwide.

This is a major topic in its own right and will not be addressed in any detail by this Subcommittee other than to direct the reader to several excellent reviews of pathophysiology, classification and the influence of topographical extent and severity on prognosis [908–912]. Current approaches rely in particular on an assessment of the extent of limbal injury and the extent and depth of corneal injury [910,911]. Gupta et al. concluded that the subdivision of grade IV injury into a further 3 subdivisions, by Dua [910], was of predictive value compared to the Roper-Hall method [912]. Although there is general recognition that the DED following extensive chemical injury contributes to the poor prognosis, there has been little formal examination of its contribution [913]. The subject would benefit from a longitudinal, multicenter study.

9.3. Hyposecretory states due to failure of the lacrimal functional unit

This section deals with DED due to lacrimal hyposecretion as

opposed to that due to organic disease of the lacrimal gland. In the healthy eye, lacrimal secretion is under the control of the LFU with additional input from higher centres. Secretory output is therefore dependent on the integrity of the afferent and efferent limbs of the reflex arc. The influence of such reflex failure on conjunctival and meibomian secretion is uncertain. The contribution of LFU failure to DED is considered below.

9.3.1. Reflex afferent block

Tear production is under neural regulation and an alteration in the trigeminal inputs from the cornea can cause DED by blocking lacrimal protein, electrolyte and water secretion [13]. Corneal nerve terminals also exert a number of trophic functions, which support epithelial cell proliferation and/or migration [914–916] and possibly immune regulation. A loss of sensory drive can come about in several ways.

9.3.1.1. Topical anesthetic use. Bilateral topical proparacaine decreases blink rate by about 30% and tear secretion by 60–75% due to a lack of trigeminal, sensorineural stimulation [217]. The chronic use and abuse of topical anesthetics can induce permanent damage to the cornea leading to corneal opacity, melting and perforation [917]. It is assumed that DED contributes to these changes, due at least to the lack of tears and to reduced blinking, but additional factors are likely to be a loss of trophic nerve functions and direct toxicity.

9.3.1.2. Trigeminal nerve injury. Damage to the trigeminal nerve, through surgical or accidental injury may occur anywhere along its course, from the trigeminal nucleus, root or ganglion, its ophthalmic branch, and at the ocular surface. The severity of its effects on the eye, depend on the extent of the damage.

9.3.1.3. Refractive surgery. Complications due to a disruption of corneal sensory innervation are a feature of refractive surgery, such as photorefractive keratoplasty (PRK) and laser in situ keratomileusis (LASIK) [918], in part the result of reduced tear secretion [259,919], a fall in blink rate [259,920], loss of trophic support [921] and changes in tear composition and stability [922]. The clinical syndrome of pain, and of punctate keratitis on the flap has been called in the past, LASIK DED, and is still referred to as such. It occurs in up to 60% of patients in the first month after surgery, declining in severity over 6–12 months postoperatively [923,924]. Tear hyperosmolarity has been recorded by one observer [925]. Punctate keratitis on the flap, but sparing the region of the hinge, has supported a causal role for sensory denervation and neuropathic firing from damaged sensory endings – termed LASIK-Induced-Neuro-Epitheliopathy, or LINE, by Wilson [926]. Also, it is suggested, that NGF and other neuropeptides such as substance P or CGRP may be key factors in the syndrome [918]. The two etiologies are not mutually exclusive and it is likely that LASIK DED and LINE can occur together, in which case a clue to the presence of DED is punctate epitheliopathy in that it affects both the LASIK flap and the cornea/conjunctiva outside it, in a distribution typical of DED. Further information is contained in the TFOS DEWS II Iatrogenic Dry Eye, and the Pain and Sensation reports [1224, 1227].

9.3.1.4. Neurotrophic keratitis. Neurotrophic keratitis (NK) is a rare disease of the cornea caused by impairment of corneal sensory innervation. The disease is characterized by decreased or absent corneal sensitivity combined with more extensive anesthesia of the globe and including at least the upper lid and nasal mucosa. Neurotrophic keratitis ranges in severity from punctate epithelial keratitis, corneal opacity with superficial neovascularization, severe inflammation and epithelial loss, persistent epithelial defect, and intractable corneal ulceration, which may proceed to perforation [927]. Because the eye is insensitive, diagnosis may be delayed. Although numerous ocular and systemic diseases may cause neurotrophic keratitis, the most common cause is viral infection, particularly, herpes zoster keratoconjunctivitis and rarely, herpes simplex keratitis. It may also be caused by nerve compression. Nowadays it is a less common outcome following surgical intervention for trigeminal neuralgia.

When the ophthalmic division of the trigeminal nerve is affected by herpes zoster, affection of the nasociliary branch of the ophthalmic nerve, heralded by a zosteriform rash at the root of the nose, is recognised as a risk factor for Herpes Zoster Ophthalmicus (HZO) [928]. DED is an important feature. In a study of neurotrophic keratitis due to HZO, sensory loss affected the cornea, upper lid and brow on the affected side and also the nasal mucosa, as indicated by a loss of the nasolacrimal reflex [255]. A diffuse punctate keratitis and a marked fall in reflex tear production occurred, the latter attributed to a loss of secretomotor drive from both the ipsilateral cornea and nasal mucosa. A lesser fall in reflex tearing on the contralateral side and a lesser degree of corneal staining, was postulated to be due to a reduction in blink rate and to an effect of cross-innervation on tear production in the fellow eye [255]. It is relevant that, in those patients with HZO without neurotrophic keratitis the nasolacrimal reflex was intact.

A loss of trophic support is considered to be a feature of neurotrophic keratitis. Such trophic factors, which promote epithelial proliferation and differentiation and corneal healing [929] are expressed by the corneal nerves and in the epithelium and include Nerve Growth Factor (NGF), SP, CGRP, NPY and Insulin-like Growth Factor (IGF-1). They are discussed further in the TFOS DEWS II Pain and Sensation report [1224].

Clinically IGF-1 combined with a SP-derived peptide, has shown promise in the treatment of neurotrophic keratitis [930] and in another preliminary study, topical application of murine NGF was effective in healing the cornea and restoring corneal sensitivity in 12 patients with neurotrophic keratitis [931]. This was later confirmed in a larger group of patients with moderate to severe neurotrophic keratitis [932]. A clinical trial of a new human recombinant NGF (hrNGF) eye drop is now active in patients with moderate to severe neurotrophic keratitis both in Europe and in the USA.

9.3.1.5. Contact lens wear. Contact lens wearers may experience ocular discomfort, frequently interpreted as dryness, as well as variable degree of decreased corneal sensation. The subject is reviewed in the TFOS Workshop on Contact Lens Discomfort [933] and further comment will be found in the report of the TFOS DEWS II Iatrogenic Dry Eye report.

9.3.2. Secretomotor blockade

9.3.2.1. Parasympathetic damage. Damage to the parasympathetic innervation of the lacrimal gland may follow injury to the *nervus intermedius* during surgery for vestibular schwannomas in the cerebellopontine angle. An associated lagophthalmos due to injury of the seventh cranial nerve may compound the resulting DED [934]. DED has also been reported as a consequence of schwannomas affecting the greater superficial petrosal nerve or injury to the nerve at the time of their removal [935,936].

9.3.2.2. Pharmacological inhibition of lacrimal secretion. A large number of systemic medications have been reported as risk factors for DED, including antidepressants, anticholinergics, antipsychotics, antispasmotics and antihistamines as well as chemotherapeutics, antihypertensive, anti-arrhythmics, antithyroid agents, opioid analgesics [937,938]. These drugs are used to treat common

conditions in the elderly such as depression, Parkinson's disease and arthritis. Approximately 76% of Americans 60 years or older used two or more prescription drugs and 37% used five or more, between 2007 and 2008 [939]. Another study also showed that patients using decongestants, antihistamines, and vitamins have a higher incidence of DED [940]. In addition it may be assumed that reporting the prevalence of DED in clinical trials may be underestimated.

A full account of iatrogenic DED is provided in the TFOS DEWS II Iatrogenic Dry Eye report [1227].

9.3.2.3. Combined afferent and efferent blockade

9.3.2.3.1. Familial dysautonomia. Familial dysautonomia (Riley Day syndrome), is an autosomal recessive disorder due to mutations in a gene encoding an IκB kinase-associated protein [941]. Lacrimal dysfunction, DED and corneal damage are major features of the disorder, in which a generalized insensitivity to pain, present from birth, is accompanied by a marked lack of both emotional and reflex tearing. There is a progressive defect in the cervical sympathetic and parasympathetic innervation of the lacrimal gland and of the sensory innervation of the ocular surface, affecting both small myelinated (Aδ) and unmyelinated (C) trigeminal neurons.

9.4. Other disorders

9.4.1. Meige syndrome: blepharospasm and dry eye

Essential blepharospasm is a disease characterized by spontaneous, excessive, intermittent or constant, contraction of the periorbital muscles, mainly of *orbicularis oculi*, occurring without other neurological or ophthalmological cause [942]. In Meige syndrome the spasm extends to include other facial muscle, the tongue, the pharynx and the cervical muscles. The cause for the blepharospasm is not known but it may sometimes be drug-induced or associated with brain disease. There are several reports which indicate some relationship between blepharospasm and DED [943,944]. Also it is reported that 57% of DED resistant to treatment is associated with Meige syndrome [945]. In the past, oral psychotropic drugs or orbicular muscle resection have been applied effectively [942,946–948], but in recent years, local injection of Botulinum toxin is considered to be the most effective treatment [944,947,949].

9.4.2. Diabetes mellitus

Patients with diabetes complain of DED symptoms. There is evidence that tear film parameters are altered in patients with diabetes, with a reduction in tear breakup time and tear secretion [950]. DED signs and symptoms have also been found to correlate with degree of peripheral neuropathy and severity of diabetic retinopathy [951]. Factors thought to contribute to reduced tear production in diabetes include microvascular damage to the lacrimal gland from hyperglycemia, reduced lacrimal innervation from autonomic neuropathy, reduction in trophic support to lacrimal tissue, and reduced reflex tearing due to impairment of corneal sensitivity [951]. Reduction in tear film stability and TBUT is likely to be due to reduced mucin production by goblet cells. Goblet cell density is thought to be dependent on corneal innervation, and reductions in corneal innervation have been observed to reduce goblet cell function [952]. This is also implicated in post- LASIK DED [918]. (See also TFOS DEWS II Sex, Gender and Hormones report [1222]).

9.4.3. Pseudoexfoliation

Pseudoexfoliation (PEX) is a basal lamina disorder encountered increasingly with age, characterized by the accumulation of clumps of micro-fibrils on the surface of the lens capsule, ciliary body, iris, trabecular meshwork and conjunctiva [953,954]. In PEX patients, both Schirmer test and tear film breakup time were significantly lower compared to a control group [955]. The number of goblet cells per unit area of conjunctiva was no different than in controls, but on electron microscopy, typical pseudoexfoliation filaments were found in the stroma in PEX patients along with remarkable changes in mucin packaging and goblet cell morphology [956].

10. Evaporative dry eye

10.1. Introduction

As noted, all forms of DED are evaporative in the sense that tear and ocular surface hyperosmolarity can only arise in response to evaporation. Hyper-evaporative loss implies that the rate of evaporative loss per unit area of the ocular surface is above the normal range, measured in an individual blinking spontaneously in standard room conditions that do not impose DES.

According to the TFOS DEWS report [1], EDE comes about as a result of a loss of evaporative barrier function of the tears or due to reduced ocular surface wettability. This has led to a subclassification into lid-related EDE and ocular surface–related DED. The latter form of EDE represents a distinct entry point into the vicious circle whereby tear instability, leading to tear film breakup in the interblink interval (and an OPI <1), is the initiator of tear hyperosmolarity. The existence of hybrid forms of DED, which include an evaporative component, is discussed elsewhere in the report and is summarised in Table 13.

10.2. Lid-related evaporative dry eye (intrinsic EDE)

10.2.1. Age-related meibomian gland changes

There is general agreement that meibomian gland acini are lost with increasing age. Arita studied meibomian gland loss by non-contact infra-red meibography in 236 healthy volunteers between the ages of between 4 and 98 years [957]. Gland dropout was expressed as a combined meiboscore for the upper and lower lids of one eye. There were few meibomian gland changes in either males

Table 13
Hybrid subtypes of dry eye disease.

Subtype	Example
Organic ADDE due to lacrimal gland pathology, combined with an organic, MGD-dependent EDE	In Sjögren syndrome
A combination of an organic ADDE, MGD-dependent EDE and EDE secondary to ocular surface disease.	GVHD or to varying degrees, other forms of cicatrizing conjunctivitis. There is obstruction to the lacrimal gland ducts, cicatrizing MGD and ocular surface disease secondary to the primary systemic disease.
Organic ADDE with a functional EDE	In severe ADDE there is defective spreading of the TFLL and a predicted functional EDE
Organic EDE with a functional ADDE.	When DED is severe, there is a fall in corneal sensitivity. It is predicted that, in EDE, this leads to a loss of compensatory, sensory drive to the lacrimal gland, and a functional aqueous-deficient state.
ADDE evolving to EDE	When tear break up occurs within the blink interval, the cornea is subjected to excessive evaporation at the site of the breakup. Thus any ADDE of sufficient severity is predicted to be converted to an EDE. Tear proteins of lacrimal origin should be at a normal level.

or females younger than 20 years, after which there was a significant dropout with age, without a statistical difference between the sexes. Den et al. [958], reported that the meibomian gland dropout score became positive after 40 years of age and a similar observation was made by Mathers et al. [763], who observed in addition, an alteration in the expressibility of meibum in keeping with obstructive MGD.

Villani et al. [390], using OCT, showed an age-related decrease in number of acini and acinar diameter with age, together with increased secretion reflectivity and acinar wall changes, in a study of 100 asymptomatic subjects aged 20–83 years. Changes were similar in men and women and were not accompanied by changes in orifice size. They were most marked at 50 and 60 years of age, contrasting with the findings of Arita et al. [959], who observed dropout by meibography from the age of 20 years. Histopathological studies by Obata et al. [624], support the occurrence of acinar atrophy without acinar dilatation, distinct from the outcome of obstructive disease.

Such studies suggest that the loss of meibomian acini with age may on the one hand be caused by a primary, age-related, non-obstructive acinar atrophy and on the other by obstructive MGD. This is in keeping with the observations of Nien et al. [960], at the cellular level, of reduced meibocyte differentiation and cell cycling, together with reduced expression of the lipogenesis factor, peroxisome proliferator-activated receptor gamma (PPAR γ), in subjects over 50 years of age. Also, there are known, age-related changes in meibum polar and neutral lipid composition [627]. This article also reports that aging in men and women was also accompanied by a significant increase in eyelid erythema, telangiectasia, scurf, keratinization, irregular posterior margins, meibomian gland orifice metaplasia, and meibomian gland secretion opacity. Potentially, both simple atrophy and obstructive MGD could provide the basis for reduced delivery of meibum with aging.

10.2.2. The influence of sex hormones on meibomian gland function

Meibomian function is strongly influenced by the sex hormones, particularly androgens. In brief, androgens stimulate the synthesis and secretion of lipids by the meibomian gland and suppress the expression of genes related to keratinization [36,49,653,961,962]. Conversely a deficiency of androgen action, such as occurs in aging, Sjögren syndrome, antiandrogen treatment and complete androgen insensitivity syndrome, is associated with MGD, altered meibum lipid profiles and evidence of decreased tear film stability [36,622,623,628]. The influence of sex hormones and other hormones on meibomian gland function and disease is dealt with in full in the TFOS DEWS II Sex, Gender and Hormones report [1222].

10.2.3. Meibomian gland dysfunction

The term 'meibomian gland dysfunction' (MGD) was introduced by Korb and Henriquez in 1981 and has been used for many years to identify the most common etiology of EDE and to distinguish it from other meibomian gland diseases [963,964]. It is established in the literature and provides a convenient label for a well-characterized condition. It may be that in its earliest stages it takes the form of a functional disorder that impairs the delivery of meibomian oil to the lid margin but in the form that presents clinically, it is a disease state, which involves pathological modifications to the gland that may be irreversible. The term *obstructive* MGD was coined by Mathers [965]. An excellent review of the history and concept of MGD and its relationship to other forms of blepharitis was published by Blackie and Korb [184].

10.2.3.1. High meibum delivery state – meibomian seborrhea. MGD has been sub-classified into high oil delivery and low oil delivery states (Fig. 12). The prevalence of high delivery states has not been reported but it is likely to be uncommon. It is referred to as meibomian seborrhea [966] and is encountered in association with seborhoeic dermatitis and rosacea. Diagnosis has been based upon the manual expression of high volumes of meibum from affected glands and inference that it is a meibomian hypersecretory state is an assumption that awaits confirmation. It would be valuable to demonstrate, in patients designated as having meibomian seborrhea that the condition of high volume expressability persists over an extended period of time. At present there are no reliable methods to evaluate meibomian secretory rate but TFLL thickness was significantly increased in a group of patients with DED associated with hypersecretory MGD and lid margin inflammation [967]. A causal role for hypersecretory MGD and DED is not established.

10.2.3.2. Low meibum delivery states - obstructive meibomian gland dysfunction. MGD is the most common cause of low meibum delivery, chiefly due to obstructive disease. Obstructive MGD is the most common cause of EDE [37,180,968] and it is believed that MGD-dependent EDE is the most common form of DED overall [36,376,506,969,970,1066,1211,1212]. It was recently defined at the TFOS Workshop on MGD, as follows and further details may be found in that report [36,506,970]: *"meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease".*

MGD may be *primary* or *secondary*. Primary MGD appears spontaneously and has no known disease association. Its prevalence increases with age. Secondary MGD has such an association, for instance with eyelid laxity [971] and eyelid tattooing [544]. In particular, MGD may regularly accompany certain skin diseases such as rosacea, atopic and seborrheic dermatitis psoriasis and icthyosis [966,972] and may be induced by inflammatory disease of the lids and ocular surface and by chemical exposures, including topical benzalkonium chloride-containing topical medications for glaucoma. The manner in which MGD contributes to and is amplified by, DED, is reviewed by Baudouin et al. [385].

MGD exists in *cicatricial* and *non-cicatricial* forms [37].

10.2.3.2.1. Cicatricial MGD. In primary, cicatricial MGD, duct obstruction results from elongation, stretching and narrowing of the terminal ducts, so that each orifice and associated duct is dragged from its position anterior to the mucocutaneous junction, into the marginal conjunctival mucosa. As this occurs, the affected terminal duct comes to lie horizontally and is visible as a characteristic, elevated ridge in the occlusal mucosa of the free margin of the lid, which represents the dragged terminal ducts exposed under a thinned mucosal epithelium [37]. Primary, cicatricial MGD may affect scattered glands in the same lid exhibiting non-cicatricial MGD. It is probably less common than obstructive MGD but the frequency of its occurrence has not been documented.

Secondary, cicatricial MGD is caused by conjunctival scarring and occurs in cicatricial conjunctival diseases. It may also accompany rosacea and vernal kerato-conjunctivitis. The process is more extensive than in primary disease and the orifices and ducts are dragged into the tarsal mucosa, where, in severe cicatricial disease they may no longer be visible, as they are absorbed into the scar tissue. In both the primary and secondary forms of the disease, even at an early stage when the ducts are still patent, once the orifices have been dragged into the mucosa, and therefore into the region of the tear meniscus, the glands are unable to deliver their oil onto the surface of the tear film. With increasing severity the process leads to duct obstruction. Cicatricial MGD has not been studied histologically and would benefit from clinicopathological study directed

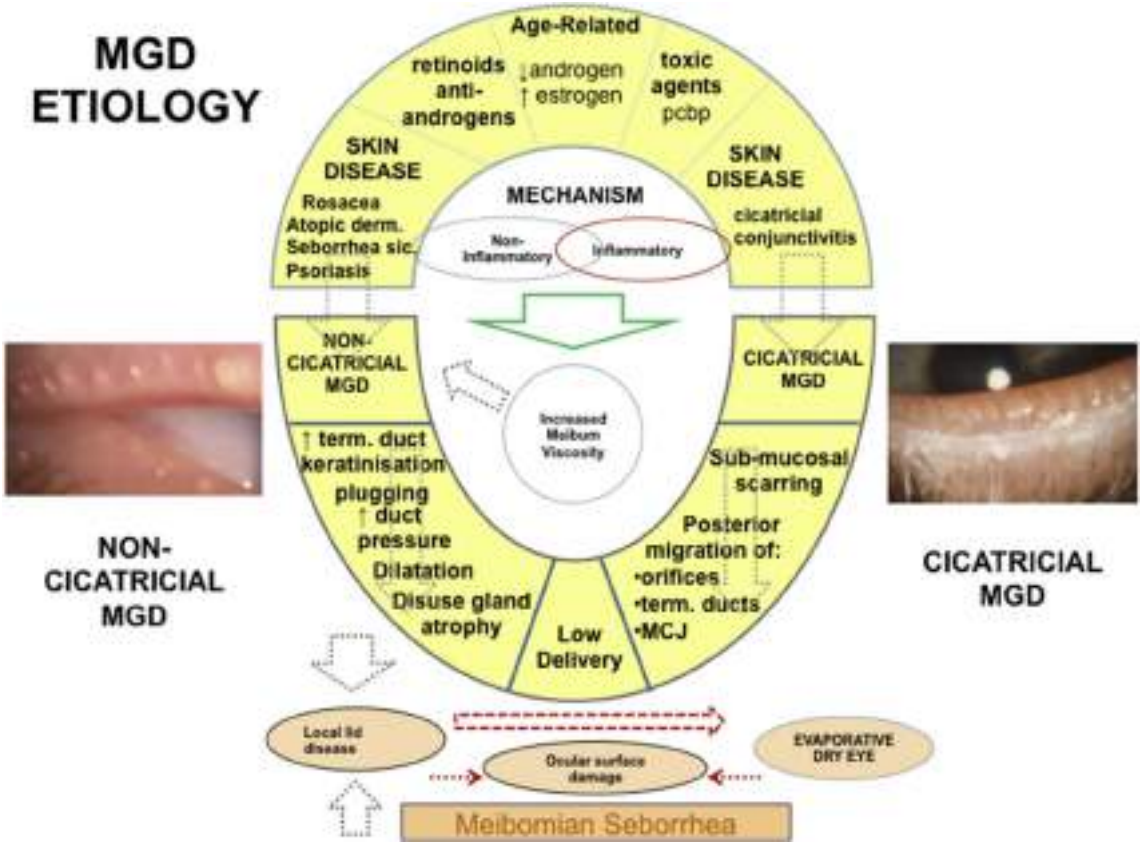

Fig. 12. A schematic diagram to show the etiology and mechanism of meibomian gland dysfunction (MGD). Although many mechanistic aspects are not yet understood, the figure attempts to summarize the current view. The upper part of the figure illustrates the etiology of the two forms of MGD which result in low delivery of meibomian oil; cicatricial and non-cicatricial MGD. With age, there is an increase in meibomian gland dropout, particularly after the age of 50 years, which correlates with the appearance of primary MGD. A fall in bioavailable androgens may contribute to these events. In youth, treatment of acne vulgaris with *cis*-retinoic acid may induce gland atrophy and MGD, while in an older age group, androgen receptor insensitivity or blockade may induce signs of MGD. Polychlorinated biphenyls may cause a systemic disorder which includes MGD-like features. Certain skin disorders are strongly associated with MGD. In general, acne rosacea, atopic dermatitis, seborrhea sicca and psoriasis are associated with non-cicatricial MGD, while cicatricial conjunctival diseases such as trachoma, erythema multiforme and pemphigoid, lead to cicatricial MGD. A key event in non-cicatricial MGD is hyperkeratinisation of the terminal duct, leading to duct obstruction, duct dilatation and disuse atrophy of the glands. Later, obliteration of the orifices may occur. Obstruction may be exacerbated by changes in oil composition which increase meibum viscosity. The degree to which inflammatory changes are found around affected glands varies in different reports, but signs of inflammation are common at the lid margin. Inflammatory mediators and lipids may be released onto the ocular surface to cause epithelial damage. In cicatricial MGD, submucosal conjunctival scarring drags the Meibomian orifices, terminal ducts and mucocutaneous junction posteriorly, across the posterior lid border and onto the tarsal plate, where the narrowed and displaced ducts can no longer deliver oil effectively to the tear film lipid layer. Low meibum delivery and changes in oil composition lead to tear film instability, increased evaporation and ultimately to evaporative dry eye (EDE). In low delivery MGD, symptoms may arise from the local lid disease itself, from lid disease with ocular surface damage and from EDE. In meibomian seborrhea, gland expression releases abundant quantities of meibum from the gland orifices, which has lead to the concept that this is a hypersecretory condition. There is less gland dropout than in obstructive MGD and there are distinctive changes in meibum composition.

specifically at orifices, ducts and glands. The Subcommittee recommends that this avenue should be pursued.

10.2.3.2.2. Non-cicatricial MGD. In non-cicatricial MGD, the terminal ducts are obstructed by a process of hyperkeratinisation [494,625] and the shedding of duct lining cells into the duct lumen to form keratotic plugs [36,39,973,974]. The hyperkeratinisation process may be linked to the significantly increased expression of keratin genes in meibomian glands of patients with MGD [505]. Further, it is likely that obstruction is compounded by an increase in meibomian lipid viscosity due to changes in meibomian lipid chemistry, and possibly interactions of lipids with cytokeratin proteins [183,975]. The relative contribution of cell debris and increased lipid viscosity to the obstructive process is not known.

The gland orifices remain located in the skin of the lid margin, initially anterior to the MCJ [37] although, with age they may come to lie behind it as the MCJ migrates forwards [454]. This has therapeutic implications, since, if gland function can be restored, the orifices remain in position for oil delivery. Obstruction is accompanied by a thickening and clouding of expressed meibum, which blocks the ducts and causes plugging of the orifices. Obstruction leads to secondary, disuse- or pressure-atrophy of the glands [494,976,977], which appears as gland 'dropout' on meibography [959]. Gland loss is similar between right and left eyes and correlated between the upper and lower lids. But there are regional differences, with less loss in the upper than lower lid [978,979] and greater losses nasally and temporally [979,980]. Dropout correlates positively with MGD grade and is inversely related to meibomian gland expressibility, TFLL thickness and TBUT [959,980–983]. In another report, dropout correlated positively with the OSDI symptom score and ocular surface staining [983]. Of interest, reduced expressibility, consistent with a diagnosis of MGD, may occur in the absence of meibographic dropout [980]. (see the TFOS DEWS II Tear Film report for further details).

Non-cicatricial MGD most commonly occurs as a primary disorder, seen with increasing frequency after the age of 50 years [626]. It also has multiple secondary associations, including dermatoses such as rosacea, seborrheic dermatitis, and atopic dermatitis [966,972]. Additionally, the retinoid, isotretinoin, used in the treatment of acne vulgaris, causes meibomian gland atrophy in a proportion of patients, which may be accompanied by features of MGD [644,648].

In non-cicatricial MGD, diagnosis is based on the morphologic changes in the meibomian orifices and gland acini observed by biomicroscopy, non-contact meibography and confocal microscopy. The orifices become narrowed and the distinctive ring that surrounds them in health becomes less visible [37,984]. In severe disease, at a stage when there is increased vascularity and the appearance of telangiectasia at the lid margin, the orifices may be distorted, finally becoming scarred and atrophic. At an earlier stage, features include plugging of the orifices by cellular debris and thickening, clouding or absence of expressed excreta. Histologically, it has been said that there is limited inflammatory reaction [624,625,978], but periglandular inflammatory cell infiltration has been reported in severe MGD, based on confocal microscopy. Infiltrates appear as roundish bodies with high reflectivity. These are reduced in number after intensive therapy with lid hygiene, topical steroids, topical non-preserved artificial tears and topical and oral antibiotics, in a comparative trial against lid hygiene and topical non-preserved artificial tears alone [985]. Hyper-reflective dots have also been observed in Sjögren syndrome-associated MGD [733]. Identification of such dots is required at histological level.

Methods exist to grade MGD [984,986,1206], by scoring the degree of gland dropout (meibography) [959,986,987], the amount of oil in the lid margin reservoir (meibometry) [186,988] and the appearance and spreading characteristics and thickness of the TFLL (interferometry) [195,989]. Confocal microscopy is being used, increasingly, to quantify the glandular changes in fine detail [390].

MGD is a symptomatic condition in its own right whose symptoms result from lid involvement and ocular surface inflammation in the absence of increased evaporation [376]. However, with progression of disease, the degree and extent of obstruction results in a reduced delivery of meibum to the tear film [36,180], a TFLL deficiency [190,978] and loss of its barrier function [175]. Lipid compositional changes, a reduced spread time and lipid layer instability also play a part in the increased evaporation rate that leads to EDE [195,375,376,965,990,991].

In their summary of the MGD literature, Blackie and Korb have emphasized that, notwithstanding the features of well-established disease, MGD may often present as an asymptomatic condition with normal lid margin appearances at the slit-lamp [184]. This form of MGD, which they call *non-obvious MGD*, (NOMGD) was recognised at the outset of the description of MGD [964] and has been noted by other authors [974]. Because there are no overt signs of disease, diagnosis must be based on a change in quality of expressed secretions. In an elderly male population over 60 years of age, a majority had at least one abnormal MGD parameter such as non-obvious meibum quality or visible lid vascularity, where lower lipid quality but not higher vascularity were significantly correlated with advancing age and DED symptoms [992].

Blackie et al. [184] emphasize the need to perform meibomian gland expression on a routine basis in order to detect NOMGD and recommend the use of standardized expression, using their custom-made expression device [993,994]. This offers the added advantage of providing a numerical score for expression, the number of Meibomian Glands Yielding Liquid Secretion (the MGYLS score). It is suggested that DED symptoms may be precipitated in patients with NOMGD in conditions of desiccating or other forms of ocular surface stress, as with contact lens wear [964], or in air-conditioned environments when performing work at video display terminals, so-called “office eye” [995–998].

10.2.3.2.3. Tear volume in meibomian gland dysfunction. In the steady state, tear meniscus dimensions such as height, radius of curvature and cross-sectional area are surrogates for meniscus volume and tear volume and flow [170]. They are, as expected, reduced in ADDE [172,477,999–1001]. In a study by Tung et al., tear meniscus height and area were reduced compared to controls, in patients with both NSDE and SSDE, and correlated negatively with epithelial corneal damage [999]. Patients with a tear meniscus height of <210 μm had a relative risk of 4.65 for developing severe corneal epithelial disease (corneal fluorescein staining > 10) with an odds ratio = 5.59.

It has been predicted that, in MGD-related EDE with normal lacrimal function, tear flow and hence tear volume and meniscus dimensions will be sustained by a compensatory response, driven by the Lacrimal Functional Unit [207]. In keeping with this, Tung et al. showed a non-significant difference between normal control values of tear meniscus height and area in a group of symptomatic MGD patients with a reduced BUT [999]. In another study it was concluded that an increase in tear production likely compensates for the loss of meibomian glands in patients with MGD [1002].

10.2.3.2.4. MGD secondary to systemic chemical exposure. Also, occurring in rare epidemics, systemic exposure to polychlorinated biphenyls, through ingestion of contaminated cooking oils, causes a chronic disorder with gross and extensive acneiform skin changes, meibomian seborrhea with thick excreta and glandular cyst formation [633,1003].

10.2.3.2.5. Anterior blepharitis-related MGD. Meibomian Gland Dysfunction may occur in conjunction with anterior blepharitis, particularly when they are both secondary manifestations of a dermatosis such as rosacea [641,966,1004–1006]. One potential source of inflammation is the commensal bacteria of the lid [1007] whose lipolytic enzymes are capable of degrading meibum, with the production of altered lipid species, such as free fatty acids, that are irritant to the tissues [1008,1009]. McCully and Dougherty [1007] reviewed the plethora of bacterial products capable of inducing inflammation, including lipopolysaccaride (LPS), chemoattractant lipids such as the aldehyde 4-hydroxynonenal (HNE) derived from unsaturated fatty acids, reactive oxygen species and lipid-derived inflammatory mediators such as arachidonic acid, which are the source of prostaglandins and leukotrienes. The role of microorganisms in the etiology of MGD is not fully established and not all studies report an increased bacterial commensal population or a consistent bacterial profile. A recent report showed significantly higher culture rates for aerobes (especially *S. Epidermidis*) and anaerobes (especially *P. Acnes*) in expressed meibum and the conjunctival sacs of patients with MGD alone, and a more complex bacterial profile compared to controls [63], but in another report, no difference in bacterial spectrum, in either lid or expressed meibum cultures, was found between MGD patients and controls despite the presence of anterior blepharitis in 76% of the MGD patients [1010]. A higher than expected frequency of *P. acnes*-positive meibum cultures reported in meibomitis-related keratoconjunctivitis (MRKC) has been invoked to explain an association with the phlyctenular-like keratitis in young girls or adolescent females, acting through a delayed-type hypersensitivity (DTH) mechanism [1011].

Another cause of anterior blepharitis is the ectoparasite Demodex, which is found increasingly with age on the surface of the human body [1012-1014]. *Demodex folliculorum*, is found in hair and eye-lash follicles and *Demodex brevis*, within sebaceous glands including the meibomian glands [1012-1014]. Demodex infestation of the lids is suggested by the presence of cyclindrical dandruff around the lash bases [1015] and may be confirmed by demonstration of the mites on epilated lashes. They have been observed non-invasively at the orifices of meibomian glands, by IVCM [1016] but their causative role in MGD [1017] and DED is not established. The subject is reviewed by Cheng et al., [1018].

10.2.3.2.6. Genetically determined meibomian gland diseases. DED may be caused by a general absence of the meibomian glands or by diffuse changes in the glands distinct from those that characterise MGD.

10.2.3.2.6.1. Meibomian agenesis and dystichiasis

Meibomian glands may be absent or partially absent as a sporadic condition [1019], or congenitally replaced by an extra row of lashes (distichiasis). Distichiasis may also occur as part of a wider, dominantly inherited syndrome of distichiasis with lower limb lymphoedema, that results from truncation mutations of the forkhead transcription factor, FOXC2 [1020]. A mouse model of this disorder exists, caused by the targeted disruption of FOXC2 [1021].

The meibomian glands may be diffusely affected in certain rare, inherited disorders such as anhydrotic ectodermal dysplasia, epidermolysis bullosa and ichthyosis, and has also been reported in Turner syndrome.

10.2.3.2.6.2. Anhydrotic ectodermal dysplasia

Anhydrotic ectodermal dysplasia refers to a group of inherited disorders accompanied by malformations of ectodermal skin appendages such as teeth, hairs, nails and glands, including the meibomian glands. Over 90% of patients show a reduction of eyebrows, alterations of eye lashes and changes to the meibomian glands. Ninety four percent of such patients were reported to suffer from DED symptoms in a large case series reported by Kaercher [1006], who suggested that meibomian gland changes, detected by meibography, are the most reliable ocular sign of ectodermal dysplasia. It is likely that the meibomian epithelial cells are affected directly by the genetic defect and that the gland and ducts are affected diffusely.

The syndrome of Ectrodactyly (split-hand or foot), Ectodermal dysplasia, and Clefting (cleft lip and or uvula and palate)-(EEC), is caused by mutations in the DNA-binding region of the gene p63, controlling a transcription factor, active during embryogenesis, and concerned with stem cell differentiation in stratified epithelia. It may occur sporadically or be inherited as an autosomal dominant disorder with variable phenotypic expression and penetrance. The condition is well reviewed by Di Iorio et al., [1022] who found an absence of the meibomian glands in almost 100% of their cohort and reduced aqueous secretion in 60%. Lacrimal drainage obstruction (including absence, stenosis or occlusion of the puncta and/or canaliculi) is reported in 59%–100% of cases. The major cause of visual morbidity, giving rise to a dense vascular keratopathy, is limbal stem cell deficiency, which was seen in 60.9% of the Di Iorio series.

10.2.3.2.6.3. Epidermolysis bullosa

EB describes a spectrum of genetically-determined, bullous, mucocutaneous disorders, characterized by fragility and rupturing of the skin in response to friction or mild mechanical trauma [1023,1024]. The level of ocular involvement generally parallels that of the skin and consists of recurrent corneal and conjunctival erosions and scarring and, in the case of the conjunctiva, symblepharon. Repeated corneal and conjunctival blistering can lead to corneal abrasion, punctate keratopathy, symblepharon, ectropion, entropion, and corneal scarring, with reduced visual acuity and even blindness [1025-1028]. Tong et al. [1029], reported the incidence of ocular complications to be 4% in the dominant form of dystrophic EB (DDEB), 12% in the most common and mildest form, EB simplex, (EBS), 40% in junctional EB (JEB) and 51% in the severe, recessive form of dystrophic EB (RDEB). Of these, JEB and RDEB are less common than DDEB and much less common than EBS.

Subtypes of EB result from mutations affecting the functional integrity of the dermo-epidermal junction and of the equivalent region of the mucosa. They are designated according to the ultrastructural level of the blister formation. In the most common form, EBS, separation occurs within the basal layer of the epithelium, with less likelihood of scarring than in the recessive form, where cleavage occurs at the level of the anchoring fibrils [1030]. In JEB the level of cleavage is within the lamina lucida of the hemidesmosomal complex and results in defective epithelial adhesion. One form of JEB (JEB Herlitz), results in extensive disease and death in infancy [1031].

The frequency of lid abnormalities in children with EB, was based in the past on retrospective studies [1030] and confined to comment on the presence or absence of 'blepharitis' [1032,1033]. This has been reported to vary from 0.37% to 17.65%, depending on EB subtype [1034]. Jones et al. [1030], in a large prospective study from Great Ormond St. London, point out that the National EB registry reports blepharitis as an uncommon finding, with highest frequencies in RDEB inversa and severe, generalized RDEB (approximately 18% in each) and in JEB subtypes (6%–7%) [1034]. In contrast, Jones et al. [1030], reported a high frequency of MGD in all subtypes of EB with the greatest frequency and severity in the more severe forms, particularly RDEB and JEB. In this carefully conducted study, diagnosis of MGD was based upon the findings of gland orifice plugging and capping, lid margin telangiectasia, lid margin rounding, and retroplacement of the mucocutaneous junction. Because of the problems associated with lid manipulation, it was not possible to perform either gland expression or meibography in this group of patients. The authors were not able to determine whether MGD was of primary origin or secondary to the EB-related ocular surface disease but they emphasized that once established, it must contribute to the frequency and severity of ocular surface disease by means of lid- and DED-related mechanisms and therefore demanded treatment in its own right.

10.2.3.2.6.4. Ichthyosis follicularis, atrichia and photophobia syndrome

Ichthyosis follicularis, atrichia and photophobia syndrome (IFAP) is a rare X-linked disorder characterized by a non-cicatricial alopecia, with absent eyebrows and lashes, with photophobia of neonatal onset and a generalized cutaneous follicular hyperkeratosis. It is an inherited disorder of lipid metabolism. Disease severity ranges from mild skin disease to severe variants with multiple extracutaneous features (brain anomalies, retardation, ectodermal dysplasia and skeletal deformities [1035].

The typical skin finding in IFAP is of 'thorn-like', follicular projections which impart a nutmeg-grater feel to the affected skin. Hyperkeratoses are sometimes seen over the elbows, knees, and dorsal fingers, while the palms and soles of the feet, the teeth, nails and sweat glands are unaffected [1035,1036]. Hair shafts and sebaceous glands are lacking [1036-1039], suggesting a failure of development of the pilosebaceous unit and Eramo reported plugged and irregularly spaced meibomian glands in an affected boy, aged 3, suggesting the presence of MGD or related meibomian gland disease [1036]. It is not yet certain whether meibomian glands as such are even present and this aspect of the disorder deserves comprehensive review. Histopathology of leg skin in this patient showed that the central lumen of all hair follicles contained only keratotic debris. There were no sebaceous glands or normal hair shafts. Well-developed sweat glands were present and mild mononuclear perivascular infiltrates. In female carriers, the trait may be non-penetrant or present with minor features.

Photophobia in this condition is likely to be due to keratitis, probably with a contribution from the MGD. Punctate epithelial erosions, pannus and progressive corneal vascularization and stromal opacification may lead to severe visual loss [1038].

IFAP is caused by mutations in the gene MBTPS2 (membrane-bound transcription factor peptidase, site 2 (S1P), located on chromosome Xp22.1 [1040], which is involved in the regulation of lipid biosynthesis. Oeffner et al. demonstrated a genotype/phenotype correlation between clinical severity and the effect mutations on peptidase activity [1041]. As discussed elsewhere in this report (Section 4.3), the proteases SIP and S2P work cooperatively to activate SREBP transcription factors and target a broad range of genes engaged in cholesterol and fatty acid metabolism. This is in

keeping with the failure of pilosebaceous development in this condition apparently also affecting the meibomian glands.

A related disorder, also inherited as an X-linked trait and due to mutations in MBTPS2, is Keratosis Follicularis Spinulosa Decalvans (KFSD) [1041,1042]. Like IFAP, KFSD exhibits the combination of follicular ichthyosis, alopecia and photophobia, but differs by reason of a later onset of, and more patchy distribution of, alopecia. The occurrence of atrophy and scarring of follicles is a later feature and the cicatricial alopecia contrasts with the scar-free alopecia of IFAP. Also, hyperkeratosis of the palms and soles and dorsal fingers occurs in KFSD but not in IFAP [1035]. Fong et al. [1035], reported an overlap in clinical and molecular features between IFAP and KSFD.

10.3. Disorders of lid aperture, congruity and dynamics

A newly reported variant of nocturnal lagophthalmos, inadequate lid seal [544], refers to the inability of apparently closed lids to exclude air from the ocular surface during sleep. It may be responsible for symptoms occurring immediately upon rising. Diagnosis is made with a "light test', using a transilluminator pressed against the closed lids. A strong correlation between a positive light test and symptoms immediately upon waking was reported in a Level 2 study.

As noted earlier, incomplete lid closure of some degree is not uncommon in normal subjects during blinking [343,409]. In normal subjects, increased ocular surface exposure and evaporation occurs in upgaze [288], so that DES may be imposed in the workplace by activities that demand attention by attending to goods placed on high shelves and to extreme elevation of the globes while the head is inclined downward as when taking aim when playing billiards. Elevations on the surface of the globe, close to the limbus, may also impair tear spreading and cause localized drying and dellen formation [1043,1044].

Incomplete lid closure or lid deformity, leading to increased exposure or poor tear film resurfacing, is accepted as a cause of ocular drying following a VIIth cranial nerve palsy (lagophthalmos) or after surgery to the lids [1045]. The relationship between VIIth cranial nerve palsy and the development of MGD [1046-1048] is of particular interest and its mechanism deserves further study. Wan et al. showed a clear correlation between the duration and severity of VIIth nerve palsy and the onset and evolution of MGD [1048]. Tear breakup time was reduced in all groups of VIIth n. palsy.

An increase in palpebral fissure width or globe prominence exposes the tear film to greater evaporation [1049] and the risk of ocular desiccation and tear hyperosmolarity. In Graves' orbitopathy, the effect of proptosis on exposure is compounded by lid retraction and lid lag, incomplete blinking or lid closure and by restriction of eye movements, each of which may compromise tear spreading [197]. Kim et al. found an increase in meibomian gland dropout in Graves' orbitopathy, correlating with a shortened TBUT, the degree of exophthalmos and palpebral aperture height [1050]. Increased gland dropout is also encountered with ocular prosthetic use [1051] and there is also an association with lid laxity [1052], with DED features including a decreased Schirmer score, reduced TBUT and increased corneal staining [971]. A parallel may be drawn between these conditions, with the proposition that gland dropout may be the consequence of meibum stasis due to incomplete or imperfect blinking. A contributing factor could also be the action of tear hyperosmolarity and inflammatory mediators at the apex of the tear menisci, close to the terminal meibomian ducts [451].

10.3.1. Other blink-related disorders

A reduced blink rate is potential basis for DED in Parkinson's disease and in progressive ophthalmoplegia [1053], where, in addition, the spreading of tears is impaired by an altered blink action and a reduction in eye movements. Other contributing factors in Parkinson's disease include reduced meibomian oil delivery, decreased reflex tearing due to autonomic dysfunction [1054] and possibly effects of androgen deficiency on the lacrimal and meibomian glands [1055].

10.4. Ocular surface-related evaporative dry eye

10.4.1. Allergic eye disease

Ocular allergies include a variety of clinical conditions (namely Seasonal Allergic Conjunctivitis-SAC, Perennial Allergic Conjunctivitis- PAC, Vernal Kerato-Conjunctivitis –VKC and Atopic Kerato-Conjunctivitis – AKC) ranging from mild, to severe and sight-threatening ocular diseases.

Although the pathophysiology of allergic eye disease, unlike that of DED, involves mostly a Th2 lymphocyte mechanism, these conditions may share some clinical and biochemical features.

Thus:

a) In each, the conjunctiva is hyperaemic or inflamed, the corneal epithelium may be damaged and the corneal nerves affected; the tear film is rich in inflammatory cytokines, mediators and neuro-mediators that can initiate and maintain chronic inflammation. MGD is reported as a feature of allergic eye disease [1056] and may be a source of DED. Fibrosis and scarring are common outcomes in severe allergic conditions such as AKC and VKC as a result of a long-standing inflammation.
b) Mucosal hyper-responsiveness to non-specific environmental stimuli has been described in both ocular allergy and DED. Patients with VKC show hyper-responsiveness to non-specific, non-allergic challenges such as histamine, air pollution or other environmental agents [1057-1060]. Similarly, in DED, both in experimental models and in humans, signs of ocular surface damage are induced by oxidative stress [767,770,772] or commonly encountered environmental factors such as air conditioning and dust, or pollutants such as smoke [772,1061].
c) Both allergy and DED show a favorable response to topical anti-inflammatory agents such as steroids and cyclosporine. Artificial tears, that are routinely used for DED patients may improve symptoms in all the clinical varieties of ocular allergy [1,770,1062,1063].
d) Both conditions have a negative impact on the quality of life as they evolve. In particular, increasing discomfort and a reduction of the visual function may be present in the severe forms of each disease, particularly when performing visual tasks requiring continuous attention (e.g. driving, reading, computer work and attention at school).

By contrast, ocular allergy and DED represent two different clinical entities with distinct immune cells involved in their pathogenic mechanism and a different histopathology (for instance increase of goblet cells in allergy [1064] and decreased numbers in DED [434]. Ocular allergy is a disease of youth while DED is more common at an older age when signs and symptoms of allergy generally disappear. They also differ in the quality of symptoms experienced, with allergic patients complaining in particular of itching and photophobia and DED patients of grittiness and foreign body sensation.

Intense itching is typical of VKC and, together with photophobia, is the constant and major symptom of allergic eye disease [1065]. Although it is sometimes listed as a symptom of DED, its frequency intensity and topographic reference are not described. It would be of interest to know whether it is a symptom of DED secondary to some form of blepharitis rather than, specifically, to DED itself.

Corneal involvement in the form of diffuse punctate keratitis or a shield ulcer is typical of the severe forms of allergy. Conversely, DED is associated with a different fluorescein pattern including the involvement of the interpalpebral and most exposed ocular surface [74,1066].

A few biological markers of inflammation may be common to both DED and allergic eye disease but eosinophils, eosinophil-derived products and mast cells are typical findings in allergic eye disease [543,1067,1068]. Their absence in a patient with ocular surface symptoms points against a diagnosis of allergic eye disease, but their presence does not exclude DED. Demonstration of a shortened tear film breakup in patients with allergy biomarkers would support the presence of both conditions [1069]. A few clinical entities exist, such as that occurring in young women with polycystic ovaries, who show features of both conditions [1070]. Although the mechanism for this is not established, it is likely that sex hormones and insulin resistance play a part (see TFOS DEWS II Sex, Gender and Hormones report).

Allergic eye diseases and DED are distinct clinical entities but some overlapping features suggest a complex interaction of mechanisms involving the immune, endocrine and nervous systems.

10.4.2. Vitamin A deficiency

Vitamin A regulates epithelial growth, cell proliferation and differentiation [1071,1072]. Systemic vitamin A insufficiency remains an important cause of childhood mortality and blindness in many low-to middle income countries [1073,1074]. In the eyes, vitamin A deficiency induces xerophthalmia [1075], which includes night blindness [1076], conjunctival xerosis [1077], Bitot's spots [1078-1080], corneal xerosis [1081] and keratomalacia [1077]. Two forms of DED are recognised and may occur together. One is due to defective ocular surface wetting and the other to lacrimal gland insufficiency [1082]. Poor wetting can be caused by a defective epithelial glycocalyx at the ocular surface, to a loss of goblet cells, and finally to ocular surface metaplasia and epithelial keratinization. Paradoxically, in current times, xerophthalmia may be encountered in developed countries following bariatric surgery for obesity, due to decreased vitamin A absorption from the small intestine [659].

Vitamin A deficiency in the animal model can induce epithelial keratinization and squamous metaplasia (with Bitot's spot formation) [1083,1084] and also a profound decrease of conjunctival goblet cell density [1077,1083,1085]. Vitamin A is involved in the biosynthesis of glycoconjugates and is involved in mucin glycosylation in the ocular surface epithelium [1086,1087]. There is evidence of abnormal mucin synthesis in vitamin A deficiency. In the rat model, membrane-associated mucin rMUC4 mRNA and secretory mucin rMUC5AC mRNA were not detected in vitamin A deficient animals [1088]. In the human conjunctival epithelial cells, retinoic acid is associated with upregulation of MUC16 through an action on secretory phospholipase A2 Group IIA [1089]. Additionally, in a primary human corneal limbal epithelial cell culture model, retinoic acid stimulates MUC1, MUC4 and MUC16 expression and improves glycocalyx barrier function in a dose-dependent manner [1090]. Retinoic acid also destroys the meibomian gland. Please refer to the TFOS DEWS II Iatrogenic Dry Eye report [1227].

10.4.3. Short breakup time dry eye

The term short breakup time DED (SBUDE) refers to a symptomatic form of DED with a fluorescein breakup time of $\leq$5 s, occurring in the presence of a normal tear secretion and tear clearance, normal meibomian gland function and unassociated with epithelial damage [1069]. Symptoms include those of dryness, ocular fatigue and blurred vision, with a substantial effect on the quality of life (QoL).

In the study of Yamamoto et al., in those patients presenting with a “spot type” of breakup (= 0 s), females were affected more commonly than males (ratio 3:1), with a peak frequency of 60 years in women and 20 years in men [1091]. SBUDE appears to be a common form of DED in the workplace in Japan. In the Osaka study of office workers engaged in prolonged work at VDTs, 244 out of 303 recruited subjects (80.5%) were diagnosed with SBUDE [1092], which was highly symptomatic [165] and associated with decreased functional visual acuity [298], QoL [1093,1094] and loss of productivity [442]. Its elucidation is of high priority.

The mechanism of SBUDE is not yet established but current research suggests that it is precipitated by defective wetting of the ocular surface. In a study comparing patients with SBUDE or ADDE with normal controls, patients in each group had a fluorescein breakup time of $\leq$5 s and MGD was excluded [425]. Neither Schirmer test values nor vital staining scores differed significantly between subjects with SBUDE and healthy controls. The expression of mRNA for both MUC1 and MUC 16 was significantly lower in patients than in controls, but there was no difference between the two patient groups, implying that a loss of wettability was likely to have played a similar role in each group. Curiously, conjunctival impression cytology showed no significant differences in goblet cell density or level of squamous metaplasia among the 3 groups. Where it has been assessed, the tear film lipid layer is normal prior to breakup, too, suggesting that breakup is not triggered by a tear lipid deficiency. The source of symptoms in the absence of significant ocular surface staining is also intriguing and for the present it is assumed to relate to surface hyperosmolarity induced at the site of breakup.

In a study of 96 Japanese office workers working regularly with VDTs, the prevalence of definite and probable DED was 9% and 57%, respectively. The mean MUC5AC concentration was lower in the tears of VDT users with definite DED than in those with no DED and the mean MUC5AC concentration in tears was lower in the group that worked longer hours [1095]. Also, MUC5AC concentration was lower in subjects with symptomatic eye-strain than in asymptomatic individuals [1095]. These results, together, suggest that the circumstances of prolonged VDT use induces changes in mucin expression that reduce ocular surface wettability and contribute to DED symptoms in this community. The pattern of tear breakup in SBUDE is of the so-called ‘spot’ or ‘dimple’ variety and studies are underway to explore whether these patterns are specifically related to surface mucin deficiency [178]. So-called, ‘line’ and ‘area’ breakup pattern are associated with ADDE, with ‘line’ breakup seen in mild to moderate ADDE and ‘area’ breakup in severe ADDE.

Some success in the treatment of SBUDE is claimed for topical diquafosol sodium, a purinergic agonist which stimulates conjunctival water and gel mucin production [1096], and also with rebamipide, which is reported to increase goblet cell density and also, gel mucin production [1097,1098]. Both agents are claimed to increase the expression of membrane-associated mucins. (See the TFOS DEWS II Management and Therapy report for further details [1228]).

10.4.4. Ocular surface disease due to topical agents

(See the TFOS DEWS II Iatrogenic Dry Eye report[1227].)

11. Summary and recommendations

The Subcommittee has reviewed how the physiology of the ocular surface is affected by, and influences the onset and evolution of, DED. There is good information about the control of lacrimal secretion in humans but less about that of the meibomian glands, surface epithelia and goblet cells. Methods to measure their

secretory performance *in vivo* are needed.

The structure and function of the precorneal tear film is still under intense scrutiny. One current opinion suggests that the tear film lipid layer alone is not a major barrier to water loss and that its chief role is to stabilize the spreading tear film. It is nonetheless still considered that deficiency and instability of the lipid layer enhances water loss sufficiently to generate clinically important hyperosmolarity at the ocular surface and that this contributes to ocular surface damage in DED.

The question of whether there is an aqueous subphase immediately deep to the TFLL, as proposed by Wolff, is still debated. Clinical observation suggests that the fluid drawn into the menisci from the nascent tear film, in the upstroke of the blink, is more watery than the precorneal film itself and it seems likely that an aqueous layer is retained between the TFLL and the subjacent mucoaqueous layer whose behavior is distinctly gel-like. The mucoaqueous layer, deposited over the cornea during the blink, is derived chiefly from the upper tarsal conjunctiva and is likely to differ from that which coats the exposed bulbar conjunctiva, which must arise from both the bulbar and tarsal conjunctiva. This may be of relevance to SLK. In healthy eyes, zones of meniscus-induced thinning may be imprinted onto the precorneal tear film in various gaze positions and be associated with tear instability, threatening its integrity. This phenomenon should be explored further in healthy eyes in conditions of DES as well as in patients with DED.

It has been hypothesized that the physiological line of conjunctival staining at the lid margin, called Marx's line, is due to a region of hyperosmolarity at the meniscus apex. Increased permeability of the epithelium, also postulated at this site could give pro-inflammatory proteins access to the terminal meibomian ducts, explaining the association between the forward movement of Marx's line with age and the occurrence of MGD. It would be worthwhile to study the composition of the glycocalyx at this site (expressed mucins and of galectin-3) and of layer 1 tight junctions in human samples. Its permeability might be explored using fluorescent dextrans.

Partial blinks are not uncommon in both normal and dry eyes but occur more frequently in DED. Because of their effect on evaporative loss this is important to the DED mechanism. It may also direct the occurrence of punctate epitheliopathy to the lower part of the globe in DED states.

The tear film is spread over the exposed ocular surface by the blink, but eye *movements* also contribute to its deposition over the peripheral cornea and bulbar conjunctiva. Shearing events between the globe and the upper or lower lid wiper are likely to differ, with friction directed more to the upper lid wiper by the blink and more to the lower lid wiper by downgaze, with horizontal gaze movements making additional contributions. This probably explains how LWE affects both the upper and lower lid margins. Friction delivered by the blink will be greatest in the mid-zone of the upper lid where the linear velocity of the excursion is greatest.

The physical concepts of boundary lubrication and hydrodynamic lubrication are being usefully applied to the dynamics of lid and globe movement. A new boundary lubricant, lubricin, of corneal and conjunctival epithelial origin, has recently been described and may be of importance in DED. A deficiency of aqueous tears and the loss of ocular surface lubrication in various forms of DED likely explain the increased frequency of punctate epitheliopathy, SLK, filamentary keratitis and LWE in DED and the symptoms associated with these conditions. It could also explain the sensations of lid heaviness and the difficulty in opening the eye on waking, in DED.

The epithelial glycocalyx is an integral component of the apical membranes of surface epithelial cells. Its molecular composition is now better known. It imparts wettability to the ocular surface, which explains its lubricative and some of its barrier functions. The contribution of intercellular tight junctions to this barrier is also well understood. The epithelium turns over continuously and, as old cells mature and die, the integrity and barrier function of this layer for these cells is lost. It is likely that frictional forces between the lids and the globe during blinking and eye movements, participate in the shedding process. Although epithelial shedding is said to be increased in DED, the shedding rate does not appear to have been measured formally. The loss of barrier function in preshed cells is hypothesized to account for a low level of punctate staining of the normal corneal and conjunctival epithelium. About 17% of normal corneas show some degree of punctate staining after the instillation of 0.125% of fluorescein and it is assumed that, over a period of time, all corneas do so. The temporal aspects of such staining in an individual are worthy of further study. We recommend that, in clinical trials, zero staining should not be the default for normality. Because stainability is dependent on instilled dye concentration and the time of reading, methods of grading should be standardized (see TFOS DEWS II Diagnostic Methodology report [1225]).

Modeling considerations suggest that in healthy eyes the tear osmolarity of the menisci is slightly lower than that over the exposed ocular surface and that this discrepancy increases with increasing meniscus hyperosmolarity in DED. It is further predicted that, in DED, a wave of hyperosmolarity, driven by evaporative loss, spreads from the epicentre of a tear breakup, reaching high levels, of pathological and symptomatic consequence at the ocular surface, which will not be fully reflected by meniscus sampling. The earlier the onset of breakup in the blink interval, the longer the period of exposure to hyperosmolarity. In specialised clinics we recommend routine consideration of the ocular protection index in patients with DED, as a measure of this threat. A high level of osmolarity in a meniscus sample implies a much higher level at the ocular surface.

The Subcommittee found increasing evidence to support the role of tissue hyperosmolarity at the ocular surface as a central element in DED, generated by exposure to hyperosmolar tears, particularly following tear film breakup. While stressing this, the Subcommittee recognizes that the predicted high levels of osmolarity have not yet been measured directly at the corneal surface and recommend that priority be given to the development of methods to measure of molarity at the tissue level within the interpalpebral zone.

A neutrophil defence mechanism (NETosis) known to be a source of mucosal damage in other diseases such as cystic fibrosis, may be a source of ocular surface damage in DED, amplified by increased epithelial shedding, tear hyperosmolarity and a fall in tear nuclease activity. DNA released into the tears (eDNA) from desquamating epithelial cells and invading neutrophils can, independently, or combined with other components of neutrophil origin, cause damage the ocular surface. Dying neutrophils can release their cellular contents into the extracellular space to form sticky, antimicrobial, NETs. They form extracellular webs containing decondensed chromatin, histones, neutrophil elastase and antimicrobial peptides, each of which individually may be toxic for epithelial cells. Given that the tears are invaded physiologically by abundant neutrophils during overnight eye closure it would seem important to explore the relationship between the NET formation and closed eye tear phenomena. The Subcommittee recommends the investigation of closed eye tears and of conjunctival impression cytology specimens in DED patients, immediately after periods of prolonged eye closure.

In the TFOS DEWS report [1], the concept of a vicious circle of inflammatory events at the ocular surface was put forward, as a basis for the self-perpetuation of DED. Evidence indicated that tear

hyperosmolarity could initiate a damaging cascade of inflammation at the ocular surface, which could decrease wettability, induce tear film instability and breakup and thereby amplify tear hyperosmolarity. Importantly, a given etiology of DED may enter the vicious circle at any point to participate in this process (Fig. 5) Abundant supportive evidence for the concept has accumulated since this time, at an experimental and clinical level, with detailed knowledge of immune cell activation and invasion and of the inflammatory mediators and proteases involved. Further experimental evidence in a mouse model suggests that ocular surface inflammation can outlast exposure to DES and may be able to perpetuate the clinical features of the disease. The potential dissociation between cause and effect may explain in part the discrepancy between some objective signs and patient symptoms reported in the literature.

For any cause of DED, tear hyperosmolarity is initiated by either or both of two mechanisms. In ADDE there is a deficient lacrimal secretion but a normal rate of evaporation from a tear film of reduced volume. In EDE hyperosmolarity results from an excessive evaporation of tears in the presence of normal lacrimal function. Since all forms of DED are due to water loss from the tear film, the precipitation of hyperosmolarity at the ocular surface is strongly influenced by environment, including ambient humidity, airflow and temperature and also blink interval, lid aperture and globe prominence. Unfavourable conditions may either trigger the onset of DED or exacerbate its severity. The effect of environment is brought out by the newly described condition of SBUDE observed in Japanese office workers. The ergonomic and environmental factors that precipitate this form of DED require further study.

It is evident that many hybrid forms of DED exist in which lacrimal deficiency and increased evaporative loss collaborate to cause enhanced ocular surface hyperosmolarity. These are summarised in Table 13. Such hybrid states should be recognised in the inclusion criteria of clinical trials and in subgroup analyses of outcomes. Once a dry eye is of sufficient severity to cause tear breakup within the interblink interval, an additional evaporative component will be added to any form of DED, so that any ADDE will acquire an evaporative component and the evaporative basis of an existing EDE will be amplified. Studies which test this prediction by comparing the ocular protection index with evaporation rate and tear osmolarity would be of value.

This hybrid state should not obscure the initiating mechanism of the DED. It is predicted that tear levels of the lacrimal proteins, lysozyme, lactoferrin and peroxidase will remain normal where the initiating cause is EDE but will be reduced where it is ADDE, due to lacrimal acinar destruction. This hypothesis should be tested in the field. A revised language is required to accommodate these and other forms of hybrid DED.

A variety of animal models of DED exist, which address several of the pathophysiological mechanisms responsible for DED including lacrimal gland insufficiency, MGD, impairment of the innervation, humoral mechanisms and environmental stress. Genetic manipulation has been used to explore the factors influencing susceptibility. Study of these factors provides hypothesis-generating insights into the causes of human DED and, since domestic animals may suffer from spontaneous, autoimmune DED, the findings are of veterinary as well as human clinical interest. They also provide an opportunity for toxicological and pharmacokinetic study of potentially sight-saving new drugs.

Murine models of DES and SCP permit the evolution of DED to be timed from its initiation. A constellation of cytokines and chemokines has been identified in these models to cause damage to the ocular surface, with differences in outcome varying according to the experimental model.

Models of autoimmune DED simulating Sjögren syndrome are dependent on genetic susceptibility. In various models, the influence of autoreactive T cells, of disrupting TGF-β signaling or the Fas-Fas ligand system, of inducing glandular apoptosis, of manipulating sex hormones, and of generating autoantibodies encountered in human disease, has been explored. In the majority of these models the diseases evolve spontaneously over time and reaching varying levels of severity. In contrast to the DES and SCP models, the specific trigger for the onset of disease is not known. Therefore, those models in which DES is administered to genetically modified animals are of particular interest in bridging the gap in knowledge between initiation and susceptibility in different model systems. The role of genetic susceptibility in human, age-related NSDE has not yet been adequately explored.

Both aged and chronic models of DED have been developed, with sex differences in severity, including corneal damage (C57BL/6) and goblet cell density (MRL.lpr.B6), which are of great interest in relation to human disease. T helper cell (Th1 and Th2) cytokines have been shown to have opposing effects on conjunctival goblet cell development and maintenance. The Th2 cytokine IL-13 induces goblet cell differentiation and mucus production and the Th1 cytokine IFN-γ causes goblet cell loss in a DES model of DED. In some models a sex bias for sialoadenitis versus dacryoadentis has been shown.

This Subcommittee has taken some trouble to compare and contrast the clinical and pathological features of Sjögren syndrome as it affects the lacrimal and salivary glands. More work can be done at a number of levels. Fresh lacrimal tissue is scarce, but an opportunity should be taken to establish post-mortem banks of lacrimal and salivary gland tissues for research purposes, obtained from patients with well-characterized Sjögren syndrome and NSDE.

The potential role of viral triggers of Sjögren syndrome, in genetically disposed individuals, should be explored further. When exposure and infection are as common as is the case for the Epstein Barr virus, this task may at first seem disheartening, but stored blood data is potentially available for large numbers of exposed and unexposed individuals and has been used epidemiologically to study the role of EBV as a risk factor for multiple sclerosis and SLE [1099-1101]. This approach should be harnessed for the study of Sjögren syndrome.

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