

# Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes

Chairman: Michael A. Lemp, MD

## Introduction

Over the last 20 years our knowledge of the pathogenetic factors involved in dry eye states has grown significantly. It is now generally recognized that the term "dry eye" is a rubric to describe a variety of conditions of diverse origin which affect the tear film and/or the ocular surface.<sup>1</sup> Recent findings show differences between Sjögren's-associated keratoconjunctivitis sicca (KCS) and non-Sjögren's KCS.<sup>2-4</sup> Neurotransmitters,<sup>5,6</sup> viruses,<sup>7</sup> and hormones<sup>8,9</sup> are important in regulating tear production and immune activity in the lacrimal glands and the ocular surface. Finally, meibomian gland dysfunction can increase tear evaporation with an increase in tear film osmolarity and resultant ocular surface disease.<sup>10</sup>

Despite these advances, there has been a lack of consensus on the appropriate diagnostic criteria, classification of disease states, the aim of specific diagnostic tests, the role of subjective assessment, clinical trial designs, and interpretation of results. This has led to the use of diverse clinical trial designs, which hampers treatment comparisons and leads to confusion over desirable end-points.

At the International Symposium on the Lacrimal Gland, Tear Film, and Dry Eye Syndromes in 1992 (Proceedings, Plenum Press, New York and London, 1994), a call for an "academic/clinical practice/industry/governmental effort to develop a consensus" was issued.<sup>11</sup> In response to this, the National Eye Institute and leading industry groups sponsored a National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes. The workshop was organized and chaired by the author. Two 1 and one-half day meetings in December 1993 and again in December 1994 were held on the campus of the National Institutes of Health. The aim of the workshops was to provide clinical instruments for the conduct of epidemiological studies and clinical trials. This report was drafted in accordance with the recommendations of the American Medical Association concerning consensus conferences.<sup>12</sup>

The objective of the workshop was to identify areas of consensus and/or disagreement in the design and interpretation of clinical trials in dry eyes. To this end, a group of individuals from academic and clinical fields, industry, and governmental agencies met. Individuals were invited to participate based on their clinical contributions to the field, corporate responsibili-

ties, and/or regulatory functions. The format of the meeting was as follows:

A brief overview of various factors concerning dry eyes was given. This was followed by discussion. Three areas of critical interest were identified:

1. The development of a classification system for dry eyes.
2. The standardization of clinical tests used to diagnose dry eye states and assess treatment effects.
3. The development of epidemiologic data concerning dry eyes.

Participants were separated into three break-out groups, each of which submitted interim reports. Two separate committees were formed to address the first two issues, and these committees met during the following year. The large group met again one year later to hear and discuss the committee reports and any additional epidemiologic information.

## Report of the Classification Study Group

The purpose of the group was to develop a practical classification of dry eye disorders and to consider which categories of diagnostic tests might be used to discriminate between different disorders. The Standardization of Clinical Tests Group paid particular attention to the precision and accuracy of the recommended tests and their availability to clinicians and the research community.

The aims of the Classification Study Group were:

1. To produce a global\* definition of dry eye.
2. To define the major classes, subclasses, and types of dry eye.
3. To recognize the existence of dry eye states of mixed etiology.
4. To define the diagnostic tests, with examples, which might be applied.

The current terminology of dry eye is complicated by different usage between different countries. The familiar term KCS was coined by Sjögren to define the ocular surface disorder accompanying the autoimmune exocrinopathy that he defined.<sup>13</sup> This is how the term is used in some countries. However, in other

\*The term global in this context refers to the broad area of dry eyes encompassing all the subsets

countries, the term Sjögren syndrome-KCS is used to define the ocular surface disease that occurs in Sjögren syndrome, and non-Sjögren KCS is used to define ocular surface disease due to primary, age-related lacrimal insufficiency. This is an acceptable use of the term KCS as long as it is understood that there are other forms of lacrimal insufficiency that give rise to dry eye, such as that due to sarcoidosis, AIDS, or graft-versus-host disease.

The term KCS is also used as a synonym for dry eye. With this use, the term is applied equally to disorders involving lacrimal insufficiency and those associated with excessive evaporation of tears, such as meibomian gland disease.

Because of this varied use of the term KCS, it is not possible to justify one particular use as opposed to another. Therefore, in the classification that follows, the broader definition is used and KCS is taken to be synonymous with the general term dry eye.

### The global aspects of dry eye

*A Global Definition:* Dry eye is most frequently caused by a decrease of lacrimal gland function but may also occur when lacrimal gland function is normal. The various etiologies may act independently or may interact to cause dry eye. These disorders or combinations have features in common which may be embraced by this single definition:

***Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.***

Because the definition is global, it is appropriate for any etiology of dry eye and does not describe a specific cause. Although it embraces most causes, it must be recognized that it is an operational definition that may need to be modified for specific situations. Also, the definition is minimal, and it should not be concluded that the features of dry eye are limited to this definition. Thus:

1. The definition states that ocular surface damage is "interpalpebral" in dry eye. This is usually the case but should not be regarded as always so. Ocular surface damage in dry eye may spread beyond the interpalpebral region of the globe to affect the superior surface of the globe.
2. Dry eye usually causes symptoms, but the possibility is acknowledged that in some patients in whom the diagnosis is strongly suggested on the basis of signs, symptoms could be absent. Since the operational criteria usually employed for the diagnosis of dry eye would ordinarily include a symptom score, a small fraction of individuals will be excluded by the above definition. This would have to be acknowledged in certain protocols.
3. In the same way, a dry eye condition could exist, supported by symptoms and signs (e.g., reduced tear secretion), and yet it might not be possible to show ocular surface damage by current methods. This possibility should be recognized and again would need to be ac-

counted for in certain protocols.

### Global criteria for dry eye

The global definition recognizes a commonality among all forms of dry eye which can be used to develop diagnostic tests. Global criteria are required for the diagnosis of dry eye which, like the global definition, do not necessarily identify a particular etiology. The working group considered that most forms of dry eye will exhibit the following features:

1. Symptoms
2. Interpalpebral surface damage
3. Tear instability
4. Tear hyperosmolarity

### Global tests for dry eye

The above features are embodied in the following tests, which are proposed as global tests for dry eye:

1. Validated questionnaire of symptoms
2. Demonstration of ocular surface damage
3. Demonstration of tear instability
4. Demonstration of tear hyperosmolarity

*A Validated Questionnaire of Symptoms:* Because an important therapeutic goal<sup>†</sup> is to improve symptoms, all clinical trials concerning the treatment of dry eye include an assessment of symptoms, which include heaviness of the lids, foreign body sensation, burning, stinging, and photophobia.

Validated questionnaires (in certain age groups) are available which attempt to characterize dry eye in terms of symptoms and for which sensitivity and specificity information has been derived.<sup>14,15</sup> It is proposed that a positive response to such a questionnaire be included within the global criteria for dry eye.

As noted by the Epidemiological Study Group, a questionnaire can be used to obtain data that would lead to a wider understanding of the demographics of dry eye, as well as medical and other risk factors. These aspects are dealt with elsewhere.

*Demonstration of Ocular Surface Damage:* Ocular surface damage may be demonstrated in several ways. Ocular surface damage can be quantified using vital dyes. Rose bengal staining has been incorporated into international standards for the diagnosis of Sjögren's and non-Sjögren's dry eye.<sup>16-18</sup> Van Bijsterveld (1969) described a scoring system for rose bengal staining, which has high sensitivity and specificity.<sup>19</sup>

Recently Lissamine Green has been offered as an alternative that is more readily tolerated.<sup>20</sup> Fluorescein may also be used as an alternative if the fluorescence from the ocular surface or conjunctiva and cornea is viewed through yellow filters.<sup>21</sup>

It is recommended that surface damage—assessed by staining with vital dyes—be used as a global criterion of dry eye. Details of the rose bengal and other tests are described in the report of the Working Party on Diagnostic Tests.

Other forms of ocular surface damage or reaction may be encountered in dry eye. The various indices of change are listed in Table I. Most of these have not been incorporated into

<sup>†</sup> Sensitivity and specificity are specific to group studied (e.g., age, sex) and are dependent on actual criteria used to establish a diagnosis.

**TABLE I** Indices of Surface Damage in Dry Eye

- Fall in area of corneal epithelial cells
- Rise in area of conjunctival epithelial cells
- Fall in the nuclear/cytoplasmic ratio
- Presence of Snake chromatin
- Fall in goblet cell density
- Increased squamous metaplasia

diagnostic tests.

**Demonstration of Tear Instability:** Norm<sup>22</sup> and Lemp<sup>23</sup> recommended recording the break-up of the tear film after the instillation of fluorescein dye as a test of tear stability. The (fluorescein) tear break-up time (BUT or FBUT) has been shown to be dependent on the reduction of tear surface tension by mucins.<sup>24</sup> When tear mucin is reduced, as reflected by a fall in conjunctival goblet cell density<sup>25</sup> or a rise in tear surface tension,<sup>26</sup> the BUT is also reduced.

Goblet cell density is reduced in a number of forms of dry eye (e.g., in disorders of the lacrimal and of the meibomian glands) with resultant reduction in BUT. It is not known to what extent ocular surface mucin,<sup>27</sup> as opposed to goblet cell mucin, contributes to the reduced BUT of dry eye, or whether there are other contributing factors. However, BUT offers a valuable parameter to include within the diagnostic global criteria for dry eye.

It should be noted that tear surface tension would make a reasonable surrogate test for tear stability as would direct tests of tear mucin, which are currently under development. Unfortunately, neither of these tests is currently available for routine clinical use.

It is recommended that a test of tear stability (BUT) be used as a global criterion of dry eye.

**Demonstration of Tear Hyperosmolarity:** Convincing arguments have been advanced which suggest that hyperosmolarity is the common denominator between all forms of dry eye. Tear hyperosmolarity has been demonstrated in experimental studies of tear deficient and evaporative dry eye;

**TABLE II** Major classes of dry eye

**Tear-Deficient Dry Eye**

- Non-Sjögren dry eye
- Sjögren syndrome dry eye

**Evaporative Dry Eye**

- Blepharitis Associated
  - Anterior Blepharitis
  - Meibomian Gland Disease
- Ocular Mucin Deficiencies
- Blink Disorders
- Disorders of lid aperture and lid/globe congruity
- Ocular Surface Disorders
- Other Tear film disorders [Contact lens induced?]

surface disease has been shown to be dependent on and proportional to increases in tear film osmolarity and duration of disease.<sup>28-31,55</sup> It has been suggested that hyperosmolarity is the primary causative mechanism in this group of disorders, leading to discomfort, ocular surface damage, and inflammation.<sup>32</sup>

For this reason, hyperosmolarity should be regarded as an important global criterion for the diagnosis of dry eye. However, a simple technique to measure tear hyperosmolarity is not yet readily available to all researchers and clinicians. The freezing point depression method is expensive and technically difficult.<sup>28</sup> Although measurement of osmolarity by the water vapor pressure method is simple, the technique must be sufficiently tested in dry eye conditions.<sup>33</sup> For this reason, measurement of tear film osmolarity will be regarded as a secondary test until such time as a prevailing test is available.

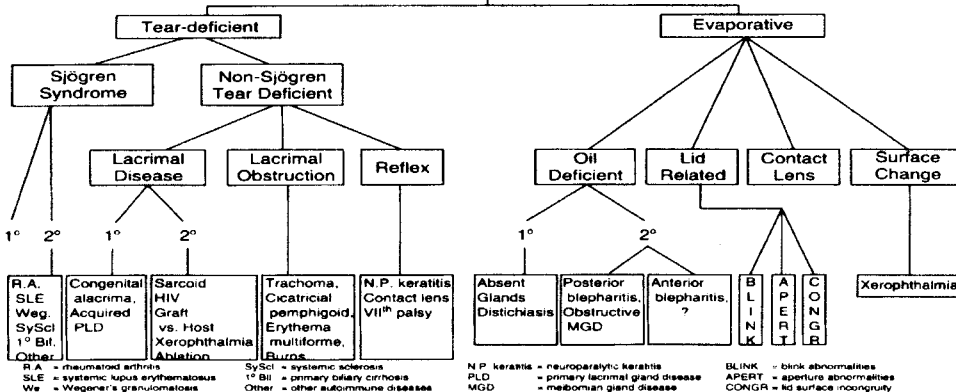
It is recommended that hyperosmolarity be used as a global criterion of dry eye by those researchers who have an accurate means of testing available.

Other criteria for the global diagnosis of dry eye may also be considered, such as the tear ferning test, which has been used for diagnostic purposes and to identify degree of severity.<sup>34</sup>

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**CLASSIFICATION OF DRY EYE**

**DRY EYE - KCS**



**Figure 1** Classification system and diagnostic algorithm for dry eye. (See text for full discussion.)

## Major classes of dry eye

Dry eyes may be assigned to two major classes: Tear-deficient dry eye and evaporative dry eye (Table II). Relationships may be more clearly seen in Figure 1, which is a diagnostic algorithm based on this classification.

1. In tear-deficient dry eye, there is a disorder of lacrimal function or a failure of transfer of lacrimal fluid into the conjunctival sac. This results in a reduction in the flow of tears and a fall in volume of tears in the conjunctival sac. Lacrimal disease is associated with a quantitative reduction in secreted lacrimal proteins.<sup>36</sup> Tear-deficient dry eye is the largest category of dry eye.
2. In tear-sufficient dry eye, lacrimal function is normal, and in most cases if not all, the tear abnormality is due to increased tear evaporation.<sup>32</sup> It may reasonably be termed evaporative dry eye.

Each of the disorders listed in Table II is considered to be independently capable of causing dry eye. Some of the disorders may occur together and act in concert to cause dry eye. An example of the latter is the common association of aqueous-deficient disease with obstructive meibomian gland disease.

Each of these disorders is considered from the dry eye aspect only, although many of them may cause changes to the external eye in addition to those that are the basis for the dry eye. The scarring of cicatricial conjunctivitis is one example. Such features help to make up the disease picture typical for this form of dry eye. In some instances there may be uncertainty as to the contribution of these accessory factors to the dry eye picture and they may act as a confounding influence in diagnosis. Thus the symptoms suffered by a patient with anterior blepharitis with dry eye are likely to be due to the inflammatory lid disease as well as to the dry eye and the signs of interpalpebral staining after trigeminal section are likely to be due to neural causes in addition to dry eye.

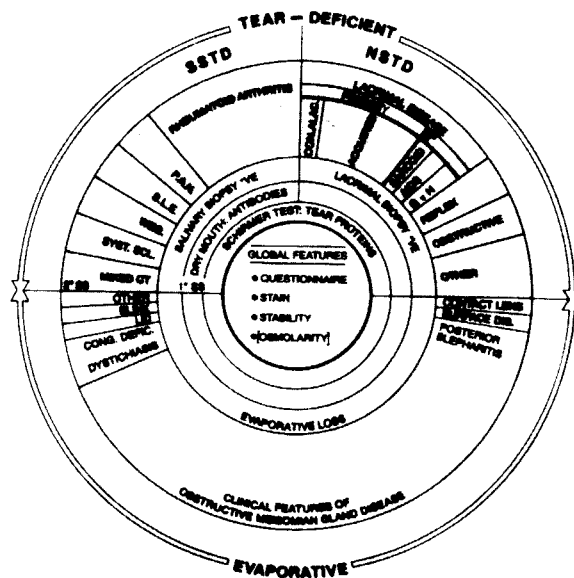
It should also be recognized that diseases which can cause dry eye may at times cause changes in the external eye which are not sufficient to give rise to dry eye. Thus lacrimal function may be reduced as part of the aging process without producing the signs or symptoms of dry eye. Sarcoidosis of the lacrimal gland need not decrease tear secretion if damage to lacrimal function is limited. Cicatrizing conjunctival disease does not always lead to dry eye, nor does obstructive meibomian gland disease. The occurrence of disease or the demonstration of selected signs alone may be insufficient to make a diagnosis (Figure 2).

**Tear-deficient Dry Eye:** There are a number of forms of tear-deficient dry eye (TDDE). This category requires the demonstration of defective lacrimal function. Defective lacrimal function is usually demonstrated by showing reduced aqueous tear volume and tear flow. The standard measure is the Schirmer test, which has been validated by van Bijsterveld<sup>19</sup> and is recommended by the Working Party on Diagnostic Tests.

Other indicators of reduced tear function include the lacrimal thread test,<sup>37</sup> the Periotron test<sup>38</sup>, fluorophotometry, or the demonstration of reduced secretion of lacrimal proteins, such as lysozyme or lactoferrin.<sup>39,40</sup> This is discussed further by the Working Party on Diagnostic Tests.

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## KCS - DRY EYE A DIAGNOSTIC PINWHEEL



**Figure 2** Dry eye diagnostic pinwheel. Criteria for the diagnosis of dry eye are presented. The hub of the pinwheel represents the criteria applied to establish the global diagnosis of dry eye. These characterize the disorder of dry eye without specifying cause. Two or more are necessary for the identification of dry eye state. The criteria for aqueous deficient dry eye are above the horizontal line; below the horizontal line are criteria for evaporative (aqueous sufficient) dry eye. Tests for Sjögren syndrome are at upper left, inner sector; tests for Non-Sjögren aqueous deficient dry eye are at upper right, inner sector. See text for full discussion. (PAN = polyarteritis nodosa; PLD = primary lacrimal gland disease; SLE = systemic lupus erythematosus; WEG = Wegener's granulomatosis; Syst Scl = systemic sclerosis; Mixed CT = mixed-combined; Cong Alac = congenital alacrima; G vs. H = Graft vs. Host disease; Cong. Defic. = congenital deficiency; Surface dis = surface disease.)

Tests for a reduction in tear secretory rate or volume may be regarded as the primary tests for the aqueous-deficient dry eye, since they are most directly related to the presumed damage mechanism. It is thought that tests for deficiency of lacrimal proteins can be regarded as surrogate tests of lacrimal dysfunction since they do not initiate ocular surface damage. It has been suggested that deficiency of lacrimal protein may be the earliest sign of aqueous-deficient dry eye.<sup>41</sup>

TDDE may be divided into two major categories: Sjögren Syndrome Tear Deficiency (SSTD) and non-Sjögren Tear Deficiency (NSTD). In NSTD there are none of the systemic signs or clinical manifestations of autoimmune disease, which are the hallmarks of SSTD.

**SJÖGREN SYNDROME TEAR DEFICIENCY:** Sjögren syndrome is an exocrinopathy affecting the lacrimal and/or salivary glands. The syndrome may be primary or secondary.

Primary Sjögren syndrome consists of the features of tear-deficient dry eye in combination with a dry mouth, the presence of autoantibodies and a positive focus score on minor salivary gland biopsy.<sup>17,18</sup> Tests for dry mouth and for the presence of

**TABLE III** Tests for dry mouth and salivary exocrinopathy\***Salivary Features**

Focus score  $\leq 1$  on minor salivary gland biopsy  
 Salivary scintigraphy  
 Parotid sialography  
 Unstimulated salivary flow ( $\leq 1.5$ ml in 15 minutes)

**Auto-Antibodies**

Anti Ro/SS-A or La/SS-B  
 Antinuclear antibodies  
 Rheumatoid factor

\*From References 16, 17, 18

autoantibodies and other serological evidence of connective tissue disease are given in Table III.

Secondary Sjögren syndrome consists of the features of primary Sjögren syndrome in conjunction with overt clinical manifestations of an autoimmune connective tissue disease. Some of the autoimmune connective tissue diseases in which Sjögren Syndrome occurs are listed in Table IV. Of these, rheumatoid arthritis is the most common. Various criteria have been established for their diagnosis.

**NON-SJÖGREN TEAR DEFICIENCY:** The various forms of non-Sjögren tear-deficient dry eye are listed in Table V.

## 1. Primary Lacrimal Deficiency (PLD)

*Congenital alacrima:* Although its specific cause is not yet known, congenital alacrima is assumed to be a primary disorder of the lacrimal gland. The most prevalent form of PLD is acquired and sometimes referred to as non-Sjögren KCS. It is more common in women, and its frequency increases with age. It results from a gradual destruction of lacrimal gland and ductal tissue by a round-cell infiltration.<sup>42,43</sup> An immune mechanism of lacrimal tissue destruction is not excluded. Since the mechanism for gland destruction is unknown, it is appropriate to refer to this condition as acquired PLD. PLD shows the features of aqueous-deficient dry eye in the absence of signs of autoimmune disease or features of other forms of aqueous-deficient dry eye (Table V).

## 2. Secondary Lacrimal Deficiency

*Sarcoidosis:* Infiltration of the lacrimal glands with sarcoid granulomata may cause dry eye.<sup>44</sup>

*Lymphoma:* In the same way, infiltration of the lacrimal glands with lymphomatous cells may cause dry eye.<sup>45</sup>

*HIV infection:* Dry eye was detected in 21% of a group of patients with AIDS, and in another study of AIDS patients with

**TABLE IV** Autoimmune connective tissue disease associated with secondary Sjögren syndrome

Rheumatoid arthritis  
 Polyarteritis  
 Wegener's granulomatosis  
 Systemic lupus erythematosus  
 Systemic sclerosis  
 Primary biliary cirrhosis  
 Mixed connective tissue disease

**TABLE V** Conditions associated with Non-Sjögren tear deficient dry eye**Lacrimal Disease**

Primary  
 Congenital alacrima  
 Acquired lacrimal disease\*  
 Secondary  
 Sarcoidosis  
 HIV  
 Graft vs. Host disease  
 Xerophthalmia  
 Dacryoadenitis  
 Lacrimal gland ablation

**Lacrimal Obstructive Disease**

Trachoma  
 Cicatricial pemphigoid  
 Erythema multiforme  
 Burns  
 Congenital lid deformity  
 Trauma  
 Atopic keratoconjunctivitis

**Reflex Hyposecretion**

Neuroparalytic keratitis  
 Chronic contact lens wear  
 Proximal VII Cranial Nerve Palsy

**Uncertain Category**

Multiple neuromatosis  
 Cri cu Chat Syndrome

\*Synonym: Non-Sjögren KCS

xerostomia, there was a positive focus score on salivary gland biopsy of 2 or more.<sup>46</sup> However, in this study, the predominant T-cell population was of suppressor lymphocytes (CD8), rather than the helper subset (CD4) characteristic of Sjögren syndrome.

*Graft versus Host Disease:* Associated with dry eye.

*Vitamin A deficiency (Xerophthalmia):* Reported to cause dry eye by two distinct mechanisms. Loss of conjunctival goblet cells and probably other surface mucin sources are responsible for one form of dry eye with normal lacrimal function. This is discussed below. A tear-deficient form of dry eye has also been reported.<sup>48</sup>

*Lacrimal Gland Ablation:* Removal of the main lacrimal gland is a further cause of tear loss.<sup>49</sup>

## 3. Reflex (neural) Causes of Evaporative Dry Eye (Table VI)

*Sensory:* Tear secretion is in part, if not wholly, reflex in origin. Reduced sensory function facilitates drying by two mechanisms: sensory loss causes decreased tear secretion<sup>50</sup> and when bilateral, reduces the blink rate. For instance, topical proparacaine applied bilaterally decreases the blink rate by about 30%<sup>51</sup> and causes a decrease in tear secretion of 60–75%.<sup>50</sup>

Loss of corneal sensation is a feature of contact lens wear and has been proposed as a mechanism for dry eye associated

**TABLE VI** Causes of corneal and conjunctival sensory loss

<b>Infective</b>	
Herpes simplex	
Herpes zoster	
<b>Corneal Surgery</b>	
Limbal incision	
Corneal graft	
Photoablative keratoplasty	
Refractive Keratoplasty	
Radial Keratoplasty	
<b>Neuroparalytic Keratitis</b>	
Injection of trigeminal ganglion	
Tumor	
Section of seventh cranial nerve	
<b>Topical Medications</b>	
Topical anesthesia	
Beta blockers	
Atropine-like drugs	
<b>Other Causes</b>	
Long-term contact lens wear	
Diabetes Mellitus	
Aging	

(modified from Gilbard JP: Dry Eye Disorders in Principles and Practice of Ophthalmology, Albert DM, Jackobic FA (eds): Philadelphia, W.B. Saunders Company, 1994, pp. 257-276.)

with long-standing contact lens wear,<sup>52,53</sup> particularly among hard and extended wear contact lens users. Increased osmolality has been demonstrated in association with contact lens wear.<sup>52</sup>

Neurotrophic keratitis, caused usually by unilateral sensory loss in the distribution of the first division of the fifth cranial nerve is associated with a severe ocular surface disorder. This is partly due to a loss of trophic function of the trigeminal nerve.<sup>54</sup> The Bengal Rose staining, decreased conjunctival goblet cell density, and loss of corneal epithelial glycogen seen in experimental neurotrophic keratitis resembles that encountered in dry eye.<sup>55</sup>

**Motor:** Seventh nerve palsy involving the nervus intermedius (as in posterior fossa tumors) interferes with the secretomotor fibers to the lacrimal gland and may cause dry eye in association with a facial nerve palsy.<sup>56</sup>

**Other:** Dry eye has also been reported with multiple neuromatosis.<sup>57</sup>

#### 4. Obstructive Lacrimal Disease

Cicatrizing conjunctival disease causes aqueous tear deficiency by scarring the orifices of the orbital and accessory lacrimal glands. Among the several causes of conjunctival scarring, those disorders that are associated with dry eye are listed in Table V and include the following:

**Trachoma:** Trachoma is one of the major causes of blindness on world-wide scale; and conjunctival and lid scarring contribute in a complex way, causing dry eye through cicatricial

conjunctivitis, lid distortion, and cicatricial meibomian gland disease.

**Cicatricial pemphigoid:** Cicatricial pemphigoid is a dermatosis characterized by blistering skin and mucosal lesions and the presence of deposits of IgG (and complement components) in the lamina lucida of the basement membrane of perilesional skin.<sup>58</sup> Subepidermal scarring affects the skin and conjunctiva and in the conjunctiva may be progressive and severe.

**Erythema multiforme:** Erythema multiforme is an acute, self-limited, blistering dermatosis which is often, but not always, precipitated by drugs, infection or malignancy. It is characterized clinically by typical target lesions in the skin which show central arteriolar and venular necrosis resembling those seen in hypersensitivity reactions. There are IgM and complement deposits in the skin

**Chemical and thermal burns:** Diffuse chemical or thermal burns may result in conjunctival scarring sufficient to cause dry eye.<sup>59</sup>

These forms of tear-deficient dry eye are distinguished from each other and from idiopathic dry eye by specific criteria. It is sufficient here to give an example of such criteria for one disorder. The dry eye caused by erythema multiforme is characterized by the features of tear-deficient dry eye, a clinical history typical of erythema multiforme, and cicatricial conjunctival changes involving the orifices of the lacrimal gland ductules. Serological and immunohistological features could be accepted in addition.

In establishing positive criteria for any disorder, it is also implied that exclusion criteria are established. These are often in an opposite sense to the inclusion criteria. In this instance, it is implied that positive features of Sjögren syndrome are exclusion criteria and there are no features suggestive of other cicatrizing conjunctival disorders.

**Evaporative Dry Eye (EDE) (Tear Sufficient):** Dry eye can occur where lacrimal function is normal and the volume and composition of the lacrimal fluid are adequate and regarded as sufficient, with the tear abnormality created by other periocular disease, usually leading to increased tear evaporation. The conditions are reasonably referred to as evaporative forms of dry eye. Each of these disorders is independently capable of producing dry eye.

**Blepharitis:** It is known that anterior blepharitis may be associated with punctate keratitis. It is less clear that anterior blepharitis, independent of other forms of lid disease, can cause dry eye. Skin lipid will break up the normal tear film.<sup>60</sup> It has been postulated that desquamated cells derived from the lid margin in squamous blepharitis may deliver such lipid to the tear film and give rise to punctate keratitis by causing tear instability and increased tear evaporation. However, there is also the view that qualitatively altered meibomian lipid may directly damage the ocular surface,<sup>60-63</sup> in which case the surface damage arises by a different mechanism.

It can be seen that the diagnosis of dry eye based solely on the administration of a questionnaire and on the presence of interpalpebral staining could be vulnerable to confounding.

**TABLE VII** Meibomian gland diseases

1. Reduced number	Congenital Deficiency <sup>54</sup>
2. Replacement	Distichiasis <sup>51</sup> Metaplastic
3. Hyposecretory*	Secondary
4. Obstructive meibomitis <sup>35,36,45,46,49</sup>	
Focal or diffuse <sup>51</sup>	
Primary, or secondary to:	
Local Disease	
Anterior Blepharitis; Conjunctivitis, e.g., Trachoma; Pemphigoid; Atopy; Chemical Burns	
Systemic Disease	
Seb. Dermatitis <sup>49</sup>	Anhydrotic Ect. Dyspl
Acne Rosacea <sup>49</sup>	Ectrodactyly Syndrome <sup>55,56</sup>
Atopy <sup>49</sup>	Turner Syndrome
Ichthyosis <sup>51</sup>	Fungal <sup>57,58</sup>
Psoriasis <sup>49</sup>	Toxic: 13-Cis Ret. Acid <sup>50,59,60</sup> Polychlorinated Biphenyls <sup>61,62,63</sup> (Rabbit) Epinephrine <sup>53</sup>
Other	
Internal Hordeolum	
Chalazion	
Concretions	
5. Hypersecretory†	Meibomian Seborrhoea <sup>32,33,34</sup>
6. Neoplastic	
7. Suppurative	

\*Hypothetical: Evidence is not yet available for primary hyposecretion

†Although there is evidence for an accumulation of meibomian oils within the glands, there is none yet for overproduction.

However, this would be avoided if hyperosmolarity were incorporated into the global diagnostic schema. The demonstration of excessive evaporative loss in the presence of anterior blepharitis would clarify the mechanism.

**Meibomian Gland Disease:** It is recognized that various forms of meibomian gland disease can independently cause dry eye. The mechanism is assumed to be insufficient tear oil for resurfacing the tear film with each blink and/or a qualitative alteration of the meibomian lipid in such a way as to destabilize the tear film. A list of meibomian gland disorders is given in Table VII.

It is assumed that the occurrence of dry eye is dependent on the severity and extent of gland dysfunction. The most common form of meibomian gland disease is obstructive. Obstructive meibomian gland disease is diagnosed on the basis of reduced expressibility of meibomian oil, qualitative abnormality of the expressed oil, and morphologic abnormality of the gland acini and ductules. Published methods exist for the grading of such changes by meibography<sup>64,65</sup> and a clinical grading approach,<sup>66</sup> and methods have been devised to measure the amount and quality of the lid oil more precisely using meibometry and a clinical grading scheme.<sup>67-69</sup>

**Blink Disorders:** Infrequent blinking as occurs with Parkinson's disease may lead to drying of the ocular surface. Subtle extensions of the interblink period may occur in relation to work and other specific activities. Methods exist to record the dynamics of the blink and relate this to the diagnosis of dry eye.<sup>70</sup>

**Disorders of Lid Aperture and Lid/Globe Congruity:** The increased width of the palpebral aperture which occurs with proptosis in thyroid disease is associated with ocular drying and tear hyperosmolarity.<sup>71</sup>

Drying of the ocular surface due to lid deformity and poor resurfacing of the ocular surface with tears, is generally accepted, but has received little study.<sup>72</sup>

**Ocular Surface Disorder:** Although any elevation of the ocular surface is associated with local surface drying, the creation of such dry spots is rarely confused with dry eye.

However, in one disorder, xerophthalmia, aqueous-adequate and aqueous-deficient dry eye can both occur, with defective surface wetting (xerosis) associated with surface metaplasia.<sup>45</sup> Ocular surface changes have been well documented and include goblet cell loss.<sup>73</sup> Although the metaplasia could be due entirely to goblet cell loss, it is also possible that it is due to a more subtle abnormality of the surface glycocalyx caused by the vitamin A deficiency itself.<sup>74</sup> It is for this reason that this category is retained.

**Other Tear Film Disorders:** This category is inserted in recognition that there may be other, as yet undetermined, causes of dry eye. This will include those disorders which cause ocular surface damage in the presence of normal lacrimal function, and whose mechanism is as yet unclear. This could include some ocular surface disorders due to contact lens wear, including drying of the ocular surface under a high water content soft lens.<sup>75</sup>

**Combined Disorder:** Any of the disorders discussed above, whether aqueous-deficient or aqueous adequate may occur in conjunction with any other, and several of them commonly do. Lacrimal gland deficiency may be accompanied by meibomian gland deficiency and cicatricial conjunctival disease may cause dry eye both by occlusion of the lacrimal gland ductules, and by causing a lid incongruity which interferes with tear resurfacing with each blink.

When the signs of more than one form of dry eye are present, it may not always be possible to differentiate their relative contribution to the dry eye state.

### Report of the Standardization of Clinical Test Study Group (Tables VIII and IX)

It has been found that lacrimal kinetics, tear secretion rate, age, questionnaire results, and non-invasive tear breakup time are not correlated in non-dry eye subjects.<sup>76</sup> In clinical treatment trials, correlation between Schirmer tests, rose bengal staining, and impression cytology have not been found.<sup>77</sup> If the results of these tests do not correlate with each other, finding a single "gold standard" may not be possible. It may be that each of the available tests measure different aspects of the dry eye or may be insensitive to anything but large changes. There may be a long time lag between some objective changes resulting in poor correlation. Further study is needed to answer these questions.

**Schirmer I Test:** The Schirmer I test<sup>†</sup> is done without

<sup>†</sup> Some clinicians prefer to perform a Schirmer test with anesthetic, but the members of this group think a Schirmer test without anesthetic is a better measure of the capacity of the lacrimal glands to produce tears.

**TABLE VIII** Tests for diagnosing dry eye

Test	Basis	Use	Units	Abnormal values
Schirmer's I	Decreased reflex tearing in lacrimal gland disease	Diagnosis of aqueous deficient dry eye	mm/5'	≤ 5 mm wetting/5'
Fluorescein tear breakup time	A measure of tear stability	Diagnosis of tear stability	seconds	≤ 10 seconds
Fluorescein staining	Indicator of corneal epithelial integrity	Diagnosis of corneal surface disease	Grade 0-3 for 5 areas	>3 out of 15
Rose bengal staining	Indicator of integrity of conjunctival surface	Diagnosis of conjunctival surface disease	Grade 0-3 for 6 areas	>3 out of 18
Lissamine green	Indicator of integrity of conjunctival surface	Diagnosis of conjunctival surface disease	Grade 0-3 for 6 areas	>3 out of 18
Tear film osmolarity	Increased osmolarity in dry eye disease	Diagnosis of dry eye	mOsm/L	≥312mOsm/L
Impression cytology	Squamous metaplasia in dry eye disease	Diagnosis of ocular surface disease	Grade 0-3	>1
Brush cytology	Squamous metaplasia in dry eye disease	Diagnosis of ocular surface disease	Grade 0-3	>1
Tear lactoferrin	Decreased levels in aqueous deficient dry eye	To confirm the diagnosis of aqueous deficient dry eye	ug/mL	≤0.9 ug/mL

anesthesia, using a specified type of paper (Whatman #41). Room temperature and humidity should be relatively consistent from test to test. The time of administration of the last drop and time of testing are recorded. The status of the meibomian glands may influence Schirmer I test results. A standardized system to assess meibomian gland status and its effect on Schirmer I test results is needed. The test is done under ambient light conditions. Only one pair of tests should be done in a given day.

The test is done without touching the paper strip directly with the finger to avoid contamination of skin oils. The strip is placed at the junction of the middle and lateral one-third of the lower eye lid. The patient is told to look forward and to blink normally while a strip is placed in the right eye followed by the left eye. Strips are removed after five minutes and the amount of wetting is recorded in millimeters.

**Tear Breakup Time:** BUT can be measured invasively by using fluorescein (FBUT) or non-invasively using a keratometer or a xeroscope (NITBUT). FBUT may not be reproducible and may not reliably reflect disease.<sup>78</sup> Fluorescein strips are wet with a standardized drop-volume of non-preserved saline solution and the strip is touched to the inferior palpebral conjunctiva. Subjects are asked to blink several times and move their eyes around to thoroughly mix the fluorescein with the tear film. Patients are asked first to close and then open their eyes. The time from opening of the eyes to the appearance of the first dry spot is measured three times and the mean is recorded. A 10 second reference value may be appropriate<sup>79</sup> with values of <10 seconds being abnormal.

NITBUT requires either a xeroscope or a keratometer. Breakup times are shorter using a keratometer compared to a xeroscope, suggesting that careful standardization of instrumental and environmental conditions is necessary.<sup>80</sup> A commercially available, standardized xeroscope is not available.

**Fluorescein Staining:** Fluorescein penetrates areas of the cornea and conjunctival epithelium where a large enough space exists.<sup>81</sup> It may also be a vital dye. Fluorescein staining can be seen in normal eyes and may be more prominent in the morning.<sup>81,82</sup> Patients who have no staining after a single administration of fluorescein may manifest corneal staining after sequential instillations of fluorescein.<sup>78</sup> A yellow Wratten filter (#11 or #12) blocks extraneous light and highlights staining patterns.<sup>83</sup> Fluorescein strips or solutions (1-2%) may be used. Critical,

unanswered questions include: Should the fluorescein be flushed from the eye after instillation? What amount and concentration should be used? How long after instillation should grading occur? Should filters be used? Should drawings or photos be used? and, What grading or scoring system should be used?

Fluorescein strips are wet with a standardized drop-volume of non-preserved saline solution. The cornea is examined three minutes after the last instillation by light passed through a cobalt blue filter and examined through a biomicroscope containing a Wratten # 12 barrier filter. Results are recorded on a cornea diagram as shown below. Punctate staining is recorded using a standardized grading system of 0-3 for each of the five areas shown in Figure 3.

The finding that sequential staining results in more staining of the cornea suggests that using a single application of fluorescein to judge corneal staining may lead to variable results. In addition, with the finding of variable staining in normal subjects over time, the importance of single observations must be questioned.<sup>84</sup>

**Rose Bengal Staining:** New information suggests that rose bengal stains areas of the ocular surface where the tear film is discontinuous.<sup>85</sup> It is commercially available as impregnated strips. At the present time, a commercial solution is not available. A 1% solution can be prepared by a local pharmacy. The drop is quite irritating to the eye, especially in patients with dry eyes, so microliter quantities should be used to avoid patient discomfort. Classically, the van Bjsterveld grading system has been used, assigning a grade (0-3) based on density of staining of the temporal and nasal conjunctiva and cornea of each eye.<sup>86</sup> Critical issues concerning its use as a diagnostic technique include: availability of ready made solutions; whether strips or drops are better; concentration and amount used; how long after instillation should grading occur; should drawings or photos be used; what grading system should be used; and is it necessary to grade the cornea? Further studies are needed to clarify these issues.

A suggested technique uses 2-5 mL of 1% rose bengal applied to the bulbar conjunctiva. After 15 seconds, the conjunctiva is examined by light passed through a green filter. As the dye may be quite uncomfortable in the dry eye patient, a drop of topical anesthetic is instilled in the dye placed on the eye. Alternatively, rose bengal strips (Smith and Nephew) may be used by first applying unpreserved saline to the impregnated

**TABLE IX** Tests for following the therapeutic effect of topical or systemic medications

Test	Basis	Use	Recorded Values
Schirmer's I	Indirect measure of tear secretion	Drugs which stimulate tear secretion	mm wetting in 5'
Fluorescein tear breakup time	A measure of tear stability	Drugs which affect tear stability	seconds
Fluorescein staining	Indicator of corneal epithelial integrity	Drugs which promote corneal epithelial healing	Grade 0-3 for 5 areas
Rose bengal staining	Indicator of integrity of conjunctival surface	Drugs which promote conjunctival epithelial healing	Grade 0-3 for 6 areas
Lissamine green	Indicator of integrity of conjunctival surface	Drugs which promote conjunctival epithelial healing	Grade 0-3 for 6 areas
Tear film osmolarity	Increased osmolarity in dry eye disease	Drugs which stimulate tear secretion/ decrease evaporation	mosm/L
Impression cytology	Squamous metaplasia in dry eye disease	Drugs which reduce squamous metaplasia	Grade 0-3
Brush cytology	Squamous metaplasia in dry eye disease	Drugs which reduce squamous metaplasia	Grade 0-3
Tear lactoferrin	Indirect measure of tear secretion	Drugs which stimulate tear secretion	ug/ml

strip and then touching the wetting strip to the inferior palpebral conjunctiva. Results are recorded for the three areas of the temporal and nasal conjunctiva of each eye and a grade of 0-3 assigned as shown in Figure 4.

**Lissamine Green Staining:** Lissamine green is reported to stain degenerated cells and mucus,<sup>87</sup> although its staining pattern appears identical to that of rose bengal. It is not available commercially. Its major benefit is that it does not sting on instillation. A similar staining technique to that of rose bengal is used.

**Tear Film Osmolarity:** Because of its overall efficacy in establishing an accurate diagnosis and because of its greater sensitivity and specificity as a single test or in combination with other tests (95-100%) in a KCS population, tear film osmolarity may represent the "gold standard."<sup>88</sup> Although its sensitivity might be high, it is unable to distinguish between tear deficient and evaporative dry eye. The technique requires determining osmolarity on basal tears and the avoidance of reflex tearing. A commercially available nanoliter osmometer is made by Clifton Technical Physics (New Hartford, NY). However, there exists a need for an instrument that is transistorized, more reliable, and more available. Reliable technique requires an experienced, trained technician. Technical errors which result in falsely abnormal values are well described.<sup>89</sup> A standardized technique has been described.<sup>88-91</sup>

**Tear pH:** Previous investigators have concluded that this test is not useful as a diagnostic tool.<sup>92,93</sup>

**Tear Ferning:** Tear ferning is dependent on the ratio of Na+ and K+ to Ca++ and Mg++. A biopolymer is needed but it need not be mucin.<sup>94</sup> One study showed that tear ferning was better at diagnosing KCS than the Schirmer's test.<sup>95</sup> Whether this technique is useful in diagnosing and following KCS patients

remains to be seen. A standardized technique needs to be developed and studied.

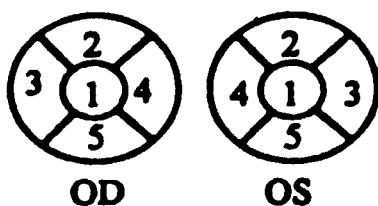
**Tear Evaporation:** Dry eye patients show an increased rate of evaporation compared to normals (0.43 mL/min vs. 0.14 mL/min).<sup>96</sup> The test is not specific for a particular type of dry eye as increased evaporation is seen in KCS, meibomian gland dysfunction and anterior surface disease. This test needs to be correlated with other tests and standardization of the measurement technique is required.

**Histologic tests**

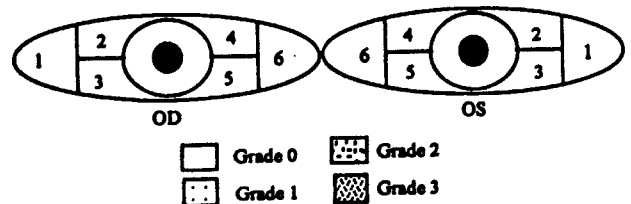
**Conjunctival Impression Cytology(CIC):** CIC allows evaluation of epithelial and goblet cells on the conjunctival surface. In patients with KCS, squamous metaplasia of the bulbar conjunctival surface is seen. Studies have consistently demonstrated that the degree of squamous metaplasia does not correlate with symptoms, fluorescein and rose bengal staining, or Schirmer tests.<sup>77,97</sup> To date in well designed clinical studies, artificial tears have not been demonstrated to reduce squamous metaplasia.<sup>77</sup> A standardized technique for CIC has been used in numerous clinical trials.

After application of topical anesthesia and irrigation of rose bengal dye if present, circular discs measuring 6-7 mm in diameter are placed on the bulbar conjunctiva nasally, temporally, superiorly and on the inferior palpebral conjunctiva. An ophtho-dynamometer is used to apply 40 gm pressure to the discs on the bulbar surface and 70 gm to discs on the palpebral surface for 3-4 seconds. The discs are removed with a forceps and placed on a glass slide with two-sided tape attached. They are oriented to allow determination of the sampling location.

The discs are fixed with a spray fixative (Spraycyte). Once



**Figure 3** Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0 to 3 is used for each of the five areas on each cornea.



**Figure 4** Diagram of the division of the conjunctival surface into six areas with a grading of rose bengal staining. A quantitative scale of 0 to 3 is used for each area of the conjunctiva of each eye. A summation of the points assigned to each area is made for each eye.

fixed, the specimens can be stained at leisure. The staining process involves PAS and a hematoxylin counterstain. Specimens are graded as shown in Figure 4.

**Brush Cytology:** Brush cytology is a technique recently described by Tsubota<sup>98</sup> to provide a minimally invasive method for sampling the conjunctival surface to evaluate the cell population for the presence of various abnormalities.<sup>99</sup> Keratinized cells are reported to be present in patients with dry eye and not in normal subjects. The limiting factor in this technology remains the availability of reagents to identify specific cell types and not the ability to sample cells.

After topical anesthesia, a modified cytobrush (Cytobrush-S) is used to sample the temporal bulbar conjunctiva. Using a gentle rotational motion against the conjunctival surface, the cells are collected using filters or a Cytospin (Shandon, Inc.) and then stained by a Papanicolaou method. The cells can be exposed to various antibodies in order to provide specific cellular information.

Kits could be manufactured providing the practitioner with reagents to identify various cells types. Further investigation is required to establish which abnormal cell types are in the dry eye as well as methods to identify them.

### Laboratory Tests of Lacrimal Gland Function

**Lysozyme:** A lysozyme diffusion agar plate, introduced by van Bijsterveld in 1969<sup>86</sup>, is used to measure lysozyme in the tears. The agar plate in which the bacterium *Micrococcus lysodeikticus* is suspended must be refrigerated. It is inoculated with tears and a standard concentration of lysozyme and incubated for 24 hours. While reliable in moderate to severe dry eyes, it is a cumbersome and relatively expensive test and not recommended.

**Lactoferrin (Lactoplate or Lactocard):** The Lactoplate test is an immunodiffusion assay performed in an agarose gel containing rabbit anti-sera to human lactoferrin. Circular discs of filter paper are placed in the inferior conjunctival cul-de-sac where they become "soaked" with tears. They are placed on the agar and incubated for three days.<sup>100</sup> While it is accurate in moderate to severe dry eye states, this method is too cumbersome and expensive to be recommended for use in clinical trials.<sup>101,102</sup>

The Lactocard test is a solid phase ELISA test requiring only 2  $\mu$ L of tears in a rapid, simple test which is colorimetrically measured by a precise reflectance spectrometer. This test is suitable for office use and has been shown to be as accurate as the Lactoplate in determining tear lactoferrin levels.<sup>101</sup> This study also demonstrated a high correlation of decreased lactoferrin levels (<0.9 mg/mL) with moderate and severe dry eye subjects. It is a rapid (15 minute) test that is easily performed in a clinician's office with minimal training. Tear samples (2  $\mu$ L) are obtained using a capillary tube from the lateral tear meniscus. The test instrument is available from Touch Scientific, Inc., Raleigh, NC.

**Tear Protein Analysis:** Many research scientists and clinicians familiar with the lacrimal gland and tears suspect that the tears from dry eye patients may contain an altered protein

composition. Many of these proteins can be measured using an ELISA assay. Although this assay is currently used in the laboratory, technology is available to develop a kit which would allow office measurement of proteins. The key question is, however, which proteins are indicative of dry eye and are there different "indicative" proteins for the different types of dry eye? This technique has been used to measure immunoglobulins (IgA, IgG, IgM) and viral antibodies in tears and salivary gland fluid.<sup>103</sup> Since constitutive protein concentration in the tears varies with flow rate, tear collection must be standardized to assure only non-stimulated tears are obtained.<sup>104,105</sup> It has been shown in dogs that if flow rate is taken into account, the value of therapy on tear composition can be measured.<sup>106</sup> Tear protein assay may become one of the most important tools available to diagnose and define the different etiologies of dry eye. If tear protein levels can be shown to correlate with patient symptom questionnaire responses, its value would be substantial.

### Conclusions

At present there is evidence that suggests that subjective and clinical findings in dry eye patients do not correlate with each other. The reasons for this are not known, but are at least partly due to the multi-factorial nature of dry eye. Relying solely on improvement in objective clinical tests to show efficacy may not be appropriate. Subjective symptom and functional life style evaluation through the use of a well-designed and validated questionnaire may be the best test to determine clinical efficacy. However, a questionnaire may not be able distinguish between the patient with KCS and meibomian gland disease, for example. Further standardization of diagnostic tests is needed. Well-designed studies are needed to clarify certain issues concerning fluorescein, rose bengal and lissamine green staining. The use of diagnostic tests should aid in the understanding of the pathophysiology of dry eye and specific treatment responses. Finally, the future of diagnostic tests may be in tear protein abnormalities found in dry eye states. Further investigation into these abnormalities and the development of specific ELISA tests for these abnormalities is needed.

Using the new diagnostic classification system, these clinical tests should be performed to determine their sensitivity, specificity and predictive values (both positive and negative) in well-defined dry eye conditions (e.g., aqueous adequate, aqueous inadequate).

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Correspondence and reprint requests to: Michael A. Lemp, MD, University Ophthalmic Consultants of Washington, 4910 Massachusetts Avenue, NW, Suite 210, Washington, DC 20016.

## Participants in the NEI/Industry Workshop on Clinical Trials in Dry Eyes

**Michael A. Lemp, MD**

CHAIRMAN

**J. Daniel Nelson, MD**

CHAIR, STANDARDIZATION OF CLINICAL TESTS GROUP

**Anthony J. Bron, BSc, FRCS, FCOphth**

CHAIR, CLASSIFICATION STUDY GROUP

**Fred Ederer, MS, FACE**

CHAIR, EPIDEMIOLOGIC GROUP

### ACADEMIC & CLINICAL

Barbara E. Caffery, OD  
 Peter C. Donshik, MD  
 Paul Driver, MD  
 R. Linsy Farris, MD  
 Gary N. Foulks, MD  
 Jeffrey P. Gilbard, MD  
 Virginia Lubkin, MD  
 Charles W. McMonnies, OD  
 Austin Mircheff, PhD  
 Juan Murube de Castillo, MD  
 Stephen C. Pflugfelder, MD  
 Peter Reinach, PhD  
 Maurizio Rolando, MD  
 Oliver D. Schein, MD, MPH  
 David Sullivan, PhD  
 Ikudo Toda, MD  
 Kazuo Tsubota, MD  
 Steven E. Wilson, MD

### INDUSTRY

Margaret Drake  
 Anne C. Petropoulos, PhD  
 David F. Power  
 T. Albert Reaves, PhD  
 Brenda Reis, PhD  
 Michael Stern, PhD  
 F. Darrell Turner, PhD  
 Koji Yamamoto, PhD  
  
 Sue Dauphin, Representative  
 The National Sjögren's Syndrome  
 Association

### GOVERNMENT

Carl Kupfer, MD  
 Director, NEI  
 Christina Braun, MD  
 Frederick L. Ferris, MD  
 Natalie Kurinji, PhD  
 Lore Anne McNicol, PhD  
 Richard Mowery, PhD  
 Wiley Chambers, MD  
 Food & Drug Administration  
 Philip Fox, DDS  
 National Institute of Dental Research