aberrometer.[206] Contrast sensitivity in soft CL wearers is significantly reduced in the middle-to-high spatial frequencies, when the precorneal lens tear film dries and breaks up. This 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 dry eye 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. 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*k*B signalling pathways[56] and the generation of inflammatory cytokines (IL-1α; -1β; 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 cells[216]; 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

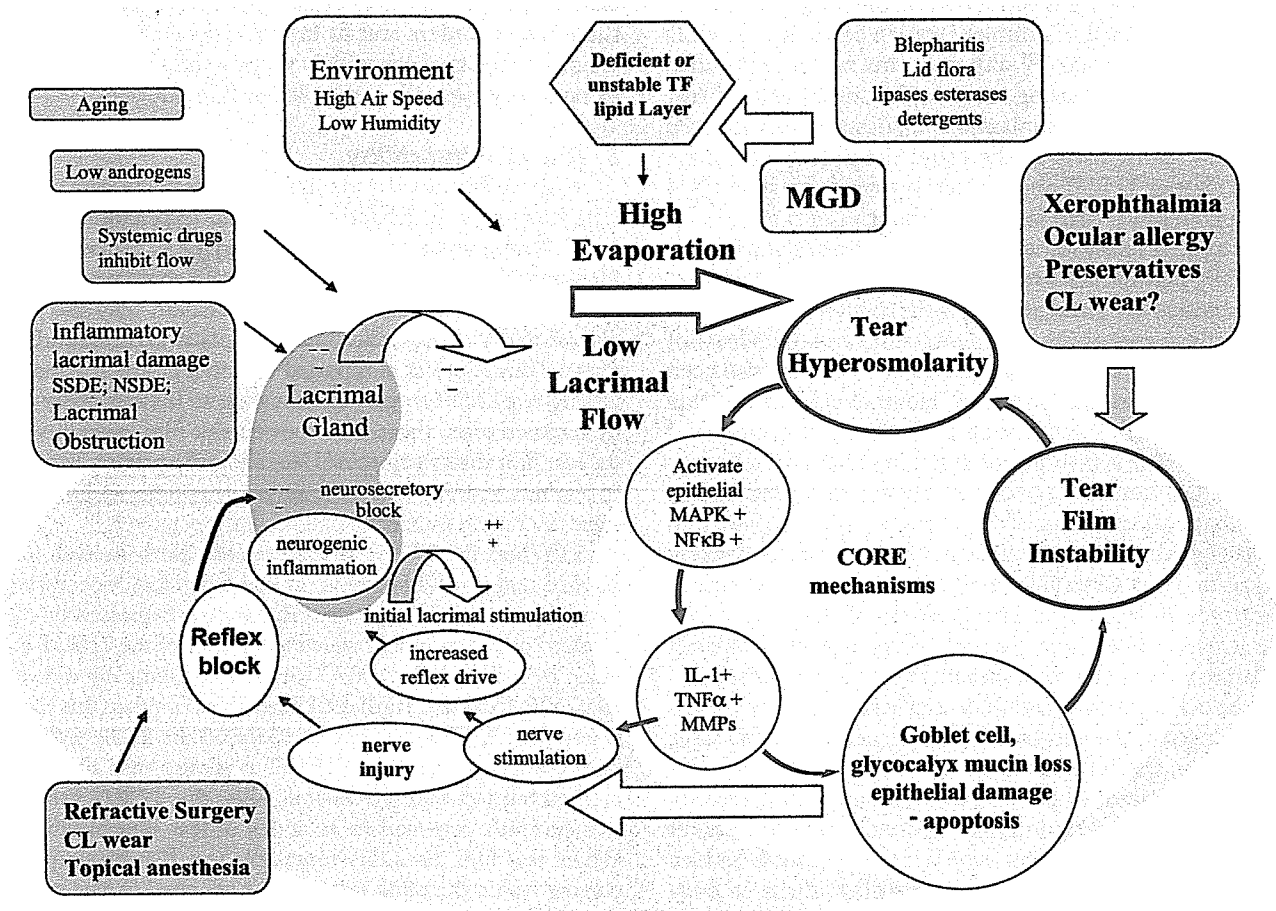

Figure 2. Mechanisms of dry eye.

The core mechanisms of dry eye are driven by *tear hyperosmolarity* and *tear film instability*. The cycle of events is shown on the right of the figure. Tear hyperosmolarity causes damage to the surface epithelium by activating a cascade of inflammatory events at the ocular surface and a release of inflammatory mediators into the tears. Epithelial damage involves cell death by apoptosis, a loss of goblet cells, and disturbance of mucin expression, leading to tear film instability. This instability exacerbates ocular surface hyperosmolarity and completes the vicious circle. Tear film instability can be initiated, without the prior occurrence of tear hyperosmolarity, by several etiologies, including xerophthalmia, ocular allergy, topical preservative use, and contact lens wear.

The epithelial injury caused by dry eye stimulates corneal nerve endings, leading to symptoms of discomfort, increased blinking and, potentially, compensatory reflex lacrimal tear secretion. Loss of normal mucins at the ocular surface contributes to symptoms by increasing frictional resistance between the lids and globe. During this period, the high reflex input has been suggested as the basis of a neurogenic inflammation within the gland.

The major causes of tear hyperosmolarity are reduced aqueous tear flow, resulting from lacrimal failure, and/or increased evaporation from the tear film. This is indicated by the arrow at the top-center of the figure. Increased evaporative loss is favored by environmental conditions of low humidity and high air flow and may be caused clinically, in particular, by meibomian gland dysfunction (MGD), which leads to an unstable tear film lipid layer. The quality of lid oil is modified by the action of esterases and lipases released by normal lid commensals, whose numbers are increased in blepharitis. Reduced aqueous tear flow is due to impaired delivery of lacrimal fluid into the conjunctival sac. It is unclear whether this is a feature of normal aging, but it may be induced by certain systemic drugs, such as antihistamines and anti-muscarinic agents. The most common cause is inflammatory lacrimal damage, which is seen in autoimmune disorders such as Sjogren syndrome and also in non-Sjogren syndrome dry eye (NSSDE). Inflammation causes both tissue destruction and a potentially reversible neurosecretory block. A receptor block may also be caused by circulating antibodies to the M3 receptor. Inflammation is favored by low tissue androgen levels.

Tear delivery may be obstructed by cicatricial conjunctival scarring or reduced by a loss of sensory reflex drive to the lacrimal gland from the ocular surface. Eventually, the chronic surface damage of dry eye leads to a fall in corneal sensitivity and a reduction of reflex tear secretion. Various etiologies may cause dry eye acting, at least in part, by the mechanism of reflex secretory block, including: refractive surgery (LASIK dry eye), contact lens wear and the chronic abuse of topical anesthetics.

Individual etiologies often cause dry eye by several interacting mechanisms. Further details can be found in the text.

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]

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 layer[229] 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 **EDITOR INSERT WEB ACCESS INFO**). 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 xerophthalmia[231] 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 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

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	
Corneal/tear signs	None to mild	Mild debris↓ meniscus	Filamentary keratitis, mucus clumping↑ tear debris	Filamentary keratitis, mucus clumping↑ tear debris
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. TBUT: fluorescein tear break-up time. MGD: meibomian gland disease

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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 MUC5 AC 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-weekly 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 consider-

able 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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The Epidemiology of Dry Eye Disease:
Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **The report of the Epidemiology Subcommittee of the 2007 Dry Eye WorkShop summarizes current knowledge on the epidemiology of dry eye disease, providing prevalence and incidence data from various populations. It stresses the need to expand epidemiological studies to additional geographic regions, to incorporate multiple races and ethnicities in future studies, and to build a consensus on dry eye diagnostic criteria for epidemiological studies. Recommendations are made regarding several characteristics of dry eye questionnaires that might be suitable for use in epidemiological studies and randomized controlled clinical trials. Risk factors for dry eye and morbidity of the disease are identified, and the impact of dry eye disease on quality of life and visual function are outlined. Suggestions are made for further prospective research that would lead to improvement of both eye and general public health.**

KEY WORDS **DEWS, dry eye, Dry Eye WorkShop, epidemiology, risk factors, questionnaire**

I. INTRODUCTION

Epidemiology is the branch of biomedical research that involves the study of the distribution and determinants of health and disease in human populations. The frequencies and types of disease in a population and the factors that influence the distribution of the disease in the population and its subgroups can be identified through epidemiologic study.

In the mid-1990s, the extent of the dry eye problem worldwide was poorly understood. A workshop co-sponsored by the National Eye Institute (**NEI**) and Industry brought together some of the leading scientists in ocular surface research and concluded that, "There is a paucity of data concerning the frequency of dry eye states in the population and how that frequency varies according to age, sex and race."[1]

Considerable progress has been made since 1994 and multiple reports have been published that address the challenge of providing epidemiological data on dry eye, including data from the Salisbury Eye Evaluation, the Beaver Dam Eye Study, the Melbourne Visual Impairment Project, and the Women's Health Study and Physicians' Health Study, among others. It is the purpose of this report to summarize the available evidence on the epidemiology of dry eye syndrome and to make recommendations for future needs and research opportunities.

II. GOALS OF THE EPIDEMIOLOGY SUBCOMMITTEE

The goals of the Epidemiology Subcommittee of the 2007 Dry Eye WorkShop (**DEWS**) were 1) to assess and summarize current knowledge on the epidemiology of dry eye, obtaining prevalence and incidence data from various populations, 2) to describe the risk factors for dry eye, and 3) to review and evaluate dry eye questionnaires.

A. Goal 1: Assess and Summarize Current Knowledge on the Epidemiology of Dry Eye Disease

1. Dry Eye Definitions and Ascertainment

To characterize the prevalence of a disease (ie, the proportion with disease within a population at a given point in time) or its incidence (ie, the number of new cases of disease that emerge from a population of initially disease-free individuals over a defined period of time), it is necessary to agree upon a definition. Dry eye is a multifactorial disease that can result from and present in a variety of ways. In 1995, the NEI/Industry workshop broadly defined dry eye as "a disorder of the tear film due to tear deficiency

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Proprietary interests of Subcommittee members are disclosed on pages (EDITOR; INSERT PAGE NUMBERS)

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or excessive tear evaporation which causes damage to the interpalpebral ocular surface associated with symptoms of ocular discomfort."[1] In this definition, the term *tear deficiency* implied a deficiency of aqueous tears secreted by the lacrimal gland. The requirement of symptoms in the definition is noteworthy, as it was not included in the definitions established in all nations; for instance, it was absent from the Japanese definition of dry eye until recently.[2]

2. Challenges in Dry Eye Epidemiology

No single diagnostic test can be performed in the field or in the clinic to reliably distinguish individuals with and without dry eye. Furthermore, although a variety of diagnostic tests are in common clinical usage, there is no consensus on which combination of tests should be used to define the disease, either in the clinic or for the purposes of a research protocol. A major stumbling block has been the reported lack of correlation between patients' irritative ocular symptoms and the results of selected clinical tests for dry eye. Much of this discrepancy can be explained by the lack of repeatability of many of the clinical tests in common use, with the implication that repeated measures of the same test on the same subjects at different times are not strongly correlated. Thus, it is not unexpected that such tests will fail to correlate with each other.

Another plausible reason for a lack of correlation between clinical tests and irritative symptoms may be the natural variability of the disease process, the "subjective" nature of symptoms, and variability in pain thresholds and cognitive responses to questions about the physical sensations in the eyes. Other factors could include the development of relative corneal anesthesia with aging and with worsening disease, and the possibility that symptoms are related to parameters not measured by the tests currently employed.

Dry eye is a symptomatic disease, and, at the present time, symptom questionnaires are among the most repeatable of the commonly used diagnostic tests. They may provide a more integrated view of the clinical condition over time. Irritative symptoms are largely responsible for the public health burden and for the care-seeking behavior of dry eye patients and their desire for therapy. Dry eye symptoms also affect activities of daily living, adversely impacting important tasks such as driving. With these important issues in mind, it should be noted that individual research groups in various reports have used different operational definitions of dry eye that are appropriate for their particular purpose. It is of great importance to consider these differences when interpreting and comparing such studies.

The Subcommittee examined data from a number of large cohort studies and paid particular attention to definitions employed and criteria used, including the requirement for a certain number, frequency, and intensity of symptoms. It was also noted whether a clinical examination was performed, or whether the study diagnosis was based on the history of dry eye diagnosed by a clinician. In some cases, measurements from objective tests were recorded, such as tear production, staining of the ocular

Table 1. Summary of population-based epidemiologic studies of dry eye

Study	N	Age range	Dry eye assessment	Prevalence
US Studies				
Salisbury Eye Study[3-5]	2420	≥ 65 y	At least 1 of 6 symptoms (dryness, gritty/sandiness, burning, redness, crusting on lashes, eyes stuck shut in morning), occurring at least often.	14.6%
Beaver Dam[6]	3722	≥ 48 y	For the past 3 months or longer have you had dry eyes?" If needed, described as "foreign body sensation with itching, burning, sandy feeling, not related to allergy).	14.4%
Women's Health Study[7]	36995	≥ 49 y	Severe symptoms of dryness and irritation, either constantly or often, and/or the physician's diagnosis of dry eye as volunteered by the patient.	7.8%
Physician's Health Studies I and II[8,9]	25655	≥ 50, 55 y	Severe symptoms of both dryness and irritation either constantly or often and/or the physician's diagnosis of dry eye as volunteered by the patient.	
Australian Studies				
Blue Mountains[10]	1075	≥ 50 y	At least 1 of 4 symptoms regardless of severity, or at least 1 symptom with a moderate to severe ranking (dryness, grittiness, itchiness, discomfort).	16.6% (at least 1 symptom) 15.3% (3 or more symptoms)
Melbourne Visual Impairment Project[11]	926	≥ 40 y	At least 1 of 6 "severe" symptoms, not attributed by the subject to hay fever (discomfort, foreign body, itching, tearing, dryness, photophobia)	5.5%
Asian Studies				
Shihpai[12]	2038	≥ 65 y	At least 1 of 6 symptoms, often or all of the time (dryness, gritty/sandiness, burning, sticky, tearing, redness, discharge, eyes stuck shut in morning).	33.7%
Sumatra[13]	1058	≥ 21 y	At least 1 of 6 symptoms, often or all of the time (dryness, gritty/sandiness, burning, redness, crusting on lashes, eyes stuck shut in morning).	27.5%

surface, and tear film breakup time. The prevalence of dry eye, using these varying definitions, was tabulated for each epidemiologic study and is listed in Table 1, along with the corresponding estimates of population prevalence.

3. Summary of Dry Eye Epidemiology Data

a. Prevalence of Dry Eye

1) Combined Prevalence Data

Based on data from the largest studies of dry eye to date, the Women's Health Study (**WHS**), and the Physicians' Health Study (**PHS**), and other studies,[3-14] it has been estimated that about 6.4 million women and 2.7 million men, for a total of 9.1 million (95% confidence interval = 7-12.6 million), Americans have dry eye.[7,14] Tens of millions more have less severe symptoms and probably a more episodic manifestation of the disease that is notable only during contact with some adverse contributing factor(s), such as low humidity or contact lens use.

Comparison of age-specific data on the prevalence of dry eye from large epidemiological studies reveals a range of about 5%[11] to over 35%[12] at various ages. However, it must be noted that different definitions of dry eye were employed in these studies, and, therefore, caution is advised in interpreting direct comparisons of these studies. Although very limited data exist on the potential effect of race or ethnicity on dry eye prevalence, data from the WHS suggest that the prevalence of severe symptoms and/or clinical diagnosis of dry eye may be greater in Hispanic and Asian, as compared to Caucasian, women. The combined data from large population-based epidemiological studies indicates that the number of women affected with dry eye appears to exceed that of men.

2) Discussion/Comments

Each of the population-based studies evaluated used a different definition of dry eye. Some studies included objective examination, but many did not. Nevertheless, in view of the poor performance (inconsistency, lack of repeatability,

etc.) of commonly used clinical tests and the importance of symptoms as an indicator of both the clinical and public impact of dry eye, these data from large epidemiological studies have provided much needed information on the prevalence of dry eye.

The studies were performed in different populations across the world and, therefore, provide some valuable information regarding potential differences in dry eye according to geographic region. In particular, data from the two studies performed in Asia suggest the possibility of a higher prevalence of dry eye in those populations.[12,13]

The weight of the evidence from large epidemiological studies indicates that female sex and older age increase the risk for dry eye; the Salisbury Eye Evaluation study is the most notable exception.[3-5]

An overall summary of data suggests that the prevalence of dry eye lies somewhere in the range of 5-30% of the population aged 50 years and older. It is thought that a proportion of the variation in observed prevalence between studies relates to differences in the definition of disease used; it is observed that the higher estimates are derived from studies in which a less restrictive definition was used, and the lower estimates are derived from those studies in which a more restrictive definition was used. Thus, one might surmise that the true prevalence of moderate-to-severe dry eye lies somewhere close to the lower bound of the range, whereas inclusion of mild or episodic cases would bring the estimate in closer proximity to the higher estimates observed.

Data from the largest US studies, the WHS[7] and the PHS,[8,9] yield estimates that 3.2 million women and 1.6 million men aged 50 years or older suffer from moderate-to-severe dry eye.

b. Incidence of Dry Eye

Epidemiologic data on dry eye can be extracted from data repositories and federal or public databases, eg, the Medicare/Medicaid databases or other data sources, such as health maintenance organizations. Ellwein and colleagues found that the dry eye case incidence per 100 fee-for-service Medicare beneficiaries increased by 57.4% from 1.22 in 1991 to 1.92 in 1998.[15] For comparison, cataract case incidence increased from 23.44 to 27.29 (16.4%), while that of diabetic retinopathy increased from 1.36 to 2.55 (87.5%) in the same time period. Case incidence may be particularly useful in evaluating the prevalence for chronic conditions for which yearly or more frequent visits are common.[15]

c. Natural History

There is a paucity of data on the natural history of untreated and treated dry eye. Data regarding the clinical course of dry eye of varying severity and rates of progression from mild to severe disease are also lacking. Such information could be obtained from clinic-based populations with use of standardized tests, and, similarly, baseline data from clinical trials and other clinical studies could be employed to obtain useful data. However, such information is not yet available. Data from randomized controlled trials (**RCTs**) include a wealth of information, which could be garnered from the placebo or vehicle-treated groups, both at baseline and at end of study; this would provide some crude natural history data, albeit from a selected population. At the DEWS meeting in Miami, Florida, in May 2006, industry representatives to the DEWS group and attendees were invited to work collaboratively to establish procedures for sharing this valuable clinical data without compromise to proprietary information. The natural history of dry eye remains to be determined, including prognostic factors, the likelihood of disease progression, and the rates of treatment adherence and discontinuation and the effect of the use of lubricants.

Epidemiologic data can also be garnered from medical claims data. This should be interpreted with the caveat that prevalence estimates based on claims provide different data than population-based studies, because claims are made for symptomatic disease for which diagnosis or treatment is sought from the medical care system. Yazdani et al reviewed the PharMetrics' Integrated Outcomes database of medical claims for 10 million patients from 22 managed care plans and reported a prevalence of dry eye of 0.39% (27,289 cases) in 1989.[16] International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9 CM) codes were used to identify cases based on a diagnosis of dry eye (tear film insufficiency 375.15, keratoconjunctivitis sicca (**KCS**) 370.33, and sicca syndrome 710.2), and Current Procedural Terminology (CPT-4) procedure codes for closure of the lacrimal punctum by thermocauterization, ligation, laser surgery, or plug were used to identify surgically treated cases of dry eye. In this managed care population, dry eye was diagnosed or treated in 0.65% of women vs 0.26% of men ($P < 0.001$), and dry eye rates increased with age, reaching the highest among women 75-79 years of age and men 80-84 years of age. This is one of a few papers that report a regional variation in the prevalence of dry eye, with a high rate of 0.8% in the midwestern US, not explained by a higher proportion of women or elderly.[16] There are several ICD-9-CM codes that can be applied to dry eye cases, including: 370.33 keratoconjunctivitis sicca, non-Sjogren syndrome (**SS**); 370.34 keratoconjunctivitis, exposure; 372.52 xerosis, conjunctival; 375.15 tear film insufficiency, unspecified (dry eye syndrome); and 710.20 keratoconjunctivitis sicca, SS.

d. Effects of Magnitude of Prevalence of Disease in Population on Positive and Negative Predictive Value

Community level surveys may overestimate rates of dry eye, due to higher response rates from ill, as opposed to healthy, individuals. Medical insurance or pharmacy claims collect data related to diagnoses made by a health care provider, procedures performed, and medications dispensed within a specific population, such as a managed care population. Minority and low-income populations may be differentially affected by under-reporting associated with reduced access to health care or decreased participation in research studies. Epidemiologic studies report varying prevalence of

dry eye because of all of these factors and, also, differences in study populations (community-, clinic-, managed care-based), differences in disease definition, and the lack of a standardized diagnostic test or clinical algorithm of tests.

4. Morbidity of Dry Eye

The public health significance of dry eye is raised by the high prevalence of dry eye among the older age groups in multiple population-based studies combined with the aging of the population. US Census Bureau estimates suggest that in the period between 2000 and 2050, the number of people in the US aged 65-84 years will increase by 100%, and the number of people aged 85 years and older will increase by 333% (Source: U.S. Census Bureau, 2004, "U.S. Interim Projections by Age, Sex, Race, and Hispanic Origin," *http://www.census.gov/ipc/www/usinterimproj/* Internet Release Date: March 18, 2004). Similar trends are expected in many other parts of the world.

a. Financial Costs of Dry Eye

Few data exist on the direct and indirect costs of dry eye. The economic impact of dry eye includes costs due to health care system utilization, including office visits, surgical interventions, prescription medications, over-the-counter and complementary and alternative therapeutics, and purchase of specialized eye wear and other nonpharmacologic therapeutics, such as humidifiers. Indirect costs include lost work time and productivity, alteration in work type or environment, decreased work time and days of work with dry eye symptoms. In addition to the pain of dry eye, intangible costs include decreased leisure time, impaired physical functioning and quality of life, impact on social interactions, and mental and general health.[17]

b. Impact of Dry Eye on Quality of Life

The impact of dry eye on quality of life (**QoL**) is mediated through 1) pain and irritative symptoms, 2) effect on ocular and general health and well-being (general QoL), 3) effect on perception of visual function (vision-related QoL), and 4) impact on visual performance. For example, the irritative symptoms of dry eye can be debilitating and result in both psychological and physical effects that impact QoL.[18] Dry eye also limits and degrades performance of common vision-related daily activities, such as driving.[19] The need for frequent instillation of lubricant eye drops can affect social and workplace interactions. The cost of treatment and the lack of a cure for dry eye add to the impact of this important public health problem.

Various methods are available to assess the effect of dry eye on visual function and QoL. Non-disease-specific, "generic" instruments like the Medical Outcome Study Short Form-36 (**SF-36**) have been applied to dry eye. Utility assessment, a tool used widely in medicine that permits the comparison of the effect of different diseases on QoL based on strategies such as standard gamble, or trading years of life for disease-free years, and other techniques, has also been applied to dry eye.[20] Interestingly, the utility scores for dry eye were similar to those for moderate angina.[21] General vision-related questionnaires, such as the NEI-Visual Function Questionnaire (**NEI-VFQ**), have been used. Disease-specific instruments, like the Ocular Surface Disease Index (**OSDI**) and the the Impact of Dry Eye on Everyday Life (**IDEEL**) questionnaire have also been developed and validated specifically for research on the impact of dry eye. These are discussed in detail in Section C.

c. Burden of Dry Eye

In a recent study among subgroups of 450 participants in the WHS and 240 participants in the PHS,[22] investigators used a supplementary dry eye syndrome (**DES**) questionnaire to ascertain how much a patient's everyday activities were limited by symptoms of dry eye and to what degree problems with their eyes limited them in a number of common activities of modern living, including reading, driving, working at the computer, professional activity, and watching TV. By design, the study group consisted of one-third with clinically diagnosed DES or severe symptoms and two-thirds without these characteristics. In pooled analyses controlled for age, diabetes, hypertension, and other factors, patients with DES were significantly more likely to report problems with reading, carrying out professional work, using a computer, watching television, driving during the day, and driving at night. Overall, patients with DES were about three times more likely to report problems with common activities than were those without DES ($P < 0.001$). These data add further weight to the consideration of DES as a significant public health problem that deserves attention in the clinic.[22]

Mertzanis et al described the relative burden of dry eye by comparing a measure of general health-related QoL, the SF-36 responses from persons with and without dry eye against the US norm.[18] The IDEEL questionnaire was administered to dry eye patients with non-SS KCS (determined by ICD-9CM codes) or SS-related KCS (determined by San Diego diagnostic criteria) and to control subjects not meeting dry eye diagnostic codes. The *Survey Manual and Interpretation Guide* provided the US normative data. These authors found that while non-SS KCS consistently limited daily roles, caused bodily pain or discomfort, and decreased vitality or energy, this impact became clinically significant when symptoms became moderate in severity. With increased severity of symptoms, other domains were adversely affected, such as perceptions of health, physical functioning, social functioning, and role-emotional limitation. Non-SS KCS had lower role-physical (effect size **[ES]** = –0.07), bodily pain (ES = –0.08), and vitality (ES = –0.11) scores than norms, but higher scores for general health, physical functioning, role-emotional and mental health, and social functioning. All SF-36 domains were lower (ES ranged from –0.14 to 0.91) for the SS patients than adjusted norms except mental health (ES = 0.12) and role-emotional (ES = –0.13). Regardless of severity of dry eye, patients reported more limitations in roles due to physical problems and bodily pain likely to affect daily activities. With

increased severity, patients also reported deficits in general health perception and vitality, and the most severely affected patients reported worse health-related QoL over all scales. The IDEEL showed greater discriminative validity for severity levels of dry eye than the SF-36 or EuroQoL (**EQ**)-5D.[23]

d. Quality of Life in Sjogren Syndrome

Sjogren syndrome is an autoimmune exocrinopathy that may be associated with immunologic abnormalities and a severe form of dry eye. Vitale et al used a disease-specific instrument, the OSDI, and a generic instrument developed for ocular disease, the NEI-VFQ, to evaluate the effect of dry eye in patients with SS on vision-targeted QoL. Despite the less heterogeneous study population of a single disease with severe dry eye, they found correlations of ocular surface parameters with vision-targeted health-related QoL to be weak or nonexistent, consistent with other studies demonstrating poor correlations between signs and symptoms of dry eye. Interestingly, the NEI-VFQ correlations with objective ocular surface parameters were higher than those of the OSDI, which may have been due to the capture of symptom intensity in addition to frequency in the generic instrument. Furthermore, the OSDI is targeted to how symptoms affect current status, a 1-week recall period, whereas the NEI-VFQ may be more suited to capturing overall impact of chronic ocular disease. It is important to include assessments of Vision-Targeted Health-Related Quality of Life (**VT-HRQ**) and visual function to fully characterize the impact of dry eye on health status. The poor correlations with conventionally measured signs indicate that an additional component of disease not captured by clinical examination is being captured.[24]

Sjogren syndrome can affect many organ systems, and afflicted patients have a reduced quality of life. Several studies have measured various aspects of this reduced QoL. Fatigue, anxiety, and depression are major aspects of SS. Thomas et al[25] studied the impact of SS in terms of disability and QoL in a community-based sample. The majority of women with SS reported interference in leisure activities and lifestyle.[26] Higher levels of depression/anxiety and fatigue were evident in SS patients compared with non-SS patients. SS patients had significantly lower scores on the SF-36, indicating a greater impact on health status. The SF-36 has been used by Sutcliffe et al,[27] Strombeck et al,[28] and others[29] to show that disabling fatigue is an important symptom for many of these patients.

Godaert et al used the multi-dimensional fatigue inventory (**MFI**) to confirm that SS patients had substantially higher levels of daily fatigue and that their fatigue increased in the evening.[30] Giles and Isenberg also noted increased fatigue in SS patients, even compared to a population of lupus patients.[31] Depression is also a prominent feature of SS. Stevenson et al used the Hospital Anxiety and Depression Scale (**HADS**) to evaluate 40 SS patients and 40 controls. SS patients showed significantly higher scores.[32] Valtysdottir et al also observed more psychiatric symptoms and worse well-being in patients with primary SS.[33]

e. Impact on Visual Function

Knowledge is increasing about how dry eye limits and degrades visual performance, including the conduct of common vision-related daily activities. New methods of measuring functional visual acuity have demonstrated the effect of dry eye on visual performance. Distinct from high-contrast visual acuity, measured in a standardized way at a practitioner's office, visual function is a measure of one's ability to perform vision-intensive tasks, such as reading, using a computer, professional work, driving at night, or watching television. Visual complaints are highly prevalent among dry eye patients.[22,34,35] These are usually described as disturbed vision or blurry, foggy vision that clears temporarily with the blink.[34] These transient changes can be profound, resulting in marked drops in contrast sensitivity and visual acuity,[36] thus affecting workplace productivity and vision-related QoL.[19,37]

Corneal surface irregularity due to epithelial desiccation, tear film instability, and evaporation can be visualized and quantified with use of tools ranging from corneal topography (surface regularity index) to complex instruments like wavefront analysis that quantify optical aberrations that can degrade the quality of vision and affect non-acuity visual function. An uneven, disrupted tear film in the central cornea can result in transient vision changes in the dry eye patient.[37,38] Optical aberrations created by tear film breakup between blinks contribute to a decline in retinal image quality that can be measured by both objective and subjective methods. The Shack-Hartmann aberrometer measures real-time changes in whole eye, higher order aberrations that can be attributed to the tear film,[38,39] whereas aberrations modeled by changes in corneal topography are based on the front surface of the eye only.[40] Subjective methods can also be used to track changes in contrast sensitivity and visual acuity due to tear film disruption.[41] Both topical application of artificial tears and punctal occlusion in dry eye patients have been demonstrated to improve visual acuity, contrast sensitivity, and corneal epithelial regularity.[36,42,43]

f. Ocular Morbidity Associated With Dry Eye Disease

Dry eye is associated with contact lens intolerance and discontinuation of contact lens wear,[45,46] can adversely affect refractive surgery outcomes,[46,47] and may be associated with increased risk of infection and complications with ocular surgery. Few data exist on the risk of infection due to dry eye. Cataract surgery in patients with dry eye can be associated with ocular morbidity, especially in patients with connective tissue disorders.[48] The large incision required for extracapsular cataract extraction was associated with decreased corneal sensation, which can impair wound healing, interrupt normal trophic factors, and render the cornea more vulnerable to epithelial breakdown in predisposed cases.[49] In contrast, small incision cataract surgery with phacoemulsification in patients with dry eye has not been associated with a higher risk of complications in dry eye patients; Ram et al reported postoperative punctate epitheliopathy in 8/25

Table 2. Risk factors for dry eye

Level of Evidence		
Mostly consistent*	Suggestive†	Unclear‡
Older age	Asian race	Cigarette smoking
Female sex	Medications	Hispanic ethnicity
Postmenopausal estrogen therapy	Tricyclic antidepressants	
Omega-3 and Omega-6 fatty acids	Selective serotonin reuptake inhibitors	Anti-cholinergics
Medications	Diuretics	Anxiolytics
Antihistamines	Beta-blockers	Antipsychotics
Connective tissue disease	Diabetes mellitus	Alcohol
LASIK and refractive excimer laser surgery	HIV/HTLV1 infection	Menopause
Radiation therapy	Systemic chemotherapy	Botulinum toxin injection
Hematopoietic stem cell transplantation	Large incision ECCE and penetrating keratoplasty	
	Isotretinoin	Acne
Vitamin A deficiency	Low humidity environments	Gout
Hepatitis C infection	Sarcoidosis	Oral contraceptives
Androgen deficiency	Ovarian dysfunction	Pregnancy

* Mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

† Suggestive evidence implies the existence of either: 1) inconclusive information from peer-reviewed publications or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal

‡ Unclear evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale

eyes, epithelial defect in 8/25 eyes of 23 patients, and no cases of infection or keratolysis.[50]

g. *Future Research Directions*

A number of questions should be addressed in future research on the epidemiology of dry eye.

What is the natural history of dry eye syndrome? Is the tissue damage to the ocular surface progressive? Do irritative symptoms progress, or might they wane over time with the development of relative corneal anesthesia?

Can we quantify the risk of ocular surface infection among patients with dry eye? Is the amount of corneal staining correlated with visual function/functional visual acuity?

What is the incidence of dry eye syndrome in the population, and are there any identifiable demographic correlates (eg, age, sex, race/ethnicity)?

Suggested risk factors for dry eye need to be verified and quantified (diabetes mellitus, HIV/HTLV1, medications, menopause, alcohol, smoking, pollution, low humidity, various medical conditions, refractive surgery, androgen deficiency, and others). It needs to be determined whether predisposing genetic factors contribute to dry eye.

The effects of dry eye should be further defined in terms of QoL, impact on vision, impact on driving, psychological issues, cost of care, impact on the health care system, and overall economic impact.

New diagnostic tests and disease biomarkers should be developed to facilitate epidemiological and clinical research.

B. Goal 2. Describe the Risk Factors for Dry Eye Disease

In 1995, the NEI/Industry Workshop found "virtually no data in reference to risk factors for the development of dry eye."[1] Since that time, epidemiological studies have only begun to address the evidence for potential lifestyle, dietary, behavioral, and other risk factors for dry eye, and further study is clearly needed. The Epidemiology Subcommittee noted that risk factors might differ among certain subtypes of dry eye, which could dilute associations in population-based studies, in which all forms of dry eye are considered together. Findings from studies in which a purely statistical, non-hypothesis-driven approach was used to study risk factors must be viewed cautiously, as spurious results are likely, and, at the same time, important associations could have easily been overlooked.

The Subcommittee recommends that future studies of risk factors for dry eye should concentrate on the examination of biologically compelling hypotheses in a detailed fashion, with appropriate attention to all aspects of good epidemiological study design (including sufficient study power), analysis, and data presentation.

Substantiated risk factors for dry eye include female sex, older age, postmenopausal estrogen therapy,[51] a diet that is low in omega 3 essential fatty acids or has a high ratio of omega 6 to omega 3 fatty acids,[52] refractive surgery,[53] vitamin A deficiency, radiation therapy, bone marrow transplantation, hepatitis C,[54] and certain classes of systemic and ocular medications, including anti-histamines (Table 2). Vitamin A deficiency is a well-recognized risk factor for dry eye,[55]

and the etiology of the nutritional deficiency now extends from inadequate intake due to unavailability of food to alcoholism-related nutritional deficiency, bariatric surgery,[56] malabsorption, eating disorders,[57] and vegan diet.[58]

Other risk factors may include diabetes mellitus,[59] human immunodeficiency virus, HIV[60] and human T cell lymphotropic virus- 1 infection,[61] connective tissue diseases, systemic cancer chemotherapy, and other medications, such as isotretinoin,[62] antidepressants, anxiolytics, beta-blockers, and diuretics. However, systematic, comprehensive study of many of these factors is lacking. Conflicting results have been reported on the associations between dry eye and some factors, including alcohol, cigarette smoking, caffeine, acne,[63] and menopausal status. Very few reports exist on the risk of dry eye with use of oral contraceptives and pregnancy and the role of ethnicity in dry eye.[64]

1. Bone Marrow Transplantation and Cancer

Allogeneic bone marrow transplantation has increased in frequency, the indications for the procedure have expanded, and the survival rate is higher than ever before. Conditioning regimens and the use and amount of radiation therapy have also changed, which has altered the clinical spectrum of ocular graft vs host disease. Dry eye due to radiation therapy,[65] systemic chemotherapy, or ocular graft vs host disease as a complication of bone marrow transplantation can be seen in cancer survivors.[66,67] A significant pediatric population has undergone bone marrow transplantation and is surviving to develop chronic graft vs host disease and dry eye.[68]

2. Menopausal Hormone Therapy (MHT)

In a study of over 25,000 women, postmenopausal estrogen therapy was found to be associated with an increased prevalence of dry eye; the prevalence of dry eye was 5.93% in women not receiving therapy, 6.67% in those receiving estrogen combined with progesterone, and 9.05% in those taking estrogen alone.[51] In post-menopausal women, for each additional 3 years of MHT, the odds ratio (**OR**) for risk of dry eye was 1.16 (1.09-1.24) after adjusting for age and other possible confounding factors. A prospective analysis of data from this study showed that the initiation of estrogen therapy preceded the diagnosis of dry eye syndrome. Corroborating evidence was subsequently found in the Shihpai study,[12] in which menopausal hormone therapy was associated with an increased risk of dry eye, OR=1.28, and in the Blue Mountains Eye Study, OR=1.7.[10]

3. Sex Hormones

The role of sex hormones in ocular surface homeostasis has been recognized and the pathologic mechanism(s) by which disturbances may result in dry eye are being investigated. Androgen levels decrease with aging in both men and women.[69] Sex steroid deficiency, specifically involving androgens, has been associated with dry eye in several distinct clinical entities, such as congenital androgen insufficiency syndrome,[70,71] SS,[72] premature ovarian failure,[73] and anti-androgen medication treatment.[74-76] The complex role of sex hormones in ocular surface health and disease warrants further study. There are conflicting reports of small studies of the risk of dry eye with oral contraceptive use, and minimal data are available regarding the effect of pregnancy, hysterectomy, oophorectomy and ovarian dysfunction on the ocular surface.[77-79]

4. Essential Fatty Acids

A role for essential fatty acids in dry eye is supported by largely consistent evidence. In a study of over 32,000 women, Miljanovic et al demonstrated about a 30% reduction in risk for dry eye with each additional gram of omega-3 fatty acids consumed per day.[52] Those who consumed 5 or more 4-ounce servings of tuna per week had a >60% reduction in risk of dry eye. A higher ratio of omega-6 to omega-3 fatty acid consumption in the diet was associated with a significantly increased risk of DES (OR: 2.51; 95% confidence interval [**CI**]: 1.13, 5.58) for >15:1 versus <4:1 (*P* for trend = 0.01). Thus, the higher the level of intake of omega-3 fatty acids in relation to the most commonly consumed types of omega-6 fatty acids, the lower the risk of dry eye. In support of a role for essential fatty acids, another study showed that women with SS had a significantly lower intake of omega-3 fatty acids (with or without adjustment for energy intake), as compared to age-matched controls.[80] Furthermore, intake of omega-3 fatty acids has been correlated with the polar lipid pattern of meibomian gland secretions in women with SS.[81]

5. Low Humidity Environments

Ocular irritative complaints, such as burning, dryness, stinging, and grittiness, are often reported in epidemiologic studies of indoor environment, especially in offices where highly demanding visual and cognitive tasks are performed.[82] While the exact cause of these symptoms remains unclear, ocular dryness due to increased tear evaporation may be due to low humidity, high room temperature and air velocity, decreased blink rate, or indoor pollution or poor air quality.[83,84] Other ultra-low humidity environments, such as aircraft cabins, have also been associated with dry eye symptoms.[85,86]

6. Computer Use

Computer users often complain of eye strain, eye fatigue, burning, irritation, redness, blurred vision, and dry eyes, among other repetitive strain symptoms.[87] This constellation of ocular complaints resulting from video display terminal operation and sustained visual attention to a computer monitor, with an associated decreased blink rate, can be regarded as a repetitive strain disorder, *computer vision syndrome* (**CVS**). While asthenopia, glare, and accommodative difficulty are all aspects of CVS, dry eye appears to contribute to a major component of symptoms reported.[88]

7. Contact Lens Wear

Contact lens (**CL**) wear has often been reported to be associated with dry eye,[89] and a significant number of CL-wearing patients experience dryness. Symptoms of dry eye

are common in CL wearers, with 50-75% of wearers reporting symptoms of ocular irritation.[44,90-93] If a conservative estimate is used (50%), approximately 17 million Americans have CL-related dry eye. A comprehensive study of 415 CL wearers revealed that several factors are associated with dry eye status in multivariate regression analyses, including female gender ($P = 0.007$), lenses with higher nominal water content ($P = 0.002$), rapid prelens tear film thinning time ($P = 0.008$), frequent usage of over-the-counter pain medication ($P = 0.02$), limbal injection ($P = 0.03$), and increased tear film osmolality ($P = 0.05$).[45]

Symptoms of dryness and discomfort are often reported as factors contributing to contact lens discontinuation. In a study by Prichard and coworkers, 12% of contact lens patients discontinued lens wear within 5 years of the initial fitting due to these symptoms.[94] Similar findings have been reported in other studies. In one study performed at a university-based ophthalmic clinic, 109 (24%) of 453 subjects with a history of contact lens wear discontinued lens wear permanently and 119 current contact lens wearers expressed contact lens dissatisfaction; both groups ranked dryness as the most common ocular symptom.[95]

8. Refractive Surgery

Dry eye is recognized to occur following refractive surgery, and our understanding of its etiology and clinical significance is evolving. Decreased corneal sensation has been proposed as the basis of reduction in blinking[96] and lacrimal secretion[96] after laser assisted in situ keratomileusis (**LASIK**) surgery, both of which may contribute to an aqueous-deficient state. Alternatively, it has been proposed that this symptomatic condition is due to the disruption of trophic sensory support to the denervated region. This condition has been termed *LASIK-Induced NeuroEpitheliopathy* (**LINE**).[97] An analogous condition of milder degree may occur following photorefractive keratoplasty (**PRK**). Limited epidemiologic data are available on refractive surgery-induced dry eye, and the magnitude, severity, and duration of the disease require further controlled prospective study. Reports of the prevalence of dry eye in LASIK patients without a prior history of dry eye vary according to the definition of dry eye, but range from 0.25%[98] up to 48%.[53]

The rate of dry eye appears to be highest in the period immediately following surgery; some, but not all, authors report a return of the Schirmer 1 to baseline level by 1 year postoperatively.[53,96,99] De Paiva and co-authors, using a definition of corneal staining of 3 or more in a small study of 35 patients, found an incidence of dry eye of 33.36% at 6 months after LASIK, and the risk of dry eye was significantly associated with extent of preoperative myopia (0.88/D. $p = 0.04$) and ablation depth (RR 1.01/micometer, $p = 0.01$).[100] Interestingly, surface ablation appears to be associated with a decreased risk of post-LASIK dry eye.[101] Dry eye may compromise wound healing and has been associated with an increased risk of refractive regression. Some authors have reported a greater risk of dry eye and refractive regression in women than in men and a higher prevalence in Asian (28%) than in Caucasian (5%) persons.[46,47] Dry eye before LASIK and long-term CL wear before LASIK may be associated an increased prevalence of dry eye after LASIK.[102]

Further research is needed to identify the risk factors for dry eye after refractive surgery, to examine the effect of pre-existing conditions (CL wear, tear instability, and ocular surface disease), and to distinguish true LASIK dry eye from LINE.[97] There is also a need to identify the value of pretreatment strategies to reduce the incidence and duration of LASIK–induced ocular surface disease.

More information is needed regarding other risk factors, such as directly comparative data to assess possible racial and/or ethnic differences, other possible nutritional and environmental risk factors, the role of sex hormones, and the possible contribution of an underlying genetic predisposition to dry eye.

C. Goal 3. Review of Dry Eye Questionnaires

Questionnaires are employed in clinical research to screen individuals for the diagnosis of dry eye or in clinical practice to assess the effects of treatments or to grade disease severity. In epidemiologic research, questionnaires can be used for population-based studies or to study the natural history of disease. The purpose of a questionnaire affects the content and nature of the instrument.

At the Puerto Rico DEWS meeting in 2004, the Epidemiology Subcommittee evaluated published dry eye symptom questionnaires. Each member of the committee received electronic files of the publications prior to the meeting. The questionnaires and publications were reviewed before the meeting, and the instruments were presented and reviewed at the Puerto Rico meeting (Table 3). The terms "dry eye" AND "questionnaire" were searched in PubMed and limits of "English language" and "human" were applied.

The following general criteria for questionnaire selection were employed for review.

1) The questionnaire has been used in randomized clinical trials (**RCTs**).
2) The questionnaire has been tested or used in epidemiologic studies.
3) The questionnaire has had some psychometric testing.
4) The questionnaire is available and appropriate for generic, non-disease-specific dry eye populations.
5) The questionnaire must have met 1 OR 2, and 3 and 4.

Fourteen questionnaires were identified that met these criteria:

1) McMonnies Dry Eye History Questionnaire (Nichols, McMonnies),[103,104]
2) Canada Dry Eye Epidemiology Study (CANDEES [Doughty]) [91]
3) Ocular Surface Disease Index (OSDI [Schiffman]),[105]
4) Salisbury Eye Evaluation (Schein, Bandeen-Roche) [106,107]
5) Dry Eye Epidemiology Projects (DEEP) questionnaire (Oden)[108]
6) Women's Health Study questionnaire (Schaumberg)[7]
7) National Eye Institute-Visual Function Questionnaire (NEI-VFQ [Mangione)[109]

Table 3. Symptoms and quality of life instruments

Instrument Title/Description/Reference	Authors/Report	Questionnaire Summary	Description/Use
McMonnies Reliability and validity of McMonnies Dry Eye Index. (Nichols et al)[103]	Nichols, Nichols, Mitchell. *Cornea* 2004;23(4):365-71	Previously described	Screening questionnaire Dry eye clinic population
McMonnies Key questions in a dry eye history (McMonnies)[104]	McMonnies. *J Am Optometric Assoc* 1986; 57(7):512-7	15 questions	Screening questionnaire—used in a clinic population
***CANDEES** A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada (CANDEES)[91]	Doughty, Fonn, Richter, et al. *Optom Vis Sci* 1997;74(8):624-31	13 questions	Epidemiology of dry eye symptoms in a large random sample
OSDI The Ocular Surface Disease Index[105]	Schiffman, Christianson, Jacobsen, et al. *Arch Ophthalmol* 2000;118:615-21	12-item questionnaire	Measures the severity of dry eye disease; end points in clinical trials, symptoms, functional problems and environmental triggers queried for the past week
OSDI and NEI-VFQ comparison[24]	Vitale, Goodman, Reed, Smith. *Health Quality Life Outcomes* 2004,2:44	Comparison of existing questionnaires	Tested in Sjogren's Syndrome population
IDEEL Comparing the discriminative validity of two generic and one disease-specific health-related quality of life measures in a sample of patients with dry eye[23]	Rajagopalan, Abetz, Mertzanis, et al. *Value Health* 2005 Mar-Apr;8(2):168-74	3 modules (57 questions): 1. Daily Activities 2. Treatment Satisfaction 3. Symptom Bother	Epidemiologic and clinical studies
Salisbury Eye Evaluation Relation between signs and symptoms of dry eye in the elderly[106]	Schein, Tielsch, Munoz B, et al. *Ophthalmology* 1997;104:1395-1401	Standardized 6-question questionnaire*	Population-based prevalence survey for clinical and subjective evidence of dry eye
Salisbury Eye Evaluation Self-reported assessment of dry eye in a population-based setting[107]	Bandeen-Roche, Munoz, Tielsch, et al. *Ophthalmol Vis Sci* 1997;38(12): 2469-2475	Standardized 6-question questionnaire*	Population-based prevalence survey for clinical and subjective evidence of dry eye
Dry Eye Epidemiology Projects (DEEP) Sensitivity and specificity of a screening questionnaire for dry eye[108]	Oden, Lilienfeld, Lemp, et al. *Adv Exp Med Biol* 1998;438; 807-20	19 questions	Screening
Women's Health Study questionnaire Prevalence of dry eye syndrome among US women[7]	Schaumberg, Sullivan, Buring, Sullivan. *Am J Ophthalmol* 2003 Aug;136(2):318-26	3 items from 14-item original questionnaire	Women's Health Study/ Epidemiologic studies
National Eye Institute Visual Function Questionnaire (NEI-VFQ)[109]	Mangione, Lee, Pitts, et al. *Arch Ophthalmol* 1998;116:1496-1504	51-item questionnaire: 2 ocular pain subscale questions	Useful tool for group-level comparisons of vision-targeted, health-related QOL in clinical research; not influenced by severity of underlying eye disease, suggesting use for multiple eye conditions.
Dry Eye Questionnaire (DEQ) Habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity[34]	Begley, Chalmers, Abetz, et al. *Invest Ophthalmol Vis Sci* 2003 Nov;44(11):4753-61	21 items on prevalence, frequency, diurnal severity and intrusiveness of sx	Epidemiologic and clinical studies
Dry Eye Questionnaire (DEQ) Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye[110]	Begley, Caffery, Chalmers, et al. *Cornea* 2002;21(7):664-70	As above	As above

Table 3 continues on following page

Table 3. Symptoms and quality of life instruments *(continued)*

Instrument Title/Description/Reference	Authors/Report	Questionnaire Summary	Description/Use
Contact Lens DEQ Responses of contact lens wearers to a dry eye survey[93]	Begley, Caffery, Nichols, Chalmers. *Optom Vis Sci* 2000; 77(1): 40-6	13 questions	Screening questionnaire for dry eye symptoms in contact lens wearers
MelbourneVisual Impairment Project The epidemiology of dry in Melbourne, Australia[11]	McCarty, Bansal, Livingston, et al. *Ophthalmology* 1998;105:1114-9	Self-reported symptoms elicited by interviewer-administered questionnaire	Epidemiologic studies
National Eye Institute 42-Item Refractive Error Questionnaire[111]	Hays, Mangione, Ellwein, et al. *Ophthalmology* 2003;110(12):2292-301	42-item questionnaire: 4 related questions: ocular pain or discomfort, dryness, tearing, soreness or tiredness	QoL due to refractive error
Sicca/SS questionnaire Validation of the Sicca symptoms inventory for clinical studies of Sjogren's syndrome[112]	Bowman, Booth, Platts, et al. Sjogren's Interest Group. *J Rheumatol* 2003;30(6):1259-66	Inventory of both symptoms and signs of Sjogren's Syndrome	Epidemiologic studies for Sjogren's Syndrome
Bjerrum questionnaire Study Design and Study Populations[113]	Bjerrum. *Acta Ophthalmologica* (Scand) 2000:10-3	3-part questionnaire which includes an ocular part with 14 questions	QOL due to SS dry eye, diagnosis of dry eye, epidemiology of SS
Bjerrum questionnaire Dry Eye Symptoms in patients and normals[114]	Bjerrum. *Acta Ophthalmologica* (Scand) 2000, 14-5.	As above	Screening questionnaire
Bjerrum questionnaire Test and symptoms in keratoconjunctivitis sicca and their correlation[35]	Bjerrum. *Acta Ophthalmol* (Scand) 1996:74:436-41	Dry eye tests Ocular symptom questionnaire (14 questions)	Examine correlation between dry eye test and ocular symptom questionnaire responses
Utility assessment questionnaire Utility assessment among pts with dry eye disease[21]	Schiffman, Walt, Jacobsen, et al. *Ophthalmology* 2003;110(7):1412-9	Utility assessment	Utility assessment
Japanese dry eye awareness study Results of a population-based questionnaire on the symptoms and lifestyles associated with dry eye[115]	Shimmura, Shimazaki, Tsubota. *Cornea* 1999; 18(4):408-11	30 questions relating to symptoms and knowledge of dry eye	Population-based, self-diagnosis study to assess public awareness and symptoms of dry eye
Sicca/SLE questionnaire Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus[116]	Jensen, Bergem, Gilboe, et al. *Oral Pathol Med* 1999;28:317-22	6-question symptom questionnaire	Screening for dry eye symptoms in SLE patients
The Eye Care Technology Forum Impacting Eye Care[117]	Ellwein. *Ophthalmology* 1994;101:199-201	Issues: Standardizing clinical evaluation	Decree for change
American-European Consensus Group Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group[118]	Vitali C, Bombardieri S, Jonnson R, et al. *Ann Rheum Dis* 2002;1:554-8		Clarification of classification of primary and secondary Sjogren syndrome, and of exclusion criteria.

8) Dry Eye Questionnaire (DEQ [Begley et al])[34,110]
9) Contact Lens DEQ (Begley et al),[93]
10) Melbourne Visual Impairment Project (McCarty)[11]
11) NEI-Refractive Error questionnaire [111]
12) Sicca Symptoms Inventory (Bowman)[112]
13) Bjerrum questionnaire[35,113,114]
14) Japanese dry eye awareness questionnaire (Shimmura)[115]

The Impact of Dry Eye on Everyday Life (IDEEL) was added to the list when it became publicly available.

A number of questionnaires were selected for detailed review, and these are summarized below. Appendix I, available at www.tearfilmocularsurface.org **(EDITOR: INSERT COMPLETE TFOS SITE INFO)** provides additional details of the McCarty symptom questionnaire, Ocular Surface Disease Index (OSDI), Salisbury Eye Evaluation questionnaire, Impact of Dry Eye on Everyday Life (IDEEL) questionnaire, and the McMonnies questionnaire.

During the meeting, the strengths and weaknesses of existing surveys were discussed, and it was noted that information is limited for each of them. The group agreed that a set of several standardized, validated questionnaires suitable for a variety of purposes and available to investigators would be desirable. Data from completed clinical trials could be used to validate existing instruments and maximize the ability to improve instruments for use in clinical trials and epidemiologic studies.

1. Features of Dry Eye Questionnaires

The instruments varied in length, intended use, population in which they were tested, mode of administration (self, interviewer, and phone) and extent of validation. Common elements in questionnaires (two or more instruments) included query of: clinician-based or other diagnosis of dry eye; frequency and/or intensity of symptoms; effect of symptoms on activities of daily living; effect of environmental triggers on symptoms; presence of dry mouth; effect of visual tasks on symptoms (eg, computer use); effect of treatment on symptoms; contact lens wear; medications; and allergies. Items infrequently included were queries related to the use of drops, arthritis, thyroid disease, dry nose or vagina, emotional triggers, and global assessment by the patient. The recall period was not specified in most questionnaires, but it ranged from 1-2 weeks in those in which a period was specified. Below is a summary of the general features of ten questionnaires:

a. McMonnies Dry Eye History Questionnaire

- 12 items- most dichotomous yes/no, weighted scoring.
- Screening, used in dry eye clinic population.
- Includes age, sex, contact lens wear.
- Previous diagnosis of dry eye, triggers (environment, swimming, alcohol).
- Frequency of symptoms: dryness, grittiness, soreness, redness, tiredness (Answers: *Never, sometimes, often, constantly*).
- Medications, arthritis, dry mouth, thyroid status.

b. Canadian Dry Eye Epidemiology Study (CANDEES)

- 13 questions: age, sex, CL wear and effect on symptoms, dry eye diagnosis.
- Epidemiologic study of prevalence of symptoms.
- Frequency and intensity of symptoms combined (Answers: *Occasional and mild, Occasional and moderate, Constant and mild, Constant and moderate, Severe*).
- Medications, time of day, allergies, dry mouth, itchy/swollen/red eyelids.

c. Ocular Surface Disease Index (OSDI)

- 12 items: visual function (6); ocular symptoms (3); environmental triggers (3)
- Frequency with 1-week recall period (Answers: *None of the time, Some of the time, Half of the time, Most of the time, All of the time* [0-4]).
- Scoring algorithm published: 100 = complete disability; 0 = no disability.
- Validated in dry eye population and used as outcome measure in RCT.

d. Impact of Dry Eye on Everyday Life (IDEEL)

- 3 modules (Daily activities, Treatment satisfaction, and Symptom bother) with a total of 57 questions.
- 2-week recall period.
- 5-point scales on frequency, bother, or limitation for most questions.
- Daily Activities includes vision, environmental triggers, emotional triggers, and work.
- Validated in dry eye population of 210 subjects with range of dry eye severity.
- Questionnaire is now available from MAPI Values, Boston, MA.

e. Salisbury Eye Evaluation Questionnaire

- 6 items: Frequency of symptoms and 3 signs (Answers: *Rarely, Sometimes, Often, All of the time*)
  Do your eyes ever feel dry?
  Gritty or sandy sensation in eyes?
  Burning sensation?
  Red, crusting lashes, stuck shut in morning.
- Self-reported population-based prevalence survey in elderly for signs and symptoms.
- Latent class analysis of symptom patterns.
- Low correlations with dry eye signs.

f. Dry Eye Epidemiology Project Questionnaire

- 19 items: treatments, symptoms, others
- Screening questionnaire (phone interview)
- Use of eye washes, compresses, drops
- Frequency of symptoms
- Itchy, sore, dry, scratchy, gritty, burning, irritated, watering, photophobia, red, sticky, achy (*Never, Sometimes, Often, Constantly*)
- Dry mouth, ocular allergies, contact lens wear frequency, physician diagnosis of dry eye

g. Women's Health Study Questionnaire

- 3 items (Answers: *Constantly, Often, Sometimes, Never*).
  Previous diagnosis of dry eye from clinician—yes or no.
  How often eyes feel dry (not wet enough)?
  How often eyes feel irritated?
- Large population-based prevalence survey..
- Case definition: Both dryness and irritation constantly or often.
- Similar sensitivity and specificity as 14 items including: sandy or gritty, burning or stinging pain, itching, light sensitivity, blurry vision, tiredness, soreness, scratchiness, redness, stickiness, achy feeling watery eyes and swollen eyelids.
- Validated against standardized clinical exam.

h. National Eye Institute-Visual Function Questionnaire (NEI-VFQ)

- 25 items of frequency and severity of symptom and effects on activities of daily living
- Multiple domains: ie, near vision, general health, social problems, distance vision...
  How often does pain or discomfort affect activities of daily living (Answers: *All, Most, Some, A little, None of the time* [5-point scale])
  —How much pain (ie, burn, itch, ache)? (Answers: *None, Mild, Moderate, Severe, Very severe* [5-point scale]).
- Not developed for dry eye; however, tested in several