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

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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.[1] Recent findings show differences between Sjögren's-associated keratoconjunctivitis sicca (KCS) and non-Sjögren's KCS.[2-4] Neurotransmitters,[5,6] viruses,[7] and hormones[8,9] 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.[10]

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.[11] 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.[12]

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 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.[13] This is how the term is used in some countries. However, in other

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

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† 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.[14,15] 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.[16–18] Van Bijsterveld (1969) described a scoring system for rose bengal staining, which has high sensitivity and specificity.[19]

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

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

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

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?]

diagnostic tests.

Demonstration of Tear Instability: Norn[22] and Lemp[23] 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.[24] When tear mucin is reduced, as reflected by a fall in conjunctival goblet cell density[25] or a rise in tear surface tension,[26] 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,[27] 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; surface disease has been shown to be dependent on and proportional to increases in tear film osmolarity and duration of disease.[28–31,55] It has been suggested that hyperosmolarity is the primary causative mechanism in this group of disorders, leading to discomfort, ocular surface damage, and inflammation.[32]

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.[28] Although measurement of osmolarity by the water vapor pressure method is simple, the technique must be sufficiently tested in dry eye conditions.[33] 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.[34]

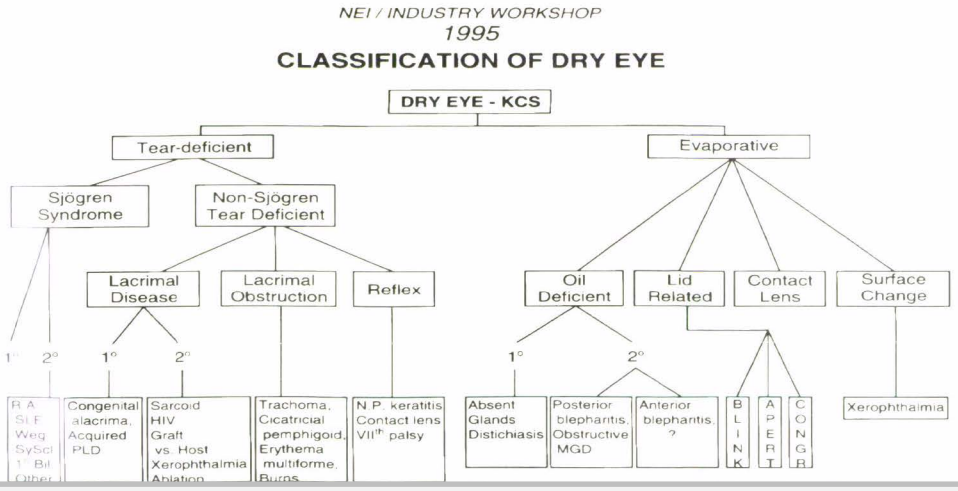

Figure 1 *Classification system and diagnostic algorithm for dry eye. (See*

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.[36] 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.[32] 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[19] and is recommended by the Working Party on Diagnostic Tests.

Other indicators of reduced tear function include the lacrimal thread test,[37] the Periotron test[38], fluorophotometry, or the demonstration of reduced secretion of lacrimal proteins, such as lysozyme or lactoferrin.[39,40] This is discussed further by the

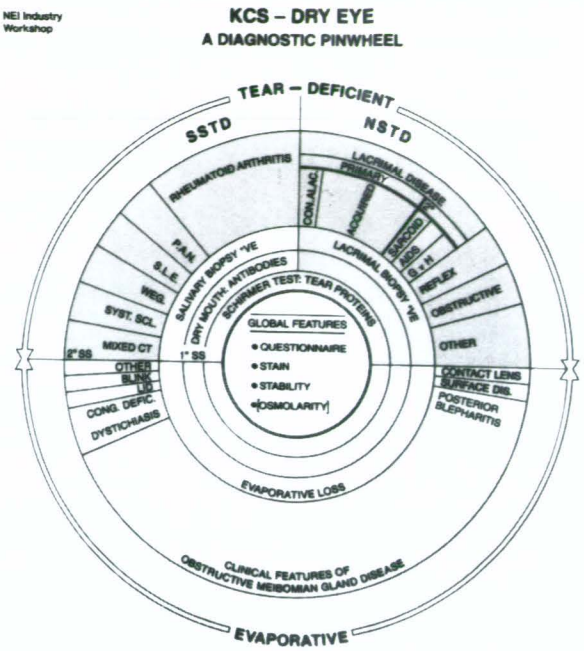

Figure 2 *Dry eye diagnostic pinwheel. Criteria for the diagnosis of dry eye are presented. The hub of the pinwheel represents the criteria applied to establish the global diagnosis of dry eye. These characterize the disorder of dry eye without specifying cause. Two or more are necessary for the identification 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; Con 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.[41]

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

TABLE III Tests for dry mouth and salivary exocrinopathy*

Salivary Features
Focus score ≤ 1 on minor salivary gland biopsy
Salivary scintigraphy
Parotid sialography
Unstimulated salivary flow (≤ 1.5ml 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.[42,43] 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.[44]

Lymphoma: In the same way, infiltration of the lacrimal glands with lymphomatous cells may cause dry eye.[45]

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 bilary cirrhosis

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.[46] 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.[48]

Lacrimal Gland Ablation: Removal of the main lacrimal gland is a further cause of tear loss.[49]

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[50] and when bilateral, reduces the blink rate. For instance, topical proparacaine applied bilaterally decreases the blink rate by about 30%[51] and causes a decrease in tear secretion of 60–75%.[50]

Loss of corneal sensation is a feature of contact lens wear

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