

DEWS Definition and Classification

The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT The aim of the DEWS Definition and Classification Subcommittee was to provide a contemporary definition of dry eye disease, supported within a comprehensive classification framework. A new definition of dry eye was developed to reflect current understanding of the disease, and the committee recommended a three-part classification system. The first part is etiopathogenic and illustrates the multiple causes of dry eye. The second is mechanistic and shows how each cause of dry eye may act through a common pathway. It is stressed that any form of dry eye can interact with and exacerbate other forms of dry eye, as part of a vicious circle. Finally, a scheme is presented, based on the severity of the dry eye disease, which is expected to provide a rational basis for therapy. These guidelines are not intended to override the clinical assessment and judgment of an expert clinician in individual cases, but they should prove helpful in the conduct of clinical practice and research.

KEYWORDS definition, DEWS, dry eye disease, Dry Eye WorkShop, etiopathogenesis, mechanism, severity grading

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Proprietary interests of Subcommittee members are disclosed on pages 202 and 204.

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I. INTRODUCTION

The Definition and Classification Subcommittee reviewed previous definitions and classification schemes for dry eye, as well as the current clinical and basic science literature that has increased and clarified knowledge of the factors that characterize and contribute to dry eye. Based on its findings, the Subcommittee presents herein an updated definition of dry eye and classifications based on etiology, mechanisms, and severity of disease.

II. GOALS OF THE DEFINITION AND CLASSIFICATION SUBCOMMITTEE

The goals of the DEWS Definition and Classification Subcommittee were to develop a contemporary definition of dry eye disease and to develop a three-part classification of dry eye, based on etiology, mechanisms, and disease stage.

The manner of working of the committee is outlined in the introduction to this issue of *The Ocular Surface*. Further details are published on the TFOS-DEWS web-site (www.tearfilm.org).

III. DEFINITION OF DRY EYE DISEASE

The committee reviewed the definition and classification presented at the 1995 National Eye Institute (NEI)/Industry Dry Eye Workshop, which was: *Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.*¹

The committee agreed that the definition could be improved in the light of new knowledge about the roles of tear hyperosmolarity and ocular surface inflammation in dry eye and the effects of dry eye on visual function. Initially two definitions were developed and presented to members of the workshop. These “general” and “operational” definitions overlapped to some extent, and, therefore, in this final report, these versions have been combined to produce the following definition:

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,²⁻⁴ visual disturbance,⁵⁻⁷ and tear film instability⁸⁻¹⁰ with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film¹¹⁻¹⁴ and inflammation of the ocular surface.^{15,16}

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Dry eye is recognized as a disturbance of the *Lacrimal Functional Unit (LFU)*, an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them.¹⁷ Trigeminal sensory fibers arising from the ocular surface run to the superior salivary nucleus in the pons, from whence efferent fibers pass, in the *nervus intermedius*, to the pterygopalatine ganglion. Here, postganglionic fibers arise, which terminate in the lacrimal gland, nasopharynx, and vessels of the orbit. Another neural pathway controls the blink reflex, via trigeminal afferents and the somatic efferent fibers of the seventh cranial nerve. Higher centers feed into the brainstem nuclei, and there is a rich sympathetic supply to the epithelia and vasculature of the glands and ocular surface.

This functional unit controls the major components of the tear film in a regulated fashion and responds to environmental, endocrinological, and cortical influences. Its overall function is to preserve the integrity of the tear

film, the transparency of the cornea, and the quality of the image projected onto the retina.¹⁷⁻²⁰ At the 2007 Dry Eye WorkShop, it was noted that the corneal and conjunctival epithelia are in continuity, through ductal epithelia, with the acinar epithelia of the main and accessory lacrimal glands and the meibomian glands, which themselves arise as specialized invaginations from the ocular surface. Also, these epithelia have the same embryological derivation. This broader concept, which has additional features, has been termed the *Ocular Surface System* and is discussed further in the "Research" chapter of this issue.²¹

An important aspect of the unit is the part played by sensory impulses, which arise from the ocular surface, in the maintenance of resting tear flow. Currently, it is considered that waking tear flow is a reflex response to afferent impulses deriving particularly, but not entirely, from the ocular surface.²² Sensory input from the nasal mucosa also makes a contribution.²³ Disease or damage to any component of the LFU (the afferent sensory nerves, the efferent autonomic and motor nerves, and the tear-secreting glands) can destabilize the tear film and lead to ocular surface disease that expresses itself as dry eye. Tear film stability, a hallmark of the normal eye, is threatened when the interactions between stabilizing tear film constituents are compromised by decreased tear secretion, delayed clearance, and altered tear composition. Ocular surface inflammation is a secondary consequence. Reflex tear secretion in response to ocular irritation is envisioned as the initial compensatory mechanism, but, with time, inflammation accompanying chronic secretory dysfunction and a decrease in corneal sensation eventually compromises the reflex response and results in even greater tear film instability. Perturbation of the LFU is considered to play an important role in the evolution of different forms of dry eye.

The distinctions *aqueous-deficient dry eye* and *evaporative dry eye* were removed from the definition, but are retained in the etiopathogenic classification.

IV. CLASSIFICATION OF DRY EYE DISEASE**A. Background**

Vitali, writing about the harmonized classification criteria for Sjogren syndrome (**SS**) remarked that classification criteria are not necessarily appropriate for use in diagnosis and may lead to misclassification of a disease, particularly in its early stages.²⁴ In an individual patient, a classification scheme can provide a guide, but an expert clinician, applying appropriate diagnostic criteria, is needed to establish a diagnosis.

Although the NEI/Industry Workshop classification¹ has served as a useful and durable scheme for over a decade, it does not reflect newer knowledge on pathophysiological mechanisms, effects on vision, and the utility of an assessment of severity of disease. Recently, two new classification schemes were published, and these were used as source documents by the committee. These include: the Triple Classification^{25,26} and the report of the Delphi panel.²⁷

The Triple Classification evolved from reports presented

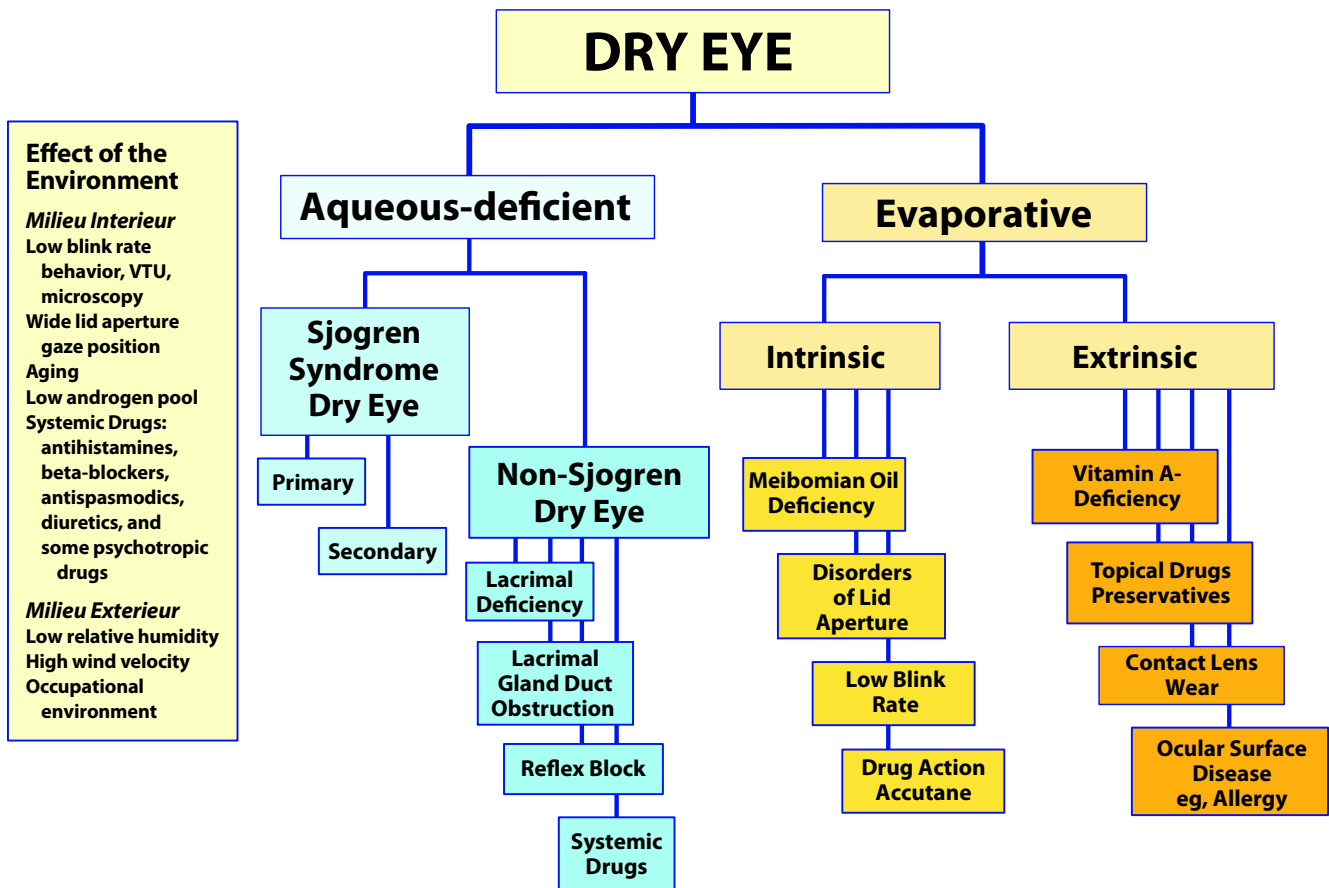


Figure 1. Major etiological causes of dry eye.

The left hand box illustrates the influence of environment on the risk of an individual to develop dry eye. The term “environment” is used broadly, to include bodily states habitually experienced by an individual, whether it reflects their “milieu interieur” or is the result of exposure to external conditions which represent the “milieu exterieur.” This background may influence the onset and type of dry eye disease in an individual, which may be aqueous-deficient or evaporative in nature.

Aqueous-deficient dry eye has two major groupings, Sjogren syndrome dry eye and non-Sjogren syndrome dry eye.

Evaporative dry eye may be intrinsic, where the regulation of evaporative loss from the tear film is directly affected, eg, by meibomian lipid deficiency, poor lid congruity and lid dynamics, low blink rate, and the effects of drug action, such as that of systemic retinoids. Extrinsic evaporative dry eye embraces those etiologies that increase evaporation by their pathological effects on the ocular surface. Causes include vitamin A deficiency, the action of toxic topical agents such as preservatives, contact lens wear and a range of ocular surface diseases, including allergic eye disease. Further details are given in the text.

at the 14th Congress of the European Society of Ophthalmology.²⁵ After further clinical experience, an updated version was published in 2005, which presented three separate schemes: one based on etiopathogenesis; one based on the glands and tissues targeted in dry eye; and one based on disease severity.²⁶

The committee felt that the concept of three different schemes serving different purposes was attractive, but it was noted that evidence-based referencing was limited. For this reason, the scheme as a whole was not adopted, but many conceptual aspects were incorporated into the committee’s final schemes.

The Delphi Panel was a consensus group that met to review the classification of dry eye.²⁷ The panel proposed changing the name of *dry eye disease* to *dysfunctional tear syndrome*, suggesting that the name more accurately reflected pathophysiological events in dry eye. However, although the committee felt that the term embraced the essential

features of the disease, they concluded that retention of the name *dry eye* had much to recommend it and that its use was embedded in the literature. The committee also rejected a subdivision based on the presence or absence of lid disease, because it is frequently difficult to identify the relative contribution of lid disease to a particular case of dry eye.

The majority of the Definition and Classification Subcommittee was in favor of adopting a severity grading based on the report of the Delphi Panel, recognizing it as a comprehensive approach that could form the basis of therapy according to severity of the disease. As noted above, the Triple Classification also presented a severity grading.

B. Etiopathogenic Classification of Dry Eye Disease

The etiopathogenic classification developed by the Subcommittee is an updated version of that presented in the NEI/Industry Workshop Report and reflects a more contemporary understanding of dry eye disease (Figure 1).

As in the 1995 report, the term *dry eye* is regarded as synonymous with the term keratoconjunctivitis sicca (**KCS**).

The classification has the following features:

The left hand box in Figure 1 illustrates the influence of environment on an individual's risk of developing dry eye. The term *environment* is used broadly to include physiological variation between individuals (their *milieu interieur*), as well as the ambient conditions that they encounter (their *milieu exterieur*).

The *milieu interieur* implies physiological conditions particular to an individual that could influence their risk of dry eye. For instance, a normal subject may have a low natural blink rate, or the blink rate may be slowed for behavioral or psychological reasons.²⁸ Slowing of the blink rate increases the blink interval and increases the period of evaporative loss between each blink.²⁹

Similarly, the natural height of the palpebral aperture in the primary position varies between individuals and between ethnic groups.³⁰ The aperture is also wider in upgaze than downgaze.³¹ Evaporative loss per eye increases with increasing palpebral width and is, therefore, increased in upgaze.³²

Extensive evidence supports a role for the sex hormones in the etiology of dry eye³³ with the generalization that low levels of androgens and high estrogen levels are risk factors for dry eye. Biologically active, androgens promote lacrimal and meibomian gland function.³³ Androgen deficiency is associated with dry eye³⁴ and may be prevented by topical or systemic androgen therapy.³⁵⁻³⁸ Dry eye occurs in patients exposed to anti-androgens in the treatment of prostatic cancer,^{39,40} and women with complete androgen insensitivity syndrome show an increase in the signs and symptoms of dry eye, associated with evidence of meibomian gland and goblet cell dysfunction.⁴¹⁻⁴³ A significantly depleted androgen pool in "non-autoimmune" dry eye associated with meibomian gland dysfunction (**MGD**) has been reported.⁴⁴ Also, as noted elsewhere in this issue,⁴⁵ female sex and postmenopausal estrogen therapy are important risk factors for dry eye,^{46,47} and women with premature ovarian failure suffer from the symptoms and signs of dry eye, although their tear production is not affected.⁴⁸

Lacrimal tear secretion is reduced by a number of systemic drugs, and these effects may be looked upon as disturbances of the *milieu interieur*. Their details are discussed later in this report. Aging is associated with physiological changes that may predispose to dry eye, including decreased tear volume and flow, increased osmolarity,⁴⁹ decreased tear film stability,⁵⁰ and alterations in the composition of the meibomian lipids.⁵¹

The *milieu exterieur* involves the occupational and external environments, which may represent risk factors for the development of dry eye. Evaporative water loss from the eye is increased in conditions of low relative humidity, occurring either as part of natural variation at different geographic locations or in special circumstances created by air-conditioning, air travel, or other artificial environments.⁵² Similarly, tear evaporation is increased by exposure to high wind velocity, and this mechanism has

been incorporated into some of the newer experimental models of dry eye.

Occupational factors may cause a slow blink rate, representing a risk for dry eye in those working with video display terminals.⁵³ Other activities associated with decreased blinking and an increase in palpebral width, including that associated with upgaze, have been reported to carry a risk for the development of dry eye symptoms.

The major classes of dry eye, as in the 1995 workshop,¹ are still held to be aqueous tear-deficient dry eye (**ADDE**) and evaporative dry eye (**EDE**). The category ADDE refers chiefly to a failure of lacrimal secretion, and this approach is retained. However, it should be recognized that a failure of water secretion by the conjunctiva could also contribute to aqueous tear deficiency. The class EDE has been subdivided to distinguish those causes that are dependent on intrinsic conditions of the lids and ocular surface and those that arise from extrinsic influences.

Dry eye can be initiated in any of these classes, but they are not mutually exclusive. It is recognized that disease initiated in one major subgroup may coexist with or even lead to events that cause dry eye by another major mechanism. This is part of a vicious circle of interactions that can amplify the severity of dry eye. An example might be that all forms of dry eye cause goblet cell loss and that this, in turn, will contribute to loss of tear film stability, to surface damage and evaporative water loss, and to symptoms resulting from a loss of lubrication and surface inflammatory events.

The major classes and subclasses of dry eye are described below.

1. Aqueous Tear-Deficient Dry Eye (Tear Deficient Dry Eye; Lacrimal Tear Deficiency)

Aqueous tear-deficient dry eye implies that dry eye is due to a failure of lacrimal tear secretion. In any form of dry eye due to lacrimal acinar destruction or dysfunction, dryness results from reduced lacrimal tear secretion and volume.^{54,55} This causes tear hyperosmolarity, because, although the water evaporates from the ocular surface at normal rates, it is from a reduced aqueous tear pool. Tear film hyperosmolarity causes hyperosmolarity of the ocular surface epithelial cells and stimulates a cascade of inflammatory events involving MAP kinases and NF κ B signalling pathways^{56,57} and the generation of inflammatory cytokines (interleukin (**IL**)-1 α ; -1 β ; tumor necrosis factor (**TNF**)- α) and matrix metalloproteinases (**MMP**-9).⁵⁸ When lacrimal dysfunction is due to lacrimal gland infiltration and inflammation, inflammatory mediators generated in the gland are assumed to find their way into the tears and be delivered to the ocular surface. However, when such mediators are detected in the tears, it is not usually possible to know whether they derive from the lacrimal gland itself or from the ocular surface (conjunctiva and cornea).

It is uncertain whether evaporation is reduced⁵⁹ or increased⁵⁹⁻⁶⁴ in ADDE. It is possible that this is determined by the stage of the disease. Some studies suggest that the reservoir of lid oil is larger in non-Sjogren syndrome dry

Table 1. Revised international classification criteria for ocular manifestations of Sjogren syndrome

I. Ocular symptoms: a positive response to at least one of the following questions: <ol style="list-style-type: none"> 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions: <ol style="list-style-type: none"> 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests: <ol style="list-style-type: none"> 1. Schirmer I test, performed without anesthesia (≤ 5 mm in 5 minutes) 2. Rose bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)
IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1 , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm ² of glandular tissue ¹⁸
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: <ol style="list-style-type: none"> 1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes) 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts¹⁹ 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer²⁰
VI. Autoantibodies: presence in the serum of the following autoantibodies: <ol style="list-style-type: none"> 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Reprinted with permission from: Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;1:554-8.

antibody) directed against muscarinic receptors within the glands.⁷¹⁻⁷³

There are two forms of SS, and classification criteria have recently been harmonized in a European-American collaboration.⁷⁴ *Primary SS* consists of the occurrence of ADDE in combination with symptoms of dry mouth, in the presence of autoantibodies, evidence of reduced salivary secretion and with a positive focus score on minor salivary gland biopsy.^{75,76} Details of the criteria are presented in Table 1. *Secondary SS* consists of the features of primary SS together with the features of an overt autoimmune connective disease, such as rheumatoid arthritis, which is the most common, or systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis, or mixed connective tissue disease.

Diagnostic criteria for each of these connective tissue disorders have been published.⁷⁷

The precise triggers leading to autoimmune acinar damage are not known in full, but risk factors include genetic profile,⁷⁸ androgen status⁷⁹ (a low androgen pool favoring an inflammatory environment within the target tissues), and exposure to environmental agents, ranging from viral infections affecting the lacrimal gland to polluted environments. A nutritional deficiency in omega-3- and other unsaturated fatty acids and unsupplemented intake of vitamin C has also been reported in patients with SS.⁸⁰ It is generally accepted that environmental factors leading to increased evaporative water loss from the eye (eg, low humidity, high wind velocity, and increased exposure of the ocular surface) may act as a trigger by invoking inflammatory events at the ocular surface through a hyperosmolar mechanism (see Section V).

The ocular dryness in SSDE is due to lacrimal hyposecretion and the accompanying characteristic inflammatory changes in the lacrimal gland, together with the presence of inflammatory mediators in the tears and within the conjunctiva.⁸¹ It is not known whether the conjunctival changes are due to an autoimmune targeting of this tissue or whether they are due to the effect of inflammatory mediators released from the lacrimal glands into the tears.

eye (**NSSDE**)⁶⁵ and that the tear film lipid layer is thicker,⁶⁶ but dynamic studies of the tear film lipid layer in ADDE have shown that spreading of the lipid layer is delayed in the interblink.^{67,68} Additionally, in severe ADDE, spreading may be undetectable by interferometry, suggesting a major defect in the tear film lipid layer. Delayed or absent spreading of the tear film could lead to an increase in water loss from the eye.

ADDE has two major subclasses, SS dry eye (**SSDE**) and non-SS dry eye.

a. Sjogren Syndrome Dry Eye

Sjogren syndrome is an exocrinopathy in which the lacrimal and salivary glands are targeted by an autoimmune process; other organs are also affected. The lacrimal and salivary glands are infiltrated by activated T-cells, which cause acinar and ductular cell death and hyposecretion of the tears or saliva. Inflammatory activation within the glands leads to the expression of autoantigens at the surface of epithelial cells (eg, fodrin, Ro and La)⁶⁹ and the retention of tissue-specific CD4 and CD8 T-cells.⁷⁰ Hyposecretion is amplified by a potentially reversible neurosecretory block, due to the effects of locally released inflammatory cytokines or to the presence of circulating antibodies (eg, anti-M3

The frequency of MGD is higher in patients with SS than in the normal population; thus, a defective tear film lipid layer may contribute to dry eye by leading to excess evaporation.⁸²

b. Non-Sjogren Syndrome Dry Eye

Non-Sjogren syndrome dry eye is a form of ADDE due to lacrimal dysfunction, where the systemic autoimmune features characteristic of SSDE have been excluded. The most common form is age-related dry eye, to which the term KCS has sometimes been applied in the past. However, as noted earlier, the term KCS is now used to describe any form of dry eye. In the 1995 Dry Eye Workshop report, it was referred to as *primary lacrimal disease*,¹ but this term has not been generally adopted. The different forms of NSSDE are briefly discussed below (Table 2).

1) Primary Lacrimal Gland Deficiencies

Age-Related Dry Eye (ARDE): There is some uncertainty as to whether tear dynamics are affected by age in the normal population.⁸³ Mathers et al showed significant age-related correlations for tear evaporation, volume, flow, and osmolarity,⁴⁹ but no such relationship was noted by Craig and Tomlinson⁸⁴ or in other reports of tear turnover,⁸⁵ tear evaporation^{86,87} and lipid layer.⁸⁸ ARDE is a primary disease.

With increasing age in the normal human population, there is an increase in ductal pathology that could promote lacrimal gland dysfunction by its obstructive effect.^{89,89a} These alterations include periductal fibrosis, interacinar fibrosis, paraductal blood vessel loss and acinar cell atrophy.^{89,89a} Damato et al found lymphocytic glandular infiltrates in 70% of lacrimal glands studied and considered this to be the basis of the fibrosis. Appearances were likened to the less severe grades of Sjogren syndrome. They postulated a sequence of periductal fibrosis, interacinar fibrosis and, finally, acinar atrophy. It has been suggested that the low-grade dacryoadenitis could be caused by systemic infection or conjunctivitis⁸⁹ or, alternatively, that subclinical conjunctivitis might be responsible for stenosis of the excretory ducts.^{89a}

Congenital Alacrima: Congenital alacrima is a rare cause of dry eye in youth.⁹⁰ It is also part of certain syndromes,⁹¹ including the autosomal recessive, triple A syndrome (Allgrove syndrome), in which congenital alacrima is associated with achalasia of the cardia, Addison's disease, central neurodegeneration, and autonomic dysfunction. It is caused by mutations in the gene encoding the protein ALADIN, which plays a role in RNA and/or protein trafficking between the nucleus and cytoplasm.^{92,93}

Familial Dysautonomia: Lacrimal dysfunction is a major feature of the autosomal recessive disorder, familial dysautonomia (Riley Day syndrome), in which a generalized insensitivity to pain is accompanied by a marked lack of both emotional and reflex tearing, within a multisystem disorder. There is a developmental and progressive neuronal abnormality of the cervical sympathetic and parasympa-

Table 2. Conditions associated with non-Sjogren syndrome dry eye

Primary lacrimal gland deficiencies

Age-related dry eye
Congenital alacrima
Familial dysautonomia

Secondary lacrimal gland deficiencies

Lacrimal gland infiltration
Sarcoidosis
Lymphoma
AIDS
Graft vs host disease
Lacrimal gland ablation
Lacrimal gland denervation

Obstruction of the lacrimal gland ducts

Trachoma
Cicatricial pemphigoid and mucous membrane pemphigoid
Erythema multiforme
Chemical and thermal burns

Reflex hyposecretion

Reflex sensory block
Contact lens wear
Diabetes
Neurotrophic keratitis
Reflex motor block
VII cranial nerve damage
Multiple neuromatosis
Exposure to systemic drugs

thetic innervations of the lacrimal gland and a defective sensory innervation of the ocular surface, which affects both small myelinated (A δ) and unmyelinated (C) trigeminal neurons.^{94,95} The chief mutation affects the gene encoding an I κ B kinase-associated protein.

2) Secondary Lacrimal Gland Deficiencies

Lacrimal gland infiltration: Lacrimal secretion may fail because of inflammatory infiltration of the gland, as in:

Sarcoidosis: Infiltration of the lacrimal gland by sarcoid granulomata may cause dry eye.⁹⁶

Lymphoma: Infiltration of the lacrimal gland by lymphomatous cells causes dry eye.⁹⁷

AIDS: Dry eye may be caused by lacrimal gland infiltration by T-cells. However, in AIDS-related dry eye, unlike the situation in SSDE, there is a predominance of CD8 suppressor cells, rather than CD4, helper cells.⁹⁸

Graft vs host disease (GVHD): Dry eye is a common complication of GVHD disease, occurring typically around 6 months after hematopoietic stem cell transplantation. It is caused in part by lacrimal gland fibrosis due to colocali-

zation of periductal T-lymphocytes (CD4 and CD8) with antigen-presenting fibroblasts.^{99,100}

Lacrimal gland ablation: The ducts of the main lacrimal gland pass through its palpebral part, so that excision of the palpebral part will be expected to have the same effect as excision of the main gland. Dry eye may be caused by partial or complete ablation of the lacrimal gland at any age, but is not an obligatory consequence, presumably because accessory gland and conjunctival secretion may compensate in some cases.⁵⁵ It is, therefore, of interest that ablation of the main lacrimal gland in squirrel monkeys, while reducing both basal and reflex tear secretion, does not in itself lead to dry eye in that species.¹⁰¹

Lacrimal gland denervation: Parasympathetic denervation of the human lacrimal gland may cause dry eye,¹⁰² and, experimentally in the rat, it causes reduced tear flow and lacrimal protein secretion and activates inflammatory changes in the gland.¹⁰³ The accessory glands are innervated similarly to the main and palpebral lacrimal glands¹⁰⁴ and are assumed to be under similar reflex control; however, evidence for this is lacking.

3) Obstruction of the Lacrimal Gland Ducts

Obstruction of the ducts of the main palpebral and accessory lacrimal glands leads to aqueous-deficient dry eye and may be caused by any form of cicatrizing conjunctivitis (Table 2). In these disorders, it is not uncommon for conjunctival scarring to cause a cicatricial obstructive MGD. In addition, lid deformity influences tear film spreading by affecting lid apposition and dynamics. Specific conditions are discussed below.

Trachoma: Trachoma is a cause of blindness on a global scale, in which corneal opacity and blindness are caused by a combination of tarsal and conjunctival scarring, trichiasis and a cicatrizing meibomian gland obstruction. Dry eye is part of the overall picture, resulting from lacrimal duct obstruction, lid malapposition, and a deficient tear film lipid layer.¹⁰⁵

Cicatricial pemphigoid and mucous membrane pemphigoid: Cicatricial and mucous membrane pemphigoid are mucocutaneous disorders characterized by blistering of the skin and mucous membranes, leading to severe and progressive conjunctival scarring. Dry eye may be caused by lacrimal obstruction, cicatricial MGD, and/or poor lid apposition.¹⁰⁶⁻¹⁰⁸

Erythema multiforme: This is an acute, self-limited mucocutaneous disorder usually precipitated by drugs, infection or malignancy. Conjunctival scarring can lead to dry eye in the manner outlined above.¹⁰⁹

Chemical and thermal burns: Diffuse burns may cause sufficient scarring to cause dry eye.¹¹⁰

4) Reflex Hyposecretion

a) Reflex Sensory Block (Tables 2 and 3)

Lacrimal tear secretion in the waking state is due in large part to a trigeminal sensory input arising chiefly from the nasolacrimal passages and the eye. When the eyes open, there is an increased reflex sensory drive from the exposed

Table 3. Causes of ocular sensory loss

Infective
Herpes simplex keratitis
Herpes zoster ophthalmicus
Corneal surgery
Limbal incision (extra-capsular cataract extraction)
Keratoplasty
Refractive surgery
PRK
LASIK
RK
Neurotrophic Keratitis
Vth nerve/ganglion section/injection/compression
Topical agents
Topical anaesthesia
Systemic medications
Beta blockers
Atropine-like drugs
Other causes
Chronic contact lens wear
Diabetes mellitus
Aging
Trichlorethylene toxicity

ocular surface. A reduction in sensory drive from the ocular surface is thought to favor the occurrence of dry eye in two ways, first, by decreasing reflex-induced lacrimal secretion, and, second, by reducing the blink rate and, hence, increasing evaporative loss.¹¹¹ Experimental evidence has shown that trigeminal denervation in the rabbit modifies the regulation of lacrimal protein secretion.¹¹²

Bilateral sensory loss reduces both tear secretion and blink rate. Bilateral, topical proparacaine decreases the blink rate by about 30% and tear secretion by 60-75%.²² It should be kept in mind that part of the reduction in secretion may be due to local anesthesia of secretory nerve terminals supplying the palpebral and accessory lacrimal glands (Belmonte C: personal communication).

Contact Lens Wear: A reduction in corneal sensitivity occurs in wearers of hard- and extended wear- contact lenses (CLs), possibly contributing^{11,113} to dry eye symptoms in this group of patients. In some studies, increased tear osmolarity has been recorded in association with CL wear.^{113,114} In a rabbit model, trigeminal denervation increases tear film osmolarity and causes the morphological changes characteristic of dry eye.¹¹⁵ Similar arguments have been put forward to advance the concept of LASIK dry eye^{116,117}; although there is evidence to support the concept, counter arguments have been put forward to suggest that at least some of the patients who are symptomatic after LASIK surgery have a neurotrophic deficiency¹¹⁸ or neuralgic disorder.¹¹⁹

Diabetes: Diabetes mellitus has been identified as a risk factor for dry eye in several studies, including large population studies.¹²⁰⁻¹²³ The prevalence was 18.1% in diabetics compared to 14.1% in non-diabetics in the Beaver Dam study,^{121,122} in which the diagnosis of dry eye or dry eye symptoms were self-reported. A similar prevalence (diabetics 20.6%, non-diabetics 13.8%) was reported in a study based on frequency of use of ocular lubricants.¹²³ This

study also noted an association between poor glycemic control (as indicated by serum HbA1C) and frequency of drop use. Goebels¹²⁴ found a reduction in reflex tearing (Schirmer test) in insulin-dependent diabetics, but no difference in tear film breakup time or basal tear flow by fluorophotometry.

It has been suggested that the association may be due to diabetic sensory or autonomic neuropathy, or to the occurrence of microvascular changes in the lacrimal gland.¹²³

Neurotrophic keratitis: Extensive sensory denervation of the anterior segment, involving the cornea and the bulbar and palpebral conjunctiva, as a component of herpes zoster ophthalmicus or induced by trigeminal nerve section, injection, or compression or toxicity, can lead to neurotrophic keratitis. This condition is characterized by features of dry eye, such as tear instability, diffuse punctate keratitis, and goblet cell loss, and also, most importantly, the occurrence of an indolent or ulcerative keratitis, which may lead to perforation.^{115,125}

The sensory loss results in a reduction of lacrimal secretion¹²⁶ and a reduction in blink rate. In addition, it is envisaged that there is a loss of trophic support to the ocular surface¹²⁵ after sensory denervation, due to a deficient release of substance-P or expression of nerve growth factor.¹²⁷⁻¹³¹

b) Reflex Motor Block

Central damage to the VII cranial nerve, involving the nervus intermedius, leads to dry eye due to loss of lacrimal secretomotor function. The nervus intermedius carries postganglionic, parasympathetic nerve fibers (of pterygopalatine ganglion origin) to the lacrimal gland. Dry eye is due to lacrimal hyposecretion in addition to incomplete lid closure (lagophthalmos). Multiple neuromatosis has also been reported as a cause of dry eye.¹³²

An association between systemic drug use and dry eye has been noted in several studies, with decreased lacrimal secretion being the likely mechanism. Responsible agents include: antihistamines, beta blockers, antispasmodics, and diuretics, and, with less certainty, tricyclic antidepressants,

selective serotonin reuptake inhibitors, and other psychotropic drugs.¹²² Additional associations with drying medications were reported by Schein et al, unrelated to the disease for which they were used.¹³³ Use of ACE (angiotensin converting enzyme) inhibitors was associated with a lower incidence of dry eye, and no relationship was found with calcium channel blockers or cholesterol-lowering drugs.¹²²

2. Evaporative Dry Eye

Evaporative dry eye is due to excessive water loss from the exposed ocular surface in the presence of normal lacrimal secretory function. Its causes have been described as *intrinsic*, where they are due to intrinsic disease affecting lid structures or dynamics, or *extrinsic*, where ocular surface disease occurs due to some extrinsic exposure. The boundary between these two categories is inevitably blurred.

a. Intrinsic Causes

1) Meibomian Gland Dysfunction

Meibomian gland dysfunction, or posterior blepharitis, is a condition of meibomian gland obstruction and is the

Table 4. Meibomian gland diseases causing evaporative dry eye

Category	Disease	References
Reduced number	Congenital deficiency	Bron et al ¹³⁷
	Acquired—MGD	
Replacement	Dystichiasis	Bron et al ¹³⁷
	Dystichiasis lymphedema syndrome	Brooks et al ¹³⁸ Kiederman et al ¹³⁹
	Metaplasia	
Meibomian Gland Dysfunction		
Hypersecretory	Meibomian seborrhoea	Gifford ¹⁴⁰ Cowper ¹⁴¹
Hyposecretory MGD	Retinoid therapy	Mathers et al ¹⁴²
Obstructive MGD	Primary or secondary	Bron et al ¹⁴³
	Focal or diffuse	Bron et al ¹⁴³
	Simple or cicatricial	Foulks and Bron ¹³⁴
	Atrophic or inflammatory— note association with dermatoses	Pflugfelder et al ¹⁴⁴
Simple MGD: Primary, or Secondary to:		
Local disease	Anterior blepharitis	
Systemic disease	Acne rosacea; seborrhoeic dermatitis; atopy; ichthyosis; psoriasis;	McCulley Dougherty ¹⁴⁵ McCulley ¹⁴⁶
Syndromes	Anhydrotic ectodermal dysplasia; ectrodactyly syndrome; Turner syndrome	Baum et al ¹⁴⁷ Mondino et al ¹⁴⁸
Systemic toxicity	13-cis retinoic acid	Mathers et al ¹⁴² Lambert and Smith ^{149,150}
	Polychlorinated biphenyls	Iku ¹⁵¹ Ohnishi et al ^{152,153}
	Epinephrine (rabbit)	Jester et al ¹⁵⁴
Cicatricial MGD: Primary, or Secondary to:		
Local disease	Chemical burns; trachoma; pemphigoid; erythema multiforme; acne rosacea; VKC and AKC	

most common cause of evaporative dry eye.¹³⁴⁻¹³⁶ Its multiple causes and associations are listed in Table 4 and include dermatoses, such as acne rosacea, seborrheic dermatitis, and atopic dermatitis. Less common but important associations include the treatment of acne vulgaris with isotretinoin, which leads to a reversible meibomian gland atrophy, loss of acinar density on meibography, and reduced volume and increased viscosity of expressed excreta.¹⁴² Additionally, exposure to polychlorinated biphenyls, through ingestion of contaminated cooking oils, causes a chronic disorder with gross and extensive acneiform skin changes, meibomian seborrhoea with thick excreta and glandular cyst formation. Other organs are affected.^{152,153,155} Meibomian duct keratinization occurs in the experimental model.^{149,150}

MGD can be primary or secondary, simple or cicatricial. In simple MGD, the gland orifices remain located in the skin of the lid, anterior to the mucocutaneous junction. In cicatricial MGD, the duct orifices are drawn posteriorly onto the lid and tarsal mucosa and, hence, are unable to deliver oil to the surface of the tear film. Diagnosis is based on morphologic features of the gland acini and duct orifices, presence of orifice plugging, and thickening or absence of expressed excreta. Methods exist to grade the degree of MGD,¹⁴³ measure the degree of gland dropout (meibography),^{156,157} and the amount of oil in the lid margin reservoir (meibometry).^{65,158} Evidence from several sources suggests that MGD of sufficient extent and degree is associated with a deficient tear film lipid layer, an increase in tear evaporation, and the occurrence of an evaporative dry eye.

It is important to recognize the effect of lid commensal organisms on meibomian lipid composition and its potential effect on tear film lipid layer stability. Shine and McCulley have shown that constitutional differences in meibomian lipid composition exist in different individuals.^{159,160} They identified one group of subjects with low levels of cholesterol esters and esters of unsaturated fatty acids (ie, the "normal-cholesterol absent" group: N[CA]), and another group with high levels of these fractions ("normal-cholesterol present" group: N[CP]). In the latter group, esterases and lipases produced by normal lid commensals (coagulase-negative staphylococci [CoNS], *Propionibacterium acnes* and *S aureus*) can release fatty acids and mono- and diglycerides into the tear film, which may be a source of irritation or of soap formation, said to be responsible for producing "meibomian foam."¹⁶¹ It should also be noted that *S. aureus* growth can be stimulated by the presence of cholesterol and that, in a study by Shine and McCulley, there were twice as many staphylococcal strains on the lid margins of those normal subjects whose meibomian lipid was cholesterol-rich, than in the cholesterol-poor group.¹⁶⁰ Factors such as these may influence the microbial load and type on normal lid margins and influence the development of blepharitis.

2) Disorders of Lid Aperture and Lid/Globe Congruity or Dynamic

An increase in the exposed evaporative surface of the eye occurs in craniostenosis, endocrine and other forms of

proptosis, and in high myopia. Endocrine exophthalmos and, specifically, increased palpebral fissure width, is associated with ocular drying and tear hyperosmolarity.¹⁶² Increasing palpebral fissure width correlates with increased tear film evaporation.⁶¹ Increased ocular surface exposure also occurs in particular gaze positions, such as upgaze,¹⁶³ and in activities that induce upgaze, such as playing pool, where, while aiming, the head is inclined downward and the eyes are in extreme upgaze.

Drying of the ocular surface due to poor lid apposition or to lid deformity, leading to exposure or poor tear film resurfacing, are accepted causes of ocular surface drying, but they have received little formal study.¹⁶⁴ Dry eye problems may be caused by problems of lid congruity after plastic surgery of the lids.¹⁶⁵

3) Low Blink Rate

Drying of the ocular surface may be caused by a reduced blink rate, which lengthens the period during which the ocular surface is exposed to water loss before the next blink.¹⁶⁶ Methods have been developed to record the blink rate and to relate this to the development of dry eye.¹⁶³ This may occur as a physiological phenomenon during performance of certain tasks of concentration, eg, working at video terminals¹⁶⁷ or microscopes, or it may be a feature of an extrapyramidal disorder, such as Parkinson disease (**PD**).

The reduced blink rate in PD is due to a decrease in the dopaminergic neuron pool of the substantia nigra and is proportional to disease severity.¹⁶⁸ Reduced blink rate is regarded by some authors as the basis of dry eye in PD.¹⁶⁹ Biousse et al found blink rate and tear film breakup time (**TFBUT**) to be significantly reduced in untreated, early-onset PD patients with a significantly increased frequency of dry eye symptoms, whereas the Schirmer test and rose bengal staining measurements were no different in PD patients than in controls.¹⁷⁰ However, other authors report a reduced lacrimal secretion in PD,¹⁷¹⁻¹⁷³ and abnormalities of tear film stability, fluorescein and rose bengal staining, tear meniscus height, and meibomian gland function.¹⁷³

Tamer et al reported dry eye symptoms in 87.5% of PD patients versus 20.6% of age-matched controls, with a mean total number of abnormal dry eye tests of 3.10 ± 1.8 in PD, versus 0.35 ± 0.9 in controls. ($P < 0.001$). Each test was significantly abnormal in PD patients versus controls, and all the tear tests (except meibomian gland function and meniscus height) showed a significant correlation with a PD severity index. The overall number of abnormal tests in PD patients was inversely related to the blink rate.

On the basis of these findings, Tamer et al postulated several mechanisms by which PD may induce dry eye. 1) Reduced blink rate and impaired meibomian oil delivery to the tear film can increase evaporative loss. They also suggest that a reduced blink rate could impair the clearance of lipid-contaminated mucin.¹⁷⁴ 2) Experimentally, androgens are required for the normal functioning of both the lacrimal^{175,176} and meibomian glands,^{177,178} and there is clinical evidence that dry eye symptoms are promoted by

blockade of androgen receptors.⁴³ The levels of circulating androgens are low in a large proportion of PD patients,¹⁷⁹ and it is suggested that this may contribute to lacrimal and meibomian dysfunction. 3) In addition, decreased reflex tearing in PD has been attributed to autonomic dysfunction, reflecting the presence of Lewy bodies in the substantia nigra, sympathetic and peripheral parasympathetic ganglia.¹⁸⁰ Magalhaes et al found evidence of autonomic failure in about a third of patients with PD.

In conclusion, it is possible that dry eye disease in PD has multiple causes.

b. Extrinsic Causes

1) Ocular Surface Disorders

Disease of the exposed ocular surface may lead to imperfect surface wetting, early tear film breakup, tear hyperosmolarity, and dry eye. Causes include vitamin A deficiency and the effects of chronically applied topical anesthetics and preservatives.

Vitamin A Deficiency: Vitamin A deficiency may cause dry eye (xerophthalmia) by two distinct mechanisms. Vitamin A is essential for the development of goblet cells in mucous membranes and the expression of glycoconjugate mucins.^{181,182} These are deficient in xerophthalmia, leading to an unstable tear film characterized by early tear film break up. Vitamin A deficiency can cause lacrimal acinar damage, and, therefore, some patients with xerophthalmia may have a lacrimal, aqueous tear-deficient dry eye.¹⁸³

Topical Drugs and Preservatives: Many components of eye drop formulations can induce a toxic response from the ocular surface. Of these, the most common offenders are preservatives, such as benzalkonium chloride (**BAC**), which cause surface epithelial cell damage and punctate epithelial keratitis, which interferes with surface wettability. Use of preserved drops is an important cause of dry eye signs and symptoms in glaucoma patients, and it is usually reversible on switching to nonpreserved preparations.¹⁸⁴ Therefore, frequent applications of preserved artificial tear preparations should be avoided.

Topical anesthesia causes drying in two ways. It reduces lacrimal secretion by reducing sensory drive to the lacrimal gland and also reduces the blink rate. It has also been suggested that anesthesia of those lacrimal secretory nerve terminals close to the surface of the upper fornix (innervating the palpebral and accessory portions of the lacrimal gland) may also be blocked by topical anaesthetics (Belmonte C: personal communication).

Chronic use of topical anesthetics can cause a neurotrophic keratitis leading to corneal perforation.^{185,186}

2) Contact Lens Wear

Contact lens wear is prevalent in the developed world, with 35 million wearers cited in the USA in the year 2000.¹⁸⁷ The causes of CL-related symptoms and of lens intolerance are, therefore, of personal and general economic importance. The primary reasons for CL intolerance are discomfort and dryness.^{188,189} In recent years, a number

of questionnaires have been developed to identify dry eye symptoms in CL wearers.^{45,190-192} Use of such questionnaires has indicated that about 50% of CL wearers report dry eye symptoms.¹⁹¹⁻¹⁹⁴ CL wearers are 12 times more likely than emmetropes and five times more likely than spectacle-wearers to report dry eye symptoms.¹⁹⁵

In a large cross-sectional study of CL wearers (91% hydrogel and 9% gas permeable lenses), several factors were found to be associated with dry eye diagnosed using the Contact Lens Dry Eye Questionnaire (**CLDEQ**). Pre-lens tear film (**PLTF**) thinning time was most strongly associated with dry eye (dry eye: 8.23 ± 5.67 seconds; non-dry eye: 11.03 ± 8.63 seconds. [$P = 0.0006$]), followed by nominal CL water content and refractive index.¹¹⁴

The pre-lens lipid layer thickness was less in dry eye subjects and correlated well with the pre-lens tear film thinning time. This, together with poor lens wettability, could be a basis for a higher evaporative loss during lens wear and was attributed to potential changes in tear film lipid composition, rather than to a loss of meibomian gland oil delivery.

Patients wearing high water-content hydrogel lenses were more likely to report dry eye. This is a controversial area in the literature. In a study of the effects of five hydrogel lenses on tear film physiology, Thai et al found that all the examined soft CL materials increased the evaporation rate and decreased the tear film thinning time.¹⁹⁶ The surface wetting ability of the CL materials was the same, regardless of special surface lens treatments. Efron et al found that patients wearing low water CLs, which maintained their hydration, were free from symptoms.¹⁹⁷ However, other studies reported no correlation between CL hydration and dry eye symptoms¹⁸⁹ and no relationship between lens hydration and tear film thinning time and dry eye symptoms¹⁹⁸ or evaporative water loss.¹⁹⁹ Dry eye was associated with a higher tear osmolarity, but not in the range normally associated with dry eye tear hyperosmolarity. The authors commented that this lower value might have been caused by reflex tearing at the time of sampling.¹¹⁴

Women were found to report dry eye more frequently than men, with 40% of the men and 62% of the women classified as having dry eye ($P < 0.0001$).¹¹⁴ The reasons for this were not explored, but potential contributing factors were considered to be hormone fluctuations during the menstrual cycle or after menopause and use of oral contraceptives or hormone replacement therapy. It was also noted that symptom reporting by women, in general, tends to be higher than that by men.²⁰⁰ Some studies show no effect of oral contraceptives or hormone levels on a range of tear parameters.²⁰¹

Glasson et al²⁰² showed that intolerance to hydrogel lenses in normals correlates with a shorter blink interval, noninvasive TFBUT and phenol red thread test length and a lower tear meniscus height and area; this has had predictive power in people presenting for CL fitting. A formula linking symptoms (using the McMonnies Dry Eye Questionnaire), non-invasive tear break up time (NITFBUT), and tear meniscus height predicted potential intolerant subjects with a sensitivity of 100%, specificity of 57%, and accuracy of 78%. Intolerance was also associated with an increase in degraded

could account for complaints of intermittent blurred vision in some CL wearers and may provide a stimulus to blink.²⁰⁷

3) Ocular Surface Disease

There is evidence that various forms of chronic ocular surface disease result in destabilization of the tear film and add a dry eye component to the ocular surface disease. Allergic eye disease offers a well-studied example.²⁰⁸ Also, any form of dry eye, whatever its origins, may cause at least a loss of goblet cell numbers, so that an ocular surface element is added.²⁰⁹

4) Allergic Conjunctivitis

Allergic conjunctivitis takes several forms, which include seasonal allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. The general mechanism leading to disease is that exposure to antigen leads to degranulation of IgE-primed mast cells, with the release of inflammatory cytokines. A Th2 response is activated at the ocular surface, initially in the conjunctival and, later, in the corneal epithelium, subsequently leading to submucosal changes. There is stimulation of goblet cell secretion and loss of surface membrane mucins.²¹⁰ Surface epithelial cell death occurs, affecting conjunctival and corneal epithelium (punctate keratoconjunctivitis). Surface damage and the release of inflammatory mediators leads to allergic symptoms and to reflex stimulation of the normal lacrimal gland.

Surface irregularities on the cornea (punctate epithelial keratitis and shield ulcer) and conjunctiva can lead to tear film instability and, hence, to a local drying component to the allergic eye disease. In chronic disease, there may be meibomian gland dysfunction, which could exacerbate surface drying by interfering with the tear film lipid layer. Lid swelling, eg, in vernal catarrh and atopic keratoconjunctivitis, can interfere with lid apposition and tear film spreading, thus exacerbating the dry eye.

Ocular allergy was noted to be a risk factor for dry eye in the Beaver Dam study, although the concomitant use of systemic medications, such as antihistamines, was recognized as a potential contributor.¹²² Factors leading to a dry eye state in allergic eye disease are discussed by Fujishima et al.²¹¹

C. The Causative Mechanisms of Dry Eye

From the above discussion, it can be seen that certain core mechanisms are envisaged at the center of the dry eye process that can initiate, amplify, and potentially change the character of dry eye over time. These are *tear hyperosmolarity* and *tear film instability*. This section is intended to show how the several subclasses of dry eye activate these core mechanisms and explain the features of various forms of dry eye. The interactions of various etiologies with these core mechanisms are summarized in Figure 2.

It should be noted that an attractive mechanistic schema for dry eye has been presented in detail by Baudouin.²¹² In this concept, two levels of involvement are identified. The first level includes the known risk factors or causes of dry eye that ultimately lead to a series of secondary biological cascades, resulting in breakdown of the tear film and ocular

surface. This pathbreaking conceptual approach describes the relationship of early disparate events to biological responses common to all forms of dry eye, many of which are mutually reinforcing. This leads to a vicious circle or loop. It is thought that early therapeutic intervention may disrupt this loop. The schema in Figure 2, developed from the discussion of our Subcommittee, emphasizes the core biological mechanisms described in this text.

1. Tear Hyperosmolarity

Tear hyperosmolarity is regarded as the central mechanism causing ocular surface inflammation, damage, and symptoms, and the initiation of compensatory events in dry eye. Tear hyperosmolarity arises as a result of water evaporation from the exposed ocular surface, in situations of a low aqueous tear flow, or as a result of excessive evaporation, or a combination of these events. Nichols et al have demonstrated the wide variation of tear film thinning rates in normal subjects, and it is reasonable to conclude that, for a given initial film thickness, subjects with the fastest thinning rates would experience a greater tear film osmolarity than those with the slowest rates.¹¹⁴ Rapid thinning may be hypothesized as a risk factor for tear hyperosmolarity.

Since the lacrimal fluid is secreted as a slightly hypotonic fluid, it will always be expected that tear osmolarity will be higher in the tear film than in other tear compartments. There are also reasons to believe that osmolarity is higher in the tear film itself than in the neighboring menisci. One reason for this is that the ratio of area to volume (which determines the relative concentrating effect of evaporation) is higher in the film than the menisci.²¹³

Hyperosmolarity stimulates a cascade of inflammatory events in the epithelial surface cells, involving MAP kinases and NF κ B signalling pathways⁵⁶ and the generation of inflammatory cytokines (IL-1 α ; -1 β ; TNF- α) and MMPs (MMP9),⁵⁸ which arise from or activate inflammatory cells at the ocular surface.²¹⁴ These concepts are supported by studies of desiccating stress in the experimental model,²¹⁵ which have demonstrated the evolution of inflammatory cytokine release and MMP activation.⁵⁷ There is evidence that these inflammatory events lead to apoptotic death of surface epithelial cells, including goblet cells²¹⁶; thus, goblet cell loss may be seen to be directly related to the effects of chronic inflammation.^{217,218} Goblet cell loss is a feature of every form of dry eye, and consistent with this is the demonstration of reduced levels of the gel mucin MUC5AC in dry eye.^{219,220} With the evolution of dry eye, other factors are likely to amplify these initiating inflammatory events, and the contribution of direct autoimmune targeting of the ocular surface cannot be excluded.

In the initial stages of dry eye, it is considered that ocular surface damage caused by osmotic, inflammatory or mechanical stresses (loss of surface lubrication) results in reflex stimulation of the lacrimal gland. Reflex trigeminal activity is thought to be responsible for an increased blink rate and a compensatory response, increased lacrimal secretion. In the case of lacrimal gland insufficiency (SSDE or NSSDE), the

reflex secretory response will be insufficient to fully compensate for the tear film hyperosmolarity, and in the steady state, this form of dry eye will be characterized by a hyperosmolarity state with low tear volume and flow. In evaporative dry eye (eg, caused by MGD), it can be hypothesized that, since the lacrimal gland is initially healthy in this situation, lacrimal secretory compensation is at first able to compensate for tear film hyperosmolarity. Ultimately it would be expected that in the steady state, dry eye would be a condition of hyperosmolarity with a tear volume and flow greater than normal. This possibility of a high volume dry eye is supported by the increased tear secretion (based on the Schirmer I test) in patients with MGD compared to normals,²²¹ although this evidence requires support by studies using more sophisticated tests of tear flow. In the study of Shimazaki et al, despite the increased tear flow, particularly in the gland dropout group, there was a shorter TFBUT and greater degree of dye staining in those with MGD than in those without.

Excessive reflex stimulation of the lacrimal gland experimentally may induce a *neurogenic inflammatory cytokine response* within the gland, leading to the sequence of glandular autoantigen expression, T-cell targeting, and the release of inflammatory mediators into the tears.^{20,222} It has also been considered to induce a state of "lacrimal exhaustion" due to excessive reflex stimulation of the lacrimal gland.^{223,224} However, these provocative hypotheses await experimental support.

Knowledge is insufficient regarding the natural history of different forms of dry eye in relation to ocular surface sensitivity. Most reports,^{144,225,226} but not all,¹¹⁹ suggest that corneal sensitivity is impaired in chronic dry eye disease, suggesting that an initial period of increased reflex sensory activity is followed by a chronic period of reduced sensory input. This is likely to be the result of the longterm effects of inflammatory mediators on sensory nerve terminals supplying the ocular surface, and there is evidence of morphological changes in the sub-basal nerve plexus.²²⁷ At this stage of dry eye, the reflex sensory drive to lacrimal secretion becomes reduced, which would reverse any compensatory drive to lacrimal secretion that is postulated for the earlier phase of the disease. This would be expected to reduce the lacrimal secretory response, regardless of the etiology of the dry eye, and would therefore exacerbate both ADDE and EDE by reinforcing the low volume state in ADDE and converting a potentially high volume state in MGD-based EDE to a normal or low volume state due to an added lacrimal deficiency. The sensory drive to the blink reflex might be expected to be similarly affected, although there is no evidence to this effect and this area requires further study.

The above proposal may explain why a clear clinical separation between ADDE and EDE may at times be difficult to support on the basis of substantive tests. Thus, while there are studies that indicate, as expected, that *tear evaporation rate is increased* in MGD,^{62,63,82,83,221,228} or where there is an incomplete or absent tear film lipid layer²²⁹ in some groups of MGD, evaporation rate may be normal.²²¹ Similarly, an increased evaporation rate has been reported by some authors

in ADDE,⁵⁹⁻⁶³ and a decreased rate by others.⁵⁹ Again, whereas a *reduction in tear flow* is the hallmark of ADDE,^{63,83,124} a reduction in flow has also been reported with MGD.^{63,83}

These findings appear contradictory, but may simply highlight our ignorance of the natural history of the primary disorders. Thus, there is evidence that spreading of the tear film lipid layer is retarded in severe ADDE, which has been attributed to the effect of the thinned aqueous phase of the tear film. Conversely, as noted earlier, it may be conceived that a loss of corneal sensitivity in EDE could reduce the reflex drive to tear secretion and, hence, result in a combined form of dry eye. These postulated interactions, occurring over time, may explain the overlap of findings in these two disorders and fit in to the general concept of a vicious circle in which widely varying influences combine to cause dry eye with a complex profile.

2. Tear Film Instability

In some forms of dry eye, tear film instability may be the initiating event, unrelated to prior tear hyperosmolarity.

1) While frank tear film instability in the form of early tear film break up may readily be accepted as a component of dry eye, more subtle degrees of tear film instability may also predispose to dry eye complications in response to ocular surface stress. Thus, Goto et al reported that in a group of patients undergoing LASIK surgery and showing no features of dry eye by standard tests, those who showed tear film instability by the tear film analysis system (TMS) showed a greater decrease in tear film stability and more severe symptoms and dry eye signs, including punctate keratitis, postoperatively.¹⁰

2) Where the TFBUT is less than the blink interval, it is implied that tear film breakup in that individual is occurring normally in the waking state. (This state is expressed by the Ocular Protection Index, which is the ratio of the TFBUT divided by the blink interval.²³⁰ (See relevant template website [www.tearfilm.org]). When this value is less than 1, then tear film breakup occurs in the waking, open-eye condition. If the TFBUT is greater than the blink interval but less than 10 seconds, then this TFBUT value is still currently regarded as an index of tear film instability. Where tear film instability represents tear film breakup occurring within the blink interval, it is assumed to give rise to local drying and hyperosmolarity of the exposed surface, to surface epithelial damage, and to a disturbance of glycocalyx and goblet cell mucins. The latter consequently exacerbates the tear film instability as part of a vicious circle of events.

Two examples of this clinical sequence, where tear film instability is due to a disturbance of ocular surface mucins, are xerophthalmia²³¹ and allergic eye disease.²¹¹ The initial loss of tear stability in vitamin A deficiency results from a reduced expression of mucins at the ocular surface and a loss of goblet cells.^{183,232} In seasonal allergic conjunctivitis or vernal keratoconjunctivitis, a disturbance of mucin expression at the surface of the eye is due, initially, to an IgE-mediated type I hypersensitivity mechanism, leading to the release of inflammatory mediators in response to allergen challenge.

Other examples include the actions of topical agents, in particular, preservatives such as BAC, which excite the expression of

Table 5. Dry eye severity grading scheme

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+ / ++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

*Must have signs AND symptoms. TFBUT: fluorescein tear break-up time. MGD: meibomian gland disease

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inflammatory cell markers at the ocular surface, causing epithelial cell damage, cell death by apoptosis, and a decrease in goblet cell density.²³³ There is both clinical and experimental evidence to support such events.²³⁴⁻²³⁸ In a study of patients treated for glaucoma for at least one year, flow cytometry demonstrated a greater expression of inflammatory markers (HLA-DR and ICAM-1) in those receiving preserved drops (BAC) than in normals or those receiving unpreserved drops. Use of preservative was associated with a lower expression of MUC5AC and the lowest MUC5AC levels were associated with the highest ICAM-1 and HLA-DR levels.²³⁹ This negative correlation suggested inflammation as a possible basis for the decreased mucin expression, in addition to any direct effect of BAC on goblet cells themselves.

Considering the possible relationship between these findings and dry eye, Pisella et al, in an unmasked study of 4107 glaucoma patients, found that the frequency of ocular surface changes was twice as high in those receiving preserved drops than in those receiving unpreserved drops, and the frequency of signs and symptoms was dose-related.¹⁸⁴

CL wear may also provide a route of entry into the dry eye mechanism, a route in addition to reduced corneal sensitivity. For a considerable time, CL wear has been recognized to cause changes to the ocular surface epithelia. Knop and Brewitt demonstrated surface epithelial metaplasia and a reduced goblet cell density with hydrogel lens wear.^{240,241} Other studies have shown an increase in goblet cell density evolving over a period of 6 months in subjects wearing polymacon, galyfilcon, and silicone hydrogel lenses.^{242,243} In another study, no change in goblet cell density was found after 6 months wear of a daily

disposable lens with a 2-week wearing schedule, and further studies suggest that the goblet cell responses may differ between hard and soft CLs.²⁴⁴

A recent study combining impression cytology with flow cytometry demonstrated an increase in inflammatory markers (HLA-DR and ICAM-1) at the ocular surface and a nonsignificant trend toward a decrease in the expression of mucin markers (MUC5AC) in patients with a history of chronic CL wear.²⁴⁵ A later study has shown no difference between CL wearers and non-CL wearers in mucin expression (MUC5AC and the carbohydrate epitope H185, a marker for MUC 16) in tears or impression cytology samples.¹⁸² In summary, it appears that CL wear may activate proinflammatory markers and stimulate the ocular surface epithelia to a variable degree. It is not yet possible to say whether these changes alone predispose individuals to the occurrence of dry eye with CL wear.

D. The Basis for Symptoms in Dry Eye

The basis for symptoms in dry eye is not truly known but may be surmised from a consideration of the etiologies, mechanisms, and responses of dry eye to therapy.²⁴⁶ The occurrence of symptoms implies the activation of sensory nerves subserving nociception at the ocular surface.^{247,248} Candidates include tear and ocular surface hyperosmolarity – including tear film break-up in the interblink, shear-stress between the lids and globe in response to reduced tear volume, and/or the reduced expression of mucins at the ocular surface, the presence of inflammatory mediators at the surface of the eye, and, finally, hypersensitivity of the nociceptive sensory nerves.

E. Classification of Dry Eye on the Basis of Severity

The Subcommittee considered that there was considerable clinical utility to adopting a classification of disease based on severity. The basic scheme of the Delphi Panel Report was adopted and modified to produce the third component of the recommendation (Table 5).

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