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THE Ocular Surface

A JOURNAL OF REVIEW LINKING LABORATORY SCIENCE, CLINICAL SCIENCE, AND CLINICAL PRACTICE

A peer-reviewed journal, indexed in MEDLINE/PubMed and EMBASE

SPECIAL ISSUE

2007 Report of the International Dry Eye WorkShop (DEWS)

Sponsored by the Tear Film & Ocular Surface Society

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DEWS Report: A Mission Completed

This issue of *The Ocular Surface* is very unusual. As the official report of the Dry Eye Work-Shop (DEWS), it is an encyclopedic review of dry eye disease and, additionally, a guide to resources archived on the internet. It is the product of a team of international experts who have labored over 3 years to compile an evidence-based review of the present state of knowledge for dry eye disease and the methods used to evaluate, diagnose, and manage the disorder. It summarizes the findings of current research and identifies future needs for a better understanding of the etiology, pathogenesis, and potential therapy of the disease.

The process of deliberation and discussion that underpins this arduous endeavor is described in the "Introduction" and in various chapters of the volume. Suffice it to say that an international community of clinicians and scientists with expertise in all aspects of dry eye disease collaborated to search the literature, collect and validate data, and incorporate it into reports. The process of commentary and adjudication of differing opinions was open, yet subject to several levels of validation. The product is a written document that serves as a guide to a vast amount of information that is archived both in this special issue and on a supporting website (www.tearfilm.org) that is accessible to all.

The chapter on Definition and Classification expands the characterization of dry eye disease and places it within the perspective of ocular surface disease. The chapter on Epidemiology provides commentary on the implications of the disease, as well as comparison of the methods available to evaluate symptoms and factors contributory to the disease. The Diagnostic Methodologies chapter not only provides valuable discussion of the parameters of dry eye disease, but also catalogs and validates a vast collection of clinical and research methods, including questionnaires, to monitor the disease. The Research chapter summarizes past and present findings, and identifies areas whose further study will contribute to the understanding of the etiopathogenesis and consequences of dry eye disease. The chapter on Clinical Trials provides recommendations with regard to both general and specific guidelines for clinical trials in dry eye disease and identifies the idiosyncrasies and confounding outcome variables for such trials. The chapter on Management and Therapy catalogs the options for therapy and recommends a contemporary strategy for management of dry eye disease.

As would be expected for a multifactorial disease that has many nuances in clinical and pathological expression, opinions differ even amongst the experts as to the most appropriate way to characterize and label some aspects of the disease. This proved true for the definition and classification of the disease. Some key concepts in the appreciation of dry eye were identified from the literature. One such concept was the characterization of the *Lacrimal Functional Unit*,[1] which has highlighted the interdependence of components of the lacrimal system in maintaining the integrity of the ocular surface. Some new concepts were constructed in the deliberation process of the Subcommittee work, including a concept suggested by Dr. Christophe Baudoin—a *Vicious Circle* of dry eye disease, by which various risk factors may interact to precipitate and perpetuate the condition.[2] The concept of the *Ocular Surface System*, developed by the Research Subcommittee, extends the scope of the ocular surface to a collection of contiguous tissues that share embryonal, innervational, histological, and hormonal background.

The time and effort necessary to compile and collate this project and the summary document was extraordinary. The endeavor could never have been completed without the sponsorship and commitment of The Tear Film & Ocular Surface Society and the officers and staff of that organization. The planning and execution of the organizational meetings, the coordination of the conferences for presentation of the collected information, the facilitation of the discussions of the DEWS participants, and the administrative direction of the publication process were achieved through the tireless efforts of Dr. David A., Rose M. and Amy G. Sullivan. The deliberations of the Steering Committee were essential to the completion of the task. Likewise, the leaders of the various Subcommittees were instrumental in providing the building blocks for construction of the final product. A special congratulations and thank you is due Professor Anthony J. Bron, who devoted endless hours and energy to leading the writing team through multiple iterations of the text and the references to provide a harmonization of the various reports. The ultimate coordination and editing of the document was in the capable hands of Susan Erickson, for whom we are most appreciative. Particular appreciation is extended to Ethis Communications, Inc. for embracing the publication of this work, which should serve as a valuable reference for all those who investigate and manage patients with dry eye disease. Last but far from least is a heartfelt thank you to the Corporate Sponsors of the Dry Eye WorkShop, who provided the financial resources and encouragement to complete this project.

I wish you good reading and great referencing.

Gary N. Foulks, MD, FACS
Editor-in-Chief

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SPECIAL ISSUE

2007 Report of the International Dry Eye WorkShop (DEWS)

Sponsored by the Tear Film & Ocular Surface Society

The 2007 International Dry Eye WorkShop was sponsored by *The Tear Film & Ocular Surface Society*, which received support for DEWS from SOOFT Italia; Alcon Laboratories; Allergan; McNeil Consumer Healthcare; Pfizer; Santen Pharmaceutical Co.; Bausch & Lomb; Novartis Pharmaceuticals; Advanced Vision Research; Inspire Pharmaceuticals; Vistakon; Senju Pharmaceutical Co.; Kowa; Otsuka Pharmaceutical Co.; Alimera Sciences; Tomei; Nidek

Introduction to the Report of the International Dry Eye WorkShop (2007)

Dry eye disease is a common yet frequently under-recognized clinical condition whose etiology and management challenge clinicians and researchers alike. Advances in the understanding of the disease have been made over the past 10 years in areas of epidemiology, pathogenesis, clinical manifestation, and possible therapy. This volume represents the work of many contributors over a long period of deliberation and through an iterative process that included collection of data, presentation of summary reports in a conference format, and harmonization of reports by a writing team with interactive commentary by the entire group of participants in an international workshop.

History

In 1994, a workshop sponsored by the National Eye Institute and supported by industry convened a group of scientists, clinicians, and researchers interested in dry eye to clarify the definition and characteristics of dry eye disease and to recommend reliable parameters for conduct of clinical research and conduct of clinical trials for dry eye disease.[1] The report of that workshop has served as a solid resource in the field for over 10 years, but the explosion of information in both basic and clinical research in the interim warranted repetition of the process. An initiative was suggested by Kazuo Tsubota, MD, and endorsed by Michael A. Lemp, MD, to recruit an international panel of experts in dry eye disease to accomplish such a task, and preliminary meetings were held in 2001.[2] Selection of the participants was based upon their prior history of peer-reviewed publication, level of participation in previous dry eye meetings (including the NEI/Industry Workshop), and collaboration with acknowledged experts in the field. The immensity of the task became immediately apparent and the coordinating support of The Tear Film & Ocular Surface Society (TFOS) was solicited. David A. Sullivan, PhD, President of TFOS, committed the organizational and administrative support of TFOS and secured broad financial support from international corporations to facilitate the international Dry Eye WorkShop (DEWS).

Process

The DEWS effort was chaired by Anthony J. Bron, FRCS, and directed by a Steering Committee that proposed guidelines for the determination of acceptable levels of evidence and methods of documentation to support such evidence. The first step involved the formation of subcommittees: Definition and Classification; Epidemiology; Diagnosis; Research; Clinical Trials, and Management and Therapy, in addition to a Communications and Industrial Liaison committee. The scientific subcommittees were charged with identifying contemporary, evidence-based information about various aspects of dry eye disease and summarizing the data in a conceptual format that was well documented and well referenced. Chairpersons of the subcommittees developed goals for each of the working committees and were responsible for coordinating the work. The second step was to hold a 3-day meeting, during which committee reports were presented to the entire group and discussed in an open forum, with all participants invited to comment or suggest additions to the reports. Finally, a writing team was established to review the reports and attempt to harmonize the presentation and cross-reference the information and concepts presented. The process of review and consideration was ongoing over a period of several years. Reports were posted on an internet website for review and commentary by all participants and comments received were submitted to the subcommittee chairpersons for evaluation and response. The draft product was submitted to the Steering Committee for final review and approval. All participants were required to provide disclosures of financial arrangements or conflicts of interest, and this information is posted on the website (www.tearfilm.org) and published at the end of this issue.

Product

In addition to the report published in this special issue of *The Ocular Surface*, the DEWS findings are available in an expanded electronic form on the TFOS website (www.tearfilm.org). This latter provision has allowed the presentation of material excluded from the journal for reasons of space, such as appendices, extended bibliographies, and standardized templates describing diagnostic tests. Each chapter addresses a topic relevant to the understanding of dry eye disease and the combined publication represents a resource that will be valuable to clinicians, epidemiologists, basic and clinical scientists, and members of the pharmaceutical industry. The reader is encouraged to use these resources extensively to support and enhance discussions in the text.

Acknowledgements

Because the DEWS report represents the integrated work of many participants, individual authorship is not assigned to the overall report or its chapters. Complete listing of the DEWS membership is shown on the following pages, and Subcommittee members are designated in a footnote on the title page of each chapter. Special recognition of the efforts of several participants in the production of this report is appropriate. The officers and administrative staff of The Tear Film & Ocular Surface Society (TFOS), including David A. Sullivan, PhD, Rose M. Sullivan, and Amy G. Sullivan, were essential to the compilation and circulation of schedules and documents. Christopher Paterson, PhD, facilitated the open meeting and discussion of the preliminary reports. Elizabeth Fini, PhD, recorded and transcribed the proceedings of the open discussion at the meeting. Anthony J. Bron, FRCS, served with dedication and energy as both Chairman of the entire DEWS workshop and Chairman of the writing team. In his role as Chairman of the Communication Subcommittee and member of the writing team, Gary N. Foulks, MD, provided valuable contributions both scientifically and organizationally.

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Report of the 2007 International Dry Eye WorkShop (DEWS) Glossary

ACR50, ACR70 indices of physical and joint function developed by the American College of Rheumatology to assess functional performance and limitation due to rheumatic disease.

ADDE Aqueous Deficient Dry eye, dry eye that is due to decreased secretion of tear fluid from the lacrimal glands.

AKC atopic keratoconjunctivitis, an allergic condition associated with atopic disease productive of inflammation of the ocular surface.

ARDE Age-Related Dry Eye, dry eye disease that is concurrent with aging.

ATD Aqueous Tear Deficiency.

ATS Artificial Tear Substitute

BUT Fluorescein Break-Up Time or Test.

CAE Controlled Adverse Environment, an environment designed and constructed to provide an environmental challenge to aggravate a clinical condition under study.

CCLR Centre for Contact Lens Research, University of Waterloo, Ontario.

Challenge clinical trial a clinical trial that observes the effect of a treatment or intervention under environmental or activity conditions that stress or challenge a particular physical or mental condition.

CIC Conjunctival Impression Cytology.

CLEK Collaborative Longitudinal Study of Keratoconus.

CPT Conjunctival Provocation Test.

CPT code current procedure terminology that assigns a unique numerical code to procedures performed for conditions listed in the ICD-9 codified disease list.

CVS Computer Vision Syndrome, the symptoms and signs produced by prolonged use of a videodisplay terminal and computer that results in decreased blink, increased tear instability and symptoms of discomfort and fluctuation in vision.

DEQ The Dry Eye Questionnaire.

DES Dry Eye Syndrome, that collection of clinical conditions that produce abnormalities of the tears and ocular surface, usually by decreased tear production or increased tear evaporation.

Dysfunctional tear syndrome the term recommended by the International Delphi Panel to describe abnormalities of the tear film and the consequences to the ocular surface.

ECP Eosinophil Cationic Protein.

EDE Evaporative Dry Eye, dry eye that is due to increased evaporation of the tear fluid from the surface of the eye.

Environmental clinical trial a clinical trial that observes the effect of a treatment or intervention under the ambient environmental conditions present.

EQ-5D a standardized questionnaire for use as a measure of health outcomes.

Equipoise (clinical research) a state of uncertainty regarding whether alternative health care interventions will confer more favorable outcomes, including balance of benefits and harms. Under the principle of equipoise, a patient should be enrolled in a randomized controlled trial only if there is substantial uncertainty (an expectation for equal likelihood) about which intervention will benefit the patient most.

FBUT Fluorescein Break-Up Time or Test.

FCT Fluorescein Clearance Test. A test of tear turnover; see TCR.

FVA Functional Visual Acuity, a measure of visual acuity during a tightly controlled period of time or environmental circumstance that assesses visual acuity with the subject being unable to compensate by blinking or adjustment to a visual challenge.

GCP Good Clinical Practices, those features of conducting a clinical trial that are accepted as proper methods for conducting a clinical trial.

Goblet cells specialized cells in the ocular surface epithelium that secrete soluble and gel-forming mucins onto the ocular surface and into the tear film.

GVHD Graft Vs Host Disease, inflammation caused by engrafted immunocompetent cells that recognize as foreign and attack cells of the host.

HADS Hospital Anxiety and Depression Scale, a scale developed to evaluate anxiety and depression.

HLA Human Leukocyte Antigen.

ICAM-1 Intercellular Adhesion Molecule that enables cell-to-cell adhesion. It is often a marker of inflammation.

ICD-9 International Classification of Disease that assigns a unique numerical code to each disease.

IDEEL Impact of Dry Eye on Everyday Life, a set of questions framed to determine the level of interference with activities of daily living produced by dry eye disease.

IL Interleukin.

Incidence the frequency of occurrence of a condition per total unit of population per period of time (eg, x/100,000/yr).

International Conference on Harmonization conference that defined guidelines for ethical conduct of human clinical trials.

International Dry Eye Workshop (DEWS) the international group conference that collated evidence-based information describing the clinical condition of dry eye disease, including clinical, basic and clinical research, epidemiology and management of the condition.

IRB Institutional Review Board, institutional committee of a defined composition that is responsible for the review of the ethical construction and conduct of a clinical trial in compliance with accepted ethical guidelines.

ITT Intention To Treat population, all subjects randomized in a clinical trial based on the original treatment to which they were assigned, regardless of the treatment they actually received or their adherence to the study protocol.

KCS Keratoconjunctivitis sicca, the condition of dry eye and inflammation of the ocular surface described by Henrik Sjögren, MD. Now commonly used interchangeably with *dry eye syndrome.*

La (SSB) a specific antigen expressed on cells that is a target for antibodies developed by the immune response in Sjogren syndrome

LASIK Laser Assisted in-Situ Keratomileusis: the removal of corneal tissue by laser beneath an anterior flap of cornea performed to correct refractive error.

LFU Lacrimal Functional Unit, the integrated functional unit comprising the lacrimal system, the ocular surface and its accessory glands and their neural interconnections that is responsible for the maintenance of the tear film and protection of the transparency of the cornea and health of the ocular surface.

Likert score a method of grading a subjective symptom or objective sign of disease by use of a categorical scale.

LINE LASIK-Induced Neuro Epitheliopathy, a term used to describe the symptom complex of ocular irritation and ocular surface abnormalities following LASIK surgery.

LIPCOF Lid Parallel Conjunctival Folds, an indicator of conjunctivochalasis.

LOCF Last Observation Carried Forward, a statistical technique to correct for missing information at a data collection point by carrying forward the last clinical observation made prior to the missing data.

M3 Muscarinic receptor, type 3.

MAP kinase Mitogen-Activated Protein kinase

MBI Maximum Blink Interval.

MFI Multi-dimensional Fatigue Inventory, a questionnaire that catalogs multiple aspects of symptoms contributing to or associated with fatigue.

MGD Meibomian Gland Dysfunction

MHC Major Histocompatibility Antigens expressed on cells and determining immune recognition in transplantation allograft reaction

MHT Menopausal Hormone Therapy, systemic replacement of female sex hormones as a treatment for post-menopausal lack of estrogen and/or other hormones.

MMP Matrix Metalloproteinase Proteolytic enzymes formed by tissues and inflammatory cells.

Mod ITT Modified Intent to Treat population, all subjects randomized to a clinical trial who received at least one dose of medication or assigned intervention.

Mucins glycoproteins expressed on the ocular surface or secreted into the tear film.

MUC-4 Mucins –soluble:

MUC1, MUC11, MUC-16 Mucins-membrane spanning

MUC5AC the gel-forming mucin secreted by the goblet cells of the ocular surface.

NEI-VFQ NEI Visual Function Questionnaire, a questionnaire developed by the National Eye Institute to evaluate vision function in activities of daily life.

NIBUT Non-Invasive Break-Up Time or Test

Nocebo a treatment or intervention that has no negative direct effect on a condition under treatment.

NSATD Non-Sjogren Aqueous Tear Deficiency.

NSSDE Non-Sjogren Syndrome-associated Dry Eye, ADDE that occurs in the absence of Sjogren Syndrome.

OPI Ocular Protection Index.

OR odds ratio

OSDI Ocular Surface Disease Index, a set of questions assessing the level of discomfort and interference with activities of daily living produced by ocular surface disease. (Developed by Allergan, Inc for evaluation of dry eye disease).

OSS Ocular Surface System, the contiguous epithelia of the ocular surface which are derived embryologically from the same surface epithelia and which are continuous, through ductal epithelia, with the acinar epithelia of the main and accessory lacrimal glands, the meibomian glands and the nasolacrimal system.

Phenol red thread test measurement of tear volume or change in tear volume with time by observation of the amount of wetting of a phenol red dye impregnated cotton thread placed over the inferior eyelid.

PHS Physicians' Health Study, a large, prospective, long-term epidemiologic study of a cohort of male physicians in the United States

Placebo a treatment or intervention that has no positive direct effect on a condition under treatment.

PP Per Protocol population, all subjects randomized to an assigned treatment or intervention who completed the treatment according to protocol

Predictive value the likelihood that a test will reliably predict the presence of a given abnormality in a population.

Prevalence the frequency of occurrence of a condition or disease in a cross-sectional population sample (eg, x% of an evaluated population)

PRK photorefractive keratectomy: the removal of anterior corneal tissue by laser performed to correct refractive error.

QoL Quality of Life, the features of patient comfort and activity that can be influenced by illness or injury.

RCT Randomized Clinical Trial, a clinical study of two or more treatments or interventions that assigns subjects at random to each of the treatment options.

Regression to the mean a statistical finding that with sequential observations, subject scores tend towards the mean of the original sample.

RK radial keratotomy, incisions made in a radial pattern about the mid-peripheral cornea to correct myopic refractive error.

Ro (SSA) a specific antigen expressed on cells that is a target for antibodies developed by the immune response present in Sjogren Syndrome.

SBUT Symptomatic Tear Film Break-Up Time.

Schirmer test a test to measure change in tear volume (production) by the observed wetting of a standardized paper strip placed over the inferior eyelid over a given period of time.

Schirmer test without anesthetic the test is performed without prior instillation of topical anesthesia to the ocular surface.

Schirmer test with anesthetic the test is performed after prior instillation of a topical anesthetic to the ocular surface.

Secretagogue an agent that stimulates glandular secretion.

Sensitivity the likelihood that a clinical test will detect the presence of a given abnormality in a population.

SF-36 The 36 item Medical Outcome Study Short-Form, a set of 36 questions that evaluate the level of interference with activities of daily living by a disease.

SLE Systemic Lupus Erythematosis.

Specificity the likelihood that a clinical test will identify only the given abnormality in a population.

SSATD Sjogren Syndrome Aqueous Tear Deficiency

SSDE Sjogren Syndrome-associated Dry Eye, ADDE that is associated with and caused by Sjogren Syndrome.

S-TBUD Staring Tear Breakup Dynamics.

Surrogate marker a marker or parameter of measurement that reflects or correlates with a different parameter of disease or tissue alteration. Surrogate markers may be direct or correlative. Direct surrogate markers are those that derive from the same physical or chemical properties as the primary marker. Correlative surrogate markers are those that correlate with the primary marker but can be produced by other mechanisms as well.

TCR Tear Clearance Rate, the rate at which the preocular tear film or an instilled marker of the tear is removed from the tear film by dilution or drainage from the tear volume.

Tear Breakup Time (TBUT also: BUT, FBUT and TFBUT) The time to initial breakup of the tear film following a blink.

TFFL Tear Film Lipid Layer, the most anterior layer of the tear film, composed of meibomian lipids that limit evaporation and stabilize the tear film.

TFI a test of tear dynamics whose value is obtained by dividing the value of the Schirmer test with anesthesia by the tear clearance rate.

TFT Tear Ferning Test, a test that detects dry eye on the basis of tear ferning patterns.

TSAS Tear Stability Analyses System

VAS Visual Analog Scale, a method of grading a subjective symptom or objective sign of disease by use of a measured linear scale.

VFQ-25 NEI-devised Visual Functioning Questionnaire.

VKC Vernal Keratoconjunctivitis, an allergic condition manifested by chronic and episodic inflammation of the ocular surface and papillary reaction of the conjunctiva.

VT-HRQ Vision-Targeted Health-Related Quality of Life, a questionnaire that evaluates QOL activities related to or dependent upon vision.

WHS Women's Health Study, a large, prospective, long-term epidemiologic study of a cohort of women in the United States.

Xerophthalmia A bilateral ocular disease caused by Vitamin A deficiency, characterized by night blindness, xerosis of the ocular surface and keratomalacia.

ABBREVIATIONS USED

↑ = Increase in/increased
↓ = Decrease in/decreased
Δ = Change in/changes to
–/– = Homozygous null mouse
ACAT-1 = Acyl-CoA:cholesterol acyltransferase-1
Auto-AG = Autoantigen
BUT = Breakup time
CALT = Conjunctiva-associated lymphoid tissue
Chr Bleph = Chronic blepharitis
CIC = Cicatrizing disease
Conj = Conjunctiva/conjunctival
Cont lens = Contact lens
DE = Dry eye
DES = Dry eye syndrome
EDA = Ectodermal dysplasia
ENV STR = Environmental stress
epi = Epithelia/epithelial
Epi. Diff/sq metaplasia = Epithelial differentiation/squamous metaplasia
GVHD = Graft-versus-host disease
KCS = Keratoconjunctivitis sicca
Lac = Lacrimal
Meibom = Meibomian
↓MG = Loss of meibomian glands
MGD = Meibomian gland dysfunction
NSS = Non Sjögren's syndrome
NSS/ACQ = Aqueous deficient non Sjögren's Syndrome
Nasolac = Nasolacrimal
NLD = Nasolacrimal duct
RA-MGD = Retinoic acid induced MGD
SCOP = Scopolamine
siRNA = Small interfering RNA
Spont DE = Spontaneous dry eye
SS = Sjogren Syndrome
TALT = Tear duct-associated lymphoid tissue
TBUT = Tear breakup time
Undif KCS = undifferentiated keratoconjunctivitis sicca
↓Vit A = Vitamin A-deficient
–Vit A = Vitamin A totally depleted

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

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

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

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

Reprints are not available. Articles can be accessed at: www.tearfilm.org

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I. INTRODUCTION

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

II. GOALS OF THE DEFINITION AND CLASSIFICATION SUBCOMMITTEE

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

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

III. DEFINITION OF DRY EYE DISEASE

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

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

> *Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,*[2-4] *visual disturbance,*[5-7] *and tear film instability*[8-10] *with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film*[11-14] *and inflammation of the ocular surface.*[15,16]

OUTLINE

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

This functional unit controls the major components of the tear film in a regulated fashion and responds to environmental, endocrinological, and cortical influences. Its overall function is to preserve the integrity of the tear film, the transparency of the cornea, and the quality of the image projected onto the retina.[17-20] At the 2007 Dry Eye WorkShop, it was noted that the corneal and conjunctival epithelia are in continuity, through ductal epithelia, with the acinar epithelia of the main and accessory lacrimal glands and the meibomian glands, which themselves arise as specialized invaginations from the ocular surface. Also, these epithelia have the same embryological derivation. This broader concept, which has additional features, has been termed the *Ocular Surface System* and is discussed further in the "Research" chapter of this issue.[21]

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

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

IV. CLASSIFICATION OF DRY EYE DISEASE

A. Background

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

Although the NEI/Industry Workshop classification[1] has served as a useful and durable scheme for over a decade, it does not reflect newer knowledge on pathophysiological mechanisms, effects on vision, and the utility of an assessment of severity of disease. Recently, two new classification schemes were published, and these were used as source documents by the committee. These include: the Triple Classification[25,26] and the report of the Delphi panel.[27]

The Triple Classification evolved from reports presented

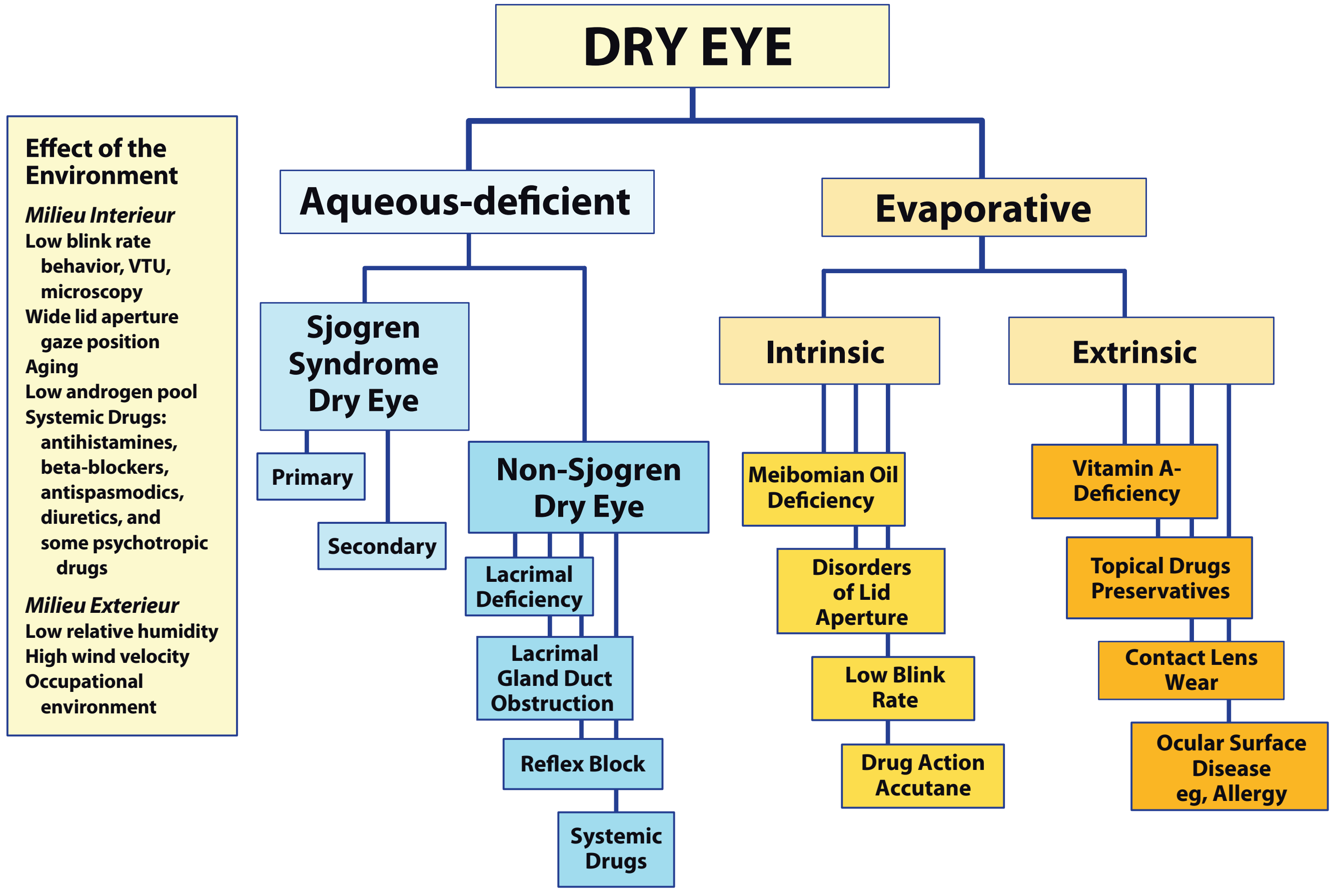

Figure 1. Major etiological causes of dry eye.

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

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

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

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

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

The Delphi Panel was a consensus group that met to review the classification of dry eye.[27] The panel proposed changing the name of *dry eye disease* to *dysfunctional tear syndrome*, suggesting that the name more accurately reflected pathophysiological events in dry eye. However, although the committee felt that the term embraced the essential features of the disease, they concluded that retention of the name *dry eye* had much to recommend it and that its use was embedded in the literature. The committee also rejected a subdivision based on the presence or absence of lid disease, because it is frequently difficult to identify the relative contribution of lid disease to a particular case of dry eye.

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

B. Etiopathogenic Classification of Dry Eye Disease

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

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

The classification has the following features:

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

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

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

Extensive evidence supports a role for the sex hormones in the etiology of dry eye[33] with the generalization that low levels of androgens and high estrogen levels are risk factors for dry eye. Biologically active, androgens promote lacrimal and meibomian gland function.[33] Androgen deficiency is associated with dry eye[34] and may be prevented by topical or systemic androgen therapy.[35-38] Dry eye occurs in patients exposed to anti-androgens in the treatment of prostatic cancer,[39,40] and women with complete androgen insensitivity syndrome show an increase in the signs and symptoms of dry eye, associated with evidence of meibomian gland and goblet cell dysfunction.[41-43] A significantly depleted androgen pool in "non-autoimmune" dry eye associated with meibomian gland dysfunction (**MGD**) has been reported.[44] Also, as noted elsewhere in this issue,[45] female sex and postmenopausal estrogen therapy are important risk factors for dry eye,[46,47] and women with premature ovarian failure suffer from the symptoms and signs of dry eye, although their tear production is not affected.[48]

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

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

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

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

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

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

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

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

It is uncertain whether evaporation is reduced[59] or increased[59-64] in ADDE. It is possible that this is determined by the stage of the disease. Some studies suggest that the reservoir of lid oil is larger in non-Sjogren syndrome dry

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

I. Ocular symptoms: a positive response to at least one of the following questions:	
	1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
	2. Do you have a recurrent sensation of sand or gravel in the eyes?
	3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions:	
	1. Have you had a daily feeling of dry mouth for more than 3 months?
	2. Have you had recurrently or persistently swollen salivary glands as an adult?
	3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:	
	1. Schirmer I test, performed without anesthesia (≤5 mm in 5 minutes)
	2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)
IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue[18]	
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:	
	1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
	2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts[19]
	3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer[20]
VI. Autoantibodies: presence in the serum of the following autoantibodies:	
	1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

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

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

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

a. Sjogren Syndrome Dry Eye

Sjogren syndrome is an exocrinopathy in which the lacrimal and salivary glands are targeted by an autoimmune process; other organs are also affected. The lacrimal and salivary glands are infiltrated by activated T-cells, which cause acinar and ductular cell death and hyposecretion of the tears or saliva. Inflammatory activation within the glands leads to the expression of autoantigens at the surface of epithelial cells (eg, fodrin, Ro and La)[69] and the retention of tissue-specific CD4 and CD8 T-cells.[70] Hyposecretion is amplified by a potentially reversible neurosecretory block, due to the effects of locally released inflammatory cytokines or to the presence of circulating antibodies (eg, anti-M3 antibody) directed against muscarinic receptors within the glands.[71-73]

There are two forms of SS, and classification criteria have recently been harmonized in a European-American collaboration.[74] *Primary SS* consists of the occurrence of ADDE in combination with symptoms of dry mouth, in the presence of autoantibodies, evidence of reduced salivary secretion and with a positive focus score on minor salivary gland biopsy.[75,76] Details of the criteria are presented in Table 1. *Secondary SS* consists of the features of primary SS together with the features of an overt autoimmune connective disease, such as rheumatoid arthritis, which is the most common, or systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis, or mixed connective tissue disease. Diagnostic criteria for each of these connective tissue disorders have been published.[77]

The precise triggers leading to autoimmune acinar damage are not known in full, but risk factors include genetic profile,[78] androgen status[79] (a low androgen pool favoring an inflammatory environment within the target tissues), and exposure to environmental agents, ranging from viral infections affecting the lacrimal gland to polluted environments. A nutritional deficiency in omega-3- and other unsaturated fatty acids and unsupplemented intake of vitamin C has also been reported in patients with SS.[80] It is generally accepted that environmental factors leading to increased evaporative water loss from the eye (eg, low humidity, high wind velocity, and increased exposure of the ocular surface) may act as a trigger by invoking inflammatory events at the ocular surface through a hyperosmolar mechanism (see Section V).

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

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

b. Non-Sjogren Syndrome Dry Eye

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

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

Primary lacrimal gland deficiencies
Age-related dry eye
Congenital alacrima
Familial dysautonomia
Secondary lacrimal gland deficiencies
Lacrimal gland infiltration
Sarcoidosis
Lymphoma
AIDS
Graft vs host disease
Lacrimal gland ablation
Lacrimal gland denervation
Obstruction of the lacrimal gland ducts
Trachoma
Cicatricial pemphigoid and mucous membrane pemphigoid
Erythema multiforme
Chemical and thermal burns
Reflex hyposecretion
Reflex sensory block
Contact lens wear
Diabetes
Neurotrophic keratitis
Reflex motor block
VII cranial nerve damage
Multiple neuromatosis
Exposure to systemic drugs

1) Primary Lacrimal Gland Deficiencies

Age-Related Dry Eye (ARDE): There is some uncertainty as to whether tear dynamics are affected by age in the normal population.[83] Mathers et al showed significant age-related correlations for tear evaporation, volume, flow, and osmolarity,[49] but no such relationship was noted by Craig and Tomlinson[84] or in other reports of tear turnover,[85] tear evaporation[86,87] and lipid layer.[88] ARDE is a primary disease.

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

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

Familial Dysautonomia: Lacrimal dysfunction is a major feature of the autosomal recessive disorder, familial dysautonomia (Riley Day syndrome), in which a generalized insensitivity to pain is accompanied by a marked lack of both emotional and reflex tearing, within a multisystem disorder. There is a developmental and progressive neuronal abnormality of the cervical sympathetic and parasympathetic innervations of the lacrimal gland and a defective sensory innervation of the ocular surface, which affects both small myelinated (Aδ) and unmyelinated (C) trigeminal neurons.[94,95] The chief mutation affects the gene encoding an IκB kinase-associated protein.

2) Secondary Lacrimal Gland Deficiencies

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

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

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

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

Graft vs host disease (**GVHD**): Dry eye is a common complication of GVHD disease, occurring typically around 6 months after hematopoietic stem cell transplantation. It is caused in part by lacrimal gland fibrosis due to colocalization of periductal T-lymphocytes (CD4 and CD8) with antigen-presenting fibroblasts.[99,100]

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

Lacrimal gland denervation: Parasympathetic denervation of the human lacrimal gland may cause dry eye,[102] and, experimentally in the rat, it causes reduced tear flow and lacrimal protein secretion and activates inflammatory changes in the gland.[103] The accessory glands are innervated similarly to the main and palpebral lacrimal glands[104] and are assumed to be under similar reflex control; however, evidence for this is lacking.

Table 3. Causes of ocular sensory loss

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

3) Obstruction of the Lacrimal Gland Ducts

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

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

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

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

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

4) Reflex Hyposecretion

a) Reflex Sensory Block (Tables 2 and 3)

Lacrimal tear secretion in the waking state is due in large part to a trigeminal sensory input arising chiefly from the nasolacrimal passages and the eye. When the eyes open, there is an increased reflex sensory drive from the exposed ocular surface. A reduction in sensory drive from the ocular surface is thought to favor the occurrence of dry eye in two ways, first, by decreasing reflex-induced lacrimal secretion, and, second, by reducing the blink rate and, hence, increasing evaporative loss.[111] Experimental evidence has shown that trigeminal denervation in the rabbit modifies the regulation of lacrimal protein secretion.[112]

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

Contact Lens Wear: A reduction in corneal sensitivity occurs in wearers of hard- and extended wear- contact lenses (**CL**s), possibly contributing[11,113] to dry eye symptoms in this group of patients. In some studies, increased tear osmolarity has been recorded in association with CL wear.[113,114] In a rabbit model, trigeminal denervation increases tear film osmolarity and causes the morphological changes characteristic of dry eye.[115] Similar arguments have been put forward to advance the concept of LASIK dry eye[116,117]; although there is evidence to support the concept, counter arguments have been put forward to suggest that at least some of the patients who are symptomatic after LASIK surgery have a neurotrophic deficiency[118] or neuralgic disorder.[119]

Diabetes: Diabetes mellitus has been identified as a risk factor for dry eye in several studies, including large population studies.[120-123] The prevalence was 18.1% in diabetics compared to 14.1% in non-diabetics in the Beaver Dam study,[121,122] in which the diagnosis of dry eye or dry eye symptoms were self-reported. A similar prevalence (diabetics 20.6%, non-diabetics 13.8%) was reported in a study based on frequency of use of ocular lubricants.[123] This study also noted an association between poor glycemic control (as indicated by serum HbA1C) and frequency of drop use. Goebbels[124] found a reduction in reflex tearing (Schirmer test) in insulin-dependent diabetics, but no difference in tear film breakup time or basal tear flow by fluorophotometry.

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

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

The sensory loss results in a reduction of lacrimal secretion[126] and a reduction in blink rate. In addition, it is envisaged that there is a loss of trophic support to the ocular surface[125] after sensory denervation, due to a deficient release of substance-P or expression of nerve growth factor.[127-131]

Table 4. Meibomian gland diseases causing evaporative dry eye

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

b) *Reflex Motor Block*

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

An association between systemic drug use and dry eye has been noted in several studies, with decreased lacrimal secretion being the likely mechanism. Responsible agents include: antihistamines, beta blockers, antispasmodics, and diuretics, and, with less certainty, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other psychotropic drugs.[122] Additional associations with drying medications were reported by Schein et al, unrelated to the disease for which they were used.[133] Use of ACE (angiotensin converting enzyme) inhibitors was associated with a lower incidence of dry eye, and no relationship was found with calcium channel blockers or cholesterol-lowering drugs.[122]

2. Evaporative Dry Eye

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

a. *Intrinsic Causes*

1) Meibomian Gland Dysfunction

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

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

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

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

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

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

3) Low Blink Rate

Drying of the ocular surface may be caused by a reduced blink rate, which lengthens the period during which the ocular surface is exposed to water loss before the next blink.[166] Methods have been developed to record the blink rate and to relate this to the development of dry eye.[163] This may occur as a physiological phenomenon during performance of certain tasks of concentration, eg, working at video terminals[167] or microscopes, or it may be a feature of an extrapyramidal disorder, such as Parkinson disease (**PD**).

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

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

On the basis of these findings, Tamer et al postulated several mechanisms by which PD may induce dry eye. 1) Reduced blink rate and impaired meibomian oil delivery to the tear film can increase evaporative loss. They also suggest that a reduced blink rate could impair the clearance of lipid-contaminated mucin.[174] 2) Experimentally, androgens are required for the normal functioning of both the lacrimal[175,176] and meibomian glands, [177,178] and there is clinical evidence that dry eye symptoms are promoted by blockade of androgen receptors.[43] The levels of circulating androgens are low in a large proportion of PD patients,[179] and it is suggested that this may contribute to lacrimal and meibomian dysfunction. 3) In addition, decreased reflex tearing in PD has been attributed to autonomic dysfunction, reflecting the presence of Lewy bodies in the substantia nigra, sympathetic and peripheral parasympathetic ganglia.[180] Magalhaes et al found evidence of autonomic failure in about a third of patients with PD.

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

b. *Extrinsic Causes*

1) Ocular Surface Disorders

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

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

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

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

Chronic use of topical anesthetics can cause a neurotrophic keratitis leading to corneal perforation.[185,186]

2) Contact Lens Wear

Contact lens wear is prevalent in the developed world, with 35 million wearers cited in the USA in the year 2000.[187] The causes of CL-related symptoms and of lens intolerance are, therefore, of personal and general economic importance. The primary reasons for CL intolerance are discomfort and dryness.[188,189] In recent years, a number of questionnaires have been developed to identify dry eye symptoms in CL wearers.[45,190-192] Use of such questionnaires has indicated that about 50% of CL wearers report dry eye symptoms.[191-194] CL wearers are 12 times more likely than emmetropes and five times more likely than spectacle-wearers to report dry eye symptoms.[195]

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

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

Patients wearing high water-content hydrogel lenses were more likely to report dry eye. This is a controversial area in the literature. In a study of the effects of five hydrogel lenses on tear film physiology, Thai et al found that all the examined soft CL materials increased the evaporation rate and decreased the tear film thinning time.[196] The surface wetting ability of the CL materials was the same, regardless of special surface lens treatments. Efron et al found that patients wearing low water CLs, which maintained their hydration, were free from symptoms.[197] However, other studies reported no correlation between CL hydration and dry eye symptoms[189] and no relationship between lens hydration and tear film thinning time and dry eye symptoms[198] or evaporative water loss.[199] Dry eye was associated with a higher tear osmolarity, but not in the range normally associated with dry eye tear hyperosmolarity. The authors commented that this lower value might have been caused by reflex tearing at the time of sampling.[114]

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

Glasson et al[202] showed that intolerance to hydrogel lenses in normals correlates with a shorter blink interval, noninvasive TFBUT and phenol red thread test length and a lower tear meniscus height and area; this has had predictive power in people presenting for CL fitting. A formula linking symptoms (using the McMonnies Dry Eye Questionnaire), non-invasive tear break up time (NITFBUT), and tear meniscus height predicted potential intolerant subjects with a sensitivity of 100%, specificity of 57%, and accuracy of 78%. Intolerance was also associated with an increase in degraded lipid products, phospholipase A2, and lipocalin in tear samples.[203] These studies suggest that features compatible with a dry eye state may predispose an individual to CL intolerance.

The variations in visual performance with soft CLs may be due to light scattering produced by changes in the hydration levels of the lens or changes in the tear film over the lens.[204,205] Decreases in retinal image quality have been inferred from the modulation transfer function induced by the drying tear film and observed with the Schack-Hartman 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 causing breakup. This

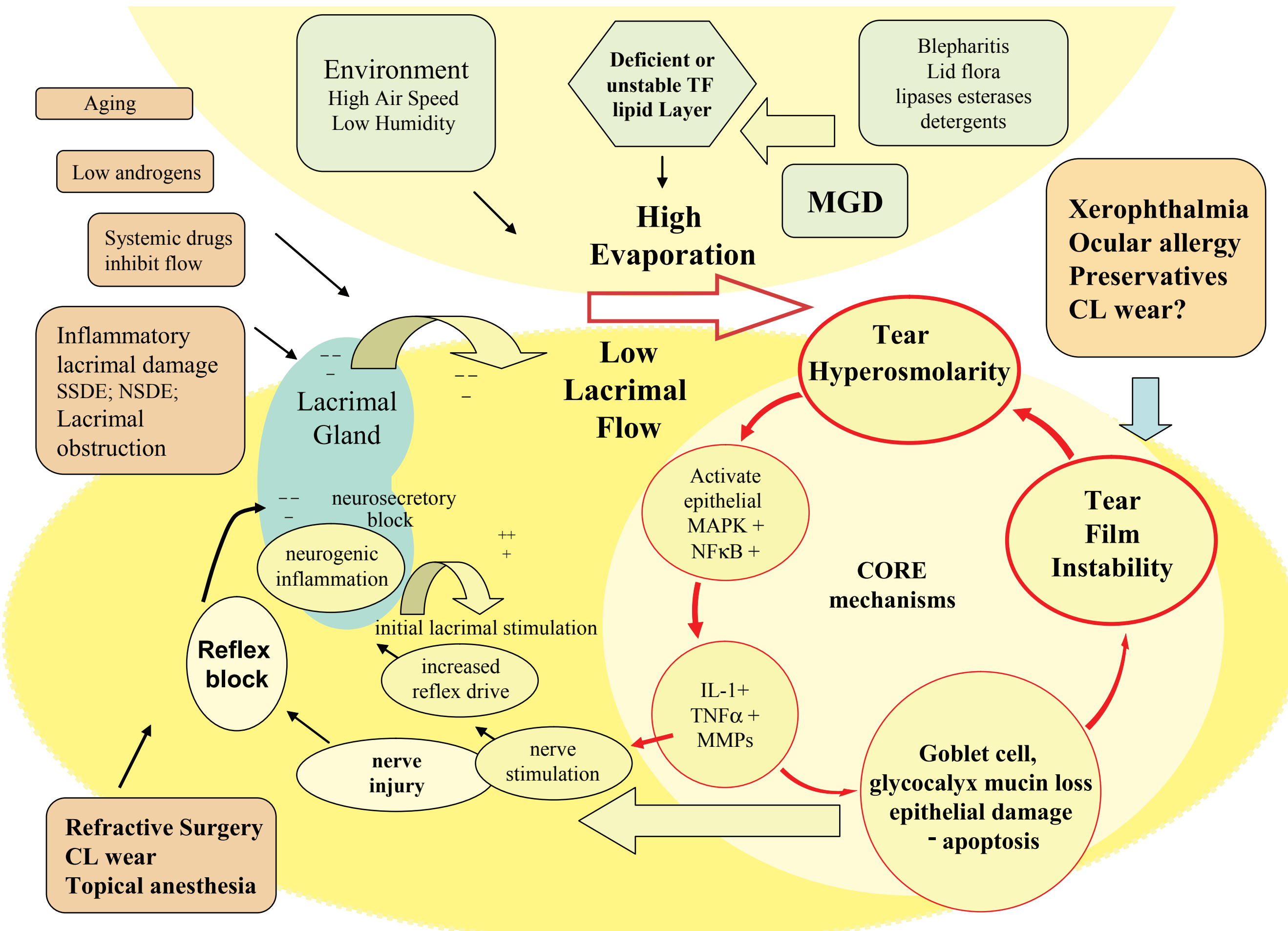

Figure 2. Mechanisms of dry eye.

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.

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

3) Ocular Surface Disease

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

4) Allergic Conjunctivitis

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

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

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

C. The Causative Mechanisms of Dry Eye

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

It should be noted that an attractive mechanistic schema for dry eye has been presented in detail by Baudouin.[212] In this concept, two levels of involvement are identified. The first level includes the known risk factors or causes of dry eye that ultimately lead to a series of secondary biological cascades, resulting in breakdown of the tear film and ocular surface. This pathbreaking conceptual approach describes the relationship of early disparate events to biological responses common to all forms of dry eye, many of which are mutually reinforcing. This leads to a vicious circle or loop. It is thought that early therapeutic intervention may disrupt this loop. The schema in Figure 2, developed from the discussion of our Subcommittee, emphasizes the core biological mechanisms described in this text.

1. Tear Hyperosmolarity

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

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

Hyperosmolarity stimulates a cascade of inflammatory events in the epithelial surface cells, involving MAP kinases and NF*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 be hypothesized that, since the lacrimal gland is initially healthy in this situation, lacrimal secretory compensation is at first able to compensate for tear film hyperosmolarity. Ultimately it would be expected that in the steady state, dry eye would be a condition of hyperosmolarity with a tear volume and flow greater than normal. This possibility of a high volume dry eye is supported by the increased tear secretion (based on the Schirmer I test) in patients with MGD compared to normals,[221] although this evidence requires support by studies using more sophisticated tests of tear flow. In the study of Shimazaki et al, despite the increased tear flow, particularly in the gland dropout group, there was a shorter TFBUT and greater degree of dye staining in those with MGD than in those without.

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

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

The above proposal may explain why a clear clinical separation between ADDE and EDE may at times be difficult to support on the basis of substantive tests. Thus, while there are studies that indicate, as expected, that *tear evaporation rate is increased* in MGD,[62,63,82,83,221,228] or where there is an incomplete or absent tear film lipid 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 [www.tearfilm.org]). When this value is less than 1, then tear film breakup occurs in the waking, open-eye condition. If the TFBUT is greater than the blink interval but less than 10 seconds, then this TFBUT value is still currently regarded as an index of tear film instability. Where tear film instability represents tear film breakup occurring within the blink interval, it is assumed to give rise to local drying and hyperosmolarity of the exposed surface, to surface epithelial damage, and to a disturbance of glycocalyx and goblet cell mucins. The latter consequently exacerbates the tear film instability as part of a vicious circle of events.

Two examples of this clinical sequence, where tear film instability is due to a disturbance of ocular surface mucins, are 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

Table 5. Dry eye severity grading scheme

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

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

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

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

CL wear may also provide a route of entry into the dry eye mechanism, a route in addition to reduced corneal sensitivity. For a considerable time, CL wear has been recognized to cause changes to the ocular surface epithelia. Knop and Brewitt demonstrated surface epithelial metaplasia and a reduced goblet cell density with hydrogel lens wear.[240,241] Other studies have shown an increase in goblet cell density evolving over a period of 6 months in subjects wearing polymacon, galyfilcon, and silicone hydrogel lenses.[242,243] In another study, no change in goblet cell density was found after 6 months wear of a daily disposable lens with a 2-week wearing schedule, and further studies suggest that the goblet cell responses may differ between hard and soft CLs.[244]

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

D. The Basis for Symptoms in Dry Eye

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

E. Classification of Dry Eye on the Basis of Severity

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

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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 disease 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 202 and 204.

Reprints are not available. Articles can be accessed at: www.tearfilm.org

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OUTLINE

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[8,9,14]	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 3.23 million women and 1.68 million men, for a total of 4.91 million Americans 50 years and older 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 wear.

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% in 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 (**RCT**s) 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 long-term 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.[22] These are discussed in detail and referenced 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,[22a] 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.[22a]

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 with 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,[44,45] 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

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

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 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 = .007), lenses with higher nominal water content (P = .002), rapid prelens tear film thinning time (P = .008), frequent usage of over-the-counter pain medication (P = .02), limbal injection (P = .03), and increased tear film osmolality (P = .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 = .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]

Table 3. Symptoms and quality of life instruments

Instrument Title/Description/Reference	Authors/Report	Questionnaire Summary	Description/Use
McMonnies Key questions in a dry eye history (McMonnies)[103]	McMonnies. *J Am Optometric Assoc* 1986; 57(7):512-7	15 questions	Screening questionnaire—used in a clinic population
McMonnies Reliability and validity of McMonnies Dry Eye Index. (Nichols et al)[104]	Nichols, Nichols, Mitchell. *Cornea* 2004;23(4):365-71	Previously described	Screening questionnaire Dry eye 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 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): 2469-75	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	25-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 Syndrome	Epidemiologic studies for Sjogren 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
American-European Consensus Group Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group[117]	Vitali C, Bombardieri S, Jonnson R, et al. *Ann Rheum Dis* 2002;1:554-8	6 areas of questions: Ocular symptoms; oral symptoms; ocular signs; histopathology; oral signs; auto-antibodies	Clarification of classification of primary and secondary Sjogren syndrome, and of exclusion criteria.
The Eye Care Technology Forum Impacting Eye Care[118]	Ellwein. *Ophthalmology* 1994;101:199-201	Issues: Standardizing clinical evaluation	Decree for change

7) National Eye Institute-Visual Function Questionnaire (NEI-VFQ [Mangione])[109]
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.tearfilm.org, 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 dry eye populations
- Useful for group level comparisons of vision-targeted health related QoL
- Can be useful for multiple eye conditions

i. *Dry Eye Questionnaire (DEQ) and Contact Lens DEQ*
- 21 items: includes contact lens wear, age, sex
- Categorical scales of prevalence, frequency, diurnal severity and intrusiveness of symptoms in typical day of one week recall period
- Frequency and intensity of symptoms: comfort, dryness, blurry vision, soreness and irritation, grittiness and scratchiness, burning and stinging, foreign body sensation, light sensitivity, itching
  Never, infrequent, frequent, constantly
  Time of day worsening
  Effect on activities of daily living
- Medications, allergies, dry mouth, nose or vagina, treatments, patient global assessment, dry eye diagnosis

j. *Melbourne, Australia, Visual Impairment Project Questionnaire*
Symptoms of discomfort, dryness, foreign body sensation, itching, tearing and photophobia were graded on a scale from 0 to 3 (0 = no history, 1 = mild, 2 = moderate, 3 = severe). For each symptom, a definition was supplied for mild, moderate and severe.

2. Summary
The Subcommittee agreed on several characteristics of a dry eye questionnaire that contribute to its suitability for use in epidemiologic studies and RCTs. The instrument must be responsive, ie, able to detect and measure a change in symptoms with effective treatment or disease progression. It should be sufficiently sensitive to detect therapeutic response by a drug. It must be reproducible; the changes detected must be real and not due to poor repeatability. The recall period should be specified, as symptoms over time are commonly integrated by patients. For example, "how do your eyes feel now?" vs "on average, over the past week, how have your eyes felt?" Other important points included the ability to set a threshold of severity of disease as an inclusion criterion (ceiling and floor effects). One may elect to use a particular instrument as a screening tool for the study qualification visit and a different questionnaire to perform at baseline and the primary outcome study visit. Specific items within the instrument may be more appropriate for screening, whereas others may be responsive to treatment effects and more relevant for efficacy analysis. Because of the possibility of worsening of dry eye symptoms over the course of the day, dry eye examinations and the questionnaire should be administered at the same time of day in clinical trials.

Vision-targeted health-related quality of life instruments quantify an aspect of dry eye disease that is not measured in other ways. Both generic and disease-specific instruments are available; utility assessment is an alternative strategy. The group recommended inclusion of an item on visual function in the definition of dry eye—for example, fluctuating vision or transient blurred vision—to capture visual effect from dryness and assist in defining a clinically meaningful situation. This is another manifestation of dry eye distinct from "irritative" symptoms.

3. Future Research
Clinically meaningful changes in questionnaire scores need to be defined. If a particular symptom is improved, does the ability to perform common activities of daily living or visual function improve as well?

The concept of the "worst" symptom, which might be defined as the most intense, the most frequent, or the most bothersome symptom, warrants further study.

The relationship between frequency and severity of dry eye symptoms must be better understood to identify a clinically meaningful change in dry eye symptoms. How does a constant but low-intensity irritative symptom compare to a periodic, severe, highly intense but infrequent pain? Although frequency and intensity of symptoms are highly correlated, frequency is relevant to RCTs, because it would be difficult to demonstrate a change in an infrequent but severe symptom.

Psychometric analysis of existing questionnaire data from interventional clinical trials or epidemiologic studies may be useful in identifying specific parameters, questions, or subscales that might be more responsive or more appropriate to demonstrate therapeutic effects from different types of treatment modalities or for dry eye of a particular type or severity. Patient satisfaction with ocular health, therapy, and impression of improvement or worsening with treatment could be explored for use in clinical research

Although important progress has been made since the 1994/1995 Dry Eye Workshop about the available evidence on the epidemiology of dry eye, there is still a need for widely accepted diagnostic criteria of dry eye for epidemiological studies and a need to conduct such studies in different geographical populations and in different races and ethnicities. We still need to clarify the role of individual dry eye questionnaires and vision-targeted and general QoL assessment tools. While certain risk factors, such as age, sex, dietary factors, refractive surgery, and others, have been related to ocular morbidity in dry eyes, the impact of other factors such as cigarette smoking, alcohol, menopause, oral contraceptives, and pregnancy, still remain unclear and will need further prospective research.

III. CONCLUSIONS
There remains a need to build consensus on appropriate dry eye diagnostic criteria for epidemiologic studies. The role of subjective assessment and vision-targeted and general QoL assessments can be clarified. More incidence studies are needed, and epidemiologic studies should be expanded to include additional geographic regions and multiple races and ethnicities. Some modifiable risk fac-

tors have been identified for dry eye, and public education resulting this regard should lead to improvement in both eye and general health, while further, prospective study is needed to elucidate other risk factors.

Detailed templates of questionnaires can be accessed at: www.tearfilm.org.

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Methodologies to Diagnose and Monitor Dry Eye Disease:
Report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **The role of the Diagnostic Methodology Subcommittee of the Dry Eye Workshop was 1) to identify tests used to screen, diagnose and monitor dry eye disease, 2) to establish criteria for test performance, and 3) to consider the utility of tests in a variety of clinical settings. The committee created a database of tests used to diagnose and monitor dry eye, each compiled by an expert in the field (rapporteur) and presented within a standard template. Development of the templates involved an iterative process between the Chairman of the subcommittee, the rapporteurs, and, at times, an additional group of expert reviewers. This process is ongoing. Each rapporteur was instructed on how to the complete a template, using a proforma template and an example of a completed template. Rapporteurs used the literature and other available sources as the basis for constructing their assigned template. The Chairman of the subcommittee modified the template to produce a standardized version and reviewed it with the rapporteur. The completed database will be searchable by an alphabetical list of test names, as well as by functional groupings, for instance, tests of aqueous dynamics, lipid functions, etc. The templates can be accessed on the website of the Tear Film and Ocular Surface Society (www.tearfilm.org). This report provides a general overview of the criteria applied in the development of tests for screening and diagnosis.**

KEY WORDS **diagnosis, dry eye, Dry Eye WorkShop, methodology for appraising dry eye tests, questionnaires, tests for dry eye, screening, Sjogren syndrome**

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

Reprints are not available. Articles can be accessed at: www.tearfilm.org.

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I. INTRODUCTION

The Diagnostic Methodology Subcommittee set out to create a detailed register of diagnostic tests used to diagnose and monitor dry eye. The aim was to perform a thorough review of the literature and other available sources, to summarize findings in a standardized fashion, and to provide the research community with a searchable database of tests, including an assessment of their diagnostic efficacy. The committee considered the feasibility and operational use of tests and questionnaires in a variety of settings, including general eye clinics, dry eye specialty clinics, clinical trials in dry eye, and non-trial clinical research in dry eye. The committee also sought to identify areas in which new tests are needed, and to provide advice on how these might be brought to clinical use.

The attempt to meet these goals has been challenged by the longstanding lack of a uniform set of criteria for the diagnosis of dry eye, for which there has been no generally agreed "gold standard." Studies of test efficacy and/or performance are influenced by the fact that subjects have often been selected based on the same tests that are under scrutiny. Similarly, the performance of any "new" test may be compromised when the test is assessed in a population of dry eye patients who have been diagnosed using unestablished criteria.

An additional challenge relates to the variety of settings in which diagnostic tests are being used. For example, tests may be applied in everyday clinical practice, or to assess eligibility in a clinical trial. Furthermore, tests may be used to follow the natural history of the disorder or to quantify clinical changes over the duration of a clinical trial (ie, in monitoring). Tests that are useful in one setting may differ from those employed in others.

OUTLINE

Table 1. Goals and objectives of the Diagnostic Subcommittee

To create a register of diagnostic tests used in dry eye diagnosis with the following characteristics:
- *A searchable register of referenced tests*
- *Variable sorting, eg,*
  - Alphabetical by test name
    - By organ system tested
      - Aqueous dynamics
      - Tear stability
      - Tear composition
      - Meibomian gland function, etc.
    - By utility, eg,
      - Diagnostic classification criteria
      - Clinical trials
        - Recruitment—entry criteria
        - Outcome measures
        - Monitoring specific drug actions, eg, anti-inflammatories; secretagogues
  - Natural history
- *Identification of evidence level*
  - [this will be a second phase of development]
  - —validation/precison and accuracy of tests
  - —system used

To consider the operational use of tests in different clinical environments
- *In general clinics*
  - What tests are feasible?
  - What questionnaires can be made available?
- *In dry eye clinics*
  - What tests are feasible?
  - What questionnaires can be made available?
- *In clinical trials*
  - Selection of tests
  - Order of tests
- *In non-trial Clinical Research*

Manuals of operation for individual tests
- Consider for selected, key tests
- Interface with industry

Future prospects
- What new tests are needed?
- How can they be brought to the general clinic?

II. GOALS OF THE DIAGNOSTIC METHODOLOGY SUBCOMMITTEE

The goals of the Diagnostic Methodology Subcommittee were to identify tests used to screen, diagnose, and monitor dry eye disease, and to establish criteria of test performance (test efficacy) and to consider their practical use in a clinical setting (Table 1).

To achieve these goals, the committee created a database of tests used in the diagnosis and monitoring of dry eye, each compiled by an expert in the field (rapporteur) and presented within a standard template. An alphabetical list of these tests can be found in Appendix 1, and Appendix 2 re-presents them in functional groupings, for instance, tests of aqueous dynamics, tests of lipid functions, etc.

III. DEVELOPMENT OF THE TEMPLATES

Templates were developed by an iterative process between the Chairman of the subcommittee and the rapporteurs. Each rapporteur was sent a set of instructions on how to complete a template, together a proforma template (Appendix 3) and an example of a completed template. Rapporteurs sent their completed templates to the Chairman of the subcommittee, who saved the original version and then modified it to correct any idiosyncrasies and produce a standardized version. A few tests have been covered by more than one rapporteur. The templates were then reformatted to remove redundant material or to add new sections, which are incorporated into the listing provided in Appendix 1. To facilitate searches, template files are titled by the test they describe. The table of functional groupings will enable investigators to identify a battery of tests that explores the influence of dry eye on a number of physiological indices (Appendix 2).

The full complement of templates can be accessed on the website of the Tear Film and Ocular Surface Society (www.tearfilm.org). It is expected that modifications will be made to these templates from time to time as new information becomes available.

Template headings (some of which are not currrently supplied with data) include the following:

1) The name of the original rapporteur;
2) The names of additional reviewers, where available;
3) The name of the test;
4) The purpose of the test;
5) The version of the test;
6) A short description of the test;
7) Details of studies conducted using the test, if relevant;
8) Details of the conduct of the test;
9) A statement of study results, if relevant;
10) A statement as to whether a web video is available, if relevant;
11) A list of the materials required for the performance of the test;
12) Variations of technique, if applicable;
13) Standardization—an indication of factors that could influence the test result, which, if standardized, could improve the efficacy of the test (eg, time of day, humidity, temperature, air flow, level of illumination, aspects of patient instruction, etc.).

The next sections relate to the performance of the test:

14) "Diagnostic value of the test" in practice, used, for instance, in conjunction with other tests;
15) Repeatability of the test;
16) Sensitivity of the test using a given cut-off value;
17) Specificity of the test using the same cut-off value (100—the false positive rate);
18) Other statistical information, if available.

Next, follows:

19) A box headed "Level of Evidence" for future use. Currently, this box is unused on all templates, since, at the time of writing, evidence criteria for the classification of tests, equivalent to those applicable to clinical trials, are not available.

The final section asked the rapporteur to identify:

20) Test problems encountered;
21) Any proposed solutions;
22) The "forward look" section, inviting suggested improvements; and
23) A final box providing a glossary of terms.

The section headed "web video" indicates whether a video-clip is available via a web link; this section is currently under development. The intention is to illustrate use of the test in field conditions in order to assist potential researchers. In the longer term, it is also intended to add links to other materials, such as schemas for protocols, Clinical Record Forms, and manuals of operation for given tests. It is hoped that Industry will consider this to be an opportunity to release nonsensitive, nonproprietary material for incorporation into the program.

IV. DEFINITION OF DRY EYE DISEASE

It was important for the Diagnostic Methodology Subcommittee to have a clear idea about the definition and classification of dry eye in order to put the tests presented into their proper context. As reported elsewhere in this supplement, the Definition and Classification committee has defined dry eye disease as follows:

> *Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.*[1]

Currently, ocular symptoms are included internationally within all definitions of dry eye, although it is acknowledged that asymptomatic patients exist who exhibit some of the objective features of dry eye and may be entitled to the diagnosis. The Japanese criteria were an exception to this,[2] but these criteria were revised in 2005 and are summarized in Appendix 4.

The issue of symptomatology in the diagnosis of dry eye is important, as one approach to the diagnosis of dry eye is based solely on the use of validated symptom questionnaires, whose administration, both in population studies and in the clinic, offer a highly accessible diagnostic instrument available to the comprehensive ophthalmologist and to the dry eye specialist alike.

V. CLASSIFICATION OF DRY EYE DISEASE

For its assignment, the Diagnostic Methodology Subcommittee regarded dry eye as a chronic, symptomatic ocular surface disease, which may, however, occasionally be asymptomatic. Asymptomatic dry eye implies that in the absence of symptoms, some objective criteria of dry eye may still be satisfied, such as tear hyperosmolarity, the presence of interpalpebral ocular surface staining, reduced tear production, or tear instability. The presence of symptoms may not always be clearcut, particularly when they develop insidiously. A patient may accept the development of irritative or visual symptoms as a matter of course (eg, as a normal part of aging), so that the symptoms are revealed only when a suitably structured questionnaire is applied.

Symptomatic ocular surface disease, (**SOSD**), is an umbrella term that includes:

1) Classical, *symptomatic dry eye*, as defined above, ie, patients experiencing the symptoms of dry eye and also exhibiting objective features of dry eye, however determined. In the current classification, this would include both *aqueous-deficient dry eye* (**ADDE**) and *evaporative dry eye* (**EDE**), as previously described[3]:

2) *Symptomatic lid disease*, including meibomian gland dysfunction (**MGD**) and anterior blepharitis, in the absence of dry eye;

3) *Symptomatic conjunctivitis and keratitis* (eg, allergic conjunctivitis, infective and noninfective keratitis and conjunctivitis) in the absence of dry eye.

The term *symptomatic ocular surface disease* has features in common with the term *dysfunctional tear syndrome* (**DTS**), a term coined by the Delphi group,[4] except that the term DTS was introduced as a *replacement* for the term dry eye, whereas, as discussed here, dry eye is seen as one component of SOSD. Any conceived form of SOSD can be expected to have its asymptomatic counterpart.

Dry eye is usually a symptomatic disorder that varies in severity and must be differentiated from other forms of SOSD. Severity ranges from a mildly irritative disorder of essentially nuisance value to the patient to a severely disabling disorder (eg, in Sjogren syndrome).[1] Although dry eye disease in its milder forms may respond to treatments that alleviate symptoms without modifying the disease process, recent pharmacological approaches are directed toward slowing, halting, or even reversing the disease process. Tests are therefore required that will discriminate between dry eye and its various subsets, identify precipitating factors, quantify disease severity, and demonstrate the effect of disease on a patients' quality of life.

It is also necessary to distinguish dry eye disease from other SOSD. Any classification scheme should address the differential diagnosis of dry eye, such as MGD occurring on its own and disorders such as allergic eye disease, chronic non-dry eye conjunctivitis, and infective conjunctivitis and keratoconjunctivitis. Meibomian gland dysfunction and these other conditions may cause or contribute to dry eye, but exist in their own right as either symptomatic or asymptomatic disorders.

Other individuals should be recognized who are "at risk" of developing dry eye but show no evidence of disease. They are related to, but fall outside, the SOSD group, as they show no objective signs of any ocular surface damage that might constitute disease. An example would be those refractive surgery patients with reduced tear stability (eg, as assessed by the tear stability analysis system [**TSAS**]), who have greater risk of post-LASIK symptomatic keratitis and have a slower recovery time than those without a preoperative tear film instability.[5] Environmental factors may also contribute to risk.[1]

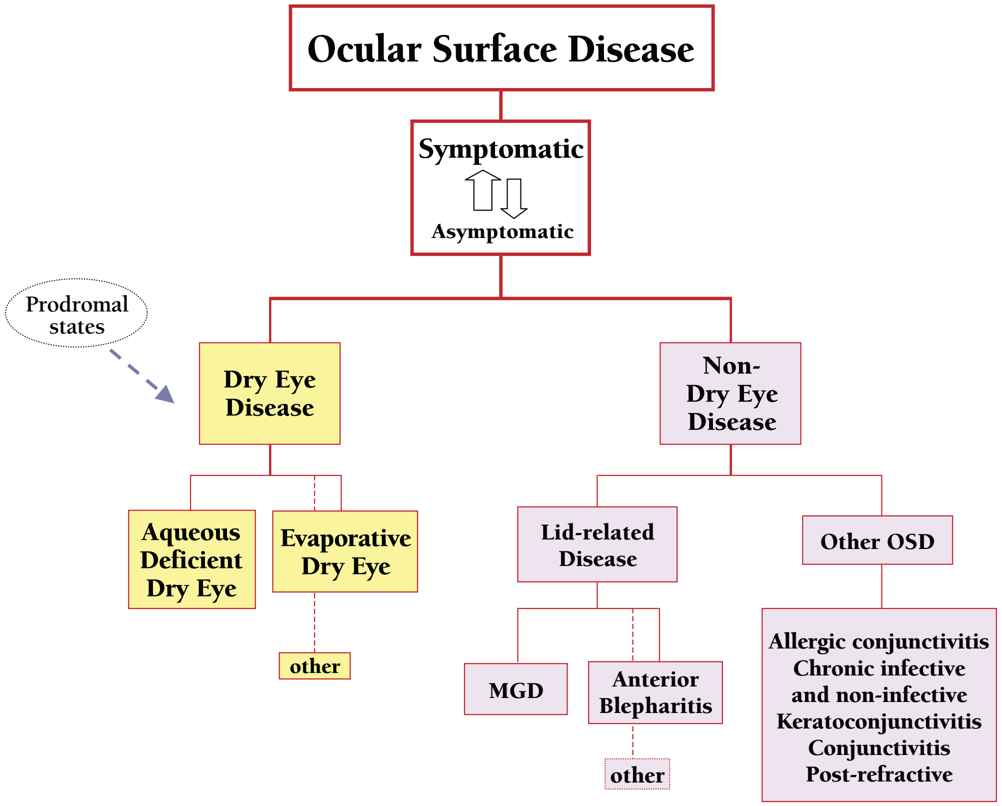

Figure 1. **Schematic illustration of the relationship between dry eye and other forms of ocular surface disease. Ocular surface disease is either symptomatic or asymptomatic, but its various subgroups may coexist and interact. Therefore, a patient may suffer from both aqueous deficient and evaporative forms of dry eye, which will consequently be more severe than in the isolated disease. Also, dry eye may coexist with non-dry eye disease. (See text for further details; see also Chapter 1: Definition and Classification.[1]) OSD = Ocular surface disease; MGD = Meibomian gland dysfunction.**

A general classification of ocular surface disease, including dry eye, is illustrated in Figure 1.

VI. TESTS USED TO DIAGNOSE AND MONITOR DRY EYE DISEASE

A. Uses of Tests

Tests are used for a variety of purposes:

1) To diagnose dry eye in everyday clinical practice.
2) To assess eligibility in a clinical trial (ie, recruitment). Such tests used in recruitment, may also be used as primary, secondary, or tertiary end points in a trial.
3) To follow quantitative changes over the duration of a clinical trial (monitoring). These tests might differ from those employed in recruitment. For instance, they might simply monitor the pharmacological action of a drug under study, eg, stimulation of mucin production.
4) To characterize dry eye as part of a clinical syndrome, eg, as in the harmonized classification criteria of Sjogren syndrome[6] (See Section VIII, Table 6).
5) To follow the natural history of the disorder. This opportunity is limited for dry eye, because treatment is so common in the population. However, the natural history of treated patients is also of interest, although they represent a heterogeneous population.

B. Shortcomings of Tests for Dry Eye

1. Selection Bias

No "gold standard" exists for the diagnosis of dry eye. Thus, when a test, eg, Schirmer test or rose bengal staining, is being evaluated for efficacy, the test population may have been classified as affected or non-affected based on those same tests. Similarly, the performance of any "new" test may be compromised when the test is assessed in a population of dry eye patients who have been diagnosed using unestablished criteria.

When studies of test efficacy look at how the test defines affected and unaffected individuals using individuals from the sample from which the diagnostic cut-offs were derived, this potentially results in a higher sensitivity and specificity rating than would have arisen from an independent sample. Also, because of the multi-factorial nature of dry eye, variable test efficacy is likely to occur from study to study.

2. Spectrum Bias

When the study sample consists of patients with either very mild or very severe disease, results are compromised because the severity of the disease in the sample studied has been highly selected.

Certain ground rules are proposed for appraising the performance of tests for dry eye diagnosis reported in the literature (Table 2).

1) Accept efficacy values on samples from which the test cut-off was derived (as is the case in most reports).
2) Exclude data from studies with selection bias due to the test being part of the original dry eye diagnostic criteria (to avoid study results with high, ie, false, sensitivity and specificity values).
3) To avoid spectrum bias, study samples should be large enough to include a range of dry eye patients with various etiologies.
4) The choice of the cut-off value for diagnosis and the test itself, unless there is some special physiological reason, should be based on a consideration of the relative consequences of having too many false-positives or too many false-negatives. Generally, in a screening test for a serious or life-threatening condition, it is desirable to have a test of high sensitivity (high detection rate)—with few false-negatives—since failure to detect the condition early can be fatal. In a mass screening test for a less serious condition or for one whose early detection is not critical, *it may be more desirable* to have a high specificity to avoid overburdening the health care delivery system with too many false-positives.
5) For dry eye screening tests, it is suggested that sensitivity and the predictive value of a positive test (**PPV**, see below) be maximized, ie, avoid high false-negative rates by "over-diagnosing" dry eye through choice of cut-off/test. This is appropriate when the patient is to be further assessed with other tests to finally diagnose dry eye. However, low false-negative rates (choice of test or cut-off maximize sensitivity) should be balanced by an acceptable PPV.
6) In diagnostic tests, optimize overall accuracy (**OA**) and combine this with a high sensitivity and PPV.
7) Simplify comparisons of screening and diagnostic tests by using single and simple terms for measuring test efficacy.

C. Appraisal of Tests Used for Screening

The purpose of screening is prevention, and it aims to identify people at high risk of a disorder. It is implicit in the screening process that a treatment is available that will reduce the morbidity of the disorder in a cost-effective manner. Screening has been defined, among persons who have not sought medical attention, as the "systematic application of a test or enquiry to identify individuals at sufficient risk of a…disorder to benefit from further investigation or…preventive action..."[26] It is implied that the disorder has serious consequences and that a remedy is available that could reduce morbidity.

Inclusion of symptoms within the definition of dry eye has an awkward implication in the context of screening. To identify those at risk of developing the disorder or who have unrecognized disease, screening is characteristically carried out on asymptomatic individuals who have not presented themselves for diagnosis; those who are symptomatic already have the disease. This "at-risk" group is likely to be represented by asymptomatic subjects whose pathophysiological background favors the development of dry eye. Perhaps, their lacrimal secretory level or their meibomian lipid secretion or delivery is at the lower limit of normal, so that with time they will pass into a state of insufficiency. They may have an unstable tear film, or they may be in the prodromal stages of a disease (eg, exhibiting nonophthalmic features of primary Sjogren syndrome), whose natural history dictates that they will eventually develop dry eyes. Members of this diverse group of subjects could be precipitated into dry eye by a number of biological, pharmacological or environmental events, ie, hormonal changes, drug exposure, high air or wind speeds, irritants, low humidity, and high temperatures. Exposure to such influences might engender dry eye symptoms in an at-risk group at a lower threshold than in subjects not at risk of dry eye disease.

At-risk subjects could be identified by "stress tests," some of which are included among the test templates that accompany this report and/or can be accessed at www.tearfilm.org. Whether or not such tests could or should become part of a "screening program" depends on whether any perceived therapeutic benefits would be economically justified. One such benefit might be to identify the suitability of individuals to work within a particular work environment, or to answer questions about the modifications of environments to avoid inducing symptomatic disease.

To be of value, a screening test should be simple, effective, applicable to a definable population, and cost-effective. In an effective screening program, a positive test ultimately leads to diagnostic tests, which, if positive, lead to timely

Table 2. Characteristics and current tests for dry eye

Test	Reference	Cut-off Value	Sensitivity (%)	FPR (%)	Specificity (%)	PPV*
Single Tests						
Questionnaires	†McMonnies[7]	Any	98	3	97	85
PRT	†Patel[8]	≤10mm	86	17	83	47
Rose Bengal	†Goren[9]	Any	25	10	90	31
Schirmer I	†Lucca[10]	<5mm/5min	25	10	90	31
Schirmer I	†Farris[11]	<3mm/5min	10	0	100	100
Schirmer I	†Bijsterveld[12]	<5.5mm/5min	85	17	83	47
Schirmer I	†Vitali[13]	<10mm/5min	83	32	68	31
F BUT	†Vitali[13]	<10s	72	38	62	25
NIBUT	†Mengher[14]	<10s	83	15	85	49
TMS-BUT	**†Goto[15]**	**<5s**	**98**	**37**	**63**	**32**
Evaporation Rate	†Khanal[16]	33 g/m²/h	51	4	96	84
Meniscus Height	†Mainstone[17]	≤0.35mm	93	33	67	33
Meniscus Radius	**†Yokoi[18,19]**	**≤0.25mm**	**89**	**22**	**78**	**42**
Tear Film Index	†Xu[20]	≤95	67	40	60	23
Tear Turnover Rate	†Khanal[16]	12%/min	80	28	72	79
Osmolarity	†Farris[21]	>312 MOsm/L	95	6	94	73
Osmolarity	†Tomlinson[22]	>316 MOsm/L	69	8	92	60
Osmolarity	‡Tomlinson[22]	>316 MOsm/L	59	6	94	63
Osmolarity	†Tomlinson[22]	>312 MOsm/L	66	16	84	42
Osmolarity	†Tomlinson[22]	>322 MOsm/L	48	1	99	89
Osmolarity	†Khanal[16]	**317** MOsm/L	78	22	78	86
Osmolarity	†Sullivan B[23§]	>318MOsm/L	94	5	95	77
Lysozyme assay	**†van Bijsterveld[12]**	**dia <21.5mm**	**99**	**1**	**99**	**95**
Ferning	†Norn[24]	Area <0.06mm²/μl	94	25	75	40
Lactoferrin	†Lucca[10]	<90	35	30	70	17
CombinedTests (Parallel)						
Sch + RB	†Farris[21]	Any/<1mm/min	77	51	49	21
Sch + BUT	†Farris[21]	<1mm/min/<105	78	44	56	24
Sch + BUT + RB	†Farris[21]	<1mm/min/<105/Any	80	51	49	22
TTR + Evap + Osmol	†Khanal[16]	<12%/>33/ >317	100	34	66	81
Combined Tests (Series)						
Sch + Osmol	**†Farris[21]**	**<1mm/min; >312**	**25**	**0**	**100**	**100**
Lacto + Osmol	**†Farris[21]**	**> 90; >312**	**35**	**0**	**100**	**100**
TTR + Evap + Osmol	†Khanal[16]	< 12%; >33; >317	38	0	100	100
Discriminant function						
Osmol + Evap + Lipid	†Craig[25]	< 0.4	96	13	87	56
TTR + Evap + Osmol	†Khanal[16]	> –0.4	93	12	88	58

The table shows the effectiveness of a range of tests, used singly or in combination, for the diagnosis of dry eye. The tests included in the table are those for which values of sensitivity and specificity are available in the literature. The predictive values of these tests (positive, negative and overall accuracy) are calculated for a 15% prevalence of dry eye in the study population. The data shown here is susceptible to bias; selection bias applies to those studies shown in dark shading, in these, the test measure was part of the original criteria defining the dry eye sample group and spectrum bias applied to those studies (shown in light shading) where the study population contained a large proportion of severe cases. Both of these forms of bias can lead to an artificially increased test sensitivity and specificity. In most of the studies listed above the efficacy of the test was shown for the data from the sample on which the cut off or referent value for diagnosis was derived (indicated by a †), again this can lead to increased sensitivity and specificity in diagnosis. Ideally test effectiveness should be obtained on an independent sample of patients, such data is shown in studies indicated by the symbol ‡.

Table 2 continues on following page

Table 2. Characteristics and current tests for dry eye *(continued)*

KEY to symbols and abbreviations used in Table 2.

*	Assumes a dry eye prevalence of 15% in the population studied.
†	Efficacy calculated in the sample from which the cutoffs were derived.
‡	Efficacy calculated in an independent sample of subjects.
§	Unpublished data

Definitions and Abbreviations

BUT	Tear break-up time
dia	Diameter of the disc observed with the radial-immuno-diffusion Lactoplate method
Evap	Tear film evaporation rate
F BUT	Fluorescein tear breakup time
FPR	False positive rate. The proportion of normals identified incorrectly as +ve by the test (Specificity is: 100-FPR)
Lacto	Lactoferrin assay using the Lactoplate method
NIBUT	Non-invasive tear breakup time
NPV	Predictive value of a negative test result
OA	Overall accuracy of test results
PPV	Positive Predictive Value: the probability of truly having dry eye among those with a positive test result
PRT	Phenol red thread test
RB	Rose Bengal staining
Selection bias	Bias built into an experiment by the method used to select the subjects who are to undergo treatment
Sensitivity	Detection rate: the proportion of patients with disease who have a positive test result
Specificity	Proportion of normal people with negative test result
Spectrum bias	Bias due to differences in the features of different populations eg, sex ratios, age, severity of disease, which influences the sensitivity and/or specificity of a test
TMS-BUT	Tear breakup time measured with the Topographic Modeling System[15]
TTR	Tear turnover rate, often measured with a scanning fluorophotometer (Fluorotron)

treatment. Where a series of tests is required to achieve a definitive diagnosis and initiate effective treatment, it is possible to assess the performance of the combination of tests. This may include a series of screening tests followed by one or more diagnostic tests, some of which may be performed simultaneously to save time.

The screening performance (efficacy) of a test can be estimated according to three parameters: 1) the *Detection Rate* (**DR**) or Sensitivity, 2) the *False-Positive Rate* (**FPR;** specificity is: 100-FPR), and 3) the ***O****dds of being* ***A****ffected in those with a* ***P****ositive test* ***R****esult* (**OAPR**). (This is the same as the PPV, if expressed as a probability.) Before a test is adopted, estimates of all three components should be available.

The relationship between affected and unaffected members of a population and the test result achieved can be represented in tabular form (Table 3).

The Detection Rate (DR) is the percentage of affected individuals who test positive. It is also referred to as the *sensitivity* of the test. The DR must be estimated using values from a continuous series of patients with the disorder, with no omissions.

$$DR = \frac{a}{a+c}$$

The False Positive Rate (FPR) is the percentage of unaffected individuals in a population who test positive. The FPR is usually estimated in a large series of apparently unaffected individuals.

$$FPR = \frac{b}{b+d}$$

The FPR, subtracted from 100, is also known as the *specificity* of the test.

The DR and FPR represent key characteristics of a test. Both are required for an assessment of its efficacy. The ideal test will have a high DR and a low FPR (ie, high specificity).

Table 3. Relationship between affected and unaffected members of population and test result achieved

		Presence of Disease				
		Yes	No	Sum		Population
Diagnostic Test Result	Positive +	a	b	a+b	=	total testing positive
	Negative –	c	d	c+d	=	total testing negative
Totals		a+c = total truly affected	b+d = total truly unaffected	a+b+c+d	=	total population

The DRs and FPRs for a number of tests used in dry eye diagnosis are presented in Table 2.

The third parameter is dependent on the prevalence of the disorder in the population studied. This is *The* ***O****dds of being* ***A****ffected in those with a* ***P****ositive test* ***R****esult* (OAPR [or PPV]). This is expressed as an odds value, eg, 1:3 or 1:100, etc. It can also be expressed as a percent probability (which in these cases would be: 1/4 × 100 = 25%, or 1/101 × 100 = 0.99%).

$$\text{OAPR} = \frac{a}{a+b}$$

D. Appraisal of Tests Used for Diagnosis

Diagnostic tests are applied to symptomatic or asymptomatic patients to obtain a diagnosis and, by inference, to exclude other diagnoses. A successful diagnosis can serve several functions, paramount of which is the opportunity for therapy. Therapy can ameliorate the symptoms of a disease, retard its progression, or produce a cure. Arrival at a successful diagnosis may also serve other functions, for instance, in relation to the natural history and prognosis of a disease, knowledge of which is of value to both patient and doctor. Also, a diagnosis, by excluding other diseases, may usefully indicate that a feared diagnosis is not present and that other kinds of therapy are not indicated.

1. Selecting a Cut-off Value

Test data may be qualitative (categorical, eg, with or without epiphora), semi-quantitative (ordinal, eg, grading by corneal staining), or quantitative (continuous, eg, the Schirmer test result in mm, intraocular pressure). For a test offering continuous data, it is appropriate to select a cut-off value to discriminate between affected and unaffected subjects. This may involve a trade-off between the DR and FPR, depending on the distribution of test values between these two groups. The DR and FPR are dependent on the selected cut-off values, and this is influenced by the overlap of values between affected and unaffected subjects. For instance, if there is no overlap in values between unaffected and affected subjects, then the cut-off will lie between the two data sets. However, where there is an overlap of values, which is usually the case, a cut-off must be chosen somewhere in the region of overlap.

The concept of choosing a cut-off is illustrated in the Figures 2a and 2b, which represent the situation in a hypothetical disorder in which the test variable is higher in the affected than in the unaffected population.[27] An example might be a staining score. When distributions are presented in this way, then the area to the right of the cut-off under the *unaffected* curve, provides the FPR, while the area to the right of the cut-off under the *affected* curve, gives the DR. Moving the cut-off to the right (as in Figure 2b) reduces the FPR but also reduces the DR.

2. The Likelihood Ratio

A useful way of expressing the interaction of DR and FPR is by calculating the *Likelihood Ratio* (**LR**), which is the ratio of those areas. The LR is a measure of the number of times individuals with positive results are more likely to have the disorder compared with individuals who have not been tested. A successful screening test might have an LR in the range of 5 to 25.

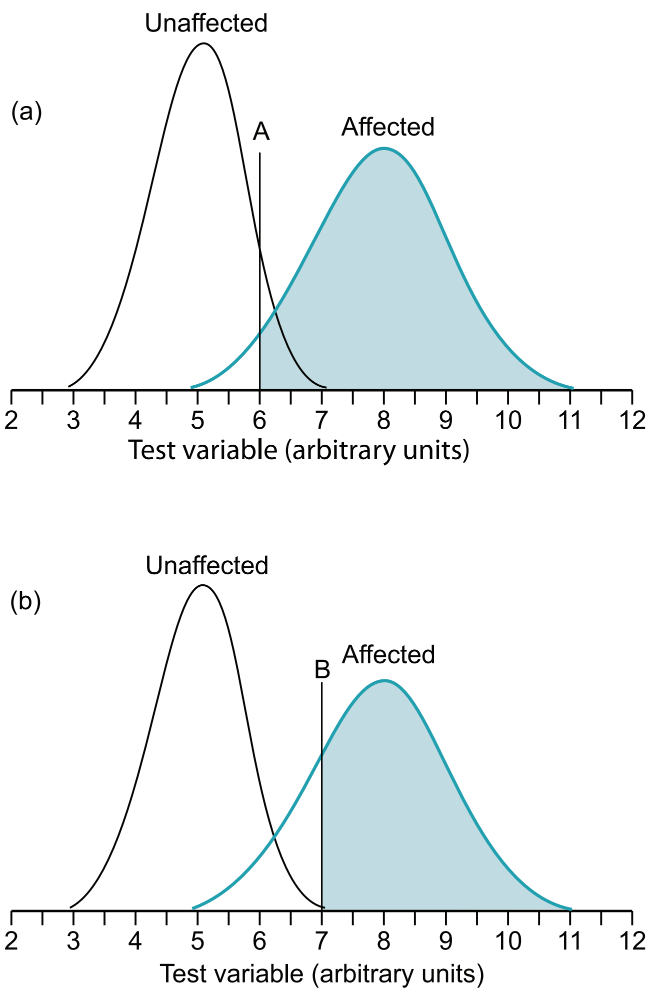

Figure 2. Illustrates how selection of the cutoff value influences the FPR and DR. See text for details.

3. Calculating the OAPR

The OAPR is a valuable parameter that represents the average chance of being affected for all individuals with a positive result by the test. It expresses the odds of the number of *true positives* to the number of *false positives*. For a given population, the OAPRs of different tests for the same condition may be compared directly with one another. There are two ways to calculate the OAPR (examples taken from Wald[26] and Wald and Cuckle[27]).

The first method uses a flow chart to estimate test performance.

Considering the total number of individuals identified as positive by a test within a defined population, a proportion will be true positives (determined by the DR of the test), and the remainder will be the false positives (determined by the FPR). The OAPR is the ratio of these two numbers, ie, OAPR = True Positives: False Positives.

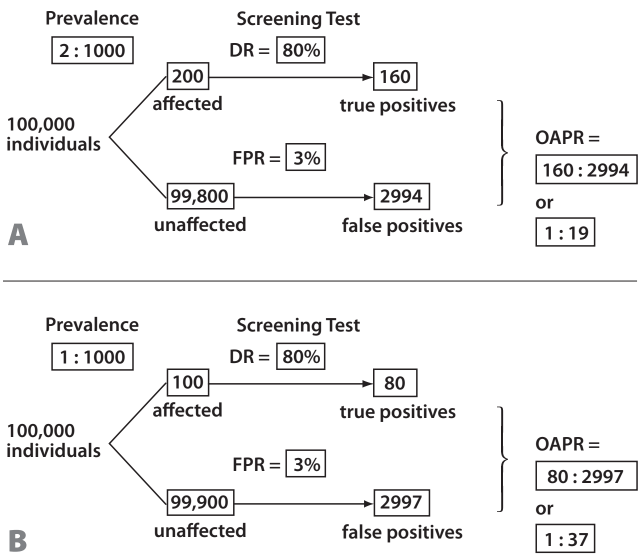

Figure 3. The influence of disease prevalence on the OAPR. See text for details.

Note that OAPR is influenced by the prevalence of the condition in the population studied.

If the test has a DR of 80% and an FPR of 3% then there are 160 true positives (80/100 x 200), and 2994 false positives (3/100 x 99,800) in the population. The OAPR can then be calculated as follows:

$$\text{OAPR} = \frac{\text{Number of true positives} = 160}{\text{Number of false positives} = 2994} = 1{:}19$$

The equivalent PPV is 5% [ie, 1/ 1+19 = 1/20 =5%] (Figure 3A).

With the same DR and FPR rates, but a prevalence of 1:1000, there are 100 affected and 99,900 unaffected.

In that case the test identifies 80 true positives and (3/100 x 99,900=) 2297 false positives, giving an OAPR that is twice that of the previous example:

$$\text{OAPR} = \frac{\text{Number of true positives} = 80}{\text{Number of false positives} = 2997} = 1{:}37$$

It can be seen that the OAPR falls as the prevalence falls (Figure 3B). The second method to calculate the OAPR uses the likelihood ratio. For a given population, the OAPR can be calculated by multiplying the LR by the prevalence of the disorder (expressed as an odds), ie, OAPR = LR x Prevalence as an odds [eg, 1:1000; 1:2000].

In the example given in Figure 4A, with a cut-off at 7, the DR is 80% and the FPR is 1%. In this case the LR is (80%/1%) = 80, and if the prevalence of the disorder is 1 per 1000 (ie, an odds of 1:999 or nearly the same as 1:1000), then:

$$\text{the OAPR} = 80 \times 1{:}1000 = 80{:}1000 = 1{:}1000 = 1{:}12.5$$

The two methods of calculating the OAPR are applicable to groups of subjects and are, therefore, of public health significance. However, it is also possible to calculate the OAPR for an *individual* with a particular positive result. This is illustrated in Figure 4B. In this situation, the LR for that individual is given by the height of *the affected population distribution curve* at the point of their test value, divided by the height of *the unaffected population distribution curve* at the same point. In the example given above, where the test value is 7 arbitrary units, the LR ratio is a/b = 12/1 = 12. Note that the vertical units are also arbitrary. Therefore, the OAPR for that individual is:

$$\text{OAPR} = \text{LR} \times \text{Prevalence as an odds [eg, 1:1000]}$$
$$= 12 \times 1{:}1000 = 12{:}1000 = 1{:}1000/12 = 1{:}83.$$

This individual has a relatively low risk of being affected.

VII. A PROTOCOL FOR EVALUATING DRY EYE DIAGNOSTIC TESTS

The following protocol is suggested as a model for evaluating diagnostic tests for dry eye. It is proposed that:

1) The diagnostic test will be applied to a study sample of normal subjects and patients with dry eyes, as defined by symptoms, and the "traditional" ophthalmological tests, Schirmer I, tear film breakup time (**TBUT**), and ocular surface staining.

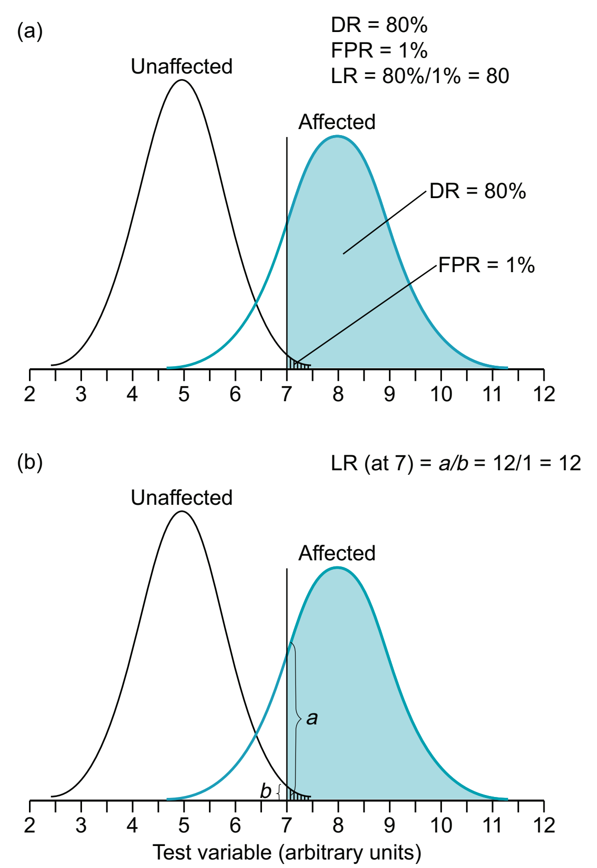

Figure 4. Calculation of the OAPR using the likelihood ratio. (a) For a group, (b) for an individual. See text for details.

2) The values obtained for the new diagnostic test in the two samples will be determined, frequency distributions of data will be compiled, and an initial cut-off value, distinguishing affected from non-affected, will be set at the intercept of the two frequency curves.

3) The sensitivity, specificity, and predictive values of a positive and negative test result and the overall accuracy of the test will be determined for this cut-off value.

4) A range of different cut-off values for the test statistic can then be analyzed by constructing a receiver-operator characteristic (**ROC**) curve to maximize the sensitivity and the specificity of the diagnostic test.

5) The proposed cut-off value thus determined for the test will then be assessed for its efficacy on a new, *independent sample* of normal and dry eye patients. An iterative process may then be required to arrive at a final cut-off value.

This approach should provide the best estimate of test performance.

Table 4A. A sequence of tests used in dry eye assessment, according to category

Group	Assessment	Technique
A	Clinical history	Questionnaire
	Symptoms eg, dry eye	Symptom questionnaire
B	Evaporation rate	Evaporimetry
C	Tear stability	Non-invasive TFBUT (or NIBUT)
	Tear lipid film thickness	Interferometry
	Tear meniscus radius/volume	Meniscometry
D	Osmolality; proteins lysozyme; lactoferrin	Tear sampling
E	Tear stability	Fluorescein BUT
	Ocular surface damage	Grading staining fluorescein; lissamine green
	Meniscus, height, volume	Meniscus slit profile
	Tear secretion turnover	Fluorimetry
F	Casual lid margin oil level	Meibometry
G	Index of tear volume	Phenol red thread test
H	Tear secretion	Schirmer I with anesthesia
	Tear secretion	Schirmer I without anesthesia
	“Reflex” tear secretion	Schirmer II (with nasal stimulation)
I	Signs of MGD	Lid (meibomian gland morphology)
J	Meibomian gland function	MG expression Expressibility of secretions Volume Quality
	Meibomian physicochemistry	Oil chemistry
K	Ocular surface damage	Rose bengal stain
L	Meibomian tissue mass	Meibography

From: Foulks G, Bron AJ. A clinical description of meibomian gland dysfunction. *Ocul Surf* 2003: 107-26. Test invasiveness increases from A to L. Intervals should be left between tests. Tests selected depend on facilities, feasibility and operational factors.

VIII. RECOMMENDATIONS OF THE DIAGNOSTIC METHODOLOGY SUBCOMMITTEE: PREFERRED SCREENING AND DIAGNOSTIC TESTS FOR DRY EYE

The following recommendations are based on the commentary provided above and on the test data presented in Table 2. Readers are reminded that when a battery of tests is performed, these should be performed in the sequence that best preserves their integrity (Table 4). The tests discussed below are presented with this in mind.

A. Current Tests

For nearly half a century, a tetrad of diagnostic tests has been universally applied to assess symptoms, tear stability, ocular surface staining, and reflex tear flow.

1. Symptom Questionnaires

Over time, a number of symptom questionnaires have been developed for use in dry eye diagnosis, epidemiological studies, and randomized controlled trials (**RCT**s), which have received some psychometric or other validation and are available to practitioners for use in their clinics. The most important of these have been summarized elsewhere in this issue, where the necessity for reproducibility and the ability to measure severity and change (“responsive-

Table 4B. A practical sequence of tests

Clinical history
Symptom questionnaire
Fluorescein BUT
Ocular surface staining grading with fluorescein/yellow filter
Schirmer I test without anesthetic, or I with anesthetic, and/or Schirmer II with nasal stimulation
Lid and meibomian morphology
Meibomian expression
Other tests may be added according to availability

Further narrative information is provided in a template on the DEWS web site, entitled “A sequence of tests.” From Foulks G, Bron AJ. A clinical description of meibomian gland dysfunction. *Ocul Surf* 2003: 107-26.

ness") have been emphasized and templates presented.[28] According to their length and composition, such questionnaires explore different aspects of dry eye disease in varying depth, ranging from diagnosis alone, to the identification of precipitating factors and impact on quality of life. The time taken to administer a questionnaire may influence the choice of questionnaire for general clinical use, and, with this in mind, the number of questions administered in various questionnaires is listed in Table 5.

These questionnaires have been validated to differing extents, and they differ in the degree to which the dry eye symptoms assessed correlate with dry eye signs. For example such correlations were identified by the extensive Dry Eye Questionnaire (**DEQ**) of Begley et al,[34] but not by the questionnaire developed by Schein et al[30] or, to any great extent, in the study McCarty et al.[36]

The Diagnostic Methodology Subcommittee concluded that the administration of a structured questionnaire to patients presenting to a clinic provides an excellent opportunity for screening patients with potential dry eye disease. Clinic time can be used most efficiently by utilizing trained auxiliary staff to administer the questionnaires. Selection of a specific questionnaire will depend on practical factors, such as available staffing, and also the intended use of the data collected, eg, whether it will be used for diagnosis alone, recruitment to a clinical trial, or as a guide to treatment.[1]

Symptomatology questionnaires should be used in combination with objective clinical measures of dry eye status, as illustrated below.

Table 5. Symptom questionnaires in current use

Report	Questions administered	Reference
Womens' Health Study (WHS)	3	Schaumberg et al[29]
International Sjogren's Classification	3	Vitali et al[6]
Schein	6	Schein et al[30]
McMonnies	12	McMonnies and Ho[31]
OSDI	12	Schiffman et al[32]
CANDEES	13	Doughty et al[33]
Dry Eye Questionnaire (DEQ)	21	Begley et al[34]
IDEEL (3 modules, 6 scales)	57	Rajagopalan et al[35]

2. Grading Ocular Surface Staining

In clinical trials in some countries, it is current practice to grade staining of the cornea using fluorescein dye and to grade staining of the conjunctiva using lissamine green. This is done for reasons of visibility and is discussed in detail elsewhere.[37] It is, however, possible to detect and score staining on both the cornea and conjunctiva together, using fluorescein alone, if fluorescence is viewed through a yellow barrier filter (eg, Wratten 12).[38]

Three systems for quantifying staining of the ocular surface are in current use, the van Bijsterveld system,[12] the Oxford system,[37] and a standardized version of the NEI/Industry Workshop system,[3]—for instance, the version developed for the CLEK study and used in the assessment of clinical methods for diagnosing dry eye (Appendices 5 and 6).[38] The Oxford and CLEK systems use a wider range of scores than the van Bijsterveld system, allowing for the detection of smaller steps of change in a clinical trial. The CLEK system, which assesses several zones of the cornea, has the advantage of scoring staining over the visual axis, providing the opportunity to relate surface changes to changes in visual function. No studies have been published that indicate that one grading system is innately better than another, but interconversion of the van Bijsterveld and Oxford scores has been estimated in an unpublished comparative study (J. Smith, personal communication).

Selection of a diagnostic cut-off for recruitment to a clinical trial is influenced by the need to identify a score that is sufficiently high to be able to demonstrate a response to treatment, but is sufficiently low to permit the recruitment of adequate numbers. Some workers have used a van Bijsterveld cut-off of ≥ 3 in recruiting dry eye patients for clinical studies. For dry eye diagnosis within the framework of Sjogren syndrome, a cut-off of ≥ 4 was derived by the American-European consensus group in a large multicenter study. [6]

3. Tear Film Stability—Tear Film Break-Up Time (TFBUT)

Details of test performance are given in Appendix 7, including the need for application of a standard volume of fluorescein and the use of a yellow barrier filter to enhance the visibility of the breakup of the fluorescent tear film. The established TFBUT cut-off for dry eye diagnosis has been < 10 seconds since the report of Lemp and Hamill in 1973.[39] More recently, values lying between ≤ 5 and < 10 seconds have been adopted by several authors, possibly based upon the 2002 report of Abelson et al,[40] which suggested that the diagnostic cut-off falls to < 5 seconds when small volumes of fluorescein are instilled in the conduct of the test (eg, using 5μl of 2.0% fluorescein in that study—many clinical trials adopt the practice of pipetting small, fixed volumes of dye). At present, sensitivity and specificity data to support this choice have not been provided, and the population in that study has not yet been defined. Refinement of this kind of data would comprise a welcome addition to the literature. Selecting a cut off below < 10 seconds will tend to decrease the sensitivity of the test and increase its specificity.

4. Reflex Tear Flow—the Schirmer Test

The Schirmer test score (length of wetting after 5 minutes) is commonly treated as a continuous variable, but it is more properly termed a pseudocontinuous variable, as wetting length values are generally taken as the nearest integer or half integer rather than as continuous fractions of a millimeter.

The Schirmer test without anesthesia is a well-standardized test that is currently performed with the patient's eyes closed (Appendix 8).[6] There is wide intrasubject, day-to-day, and visit-to-visit variation, but the variation and the absolute value decrease in aqueous-deficient dry eye, probably because of the decreased reflex response with lacrimal failure. The diagnostic cut-off employed in the past was ≤ 5.5 mm in 5 minutes, based on the van Bijsterveld study,[12,41] and the studies of Pflugfelder et al[42,43] and others[6] have made a case for using ≤ 5 mm. More recently, many authors and clinical trialists have adopted a cut-off of < 5 mm although the basis for this shift is unclear. Lowering the cut-off decreases the detection rate (sensitivity) but increases the specificity of the test. The van Bijsterveld study, although a model study in many ways, suffered from selection bias and, therefore, a refinement of this value, using appropriate studies, is needed (see above). In the meantime, it is reasonable to carry out the Schirmer test using a cut-off of ≤ 5 mm in 5 minutes.

Table 6. Revised international classification criteria for ocular manifestations of Sjogren syndrome

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

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

5. Tear Osmolarity

The place of tear osmolarity measurement in dry eye diagnosis is well established, and its adoption has several attractions. There is considerable value in assessing a parameter that is directly involved in the mechanism of dry eye. Tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of "ocular surface dryness."[1] Furthermore, in several studies, as illustrated in Table 2, development of a diagnostic osmolar cut-off value has utilized appropriate methodology, using an independent sample of dry eye patients. Thus, the recommended cut-off value of 316 mOsm/l can be said to be well validated.[22]

In the past, although the measurement of tear osmolarity has been offered as a "gold standard" in dry eye diagnosis,[11] its general utility as a test has been hindered by the need for expert technical support; thus, its use has been confined to a small number of specialized laboratories. The feasibility of this objective test is greatly enhanced by the imminent availability of a commercial device that will make the technology generally available (see below).[23,45]

6. Combined Tests in Current Use

In various RCT settings, different authors have adopted different approaches to the recruitment of dry eye patients, on an *ad hoc* basis, usually requiring subjects to satisfy entry criteria including a symptom or symptoms together with one or more positive signs (eg, a positive TFBUT test, staining grade, or Schirmer test).

The best example of the validated use of a combination of tests in dry eye for diagnosis is provided by the classification criteria of the American-European consensus group.[6] These criteria require evidence for a single ocular symptom and a single ocular sign for the diagnosis of dry eye as a component of Sjogren syndrome, as summarized in Table (Table 6).

B. Future Tests

Looking to the future and based on the currently available data (Table 2), the use of various tests, singly or in combination, can be considered as adjunctive approaches to dry eye screening and diagnosis. They are summarized briefly below:

1. Screening Tests for Dry Eye Disease

Screening tests should maximize sensitivity and "dry eye overdiagnosis." Such tests include single measures of meniscus height (using appropriate technology), tear ferning; or parallel combinations of tear turnover rate (**TTR**) + evaporation + osmolarity, or weighted combinations (by discriminant function analysis) of osmolarity + evaporation + lipid classification or TTR .

Because a screening test should be rapid and simple, the preference might be for a meniscus height or radius measure.

2. Diagnostic Tests for Dry Eye Disease

Diagnostic tests should combine high overall accuracy with good sensitivity. As noted above, the measurement of tear osmolarity may turn out to be the single most important, objective test in the diagnosis of dry eye disease. Alternative candidates as objective tests include 1) the parallel combination of TTR + evaporation + osmolarity, or the weighted combination (by discriminant function analysis) of osmolarity + evaporation + lipid classification or TTR.

The most effective test candidates are complex and not easily applicable, clinically. This might suggest noninvasive TFBUT as the clinical alternative.

Certain combinations of dry eye-related tests have been used to predict the risk of contact lens intolerance in patients presenting for fitting with hydrogel contact lenses.[1,44]

Table 7. A selected list of some emerging technologies

Invasiveness	Comment	Reference
Non-invasive	Symptom questionnaires (also see Table 2)	
	Schein	Schein et al[30]
	OSDI	Schiffman et al[32]
	DEQ	Begley et al[34]
	IDEEL	Rajagopalan et al[35]
	Utility assessment	Buchholz et al[45]
Non- to Minimal	*Optical sampling*	
	Meniscometry (Appendix 10)	Yokoi et al[46]
	Lipid layer interferometry (Appendix 11)	Yokoi et al[47]
	Tear stability analysis system (Appendix 12)	Kojima et al[48]
	High speed video—tear film dynamics	Nemeth et al[49]
	OCT tear film and tear film imaging	Wang et al[50]
	Confocal microscopy	Erdelyi[51]
	Tear fluid sampling	
	Strip meniscometry	Dogru et al[52]
	Sampling for proteomic analysis	Grus et al[53]
	Osmolarity eg, OcuSense (Appendix 9)	Sullivan[54]
Moderate	Meibomian sampling; Meibometry (Appendix 13)	Yokoi et al[55]
	Meibography (Appendix 14)	Mathers, et al[56]
Invasive non-stress	Staining: new dyes Digital photography of surface staining	Note: These techniques may reflect steady state conditions at the time of sampling, even though they disturb the steady state with respect to down-stream tests.
	Impression and brush cytology—coupled to flow cytometry (Appendices 15 and 16)	
	Lacrimal scintigraphy	
Stress Tests	Functional visual acuity	Ishida et al[57]
	Controlled Adverse Environment (CAE)	Ousler et al[58]
	S-TBUD (Areal BUT while staring)	Liu et al[59]
	Forceful blink test (Korb)	Korb[60]

DEQ = Dry Eye Questionnaire; IDEEL=Impact of Dry Eye on Everyday Life; OCT =Ocular Coherence Tomography; OSDI =Ocular Surface Disease Index; S-TBUD=Staring Tear Breakup Dynamics.

C. Emerging Technologies

The purpose of this section is to review those diagnostic technologies that show promise for advancing our ability to investigate, monitor, or diagnose dry eye disease in the future. Many of these technologies are described within the web-based diagnostic test templates, and some are at a nascent stage. Such tests start life as prototype instruments that are used by investigators within a research environment. Some of these never see broader application as inexpensive, easy-to-use tools that can be used in the clinical setting. There is particular interest is in those technologies that might be adapted and adopted for everyday clinical use. The tests discussed here are summarized in Table 7. The new technologies are at various stages of development. Some are elaborations of old technologies and some are entirely new.

Most technologies sample the eye in some fashion, and it is useful to consider whether that sampling process is noninvasive, minimally invasive, or invasive. In tear sampling, a non- or minimally-invasive technique has the major advantage that it captures data from the surface of the eye without significantly inducing reflex tearing. Reflex tearing has been a major obstacle to the interpretation of aqueous tear-sourced data from the earliest days of tear research.

There are evident advantages to the capturing of data that represent the steady state, whether these are physiological data or pathologic data.

The problem of reflex tearing has, of course, greatly influenced the interpretation of tear compositional data. For this reason, techniques that gather information from the tear film by processing reflected light or images from the tear film surface have a particular attraction as representing the "true" state of the ocular surface. This would include techniques such as interferometry, meniscometry, high-speed videotopography and optical coherence tomography (**OCT**). Some of these techniques offer the opportunity of delivering on-line data to a data capture system, allowing processing of the dynamic behavior of the tear film. In the same way, the capturing of images of cells and other materials at the ocular surface on-line seems to represent an opportunity to view the steady state.

It is the view of the Diagnostic Methodology Subcommittee that access to the steady-state presents less of a sampling problem when data are directly acquired from the ocular surface (eg, sampling cells or mucin from the ocular surface by impression cytology or brush cytology), as the sample makes an instantaneous statement about the steady state. Here, however, there may be problems in interpreting the sample because of the variable and partial nature of the sampling procedure. These problems can be handled in part by standardization. Also, although such sampling may take a "snapshot" of the steady state, such procedures (ie, impression cytology), because they are invasive, will influence subsequent sampling events. Therefore, they may need to be placed at the end of a series of tests.

It is our expectation that the sampling of expressed meibomian lipid is likely to reflect the steady state condition of the meibomian glands at the time of collection. Here we encounter other kinds of difficulties; for instance, the expressed material is all presecretory and, therefore, it does not fully reflect the nature of lipids delivered to the tear film, and in the case of meibomian gland dysfunction, the expressed material is likely to be increasingly contaminated with keratinized epithelial debris. For this reason, many publications refer to this expressed material as "meibomian excreta" or "meibum." Nonetheless, such expressed material, whether secretion or excreta, is likely to reflect the steady state of the meibomian and ductular product.

In summary, the Diagnostic Methodology Subcommittee concludes that in studying the ocular surface, there is a reasonable opportunity to obtain steady-state information about ocular surface cells and the meibomian gland and duct status. For studying the tear film, the greatest opportunity lies in the use of noninvasive techniques involving the sampling of optical radiation reflected from the tear film. However, even with noninvasive techniques, we must be cautious, as a gradual change has been observed in meniscus curvature by meniscometry in subjects sitting in apparently stable room conditions over a matter of several minutes, suggesting that it is very easy to induce minor degrees of reflex tearing under "test" conditions. Consequently, such techniques hover in a gray zone between non- and minimally-invasive in character. On the other hand, we anticipate that the designation of "minimally invasive" may be reasonably applied to direct sampling of tears under circumstances where sample volumes are in the low nanolitre range. This relates to sampling for proteomic analysis and to the depression of freezing point and "lab-on a-chip" methods for estimating tear osmolarity.

In considering noninvasiveness, it is important to note that there have been significant advances in the development of questionnaires to diagnose dry eye, identify precipitating or risk factors and explore quality-of-life implications. Nonetheless, even questionnaires are not truly non-invasive, since whenever people are observed within a study, their behavior or performance is altered (the "Hawthorne effect"[61]).

Although emerging technologies have focused on the development of noninvasive techniques to observe the steady state conditions of dry eye, there is one area where the invasive test plays a useful role. This relates to various stress tests for dry eye diagnosis, which aim to subject the eye to some sort of stress that will reveal a predisposition to dry eye. Such stress tests include the staring tear breakup dynamics (**S-TBUD**) test, forced closure test, and use of a controlled adverse environment (**CAE**).

In general, the recommended approach favors technologies that allow changes in tears at the ocular surface to be detected while causing the least disturbance to tear film dynamics during sampling. Proteomic and related techniques are examples of these. Such non- or minimally-invasive technologies offer improved acceptability to the patient and the possibility of assessment at something close to the steady-state. In addition to disturbing the tear film and altering the accuracy of the test, an invasive test is more likely to influence the outcome of another test performed sequentially, perhaps as part of a battery of tests. Some minimally invasive technologies are already in place and require only further refinement, such as the development of micro-processor-controlled systems to capture and represent data. In other technologies, the induction of reflex tearing at the time of tear sampling still exists as a problem to be overcome.

IX. SUMMARY OF RECOMMENDATIONS

A. Diagnosis of Dry Eye Disease

Two factors influence our recommendations of diagnostic tests for dry eye. First, many candidate tests derive from studies that were subject to various forms of bias (Table 2). This means that the cut-offs that they propose may be unreliable. Second, several tests with excellent credentials are not available outside of specialist clinics. We therefore offer here a pragmatic approach to the diagnosis of dry eye disease based on the quality of tests currently available and their practicality in a general clinic, but we ask readers to apprise themselves of the credentials of each test by referring to Table 2.

1) Seven sets of validated questionnaires, of differing

length, are listed in Table 5 (refer to the website, www.tearfilm.org, and the report of the Epidemiology Subcommittee[28] for further details). We recommend that practitioners adopt one of these for routine screening in their clinics, keeping in mind the qualitative differences between the tests.

2) The dry eye component of the international classification criteria for Sjogren syndrome requires one ocular symptom (out of three) and one ocular sign (out of two) to be satisfied (Table 6).[6]

3) Tear Evaluation

a) Tear osmolarity: Although techniques to measure tear osmolarity are currently inaccessible to most practitioners, the development of commercial instruments may make such measurements feasible in the near future. As an objective measure of dry eye, hyperosmolarity is attractive as a signature feature, characterizing dryness. A number of studies, including the study of an independent sample, suggest a diagnostic cut-off of ≥ 316 MOsm/L.

b) Non-invasive TFBUT: If the studies shown in Table 2 that are potentially susceptible to selection or spectrum bias are ignored, the simple clinical alternative for dry eye diagnosis might be noninvasive TFBUT measurements that give moderately high sensitivity (83%) with good overall accuracy (85%).

c) Tear function: The tear function index (**TFI**) has been used in the diagnosis of dry eye as a component of Sjogren syndrome. It is the quotient of the Schirmer value and the tear clearance rate, and a standard kit is available (see web template). The sensitivity of the test is cited as 100% with a cut off of < 40.[62]

4) Better test performance can be achieved when tests are used in combination, either in series or in parallel and the opportunity should be taken to review some of the standard tests cited above, using large, independent populations of subjects.

B. Monitoring Dry Eye Disease

Many of the tests used to diagnose dry eye are also used to monitor its progress, either in the clinic or within clinical trials. Additional tests, many of them referred to in this DEWS Report or presented on the website (www.tearfilm.org) can be used to follow the progress of the disease. In the future, these may include increasingly sophisticated techniques applied to tiny tear volumes with minimal invasiveness. Such tests will help to identify important changes in the native and inflammatory components of the tears in dry eye.

X. SUMMARY AND CONCLUSIONS

The purpose of this report was to review the literature and develop a resource of tests used in dry eye disease diagnosis and monitoring. These are displayed as templates on the TFOS website (www.tearfilm.org), which will be updated from time to time. A selection is presented herein. To give guidance as to their selection and interpretation, we have indicated some of their shortcomings and sources of bias. Our aim has been to facilitate standardization and validation. In general, with some exceptions, there is still a deficiency of symptom questionnaires and objective tests that have been adequately validated within well-defined sample populations. These deficiencies are remediable and will be a stimulus for future research. As we emphasize here, in considering emerging technologies, the way forward will be with new, minimally invasive techniques that sample the eye and preserve its steady state.

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APPENDIX 1. ALPHABETICAL LISTING OF TESTS USED TO DIAGNOSE AND MONITOR DRY EYE

Allergy conjunctival eosinophils
Allergy conjunctival provocation test
Allergy tear IGE
• • •
Basal tear volume
Brush cytology
• • •
CCLRU—Hyperemia and other grading scales
Conjunctivochalasis
• • •
Fluorescein permeability
Flow cytometry
• • •
Endocrine markers report
EQ-SD (questionnaire)
• • •
Ferning
Forceful blink test
Functional visual acuity
• • •
Grading staining—Nichols CLEK B
Grading staining—Oxford scheme
Grading staining—van Bijsterveld
• • •
Hamano thread test
• • •
Impression cytology
• • •
Lacrimal biopsy
Lid margin disease criteria
LASIK-induced Neuro-Epitheliopathy (LINE)
• • •
Meibography
Meibomian gland expression
Meibomian lipid analysis
Meibomian lipid sampling
Meibomian microbiology
• • •
NIBUT
• • •
Ocular Protection Index (OPI)
Osmolarity OcuSense overview
Osmolarity—Depression of freezing point
Osmolarity OcuSense—Sullivan
Osmolarity—Vapor pressure
• • •
Rheumatic criteria
• • •
SBUT
Schirmer I European criteria 1994
Schirmer I Farris
Schirmer I Nichols
Schirmer I van Bijsterveld
Schirmer Pflugfelder A
Schirmer Pflugfelder B
Scintigraphy
SF-36
Sicca index
Sjogren syndrome—Direct sialometry
Sjogren syndrome—Salivary-scintigraphy
Sjogren syndrome—Sialography
Sjogren syndrome—Hematology
Sjogren Serology—Martin
SSI (Sjogren Syndrome Index)—Bowman
Symptoms DEQ (questionnaire)
Symptoms IDEEL (questionnaire)
Symptoms McCarty (questionnaire)
Symptoms McMonnies (questionnaire)
Symptoms NEI-VFQ25 (questionnaire)
Symptoms OSDI (questionnaire)
Symptoms Schein (questionnaire)
Staining exam form-1 from Nichols
• • •
TBUD
Tear evaporation
Tear flow fluorimetry
Tear lipid interferometry
Tear meniscus height
Tear meniscus radius
Tear protein profiles
Tear Stability Analysis System (TSAS)
Tear turnover fluorimetry
Tear volume fluorimetry
Tests used in combination
- Combined tests—Afonso 1999
- Combined tests—Bjerrum 1997
- Combined tests—European criteria 1994
- Combined tests—Nichols 2004
- Combined tests—Pflugfelder 1998
- Combined tests—Shimazaki 1998
- Combined tests—van Bijsterveld 1969

Tear film breakup time (TFBUT)
Thermography
Time-trade-off approaches to dry eye severity

Appendix 2. Functional groupings of tests used in the assessment of dry eye

1. **Symptoms tests**
   - *Questionnaires*
     - NEI-VFQ25
     - McMonnies
     - Schein
     - McCarty
     - OSDI
     - DEQ
     - IDEEL
   - ***Visual function***
     - LogMar acuity
     - Contrast sensitivity
     - Functional visual acuity
2. **Aqueous tears**
   - ***Tear volume***
     - Fluorimetry
     - Hamano thread
     - Periotron test—"basal tear volume"
   - ***Tear meniscus***
     - Radius of curvature
     - Height
     - Area of cross-section
   - ***Tear film thickness***
   - ***Tear flow***
     - Fluoroimetry
     - Schirmer test
       - Schirmer I
       - Dynamic Schirmer
       - Schirmer II
       - Reflex Schirmer
   - ***Tear turnover***
     - Dye dilution
     - Tear clearance
     - Fluorimetry
   - ***Tear evaporation***
     - Evaporimetry
3. **Tear stability and visual function**
   - ***Visual acuity***
     - ETDRS
     - Functional visual acuity
   - ***Tear stability***
     - Breakup time (BUT)
     - SBUT: Symptomatic BUT
     - Tear film BUT fluorescein
     - Noninvasive BUT (NIBUT)
     - Tear thinning time
     - Topographic analysis
     - Tear stability analysis system
     - Wavefront analysis
4. **Tear composition**
   - ***Biological fluids***
     - Aqueous tears
       - Lactoferrin
       - Lysozyme
       - Peroxidase
       - Immunoglobulin A
       - Ceruloplasmin
       - Inflammatory mediators
       - Matrix metalloproteinases
       - Other proteins
       - Mucins
       - Lipids
   - ***Cells in biofluids***
     - Inflammatory cells
       - Epithelial cells
       - Tear debris
   - ***Surface cells***
     - Impression cytology
     - Flow cytometry
     - Brush cytology
     - Confocal microscopy
   - ***Meibomian lipids***
     - Evaporimetry
     - Interferometry
     - Thickness
     - Grading
     - Meibometry
     - Meibography
     - Morphology in MGD
     - Expressed oil quality
     - Lipid chemistry
   - ***Tears: physical***
     - Osmolarity
       - Depression of freezing point
       - Vapor pressure osmometry
       - Conductivity OcuSense
       - Electrolyte composition
     - Tear ferning
   - ***Surface damage***
     - Grading staining
     - Fluorescein stain
     - Rose Bengal stain
     - Lissamine green
     - Double staining
5. **Other criteria**
   - Tear function index (TFI)
   - Ocular protection index (OPI)
   - Conjunctivochalasis score
   - Blink characteristics
   - Distinction from allergy
   - Lid margin disease criteria
   - Microbiology and lid disease
6. **Sjogren syndrome**
   - Serological tests
     - Anti-Ro
     - Anti-La
     - Anti-M3 receptor
     - Anti-fodrin
   - Minor salivary gland biopsy
   - Lacrimal gland biopsy
   - Systemic endocrine findings
   - Tests of salivary function
     - Biscuit test
     - Sialography
7. **Tests for assorted disorders**
   - Wegener's: Positive ANCA
   - Rheumatoid arthritis: Positive Rh-F
   - Systemic lupus erythematosus
   - LASIK-Induced Neuro Epitheliopathy

Appendix 3. A proforma diagnostic template

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Please insert your name	Date:DD/MM/YY
REVIEWERS	Names of additional reviewers added here	
NAME OF TEST	eg, **Schirmer 1**	
TO DIAGNOSE	*Test used to diagnose — eg, aqueous tear deficiency (ATD).*	REFERENCES
VERSION of TEST	[V] *Please call your preferred version, version 1. Other versions should be submitted on separate templates and numbered, not necessarily in priority order.*	*Please reference the source of this version.*
DESCRIPTION	*This should be a one or two line statement saying what the test is for.*	
NATURE of STUDY	*If you wish to refer to a specific study in detail, enter the details here.*	
CONDUCT of TEST	*Please describe all steps of the test in sufficient detail to provide a template for a trainer.*	
Results of Study	*If you have described a specific study in detail, place the results here.*	
Web Video	Available [ ] *If instruction would be aided by a video of the technique, please tick this video box.*	
Materials	*Please list the nature and sources of materials used for the test as described.*	
Variations of Technique		
Standardization	Time of day: [ ] Temperature: [ ] Humidity: [ ] Air speed: [ ] Illumination: [ ] Other: [ ] *Tick the boxes if you think that such standardization would improve the repeatability of the test.*	
Diagnostic Value	This version: [ ] Other version: [ ] *Please state if these stats relate to this version or another cited version.* *Please cite statistics indicating the diagnostic value of the test in a referenced study.*	*Please cite reference to stats used*
Repeatability	Intra-observer agreement: [ ] Inter-observer agreement: [ ]	
Sensitivity	(true positives): [ ]	
Specificity	(100 – false positives): [ ]	
Other Stats	*If you have other stats for this or related versions of the test, add as many rows as necessary and cite the reference.*	
Level of Evidence		
Test Problems	*Is there a problem with this test?*	
Test Solutions	*Can you suggest an improvement?*	
Forward Look	*What future developments do you foresee?*	
Glossary	*Please explain abbreviations*	

REFERENCES
[*To be inserted*]

Appendix 4. A note on the Japanese criteria for dry eye diagnosis

The previous Japanese dry eye diagnostic criteria were revised by the Japanese Dry Eye Research Society after the 1994-95 NEI/ Industry workshop (Miyawaki S, Nishiyama S. Classification criteria for Sjogren's syndrome—sensitivity and specificity of criteria of the Japanese Ministry of Health and Welfare (1977) and criteria of European community (1993). *Nippon Rinsho* 1995;53:2371-5). The criteria, unpublished in the English literature, omitted symptoms from the diagnostic criteria at that time, because objective and subjective findings did not appear to correlate. Following the DEWS meeting of 2004, the importance of symptoms was accepted in Japan and the criteria have been modified.

The Japanese criteria prior to the 2004 DEWS meeting were:

1) Qualitative or quantitative disturbance of the tear film (quantity: Schirmer test less than 5 mm or phenol red thread test less than 10 mm; quality: BUT less than 5 sec)
2) Conjunctivocorneal epithelial damage (excluding all other etiologies other than that listed under number 1)
   Fluorescein staining greater than 1 point
   RB staining greater than 3 points
   (The presence of either fluorescein or RB staining is finding sufficient to satisfy criterion number 2)

The presence of both 1 and 2 = Definite dry eye. Presence of 1 or 2 = Probable dry eye

The Japanese diagnostic criteria have been revised by the Japan Dry Eye Research Society in August 2005, to include symptoms, as follows.

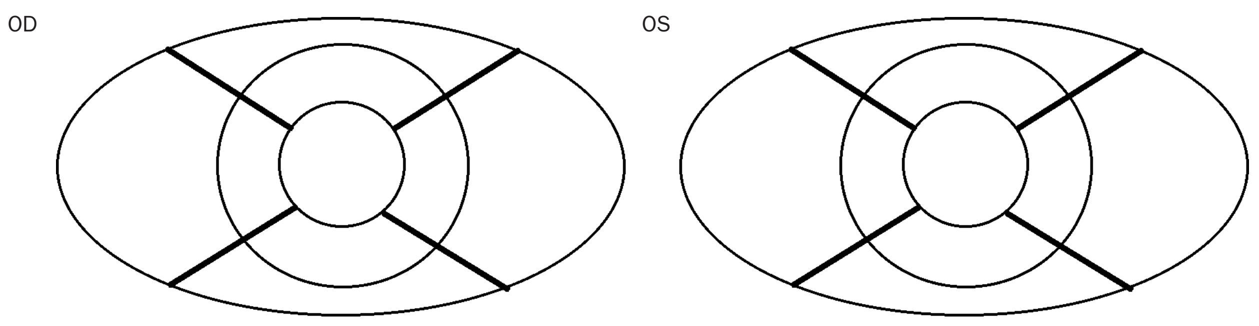
New Diagnostic Criteria of the Japan Dry Eye Research Society: Revised in August 2005

	Definite DE	Probable DE		
Symptoms	Yes	Yes	Yes	No
Tear film quality/quantity—disturbed	Yes	No	Yes	Yes
Epithelial damage	Yes	Yes	No	Yes

The phenol red thread test has been removed from the diagnostic criteria.
A fluorescein staining score of above 3 points is now required as positive staining (instead of 1 point).

APPENDIX 5

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	A.J. Bron	22nd Oct 2004
TEST	**GRADING STAINING: CLEK Schema**	
TO DIAGNOSE	The scheme is used to estimate surface damage in dry eye.	REFERENCES
VERSION of TEST	[V1] [CLEK study]	Barr et al 1999 Lemp 1995
DESCRIPTION	Surface damage to the exposed eye, assessed by staining, is graded against standard charts.	
NATURE of STUDY	**Nature of study** In this study, 75 patients regarded as having mild to moderate dry eye were assessed for symptoms, MGD, tear quality, meniscus height, blink quality, TBUT F and BR staining, phenol red test and Schirmer. 70.7% female. 61% using ATS 21.9% met European Criteria for moderate to severe dry eye. About 30% were CL wearers.	Nichols et al 2004
CONDUCT of TEST	**Fluorescein instillation:** Fluorescein strip wetted with buffered saline. Drop instilled on inferior palpebral conjunctiva. Blink several times. **Rose Bengal Staining:** A Rosets™ Rose Bengal Ophthalmic Strip is wetted with sterile buffered saline and instilled on the inferior bulbar conjunctiva. ("care taken to instill adequate dye") **STAINING:** 5 corneal regions and 4 conjunctival regions as described in the CLEK study (Barr et al. 1999). The staining scale was 0-4, with 0.5 unit steps in each of the 5 corneal regions. Photos were used as examples of severity. The "total score" could either be summed, or averaged.	Nichols et al 2004 Barr et al 1999 [CLEK study]



C I N T S = Central Inferior Nasal Temporal Superior
0–4 scale in 0.5 unit steps

	circle	location	Check appropriate box				
OD	Location	Cornea/Conj.	Punctate	FB	Coalesced	Full-Thickness	Other
Stain 1	C I N T S						
Stain 2	C I N T S						
Stain 3	C I N T S						
Stain 4	C I N T S						
Stain 5	C I N T S						
Stain 6	C I N T S						
Stain 7	C I N T S						
Stain 8	C I N T S						
Stain 9	C I N T S						

continued

<table>
<tr><td>Web Video</td><td>Not available.</td><td></td></tr>
<tr><td>Materials</td><td>• Barnes-Hind Ful-Glo® Fluorescein Sodium Ophthalmic strip
• Rosets™ Rose Bengal Ophthalmic Strip (Chauvin Pharmaceuticals)
• Source of non-preserved buffered saline.</td><td></td></tr>
<tr><td>Standardization</td><td>Nil additional</td><td></td></tr>
<tr><td>Repeatability</td><td>Intra-observer agreement.

Corneal and Conjunctival Staining
Sum of all regions:
Fluorescein stain: The weighted κ was:
0.69 (95% CI = 0.35, 0.81) and the intraclass correlation coefficient was
0.76 (95% CI = 0.58, 0.87).
Bengal rose stain: The weighted κ was:
0.33 (95% CI = 0.45, 0.93) and the intraclass correlation coefficient was
0.40 (95% CI = 0.09, 0.64).

Note that agreement was better for fluorescein than for bengal rose, perhaps because the bengal rose strip gives weaker staining than the fluorescein strip.

Note too, that agreement was less good for individual zones assessed independently as follows:
<table>
<tr><td colspan="5">Unweighted κ for presence versus absence of F and BR staining.
(κ values; [% agreement])</td></tr>
<tr><th>Zone</th><th>Cornea Fluor</th><th>Cornea Bengal R</th><th>Conj Fluor</th><th>Conj Bengal R</th></tr>
<tr><td>Inf</td><td>0.18 (58.7)</td><td>0.02 (81.3)</td><td>0.25 (70.7)</td><td>0.14 (60.0)</td></tr>
<tr><td>Nas</td><td>0.23 (70.7)</td><td>–0.02(94.7)</td><td>0.14 (56.0)</td><td>0.09 (65.3)</td></tr>
<tr><td>Temp</td><td>0.47 (82.7)</td><td>0.49 (97.3)</td><td>0.10 (54.7)</td><td>0.46 (92.0)</td></tr>
<tr><td>Sup</td><td>0.28 (82.7)</td><td>N/A</td><td>0.31 (90.7)</td><td>N/A</td></tr>
<tr><td>Centr</td><td>0.29 (81.3)</td><td>N/A</td><td></td><td></td></tr>
<tr><td colspan="5">N/A Not available because no stain
K values: 0–0.2 slight agreement; 0.21–0.40 fair agreement;
0.41–0.60 moderate agreement; 0.61–<1.0 excellent; 1.0 =perfect agreement</td></tr>
</table>
Note, even in region of most frequent corneal staining, κ = 0.21:
It was concluded that perhaps zone scores varied between visits but the total sum of scores was more constant.</td><td>Nichols et al 2004</td></tr>
<tr><td>Test problems</td><td>About 30% were CL wearers. They do not appear to have been analyzed separately.
Only a single observer was involved in the repeatability measurements.
Did patients stop ATS drops before assessment?</td><td></td></tr>
<tr><td>Glossary</td><td>CLEK = Collaborative Longitudinal Evaluation of Keratoconus</td><td></td></tr>
</table>

REFERENCES

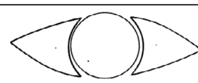
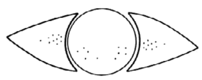
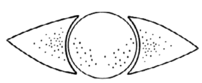
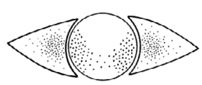
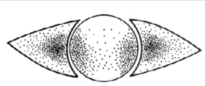
Barr JT, Schechtman KB, Fink BA, et al. Corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: baseline prevalence and repeatability of detection. *Cornea* 1999;18(1):34-46

Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes. *CLAO J* 1995;21(4):221-31

Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea* 2004;23(3):272-85

APPENDIX 6

<table>
<tr><td>DEWS</td><td>DRY EYE: DIAGNOSTIC TEST TEMPLATE</td><td></td></tr>
<tr><td>RAPPORTEUR</td><td>A.J.Bron</td><td>21st Oct 04</td></tr>
<tr><td>TEST</td><td>GRADING STAINING: Oxford Schema</td><td></td></tr>
<tr><td>TO DIAGNOSE</td><td>The scheme is used to estimate surface damage in dry eye.</td><td>REFERENCES</td></tr>
<tr><td>VERSION of TEST</td><td>[V 1]</td><td></td></tr>
<tr><td>DESCRIPTION</td><td>Surface damage to the exposed eye, assessed by staining, is graded against standard charts.</td><td></td></tr>
<tr><td>CONDUCT of TEST</td><td>
Grading Schema:
Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale

<table>
<tr><th>PANEL</th><th>Grade</th><th>Criteria</th></tr>
<tr><td>A </td><td>0</td><td>Equal to or less than panel A</td></tr>
<tr><td>B </td><td>I</td><td>Equal to or less than panel B, greater than A</td></tr>
<tr><td>C </td><td>II</td><td>Equal to or less than panel C, greater than B</td></tr>
<tr><td>D </td><td>III</td><td>Equal to or less than panel D, greater than C</td></tr>
<tr><td>E </td><td>IV</td><td>Equal to or less than panel E, greater than D</td></tr>
<tr><td>>E</td><td>V</td><td>Greater than panel E</td></tr>
</table>

Conduct of Test:

Dye is instilled.
Slit-lamp is set (eg, 16 magnification with x10 oculars with Haag-Streit).
Cornea: The upper eyelid is lifted slightly to grade the whole corneal surface,
Conjunctiva: To grade the temporal zone, the subject looks nasally; to grade the nasal zone the subject looks temporally.
(The upper and lower conjunctiva can also be graded).

Selection of dyes:
A list dyes and filters can be found in the original paper.
With fluorescein, staining must be graded as quickly as possible after instillation, since the dye then diffuses rapidly into the tissue and its high luminosity blurring the stain margin. Staining after rose bengal or lissamine green, persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography.

Fluorescein sodium
1. Quantified drop instillation
eg 2 µl of 2% sterile fluorescein instilled into each conjunctival sac with a micro-pipette (using a sterile tip). In very dry eye, larger volumes risk the possibility of inadequate dilution into the fluorescent range.
2. Unquantified instillation — impregnated paper strips
This is a convenient approach in the clinic using the following method of application:

A single drop of unit dose saline is instilled onto a fluorescein-impregnated strip.
When the drop has saturated the impregnated tip, the excess is shaken into a waste bin with a sharp flick.
The right lower lid is then pulled down and the strip is tapped onto the lower tarsal conjunctiva. A similar procedure is carried out on the left.

If too large a volume is delivered then the concentration in the tear film will be too high, and the tear film and staining pattern will be non-fluorescent.
</td><td>Bron Evans Smith 2003</td></tr>
</table>

continued

3.Timing
The fluorescein break-up time (FBUT) is usually performed prior to grading staining. Since fluorescein diffuses rapidly into tissues, punctate staining blurs after a short period. It is therefore essential to assess staining rapidly, in sequence, in the right and then the left eye, so that the staining patterns observed are equally crisp.
If it is intended to photograph the staining pattern for grading, then photography should follow immediately after each instillation.

Exciter and Barrier Filters
The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm. A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15 barrier.

Where more light is required for photographic purposes, narrow band-pass, interference filters can be used.

The use of both exciter and barrier filters allows both the cornea and conjunctiva to be assessed using a single stain. This is a major advantage in clinical trials where it is otherwise customary to employ fluorescein to grade corneal staining and rose bengal or lissamine green to grade conjunctival staining.

Disadvantages of Fluorescein Staining
Blurred pattern if reading is delayed. Delay in photographing fluorescein staining results in blurred images of the staining pattern.

Rose Bengal
The intensity of rose bengal staining is dose dependent. If drop size or concentration is reduced to minimize stinging, the amount of staining is also reduced. Use of impregnated strips will give weaker staining than use of a full drop of 1% solution. Best results are achieved with, eg. 25 µl 1%, instilled into the conjunctival sac. Because rose bengal stings, instillation is best preceded by a topical anesthetic.

Instillation Technique
1) eg, a drop of Proxymetacaine is instilled into the conjunctival sac followed, after recovery, by;
2) A drop of rose bengal 1.0%. This is instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down.
3) Since both anaesthetic and drop may stimulate reflex tearing, the test should follow measurement of the FBUT and of the Schirmer test. (Conjunctival staining due to insertion of the Schirmer paper can usually be distinguished from that due to dry eye disease).

Both eyes may be stained prior to grading, since there is no risk of the staining pattern in the first eye being obscured by the time the second eye is graded.
The cited paper gives advice about avoidance of overspill.

Visibility
Rose bengal staining on the conjunctiva shows up well against the sclera and may be enhanced using a red-free (green) light source. Corneal staining may show up well against a blue iris, but is difficult to see against a dark brown iris.

Phototoxicity
Photo-activation of rose bengal by sunlight increases post-instillation symptoms, especially in severe dry eye with heavy staining. This post-instillation pain can be minimized by liberal irrigation with normal saline at the end of the test.

Lissamine green stains the eye in a similar manner to rose bengal but is as well tolerated as fluorescein. Visibility and dose-dependency are the same as rose bengal and staining is persistant so that photography need not be performed immediately after instillation. Lissamine green is available as impregnated strips or may be ordered as a pre-prepared solution. A 25 µl 1% drop will give more intense staining. Because the drop is well tolerated, no anaesthetic is required.

continued

APPENDIX 6 *continued*

<table>
<tr><td>CONDUCT of TESTS</td><td>Visibility
As with rose bengal, lissamine green staining is easily visible on the conjunctiva. On the cornea, staining is seen well against a light blue iris background but is poorly visible against a dark brown iris background. For both rose bengal and lissamine green, because the dyes are poorly seen within the tear film, the dye in the tear film does not obscure the staining pattern. Also, since both dyes do not diffuse into the substantia propria of the conjunctiva, the staining pattern is retained for longer.

Visibility of staining may be enhanced using a white light source and a red barrier filter, to give a black pattern on a red ground. A suitable filter is a Hoya 25A, or a Kodak Wratten 92.</td><td></td></tr>
<tr><td>Web Video</td><td>Not available</td><td></td></tr>
<tr><td>Materials</td><td>Oxford grading panel; Slit-lamp; Selected dye.</td><td></td></tr>
<tr><td>Standardization</td><td>See above.</td><td></td></tr>
<tr><td>Repeatability</td><td>A small intra-inter observer study was carried out in 1986 and was presented but not published:

Intra-observer study: This study asked two trained ophthalmologists to grade a series of standard slides, showing corneal and conjunctival fluorescein staining, on 2 separate occasions. [note: -this study is only relevant to grading photographic records not patients.]

<table>
<tr><td colspan="3">Intra-observer κ for grading photographs of staining, using the Oxford scheme.
Two observers.</td></tr>
<tr><td></td><td>Cornea</td><td>Conjunctiva</td></tr>
<tr><td>Observer 1</td><td>0.86</td><td>0.69</td></tr>
<tr><td>Observer 2</td><td>0.65</td><td>0.83</td></tr>
</table>

Note that values are in the good to excellent range.

Inter-observer study: In this study, the same 2 observers graded fluorescein staining (blue exciter; yellow filter) in 13 dry eye patients at an interval within 2-3 weeks.

<table>
<tr><td colspan="3">Inter-observer κ for grading patients with dry eye, using the Oxford scheme.
Two observers. Fluorescein; bengal rose</td></tr>
<tr><td>Observer 1 v 2</td><td>Cornea</td><td>Conjunctiva</td></tr>
<tr><td>Fluorescein</td><td>0.88</td><td>0.48</td></tr>
<tr><td>Bengal rose</td><td>0.87</td><td>0.54</td></tr>
</table>

It is of interest that observations are in the excellent category for cornea, with either stain and in the fair category for conjunctiva.</td><td>Hardman Lea et al 1986 AER abstract.</td></tr>
<tr><td>Test problems</td><td>The test depends on pattern recognition applicable to dry eye states.</td><td></td></tr>
<tr><td>Test solutions</td><td>More general use to assess all forms of ocular surface staining can be achieved by scoring staining in multiple segments of the ocular surface while retaining a full number density range of dots</td><td></td></tr>
</table>

REFERENCES

Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003;22(7):640-50.

APPENDIX 7

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Mark B. Abelson and George W. Ousler III	5th Nov 2004
Reviewers	–J Paugh	27th Dec 2007
TEST	**Tear Film Break-Up Time (TFBUT)** also: BUT (Break-up Time) and FBUT (Fluorescein Break-Up Time)	
TO DIAGNOSE	Tear Film Stability	
VERSION	Version I	
DESCRIPTION	The tear film break-up time is defined as the interval between the last complete blink and the first appearance of a dry spot, or disruption in the tear film.	Lemp 1970 Lemp 1995
STUDY	100 subjects with normal ocular health and 100 patients with 'a history of dry eye'. 5 µl of 2% fluorescein were instilled. Average of 3 readings.	Abelson et al 2002
CONDUCT of TEST [V1]	Standardization of the volume instilled is important. Johnson and Murphy 2005 found that increasing the volume of fluorescein instilled from 1–2.7 µl, increased the TFBUT, but that increasing to 7.4 µl was not associated with further change. 1. Instill 1 to 5 micro-liters of non-preserved, 2% sodium fluorescein onto the bulbar conjunctiva without inducing reflex tearing by using a micro-pipette or D.E.T. strip; 2. The patient is instructed to blink naturally, without squeezing, several times to distribute the fluorescein 3. Within 10 - 30 seconds of the fluorescein instillation, the patient is asked to stare straight ahead without blinking, until told otherwise; 4. Set slit-lamp magnification at 10X, keep the background illumination intensity constant (cobalt blue light) and use a Wratten 12 yellow filter to enhance observation of the tear film over the entire cornea; 5. Use stopwatch to record time between last complete blink and first appearance of growing micelle; 6. Once TFBUT is observed, instruct patient to blink freely. Various authors advocate the use of a yellow barrier filter (Kodak Wratten 12) to enhance the visibility of the break in the fluorescent tear film. (Eliason and Maurice 1990; Cho and Brown 1993; Nichols et al. 2003; Bron et al 2003. Johnson et al 2005).	Johnson and Murphy 2005
CONDUCT of TEST [V2]	2.5 µl 1.0% fluorescein	Vitale et al 1994
Results of study	The mean TFBUT for normal subjects was 7.1 s (range 4.7 to 11.4 s) and for dry eye patients 2.2 s (range (0.9 to 5.2 s). On the basis of this, a cut-off for dry eye diagnosis of ≤ 5 s was recommended.	Abelson et al 2002
Video	*Slit-lamp, on-line video camera may be used to capture TFBUT. Video capture with an on-screen timer allows for precise measurement of the time between the last complete blink and the appearance of the first, growing micelle. This also allows masking for clinical trials purposes	Welch et al 2003
Web video	Not available	
Materials	• Non-preserved, 2% sodium fluorescein; • Micro-pipette; • Or D.E.T. strip. • Slit-lamp • Timer • Kodak Wratten filter 12. See variations, below.	
Variations of technique	Historically, the technique for evaluating TFBUT has lacked consistency. Large and varying amounts of sodium fluorescein (up to 50 µl) were used, times were determined by counting aloud and using less sophisticated instrumentation. Such techniques yield varying results.	
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] • Patient instruction; • Slit-lamp magnification; • Barrier filter.	

continued

APPENDIX 7 *continued*

Diagnostic value	This version (micro-quantities of fluorescein): TFBUT ≤ 5 seconds = dry eye; TFBUT > 5 seconds = normal. Other version (larger quantities of fluorescein): TFBUT ≤ 10 seconds = dry eye; TFBUT > 10 seconds = normal.	Lemp 1995 Abelson et al 2002
Sensitivity	(**true positives**) [72.2%] 184/255 patients (cut off ≤ 10 sec)	Vitale et al 1994
Specificity	(**100 – false positives**) [61.6%] 69/112 controls	
Test problems	Instillation of fluorescein must be done carefully so that reflex tearing is not induced. Alterations in tear volume may artificially lengthen TFBUT. Proper patient instruction is critical. If patients are not told to blink freely after TFBUT occurs, reflex tearing may occur and skew subsequent measurements. Large, uncontrolled volumes of fluorescein may also artificially lengthen TFBUT. In the reported study, the age and sex of subjects is not stated and the criteria for dry eye diagnosis are not provided and no sensitivity or specificity calculations were made for the selected cutoff value. However, there was little overlap between the normal and abnormal distribution curves.	Abelson et al 2002
Glossary	TFBUT = Tear film break-up time: BUT = Break-Up Time) and FBUT = Fluorescein Break-Up Time.	

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APPENDIX 8

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	A.J.Bron	19th Oct 2004
TEST	**Schirmer-1 Test — without anesthesia**	
TO DIAGNOSE	Dry Eye	REFERENCES
VERSION	[V1]	
DESCRIPTION	An estimation of tear flow stimulated reflexly by insertion of a filter paper into the conjunctival sac.	
NATURE of STUDY	Diagnostic value of the Schirmer 1 test, Rose bengal staining and a test of lysozyme tear level in sicca syndrome. **Normal** controls: 550 Age 20-74 years M=F in each 5 y band **Sicca** syndrome: 43 F32; M11	
CONDUCT of TEST	**Schirmer-1 test:** The unanesthetized eye Schirmer paper strips Schirmer strips inserted over the lower lid margin, midway between the middle and outer third (assumed). Closed eye (assumed). Read at 5 minutes [No further details]	van Bijsterveld 1969
RESULTS of STUDY	**Schirmer-1:** With a cut of ≤ 5.5 mm the probability of misclassification of patients was 15% and of controls was 17%. No significant differences between men and women at each 5 year age band, but Schirmer value fell with age. Note 107 controls had wetting > 30 mm	
Video need	Not available	
Materials	• Schirmer Papers (5x35mm Whatman No 1)	
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√]. Assumed to influence.	
Variations of technique	• Calibrated and dyed papers (Eagle Vision - blue) • Paper housed in impervious wrap, to reduce evaporation.	Esquivel and Holly
Sensitivity	**Differentiating 'sicca' from normals:** **(true positives) [85%] ≤ 5.5 mm cut off**	van Bijsterveld 1969
Specificity	**(100 – false positives) [83%] ≤ 5.5 mm cut off**	van Bijsterveld 1969
Test problems	Full details of Schirmer not stated in this paper. Two eye data was pooled for analysis, for all measures (ie. Including rose bengal and lysozyme	
Glossary	'sicca' = keratoconjunctivitis sicca = dry eye. In this study it probably equates with aqueous-deficient dry eye.	

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APPENDIX 9

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Michael A. Lemp	16th Oct 2004; 15th March 2006
TEST	**Tear Osmolarity**	
TO DIAGNOSE	Global test for dry eye	Sullivan 2004
VERSION of TEST	OcuSense Volume Independent Tear Osmometer	
DESCRIPTION	This "lab-on-a-chip" test uses a combination of impedance information with sophisticated mathematics to derive tear film osmolarity. A small nanoliter tear sample is obtained with a standard micropipette and is then automatically transferred to a chip surface. A precise readout is obtained in seconds after the transfer.	
CONDUCT of TEST	1. Snap microchip in place 2. Touch lower lid with microcapillary 3. Let capillary action draw a few nL 4. Place capillary in machine 5. Read osmolarity	
Web video	Available:[No]	
Materials	• 1-lambda microcapillary • microchip • Both available from OcuSense	
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] Assumed to influence Other: [Avoid reflex tearing] White et. al. Showed that use of a slit lamp has upwards of a 7 mOsm/kg effect on the value of osmolality due to the induction of reflex tearing. Overstimulation during collection is discouraged. Reflex tears have far lower osmolality (≈ 5%, Nelson, 1986) than basal tears.	White et al 1993 Nelson et al 1986
Repeatability	Intra-observer agreement. [ ] Inter-observer agreement. [< 2.6% 1st prototype]	Sullivan B 2004
Sensitivity	(true positives) [projected 94%] ≥ 318 mOsm: –provisional	Sullivan B 2004
Specificity	(100 – false positives) [projected 84%]	Sullivan B 2004
Test problems	Limited availability	
Test solutions	Commercial development	
FORWARD LOOK	This is a high throughput test that can be performed by a technician, and currently carries a miscellaneous CPT.	

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APPENDIX 10

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Mark Willcox	10th Jan 2006
TEST	**Tear meniscus radius, height and cross sectional area**	
TO DIAGNOSE	Aqueous tear deficiency (ATD).	REFERENCES
VERSION	[V 1] **Meniscometry**	Yokoi Komuro 2004
DESCRIPTION	A rotatable projection system with a target comprising black and white stripes is projected onto the lower central tear film meniscus. Images are recorded and transferred to computer in order to calculate radius of curvature	
CONDUCT of TEST	1. The subject is seated at a slit lamp 2. A rotatable projection system with a target comprising a series of black and white stripes (4 black and 5 white; each 4mm wide), is introduced coaxially using a half-silvered mirror 3. Images of the tear meniscus (of either or both eyes) are recorded with a digital video recorder 4. Images are transferred to a computer and image analysis software used to calculate the radius of curvature of the meniscus by applying the concave mirror formula	
Web Video	Not available	
Materials:	• Slit lamp • Rotatable projection system (see above) with half silvered mirror • Digital video recorder plus TV monitor • Computer plus software • Colour printer	Oguz et al 2000
Variations of technique	Several alternative methods have been published including: 1. Use of variable beam height on a slit lamp 2. Measurement and grading of meniscus integrity using slit lamp 3. Using a video slit lamp biomicroscope but no projected stripes 4. Measurement after instillation of fluorescein	Nichols et al 2004a Cermak et al 2003 Glasson et al 2003 Farrell et al 2003 Oguz et al 2000
Standardisation	Assumed to be influenced by: Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√]	
Repeatability	Intra-observer agreement. [Not recorded for V1 – but poor in Nichols et al system]	
Sensitivity	Tear meniscus height: cut off of: < 0.18 mm (true positives) Farrell et al's technique = [72.8%]	Farrell et al 2003
Specificity	(100 – false positives) Farrell's technique = [66.6%]	
Sensitivity	Tear Meniscus Height: Small vol. fluorescein: cut off < 0.35mm (true positives) Mainstone et al = [93.3%]	Mainstone et al 1996
Specificity	(100 – false positives) Mainstone et al = [66.7%]	
Other Stats	For V1 – significantly lower meniscus height in dry eye subjects. Plugging puncta significantly increased meniscus height. Significant correlation between meniscus height and Schirmer test Cermak et al – significantly lower meniscus height in androgen insensitive female subjects who demonstrated dry eyes Farrell et al – significant decrease in dry eye subjects compared with controls; significant increase in dry eye subjects with puncta occluded Correlations noted between meniscus curvature and meniscus height in presence or absence of fluorescein Tear meniscus height and area reduced in subjects intolerant to contact lens wear compared with tolerant subjects Nichols et al (2004b) demonstrated lack of association between tear meniscus height and symptoms of dry eye.	Yokoi and Komuro 2004 Cermak et al 2003 Farrell et al 2003 Oguz et al 2000 Glasson et al 2003 Nichols et al 2004b
Test problems	Positioning of subject etc and use of specialized equipment	
Forward Look	To adapt the V1 method for general use.	

continued

APPENDIX 10 ***continued***

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APPENDIX 11

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Eiki Goto, MD	15th Mar 2006
TEST	**Tear film lipid layer interferometry**	
TO DIAGNOSE	Aqueous tear deficient dry eye (ATD) or precorneal lipid tear deficiency.	REFERENCES
VERSION	[V6]	Goto et al 2003
DESCRIPTION	Superficial tear lipid layer is observed with tear interference camera. Interference images are graded on dry eye severity or analyzed to quantify lipid layer thickness.	Korb and Greiner 1994; King-Smith et al 1999; Yokoi et al 1996; Mathers et al 1997; Goto et al 2003
CONDUCT of TEST	1. The subject is seated comfortably at the tear interference camera and the head positioned on the chin rest. 2. With the eyes in normal blinking interference images are monitored. 3. After a few seconds of blinking, when the interference image becomes stable, the image is captured. 4. Lipid layer thickness is estimated using a color comparison table (Korb and Greiner). 5. Interference images are semi-quantitatively graded on the pattern and color. (Yokoi et al) 6. In a kinetic analysis, interference images are recorded on a video over several natural blink intervals for 30 seconds. In a representative blink interval, lipid spread time from eye opening to the cessation of lipid movement is measured. (Goto and Tseng) 7. When image analysis is needed, the captured, still, interference image is analyzed by its colour profile. Lipid layer thickness is quantified with the color chart system. (Goto et al)	Doane 1989; Korb and Greiner 1994; Yokoi et al 1996; Goto and Tseng 2003 Goto et al 2003 Korb et al 2005
Web Video	Not available	
Materials	• Tear interference camera (DR-1, Kowa, Nagoya, Japan), Dr. Korb's camera, Dr. Doane's camera or Tearscope (Keeler, Windsor) • Digital printer • Hopefully PC for image capturing	Yokoi et al 1996 Goto and Tseng 2003
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] Other: [blinking √]. Assumed to influence	
Variations of technique	V1, Tear lipid layer interference images were observed using devices such as Tearscope. V2, Lipid layer thickness was estimated using color comparison method. V3, Images were captured using modified specular microscope and graded on dry eye severity in Sjogren syndrome. V4, Interference camera was sophisticated (DR-1, Kowa, Japan) and images were graded on dry eye severity. V5, Kinetic analysis of interference images using DR-1 to measure lipid spread time. V6, Precorneal lipid layer thickness was quantified using colorimetric system in DR-1. V7, Lipid layer thickness topography was processed. * Tear interference patterns on contact lens are also evaluated by Guillon or Maruyama.	Guillon 1992 Korb and Greiner 1994 Danjo and Hamano 1995 Yokoi et al 1996 Tiffany et al 2001 Goto and Tseng 2003 Goto et al 2003 Goto et al 2004 Maruyama et al 2004
Diagnostic value	See references 4 and 5.	Yokoi et al 1996 Yokoi et al 1999
Repeatability	Intra-observer agreement. [+], V4 on grading and V5 on grading and Kinetic analysis Inter-observer agreement. [–]	Yokoi et al 1996; Yokoi et al 1999; Goto and Tseng 2003; Goto and Tseng 2003

continued

APPENDIX 11 *continued*		
Test problems	a. Colour intensity of interference images are influenced by the refractive indices of tear lipid and aqueous layers and specular angle. b. Interference images are influenced by how to blink, thus to record the non-invasive status of the lipid layer, it is important for the subject to blink naturally. c. Lipid quality could not be indicated by interferometry. d. Amount of meibum secretion observed at lid margin does not always correlate with the precorneal lipid layer thickness (a phenomenon, not a test problem)	Goto et al 2003 King-Smith et al 1999 Tiffany 1986
Test solutions	a. Image analysis for lipid thickness quantification need to be developed more.	
FORWARD LOOK	a. Identify cut-off for MGD, and ATD diagnosis. b. Incorporate MGD diagnosis into diagnosis of evaporative dry eye or precorneal lipid deficiency. c. Image analysis on raw interference image and quantification of lipid layer thickness in a mapping form. Clinically useful index from mapping for comparison and stats.	
Glossary	ATD = Aqueous tear deficient dry eye	

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APPENDIX 12

DEW	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Murat Dogru	24th Oct 2004
TEST	**Tear Stability Analyses System (TSAS)**	
TO DIAGNOSE	Test used to diagnose –Tear Instability Refs:	Kojima 2004 Goto 2004a,b
VERSION	[TMS-2N]	Kojima 2004
DESCRIPTION	Noninvasive and objective test for tear film stability analysis	
Study	To compare the sensitivity and specificity of TSAS with the BUT (based on slit-lamp examination and use of fluorescein), 48 volunteers without any eye disease, surgery or drug use within 1 year of study were recruited. See below.	Goto 2004a
CONDUCT of TEST	Subject seated in front of TMS-2N corneal topography unit. Subject asked not to blink for 10 seconds with test initiation Device automatically captures corneal topograms each second for 11 consecutive seconds, displayed as time plot curves of SRI, SAI, BUT area	
Results of Study	See study, above. 42.5% (34 eyes) of the 80 eyes of the volunteers studied had a normal BUT and 57.5% had an abnormal BUT. On the basis of the subjects' dry eye symptoms such as FBS, soreness, dryness etc, the sensitivity and specificity of the BUT were 75% and 60% respectively. Among 34 eyes with a normal BUT, 11 (32.35%) were found to have an abnormal TMS BUT. Of these eyes, 9 (81.8%) were from 6 subjects who had dry eye symptoms in their questionnaires. On the basis of symptomatology, the sensitivity and specificity of TMS BUT was 97.5 and 62.5% respectively. The difference of sensitivity between SLE BUT and TMS BUT was significant; however, the difference in specificity was not.	
Web Video	Not available	
Materials	TMS-2N corneal topography device TSAS software(Tomey Inc)	
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] . Assumed to influence.	
Sensitivity	(true positives) [97.5%]	Goto 2004a
Specificity	(100 – false positives) [62.5 %]	
Test problems	Although the test appears to be a promising, non-invasive method to test tear stability, it is not known whether the test is evaluating tear stability due to lipid layer or overall tear film changes. Only one study compares the test with the invasive fluorescein aided BUT measurement. Normal values of this test and age-specific cut off values on a large set of subjects not yet established. Comparative studies with other invasive and non-invasive tests of tear stability do not exist as yet. Needs a corneal topography device and the software which makes it expensive compared to fluorescein aided BUT testing.	
Test solutions	The above mentioned studies will prepare this test for general clinical prime time.	
Forward Look	The device is still being furnished with novel parameters such as BUT area. For dynamic analyses of tear functions in dry eye syndromes and ocular surface disorders, I believe that this new system is set to play an important role in the future.	
Glossary	TSAS: Tear Stability Analyses System	

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APPENDIX 13

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	John M. Tiffany	12th Nov 2004
TEST	**MEIBOMETRY**	
TO DIAGNOSE	Meibomian Gland Dysfunction — (MGD)	REFERENCES
VERSION of TEST	[V1]	Komuro et al 2002
DESCRIPTION	Lipid on the lower central lid margin is blotted onto a plastic tape and the amount taken up read by optical densitometry. This provides an indirect measure of the steady state level of meibomian lipid.	
CONDUCT of TEST	1. The subject is seated, with the head resting comfortably at the slit-lamp. 2. With the eyes in upgaze, the right lower lid is drawn down lightly without pressure on the tarsal plate. 3. A standard loop of plastic tape, held in an applanation or ultrasonography probe holder, is applied to the central third of the everted lid margin for 3 seconds, at 0 mmHg exerted pressure. 4. The tape is air dried for 3 minutes to allow tear evaporation if necessary. 5. The increase in transparency induced by the lipid blot, is read in the laser meibometer. 6. The Casual Lipid level (expressed as arbitrary optical density units) is calculated as (C-B), where C is the casual reading, B is the reading from the untouched tape (background).	Komuro et al 2002
Video need	Not available.	
Materials	• Plastic tape: 8 mm wide (Courage and Khazaka, Köln) • Tape Holder:(eg. NIDEK ultrasonographic probe holder. • Laser Meibometer. Window size (2.5 x 5.0 mm2)	
Standardization	Time of day [x] The level is highest in the first hour after waking, but thereafter settles to a constant level through most of the day	
Variations of technique	In the original version, [V2] optical density was read using an adaptation of the Courage and Khazaka sebumeter. A point reading was taken at the centre of the blot. Other methods exist in which the blot is scanned and the increase in transparency is integrated over the length of the blot . The spring-clip holding the loop of tape can be mounted with wax, modeling clay or "Blu-Tack" to the end of a thin wooden rod (eg, a bamboo kitchen skewer) held upright by a lump of wax to the ultrasonography mounting-plate; this also exerts zero pressure on the eyelid. After blotting, the loop is opened and attached to a highly-reflective surface (mirror or polished metal) for scanning.	Chew et al 1993a,b Yokoi et al 1999
Test problems	a. In normal subjects the lipid blot is uniform and results can be extrapolated to the total lid length. In MGD, focal gland obstruction may vary along the lid length so that central readings may not truly reflect the overall picture. b. Calibrations and assumptions are required to convert raw densitometry readings into meibomian lipid equivalent values.	
Test solutions	a. Measurement should be made along the whole of the lower lid length in order to reflect variation in MGD. b. If the scanning method is used, either a maximally-wide or a very narrow area across the blot should be integrated, to give either an averaged reading including regions with non-functional glands, or a reading only from a selected area of full blotting.	
Forward Look	a. Develop a system to integrate lipid along full lid length. b. Identify cut-off for MGD diagnosis. c. Incorporate MGD diagnosis into diagnosis of evaporative dry eye.	
Glossary	MGD: Meibomian gland dysfunction	

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APPENDIX 14

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Gary N. Foulks	19th Oct 04
TEST	MEIBOGRAPHY/MEIBOSCOPY	REFERENCES
TO DIAGNOSE	Meibomian gland morphology and density and drop out. Diagnosis of Meibomian gland dysfunction (MGD)	Robin et al 1985 Jester et al 1982
VERSION	[V1]	*reference 1 above*
DESCRIPTION	Meiboscopy is the visualization of the meibomian gland by transillumination of the eyelid. Meibography implies photographic documentation	Mathers et al 1994
CONDUCT of TEST	Meiboscopy: The most basic version uses white light from a Finoff transilluminator. This is applied to the cutaneous side of the everted eyelid and allows observation from the conjunctival surface The presence and morphology of the glands can be observed and gland loss, or “drop out” quantified. Meibography is the photographic documentation of the image of the gland under such illumination. Variations on the theme include the use of infrared photography or videophotography.	
Web Video	Not available	
Materials	• Finoff head light, slit lamp biomicroscope • (variation: infrared light source and sensor; videography)	
Variations of technique	1) infrared photography 2) videography Variations in scoring systems.	Pflugfelder 1998 Shimazaki 1998 Yokoi 2007
Standardization	Illumination [√]	
Diagnostic value	This version : [x] Most reliable test in patients with ectodermal dysplasia syndrome Other version: [ ]	Kaercher et al 2004
Other Stats	Greatest value is determining presence or absence of gland. Morphological variations, while interesting, are more difficult to quantify.	
Test problems	The limitation is the subjective nature of the observation.	
Test solutions	An improvement could be standardized photographs as reference.	
Forward Look	Improved photographic documentation.	
Glossary	MGD: Meibomian gland dysfunction	

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APPENDIX 15

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Kazuo Tsubota	14th Dec 2004
TEST	**Brush Cytology Technique**	
TO DIAGNOSE	A variety of ocular surface diseases	REFERENCES
VERSION	[1]	
DESCRIPTION	Brush cytology is the technique which collects conjunctival epithelial samples from the patient, clinically. This method is different from impression cytology in that brush cytology can obtain basal cells as well as superficial cells.	Tsubota 1990 (a) Tsubota 1990 (b) Tsubota, 1991 Fukagawa 1993 Fujihara 1997 Miyoshi 2001 Takano 2004
CONDUCT of TEST	Brushing cytology of the conjunctiva is a moderately invasive but can provide a valuable snapshot of the surface of the eye to evaluate many conjunctival conditions.	
Video needed	Not available	
Materials	• Small Brush (Teikokuzouki Pty. Ltd., Japan), • Hank's buffered solution, • Millipore filter (Millipore Corp., Bedford, MA)	
Standardization	The strength of the pressure applied to the conjunctiva by brush should be moderate.	
Diagnostic value	This version is useful to evaluate: 1) squamous metaplasia, 2) detecting inflammatory cells, 3) expression of several surface markers on the ocular surface epithelium.	Tsubota 1990 (b)
Test problems	The procedure is slightly invasive to the patient as the cells are detached from the ocular surface	
Test solutions	Use a very soft brush (do not use a rough brush)	
Forward Look	Since more than 100,000 cells are obtained using brush cytology, this is a very good technique to see molecular expression by each cell. Thus this technique, combined with flow cytometry can give us more detailed information about events at the ocular surface at the cellular level.	

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APPENDIX 16

DEWS	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Christophe Baudouin	7th Nov 2004
TEST	**Flow cytometry in impression cytology**	
TO DIAGNOSE	Conjunctival inflammation / apoptosis	REFERENCES
VERSION of TEST	[V 1] [V2] Also available: Brush cytology for cell collection before flow cytometry procedures (Fujihara et al., 1997).	Baudouin et al 1997 Fujihara et al 1997
DESCRIPTION	This technique is highly sensitive and specific for analyzing expression of any marker by conjunctival epithelial cells, or identification of inflammatory and goblet cells. HLA-DR normally not or weakly expressed. Strongly overexpressed in case of ocular surface inflammation	
NATURE of STUDY	Technique specially relevant in dry eye, allergy or assessment of antiglaucoma eyedrops	Brignole et al 2000, 2001
CONDUCT of TEST	1. Without or under topical anesthesia with one drop of 0.04% oxibuprocaine, one or more filters, 13 x 6.5 mm in size, are gently applied to the conjunctival surface. 2. After removal, the membranes are dipped into tubes containing 0.05% paraformaldehyde. The tubes have to be kept at 4°C before and after impression collection in order to avoid sample degradation during the phase of fixation. Under this condition the filters with the conjunctival specimens can be stored several days and sent to the laboratory in cold-conditioned containers before being processed for flow cytometry analyses. 3. Cell extraction is manually conducted by gentle agitation. After centrifugation in PBS, conjunctival cells are then immunostained and analyzed by flow cytometry. 4. Indirect or direct immunofluorescence procedures may be used. Simple or multi-color analysis can be performed commonly using 2 to 4 antibodies conjugated with different fluorochromes. A nonimmune isotype-matched mouse immunoglobulin has to be used as a negative isotypic control, fluorochrome-conjugated or not, according to direct or indirect immunofluorescence procedure. 5. At the end of incubation with specific antibodies, cells are centrifuged in PBS (1600 rpm, 5 minutes), resuspended in PBS and analysed on a flow cytometer. Intracytoplasmic markers can also be detected by using specific permeabilization techniques, such as 0.5% saponin, X100 triton X or ethanol. 6. Many markers available giving relevant information on ocular surface disorders; HLA DR expression by epithelial cells, gold standard for inflammatory assessment	Brignole et al 2004
Web Video	Not available	
Materials	1. Polyethersulfone filters (Supor®, Gelman Sciences Ann Arbor, MI, USA), 13 mm in diameter with pores of 0.20 µm 2. Paraformaldehyde freshly prepared and preserved at 4°C, monoclonal antibodies and material for immunostaining 3. Flow cytometer	
Variations of technique	[V2] Brush cytology for cell collection before flow cytometry procedures.	Fujihara et al 1997
Diagnostic value	This version : [√] HLA DR inferior to 45% of positive cells and 18,000 MESF (molecular equivalent of soluble fluorochrome) in normal eyes. Widely above these values in inflammatory ocular surface disorders Please cite statistics indicating the diagnostic value of the test.	Brignole et al 2004
Repeatability	Standardized technique reliable over time and from one laboratory to another	
Test problems	This procedure is highly technical and requires a laboratory equipped with a flow cytometer and a staff familiar with immunostaining processing and flow cytometry analysis on paucicellular specimens	
FORWARD LOOK	Many markers for a large variety of applications have yet to be tested with further improvement of pathophysiological knowledge of ocular surface diseases	
Glossary	HLA-DR: Major leukocyte antigen, human histocompatibility complex, class II cell surface receptor	

continued

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Appendix 17

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Maurizio Rolando	1st Nov 2004 11th Jan 2006
TEST	**Ferning Test (TFT)**	REFERENCES
TO DIAGNOSE	Quality of tears (electrolyte concentration), KCS, Hyperosmolarity	
VERSION of TEST	[V1] Tear ferning test (tear collection by rod) [V2] Tear collection by glass capillary)	Rolando 1984 Norn 1994
DESCRIPTION	A drop of tears is collected from the lower meniscus and dropped onto a microscope slide and allowed to dry by evaporation. Different forms of branching crystallization patterns can be observed and classified. The tear ferning test permits separation of normal from dry eyes on the basis of the ferning patterns.	Golding et al 1994 Rolando 1986-1988 Pearce, Tomlinson 2000
CONDUCT of TEST	1. The subject is seated, with the head resting comfortably, in a dim light. 2. With the eyes in upgaze, by means of a micropipette, nearly 1 microliter of tears is collected by capillarity from the lacrimal river of the lower meniscus. 3. The fluid is then dropped onto a microscope slide and exposed to evaporation at 20 ±3 C° for 10 minutes 4. The sample is then observed under a microscope at x 100-400 enlargement (better visibility is achieved with phase contrast microscopy) 5. The patterns of crystallization (ferning) are classified in 4 classes: Type 1: uniform large arborization, Type 2: ferning abundant but of smaller size; Type 3: partially present incomplete ferning; Type 4: no ferning. Types 1 & 2 are reported to be normal and Types 3 & 4 reported to be abnormal	Rolando 1984-1986
Web Video	Not available	
Materials	• capillary glass • clean microscope slides [ ] • light microscope (Phase contrast useful but not necessary)	
Standardization	Time of day: [any] Temperature: [20-28°C] Humidity: [high humidity slows down the time of appearance of the ferns] Air speed: [the effect of excessive air speed has not been studied but increasing the evaporation rate could affect the pattern of ferning]. Illumination: [the level of illumination seems irrelevant in the development of ferning patterns once the sample has been collected and dropped] Other: [Avoid excessive light and lid margin contact in order to decrease reflex tearing.]	
Variations of technique	In the original version, [V1] tear collection was acheived by capillary attraction by means of a 0.5 mm rod loop placed in contact with tears pooled in the lower fornix of the cul de sac The second version uses a capillary tube in contact with the fluid of the lower meniscus. This increases reproducibility, with a coefficient of variation of 6.4%.	Norn 1994
Diagnostic value	This version: [ ] Other version: [2] prognostic value 86.6%	Albach et al 1994
Repeatability	Intra-observer agreement. [Intraobserver agreement of 94.50% (kappa = 0.76; CI = 0.67-0.86). -] Inter-observer agreement. [Interobserver agreement 92.10% (kappa = 0.65; CI = 0.56-0.75]	Pensyl and Dillehay 1998
Sensitivity	(true positives) [82.2%] [Cut off: Type III or worse according to the previously reported classification 6-7)	Albach et al 1994
Specificity	(100 – false positives) [92.5%]	Albach et al 1994
Other Stats	94% sensitivity 75% specificity [Cut off: Type III or worse according to the previously reported classification 6-7] 92% sensitivity 83% specificity [Cut off: Type III or worse according to the previously reported classification 6-7]	Norn 1994 Rolando 1986

continued

APPENDIX 17 *continued*		
Test problems	Care should be taken not to elicit reflex tearing during collections Light microscopy is often unavailable in the office. In spite of a good clinical ability of separating normal from dry eyes, the real meaning of the results is not known [Test affected by extreme conditions of temperature and humidity]	
Forward Look	It would be interesting to explore the correlation between the patterns of crystallization (test types I to IV) and the level of tear film osmolarity	
Glossary	TFT: Tear ferning test	

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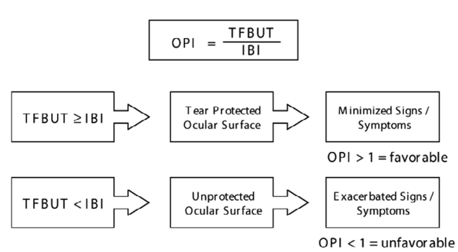
APPENDIX 18

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Mark B. Abelson and George W. Ousler III	5th Nov 2004
TEST	Ocular Protection Index (OPI)	Ousler et al 2002
TO DIAGNOSE	Ocular Surface Protection Risk of ocular surface damage	
VERSION	[V1]	
DESCRIPTION	The principle of the test is that when the tear film break up time (TFBUT) is shorter than the blink interval (IBI), the eyes are exposed to the risk of focal ocular surface damage. The Ocular Protection Index (OPI) is the ratio of the TFBUT and IBI (TFBUT/IBI). If the OPI score is < 1, then a patient's cornea is at risk of exposure and if the OPI score is ≥ 1, it's not.	Ousler et al 2002
General note	When studying the relationship between TFBUT and the inter-blink interval (IBI = time between complete blinks), it may be suggested that their interaction assists in regulating the integrity of an ocular surface. For example, the ocular surface is protected when the TFBUT either matches or exceeds than the IBI. In contrast, the surface is unprotected surface when the TFBUT is less than the IBI. This relationship can be clinically relevant since repeated, intermittent exposures of a tear film deficient cornea lead to symptoms and signs such as keratitis and redness. An index known as the Ocular Protection Index (OPI) can be used to quantify the interaction between the IBI and TFBUT. The OPI is calculated by dividing TFBUT by the IBI. If the OPI score is < 1, a patient's cornea is at risk for exposure, and if the OPI score is ≥ 1, it's not. This approach to measuring alterations in TFBUT has proven to be useful in assessing factors that cause dry eye and evaluating therapies.	
CONDUCT of TEST	1. Complete a visual count of the number of blinks per minute while your patient reads the ETDRS chart; 2. Calculate IBI = 60 divided by the number of blinks per minute; 3. Measure TFBUT; 4. Divide TFBUT by the IBI to determine OPI score – Ocular Protection Index (OPI) 	Ousler et al 2002
Web Video	Not available	
Materials	Blink Rate Recorder – • ETDRS chart or standard visual task; TFBUT Measurement – • Non-preserved, 2% sodium fluorescein; • Micro-pipette; • *Or* D.E.T. strip.	See TFBUT template for details of TFBUT test
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√]	
Diagnostic value	OPI Score ≥ 1 = protected ocular surface OPI Score < 1 = unprotected ocular surface	Ousler et al 2002 Abelson et al 2002
Glossary	OPI = Ocular Protection Index: TFBUT =Tear film break-up time: IBI = Inter-blink Interval:	

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APPENDIX 19

DEW	DRY EYE DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Alan Tomlinson	10th Jan 2006
TEST	**Fluorophotometry (Fluorimetry) – Tear Flow**	
DIAGNOSES	Changes in tear flow in aqueous tear deficiency (ATD).	REFERENCES
VERSION of TEST	[Version 1] Scanning automated fluorophotometry (Fluorotron Master, Coherent Inc, Palo, Alto, CA)	
DESCRIPTION	To calculate tear flow from measurements of tear volume and turnover.	
CONDUCT of TEST	**Tear Turnover Rate** 1) Subject is seated at the chin rest of the Fluorotron (with the anterior segment adapter fitted). Horizontal and vertical adjustments are made to align the subject's eye in the instrument's optic beam. 2) Three scans are conducted to establish the intrinsic corneal autofluorescence. 3) A 1 μl drop of 2% sodium fluorescein is instilled into the lower fornix with a pipette. 4) Initial scans are taken 1 minute post instillation, then at 2 minute intervals for a further 20 minutes. 5) The intrinsic corneal autofluorescence value is substracted from all values obtained from tear film fluorescence, prior to data analysis. 6) Fluoroscein concentration at each time point is calculated from the Fluorotron scans obtained at all time points beyond 4 minute post instillation, to avoid initial reflex tearing caused by instillation. 7) The decay in fluorescence is calculated from the log of the curve obtained from the formula: $T_0(t_0) = 100 \frac{[C_t(t_0) - C_t(t_0+1]}{C_t(t_0)}$ (%/min) Where Ct(t) = fluorescein concentration in tear film at time t(min). Assuming a monophasic decay of fluorescence from 5 mins post instillation with a decay time constant β (min^{-1}): $C_t(t) = C_t(0).e^{\beta t}$ (ng/ml) the following is obtained: $T_t(t_0) = 100 (1 - e^{\beta t})$ (%/min) This calculation can be carried out using the software package ANT_SEGMENT tear. **Tear Volume** 1) Subject is seated at the chin rest of the Fluorotron (with the anterior segment adapter fitted). Horizontal and vertical adjustments are made to align the subject's eye in the instrument's optic beam. 2) Three scans are conducted to establish the intrinsic corneal autofluorescence. 3) One μl of 2% sodium fluorescein is instilled into the lower fornix with a pipette. 4) Initial scans are taken 1 minute post instillation, then at 1 minute intervals for a further 4 minutes. 5) The intrinsic corneal autofluorescence value is substracted from all values obtained from tear film fluorescence, prior to data analysis. 6) Fluorescein concentration at each time point is calculated from all the Fluorotron scans obtained. 7) The decay in fluorescence is calculated from the log of the curve obtained from the formula: $T_0(t_0) = 100 \frac{[C_t(t_0) - C_t(t_0+1]}{C_t(t_0)}$ (%/min) Where $C_t(t)$ = fluorescein concentration in tear film at time t(min). Assuming a monophasic decay of fluorescence from 5 mins post instillation with a decay time constant β (min^{-1}): $C_t(t) = C_t(0).e^{\beta t}$ (ng/ml) the following is obtained: $T_t(t_0) = 100 (1 - e^{\beta t})$ (%/min) This calculation can be carried out using the software package ANT_SEGMENT tear. Tear volume is then calculated from: $V_t = (C_d.C_m^{-1}.k^{-1}-1) V_d$ Where C_d = fluorescein concentration in the drop C_m = initial fluoroscein concentration calculated by back extrapolation with the Fluorotron in ng/ml k = correction factor (k = 250) for the limited spatial resolution of the Fluorotron and V_d = drop volume in ml Calculation of tear flow: Tear flow = $\frac{V_t}{T_0(t_0)}$ (μl/min)	Kuppens 1992 Van Best 1995 Van Best 1995 Kuppens 1992 Van Best 1995 Kuppens 1992 Mishima 1965

continued

Appendix 19 *continued*		
Web Video	Not available	
Materials	Fluorotron Master 2% sodium fluorescein Mimims (Chauvin, UK) Air displacement pipette P2 Pipetman (Gilson, Villiers-le-Bel, France) Disposable sterile tips (Gilson, Villiers-le-Bel, France)	
Variations of technique	Varying concentrations and instillation volumes of fluorescein can be used, eg, 1% and 0.5 -2 µl.	
Standardization	Time of day [X] Temperature [ ] Humidity [ ] Air speed [still] Illumination [low ambient] Other: [Blink is initiated immediately prior to scan to ensure uniform tear thickness]	Pearce et al 2000
Diagnostic value	This version: [ ] Determination of tear flow an indication of aqueous tear deficiency. To obtain estimate of tear drainage from eye. Other version: [ ]	Mathers, Daley 1996 Mathers et al 1996 Gobbels et al 1992
Repeatability	*Intra-observer variation. [Not significant]* *Inter-observer variation. [Not significant]*	Mishima et al 1966 Van Best 1995
Test problems	High cost of basic equipment. Time required for measurement. Indirect (surrogate) measures of tear outflow and volume as it is assumed that fluorescein and aqueous tear are eliminated at the same rate from the eye. Absorption of fluorescein into the ocular tissue may be a factor in dry eye patients and may decrease apparent rate of decay.	
Test solutions	Use of high molecular weight conjugates.	McNamara et al 1998
Forward Look	Production of a cheaper automated scanning fluorophotometer. Development of reduced test incorporating 6 measurements for total of 10 minutes (tear turnover). Combination of tear flow (µl/min) with evaporation rate (µl/min) gives a value of “total tear flow” in the eye and an estimate of total tear production. This allows analysis of the proportion of tears eliminated by evaporation and/or drainage in various forms of dry eye.	Pearce et al 2000 Mathers, Daley 1996 Mathers 2004

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APPENDIX 20

DEW	**DRY EYE: DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Stephen Kaye	18th April 2006
TEST	**Tear Function Index (*Liverpool modification*)** Email: TFI@clineng-liverpool-nhs.com	
TO DIAGNOSE	To evaluate the tear dynamics of production and drainage and detect subjects suffering from dry eye	Ono et al 1991 Xu et al 1995(a) Xu et al 1995(b) Kaye et al 2001
VERSION of TEST	The test is a modification of that described by Xu et al. (1995) and depends on using prepared filter paper strips containing fluorescein. The test has been designed to allow direct measurement of the TFI using prepared tear strips.	Kaye et al 2001
DESCRIPTION	TFI is the quotient of the Schirmer test value and the Tear clearance rate (TCR).	
CONDUCT of TEST	A fluorescein-coated tear strip is placed over the lower lid margin at the junction of the middle and lateral third of the lid. 1. The eye is closed and the strip is left in place for 3 minutes 2. On removal, the distance from the strip notch to the wetted dye front is recorded, using the scale provided. 3. The strip is air dried and 4. The intensity of staining is compared with that of the calibrated panel of dilutions, (ranging from 1:1 to 1:128), to determine the TCR. 5. The TFI is defined as the quotient of the Schirmer test and the TCR.	
Web Video	Not available	
Materials	• The standard kit provides a cardboard envelope, containing a docket with 4 see-through pouches. • Each pouch contains 4 sterile, single-use, fluorescein-coated tear-strips together with a calibrated colour scale for reference. • A ruled measurement scale is printed on the envelope, together with • a nomogram and • a set of instructions The kit, containing the prepared strips, together with instructions and calibrated measuring scale and colour scale are provided by the Dept. Clinical Engineering of the Royal Liverpool University Hospital, Prescot Street Liverpool L7 8XP. For further information: Email: TFI@clineng-liverpool-nhs.com	
Variations of technique	TFI as described by Xu et al (1995)	
Standardization	The procedure is standardised. Strips are calibrated for use in each pack.	
Diagnostic value	Identification of subjects suffering from aqueous tear deficiency, for instance in Sjögrens syndrome.	
Sensitivity	A TFI of less than 40 is 100% sensitive for patients with SS dry eye	Kaye et al 2001
Specificity	Patients with Sjögren's syndrome have a TFI upper 95% confidence interval of 15 (12 if anaesthetic has been used)	Kaye et al 2001
Other Stats	Less inter-ocular difference and less variability than the original method	Kaye et al 2001
Test problems	As with the Schirmer's test, it is uncomfortable. Also, staining of the ocular surface at the sites of strip contact with the conjunctiva occur after using fluorescein or Rose Bengal.	
FORWARD LOOK	Performing the TFI using prepared filter paper strips with the matched colour dilution is very sensitive for detecting patients with SS dry eye. The test can be used by non-ophthalmically trained personel. Subjects with a TFI of less than 40 can then be referred for an ophthalmic assessment.	
Glossary	TFI: Tear function index	

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Design and Conduct of Clinical Trials:
Report of the Clinical Trials Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT This report summarizes some universal concepts with regard to clinical trials in general and other issues pertaining to clinical trials specifically tailored to the study of therapeutic intervention in dry eye disease. The report also makes recommendations for logistical design and implementation of such trials. It identifies peculiarities of dry eye disease that complicate clinical trial design, such as the lack of correlation of signs and symptoms, as well as the likelihood of control interventions having a lubricant (placebo) effect. Strategies for environmental trials and controlled adverse environment trials are reviewed.

KEY WORDS clinical trials, DEWS, dry eye, Dry Eye WorkShop

I. INTRODUCTION

Clinical trials in dry eye disease represent a challenge to clinicians, epidemiologists, and biostatisticians, as well as to those seeking regulatory approval for medications or other therapies.[1] This report summarizes some universal concepts with regard to clinical trials in general and addresses other issues pertaining to clinical trials specifically tailored to the study of therapeutic intervention in dry eye disease. The level of evidence for supporting data from clinical trials is identified in the bibliography, according to the modified American Academy of Ophthalmology Preferred Practices guidelines. The report also makes recommendations for logistical design and implementation of such trials.

II. GOALS OF THE CLINICAL TRIALS SUBCOMMITTEE

The goals of the Clinical Trials Subcommittee were to systematically review literature, procedures, and concepts related to clinical trials in general, to consider special issues related to clinical trials involving therapeutic interventions in dry eye disease, and to present guidelines for successful conduct of clinical trials.

III. GUIDELINES FOR CLINICAL TRIALS IN GENERAL

Before a clinical trial is initiated, a state of equipoise must exist. In other words, there must be sufficient doubt about the effectiveness of the particular intervention under consideration to justify withholding it from a portion of the study subjects, and, at the same time, there must be sufficient belief in the therapeutic potential of the intervention to justify its exposure to the remaining portion of willing and eligible study participants. If these conditions are met, then a number of additional issues need to be considered in the design and conduct of the clinical trial so that valid results can be obtained (Table 1). Important processes include formulation of a concise and specific study question, specification of the primary outcome measure, statistical estimation of the necessary sample-size, specification of the length of follow-up and specific schedule for baseline and follow-up evaluations, selection of the study population, definition of the primary outcome measure, random allocation of the intervention(s)/treatment(s), establishment of strategies for maintenance of compliance with the allocated intervention(s)/treatment(s) and for achievement of high and balanced rates of follow-up. In addition, it is important to establish an organizational and decision-making structure and specific procedures for intake of data, and for patient safety monitoring.

A. Design

The most desirable design of a clinical trial is a prospective, randomized, double-masked, placebo- or vehicle- con-

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

Reprints are not available. Articles can be accessed at: www.tearfilm.org

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OUTLINE

trolled parallel group or crossover study. Other acceptable designs include equivalence or superiority trials to compare a new therapy to one that is already approved or in common use. Such trials must also be constructed as prospective, randomized, masked trials.[2-5] Parallel group studies should ideally provide for demographic and environmental climate or activity comparability. With large enough sample size, randomization will tend to ensure equal distribution of demographic characteristics across treatment groups. If there is a particular concern with regard to one or more demographic factors (eg, sex, age), then equal distribution of these factors across treatment groups can be achieved by randomizing in small blocks. Unfortunately, this technique generally is impractical to implement and adds considerably to the number of patients that must be screened to find suitable matches.

In general, crossover design trials have the benefit of using the patient as their own control but are fraught with confounding problems when, as with dry eye, the potential exists for the persistent effects of one treatment to outlast that of another. Also, if one treatment interferes with another, the sequential effects of the test medications or treatments could be confounding. Three assumptions are inherent in a crossover study:

1) The treatment does not cure the disease.
2) There is no carryover between periods.
3) In order to contribute to the analysis, all patients must complete all periods.

The perceived benefit of a crossover study over a parallel study is based upon an assumption that *intra*-patient variability is less than *inter*-patient variability. This is not always true. Washout periods with placebo treatment can be used to abrogate the lingering effects of prior therapy, but the duration of the washout period must be sufficient for effective washout, and the sufficient duration may be unknown or vary, depending upon the specific agents tested. Given these concerns, an important compensatory design strategy in crossover trials is to randomize the sequence of administration of the test agent and control agent, so that some individuals will receive the active therapy first, whereas others will receive the control therapy first.

Table 1. Attributes of well-designed clinical trial

1. Formulation of a concise and specific study question
2. Specification of a primary outcome measure
3. Statistical estimation of the necessary sample-size
4. Specification of the length of follow-up and specific schedule for baseline and follow-up evaluations
5. Selection of the study population
6. Definition of the primary outcome measure
7. Random allocation of the intervention(s)/treatment(s)
8. Strategies for maintenance of compliance with the allocated intervention(s)/treatment(s), and for the achievement of high and balanced rates of follow-up
9. Establishment of an organizational and decision-making structure
10. Specification of procedures for intake of data and for patient safety monitoring

B. Inclusion and Exclusion Criteria

Appropriate inclusion and exclusion criteria are essential to assure the integrity of the trial. Inclusion criteria should identify a number of appropriate variables specifically to define the population that will be studied (Table 2). Such criteria generally include 1) the ability of subjects to provide informed consent, 2) the ability to comply with the protocol, and 3) the existence of disease severity sufficient to demonstrate a statistically significant and clinically meaningful effect of therapy. Specific diagnostic criteria are usually defined to ensure homogeneity of disease status, which can lead to a more precise study.

Exclusion criteria may be used to exclude, for example, 1) subjects with concurrent disease that could confound the response to therapy, 2) subjects unlikely to comply with the protocol or likely to be lost to follow-up, and 3) subjects with known hypersensitivity or intolerance to the proposed therapy (Table 3).

When selecting inclusion and exclusion criteria, the

Table 2. Inclusion criteria for clinical trial

1. Subjects must be capable of providing informed consent.
2. Subjects must be able to comply with the protocol.
3. Disease severity must be sufficient to demonstrate a statistically significant and clinically meaningful effect of therapy.
4. Specific diagnostic criteria must be defined to ensure homogeneity of disease status, which can lead to a more precise study.
5. Subjects must be capable of responding to the proposed mechanism of action of the intervention to be studied

Table 3. Exclusion criteria for clinical trial

1. Subjects have concurrent disease that could confound the response to therapy.
2. Subjects are unlikely to comply with the protocol or likely to be lost to follow-up.
3. Subjects have known hypersensitivity or intolerance to the proposed therapy.
4. Subjects use concomitant therapy that affects either tear function or ocular surface integrity.
5. Subjects have had surgical or other manipulation of the eye that could confound the outcome parameters or interfere with the mechanism of action of the proposed intervention to be studied.

investigator should be aware of the inherent trade-offs between the internal validity of the trial and its generalizability to the larger population of people with the disease of interest. Minimally restrictive inclusion and exclusion criteria make recruitment easier and provide a wider basis for generalization of the study findings, but treatment effects may be obscured by heterogeneity of disease status.

C. Outcome Measures

The outcome measure used to compare treatments may be either a clinical event or a surrogate outcome measure. The primary outcome measure should be selected prior to the start of data collection, as its rate of occurrence will affect various aspects of the study design, including the length of the study and the sample size. Although some clinical trials have employed post-hoc analysis of outcome variables, regulatory agencies are often reluctant to accept such analyses in pivotal trials. However, it is appropriate for most trials additionally to collect and analyze information on a number of secondary outcome measures. These can provide further information that may contribute to the overall evaluation of the study treatments.

Surrogate outcome measures are measurable features of the disease that reliably reflect an outcome parameter that is clinically relevant but difficult to precisely determine. For example, measurement of frequency of required instillation of comfort drops can be a quantifiable surrogate subjective measure of frequency/duration of discomfort occurring during the day. Similarly, an objective surrogate measure of tear film osmolarity could be the electrical conductivity of a tear sample. The surrogate outcome measure must be validated as a reliable and relevant monitor of outcome, but it may be of special value in a condition such as dry eye, where the correlation of signs and symptoms is weak, and objective evidence of change in disease is needed.

D. Sample Size, Randomization and Data Analysis

The sample size of a clinical trial should be sufficient to allow for a statistically powerful analysis of the primary study hypothesis. It may also provide for statistical comparisons within subgroups, if this is considered desirable or necessary to clarify the therapeutic response. It is essential that the trial be of sufficient size to provide power to detect a clinically meaningful treatment effect, as well as a statistically significant effect. Statistical analysis must be appropriate for the size, design, outcome measure(s), and duration of the study. The power to detect a given difference between treatments is directly proportional to the sample size and treatment difference, and indirectly proportional to the alpha level and variability. A key factor is the study planners' selection of a clinically significant difference. Then, they can determine the required number of patients to detect a difference that is at least that large, given that it exists.

Randomization to test or control treatment is generally the best strategy available in clinical trials to guard against treatment selection bias. There are numerous methods for establishing randomization. Today, most researchers use computer-generated randomization lists, which may be further stratified by study site and a pre-study characteristic (eg, disease severity). A written description of the randomization scheme used to generate treatment allocations should be recorded. This description should include sufficient detail to allow a person to reproduce the allocation schedule, and the assignment process should establish a clear audit trail.

Treatment assignments should be masked to the patient, physician, and the person issuing the assignment, until the patient has been officially enrolled and randomized into the study. Preferably, the study should be masked for patients and physicians until it is completed. This may be easiest to implement if assignments are issued by a person or group located outside of the clinic. Investigators should also be aware, particularly in small studies, that a randomization bias could occur that must be controlled or evaluated. The baseline characteristics of the study groups may also vary by chance, and if large enough, such differences can impact treatment comparisons. The strategy for the analysis of clinical trial data must be outlined in advance and must accommodate the form of the specified outcome variable(s) with appropriate methods of analysis.

The key feature in the analysis of clinical trials is adherence to the principle of "intention-to-treat." That is, the primary analysis of data in a trial must be conducted by classifying study subjects based on the original treatment to which they were assigned, regardless of the treatment they actually received or their adherence to the study protocol (Table 4). Good clinical practice dictates that assessment of qualifying patients and visits be made by the clinical management (ie, organization team) prior to unmasking of the treatment assignment. Furthermore, it should be stated a priori in the protocol and statistical analysis plan which

Table 4. Data analysis: populations to analyze

1. Intent to Treat (ITT): All subjects randomized.
2. Modified Intent to Treat (Mod ITT): All subjects randomized who received at least one dose of medication
3. Per Protocol (PP): All subjects randomized who completed the treatment according to protocol

population is primary.

Statistical methods can be used to address missing data, eg, *last observation carried forward* (**LOCF**) or end-point substitution. Ideally, the efficacy and safety results from all populations will be in general agreement. However, differences may occur, for example, when subjects drop out due to efficacy failure or safety issues. Treatment cross-over, poor compliance, and loss to follow-up are key threats to the validity of a clinical trial, and every effort should be made to ensure adherence to the study protocol and follow-up that is as complete as possible. In the presence of losses to follow-up, a series of analyses are usually conducted under various assumptions regarding the rate of events among patients lost to follow-up. Similarly, secondary analyses can account for treatment received, as well as for differences in compliance, but these are not a substitute for the primary "intention-to-treat" analysis.

Basic analytic methods for clinical trials can be found in any number of biostatistical textbooks and other resources. Outcome analyses based on comparisons of the proportion of patients who have experienced the outcome of interest are a common method for analyzing trial data. They are generally valid as long as the intensity of follow-up is comparable in the two treatment groups, losses to follow-up are low, and the treatment groups have comparable baseline characteristics.

Statistical evaluation of the difference in proportions can be carried out using Fisher's exact test, or a chi-square test, if appropriate. However, simple analysis of the proportion of patients who experience the outcome fails to take into account the length of follow-up. This may become important in the setting of many clinical trials in which patients are recruited over an extended period of time and then followed through a specific calendar time point, resulting in varying lengths of patient follow-up. Analysis of data from such studies is usually approached using lifetable analyses methods, which provide a statistical means of dealing with the variable lengths of follow-up. Adjustment for differences in baseline characteristics can be approached by either stratification or multivariable analysis. Investigators should be aware that the issue of what constitutes statistical significance is complex, and they should interpret *P*-values with caution, particularly as most trials will provide data on a number of outcome measures. These statistical comparisons cannot be considered to be mutually independent. Consideration of appropriate adjustment for multiple comparisons is imperative.

E. Administration of a Clinical Trial

Organization and administration of a clinical trial is critical to success. An organizational structure is desirable for large, multi-center clinical trials. An exemplary organizational chart is shown in Figure 1.

Advance preparation and written standardized procedures are needed for each step in the conduct of a clinical trial in order to avoid the high risk of error or missing data. Appendices cited at the end of this chapter can be accessed at: www.tearfilm.org. A Manual of Procedures should be prepared. Elements of an adequate manual are listed in Appendix 1.[6-11]

Standards of Good Clinical Practice should be exercised for quality assurance. Guidelines for sponsors and investigators are detailed in Appendix 2 and include observation of regulatory requirements, including 1) sponsor's role, 2) investigator's role, 3) clinical and functional investigation laboratory's role, 4) ethics committee or committee for the protection of persons, 5) International Conference on Harmonization, and 6) regulatory guidelines.[12-30] It is appropriate to prepare an Investigator's Brochure for the tested drug (Appendix 3).[31] Use of the investigational medical product should be outlined (Appendix 4).[32-36] Adverse events and their management should be identified (Appendix 5).[37-43] The ethics approval process should be conducted through institutional or designated Institutional Review Boards appropriate to the investigator. Data from clinical trials should be made available after completion of the study and data analysis.[43]

IV. GUIDELINES FOR CLINICAL TRIALS IN DRY EYE DISEASE

General considerations for clinical trials in dry eye disease incorporate the key concepts delineated for clinical trials in general. Clinical trials in dry eye disease can include prospective environmental and prospective challenge designs. A protocol customized to the hypothesized mechanism of action of the drug or intervention to be tested is desirable.

An environmental trial should embrace the general design guidelines listed above with prospective, randomized, double-masked, placebo/vehicle controlled features. There should be adequate duration of study to demonstrate efficacy and safety.

Inclusion and exclusion criteria should identify a potentially responsive population and be selected to avoid or minimize regression to the mean or observation bias. This approach should exclude: 1) the presence or absence of any ocular surface disease that would cause dry eyes other than the condition for which the drug or device is being tested; 2) the presence or absence of a dry eye-associated systemic disease other than the primary condition causing dry eyes; 3) use of systemic medications with possible influence on the tear film, tear secretion, or ocular surface; 4) use of concomitant or previous topical eye medications that would alter the effect of the drug or device being evaluated; 5) history of previous ocular surgery, including refractive surgery, eyelid tattooing, eyelid surgery, or corneal surgery; 6) the presence or absence of associated meibomian gland disease appropriate to study parameters; and 7) the presence or absence of contact lens wear. When patients are on a stable regimen of lubricant therapy that does not specifically interfere with the mechanism of action of the formulation of drug or intervention to be tested, it may be acceptable to enroll such patients while they continue the uninterrupted use of their background management.

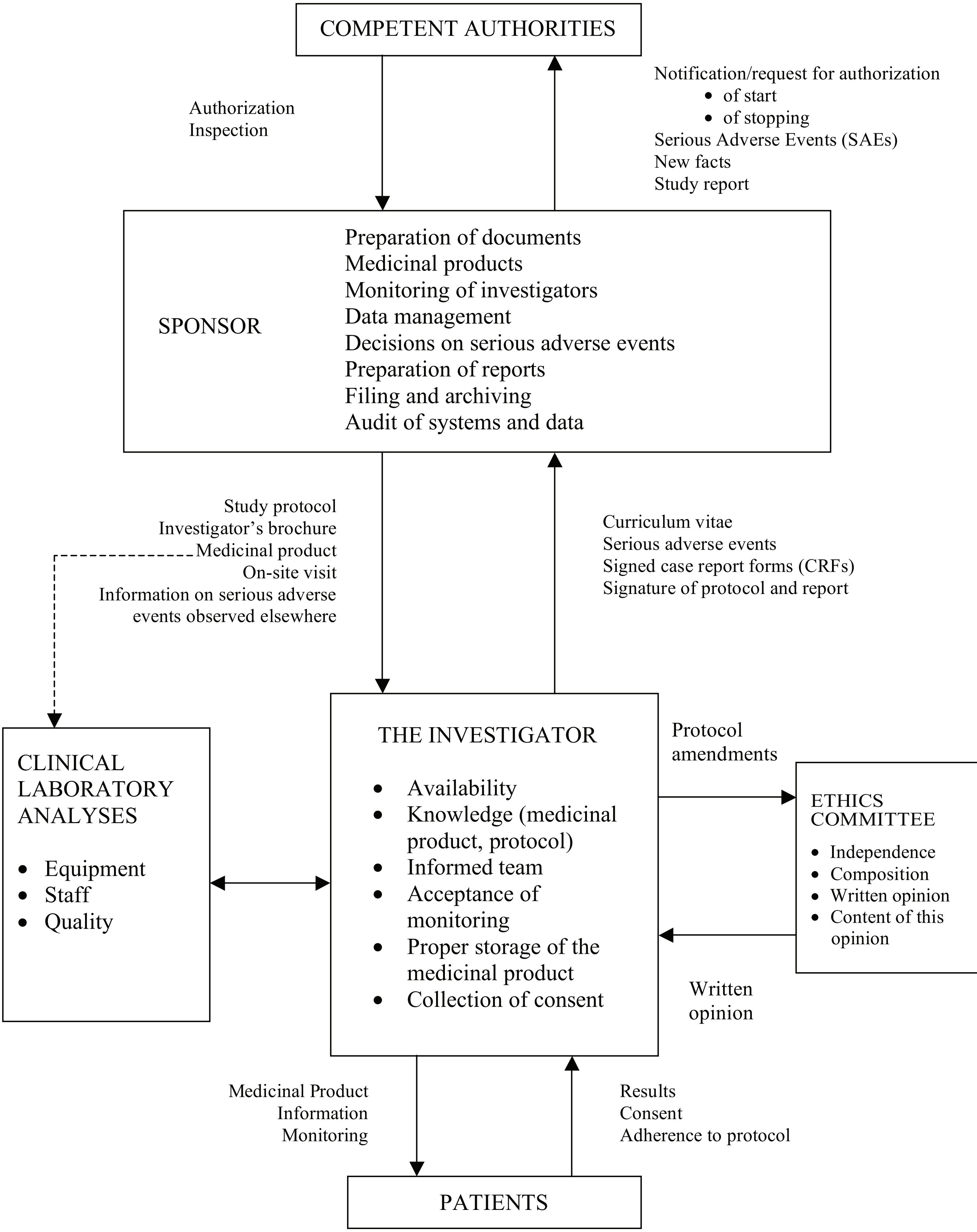

Figure 1. Overall organization of the clinical trial. Reprinted with permission from: Spriet A, Dupin-Spriet T. Clinical trials and quality (chapter 1), in *Good practice of clinical drug trials*. Switzerland, Karger, 2005, ed 3, p 7.

Monitoring the use of the background therapy would be required, however.

Sample size should be sufficient to allow valid statistical analysis and sub-group statistical comparisons, if necessary. It should provide statistical power to support the conclusions of the study. If the conclusions of the study are equivalence of the two treatment groups, then consideration of the power of the study to detect a clinically significant difference is important. Typically, a minimum of 80% power (beta) is required. Levels of disease severity should be recognized and evenly distributed so as not to skew study outcomes toward a possible positive or negative therapeutic response. The ability of subjects to comply with and complete the study should be verified.

A controlled adverse environment (**CAE**) design can be used to control the environment, the subjects' activities, or a combination of both during the clinical trial, thereby providing a stressful environment to exacerbate clinical symptoms and signs of dry eye.[44] Such a stress test is especially valuable in establishing a pharmacological effect in a short period of time. Humidity, temperature, and air-flow are environmental variables that can be monitored and manipulated. Activities can include visual tasks, and the blink rate and tear film stability can be monitored. The trial design should embrace features of a prospective, randomized, masked (to the extent possible), controlled study. Recognition of possible patient adaptation to the conditions of the environmental challenge requires corrective adjustment in data analysis.[45,46] When selecting a patient population based upon the naive response to the challenge environment, such selection may reduce the generalizability of the conclusions of the study to the entire dry eye population.

V. OBSERVATIONS FROM PREVIOUS CLINICAL TRIALS IN DRY EYE

A. Peculiarities of Clinical Trials in Dry Eye

Symptoms and signs have been observed to be closely related in some trials and not in others. Most drug trials have shown a disparity in signs and symptoms.[47-76] There is a prominent apparent placebo or vehicle response in most clinical trials evaluating a topical therapy for dry eye disease.[1] Although placebo effects have been observed in numerous trials that evaluate symptoms, there is also a notable placebo response for objective parameters observed in clinical trials for dry eye. Explanation for this prominent placebo response is not clear, but it may be partially explained by regression to the mean. Most previous clinical trials define entry criteria as a minimal level of severity in outcome parameters. Although this maneuver assures a level of severity to allow demonstration of a measurable effect, it also predisposes to regression to the mean.

The moisturizing and lubricant effect of any topically applied control may also provide an improvement from baseline in manifestations of dry eye disease. Participation in a clinical trial alone has been shown to improve compliance.[3,5] The improvement observed in both control and active trial groups after randomization to a therapy may reflect both subject and observer anticipation and desire for a favorable effect of any proposed therapy. This phenomenon has been termed "expectation of randomization" and may influence the response to either treatment assigned.

B. Evaluation and Outcome Parameters

A review of the literature reveals that Schirmer test, tear film breakup time (**TFBUT**), vital staining scores, and symptoms of discomfort are the most common endpoints used in clinical trials of dry eyes. There was also a wide range of markers used in different trials, depending on the nature of the drug, ie, tear substitutes, anti-inflammatory drugs, and secretagogues. One observation from this review was that the duration of trials was relatively short, varying between 6-8 weeks in trials involving tear substitutes and longer in trials involving anti-inflammatory agents or secretagogues (8-12 weeks with follow-up durations varying between 3-12 months).

Other than the above-mentioned endpoints, trials involving anti-inflammatory agents used tests, biomarkers, and endpoints that included impression cytology (goblet cell numbers, epithelial morphology, and expression of HLA DR, CD3,4,8, 40, Apo2.7, and cytokine profiles). Trials of secretagogues looked at osmolarity, MUC 1, 2, 4 and 5AC mRNA expressions, as well. Apart from the common endpoints mentioned above, trials on devices involving tear retention, such as goggles and punctal plugs, took into consideration the tear clearance rate, tear osmolarity, and tear functional index (**TFI**), as well as standardization of environmental humidity and temperature. These parameters have been used for evaluation of therapies with 1) artificial tears[47-52]; 2) anti-inflammatory agents, including corticosteroids[53,54] and cyclosporine[55-61]; 3) autologous serum [62-66]; secretagogues, including those for aqueous[67-72] and mucin[73-78] stimulation; 4) devices[79-86]; and miscellaneous therapy.[87-88]

C. Suggested Attributes of Clinical Trials in Dry Eye

Inclusion criteria for clinical trials in dry eye should identify, based upon the mechanism of action of the proposed treatment or intervention, a potentially responsive population in which the treatment or intervention is likely to demonstrate efficacy. Inclusion and exclusion criteria should select a specific population that avoids or minimizes confounding variables and regression to the mean. Exclusion criteria are detailed in Section IV above.

A protocol customized to the mechanism of action of the drug or intervention to be tested is most appropriate. Outcome variables should be selected consistent with the mechanism of action of the drug or intervention being tested. The Subcommittee strongly advises inclusion of biomarkers and/or surrogate markers of disease status for future trials, as appropriate with the continued development of technology, but recognizes that validation of such surrogate markers will be needed. For example, increased osmolarity of the tears is an established marker of dry eye, and there are several possible methods of measurement.

Surrogate markers may be direct or correlative. Direct surrogate markers are those that derive from the same physical or chemical properties as the primary marker, eg, tear conductivity as a measure of tear osmolarity. Correlative surrogate markers are those that correlate with the primary marker but can be produced by other mechanisms as well, eg, a single inflammatory cytokine level as a marker of inflammation.

In dry eye disease, in which variability of a sign or symptom can be greatly influenced by environmental or visual task activities at any given point in time, the measurement of reliable, durable surrogate markers of disease activity should be considered as a valid measure of effectiveness of any given therapy or intervention. The outcome measures should be measurable with adequate accuracy and reproducibility. Measurement of the primary outcome parameter should be accomplished with a well-validated test. This is true for clinical signs of disease and surrogate measures, as well as for symptoms of discomfort and visual disturbance.[89-96] The primary outcome variable may be a symptom or a sign for valid outcome analysis, but regulatory approval may require both in some countries. Symptoms should be graded in a well-defined scoring system, such as the visual analog scale (**VAS**) or with Likert scores.[2,97]

In recognition of the prominence of placebo and vehicle response in clinical trials in dry eye, the Subcommittee made several observations. Because a true placebo has not been found that lacks inherent lubricant effect, consideration of a non-treatment arm could be considered. Although such a design has limitations of possible institutional review board constraints, and given that patients may be prone to intermittent use of over-the-counter lubricants that could confound the outcome, consideration of such a design has merit. In the absence of such a protocol, the Subcommittee recommends consideration of 1) a randomized, masked trial, in which the initiation of treatment is also masked both to investigator and subject, or 2) a withdrawal study, in which all patients initially receive active medication, followed by randomization to vehicle. One benefit of such a design is that all subjects receive active medication at some point in the trial, and this may serve to improve willingness of subjects to enroll in a well-designed trial.

The Subcommittee recommends inclusion of the following outcome parameters:

1. An objective measure of visual function (eg, Functional Visual Acuity);
2. Determination of tear volume and production (eg, Schirmer test or fluorescein dilution test);
3. Determination of tear stability (eg, tear breakup with fluorescein TFBUT or a non-invasive TFBUT device such as videokeratography)[96];
4. Measurement of tear composition (eg, osmolarity, determination of specific protein content, or the measurement of inflammatory mediators in tears);
5. Measurement of ocular surface integrity.

There is consensus that the determination of ocular surface integrity is at this time best performed by staining of the ocular surface with fluorescein and lissamine green or rose bengal (see parameters from the Diagnostic Methodology Subcommittee Report in this issue for appropriate concentrations and use of barrier filters),[98] although the limitations of such evaluation have been documented in previous clinical trials.[58,69,76] A standardized grading system should separately grade corneal and conjunctival staining and record individual area scores, as well as combined area scores, for analysis (see the Diagnostic Methodology Subcommittee Report for appropriate grading system).[98] The grading system should allow for one or two dots of staining in the inferonasal quadrant of the cornea, because such staining may occur in normal subjects.[99-107] Staining of the conjunctival caruncle and semilunar fold should not be counted, as this occurs in a majority of normal subjects.[101]

Other tests that could be used as outcome measures in specific protocols might include impression cytology and flow cytometry (for selected trials, see parameters from the Diagnostic Methodology Subcommittee Report for appropriate method and staining procedure).[98] Technological advances in measurement of tear film stability, measurement of the tear meniscus volume, or measurement of ocular surface protection and epithelial permeability may in the future allow more precise determination of tear function and ocular surface integrity. However, at present, they are not well validated in clinical trials.

Outcome analysis in a multi-factorial disease with several clinical parameters of tear film abnormality, ocular surface damage, and functional impairment may be amenable to composite indices of disease severity. This approach has been utilized in evaluation of rheumatic disease, with consensus development of the American Congress of Rheumatology (ACR) indices (ACR50 and ACR70) that evaluate multiple descriptors of disease severity. Currently, there has been inadequate evaluation of such composite indices in dry eye disease, and validated indices are not available. The committee identifies as a need and an area for future deliberation the development and validation of such indices for evaluation of dry eye disease.

Appropriate and carefully planned statistical analysis is critical in evaluating clinical trial data. The analysis strategy will depend on the primary outcome variable selected for the trial, and it must be chosen prior to the beginning of data collection. The general principle of the intent-to-treat analysis should be adhered to for the primary analysis of data.

VI. FEATURES TO FACILITATE MULTICENTER AND INTERNATIONAL COLLABORATIVE CLINICAL TRIALS

The Subcommittee recommends the development of criteria to be used in multinational venues. Important aspects to consider for such international trials are the use of uniform terminology. This may require that terms are translated and back-translated for clarity and accuracy.

It is necessary to resolve cultural or ethnic connotations or implications in terminology. There should be uniform interpretation of outcome variables with standardized protocols for measurement and recording of data. Testing procedures should be uniform, with use of standardized reagents, standardized protocols, and consistent recording of results. It is necessary to maintain skill levels of data collectors and observers, including certification of investigators and research coordinators and technicians. Attempts should be made to reduce biases related to population differences (race, ethnicity, climatic).

These appendices can be accessed at www.tearfilm.org:

- Appendix 1. *Outline of a manual of procedures*
- Appendix 2. *Guidelines for Good Clinical Practices*
- Appendix 3. *Writing the Investigator's Brochure for the tested drug*
- Appendix 4. *Using the investigational medicinal product*
- Appendix 5. *Adverse events and management issues*

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Management and Therapy of Dry Eye Disease:

Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT The members of the Management and Therapy Subcommittee assessed current dry eye therapies. Each member wrote a succinct evidence-based review on an assigned aspect of the topic, and the final report was written after review by and with consensus of all subcommittee members and the entire Dry Eye WorkShop membership. In addition to its own review of the literature, the Subcommittee reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on Dry Eye. The Subcommittee favored the approach taken by the ITF, whose recommended treatments were based on level of disease severity. The recommendations of the Subcommittee are based on a modification of the ITF severity grading scheme, and suggested treatments were chosen from a menu of therapies for which evidence of therapeutic effect had been presented.

KEYWORDS DEWS, dry eye disease, Dry Eye WorkShop, management, therapy

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

Reprints are not available. Articles can be accessed at:www.tearfilm.org.

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I. INTRODUCTION

This report summarizes the management and therapeutic options for treating dry eye disease. The level of evidence for supporting data from the literature is evaluated according to the modified American Academy of Ophthalmology Preferred Practices guidelines (Table 1).

II. GOALS OF THE MANAGEMENT AND THERAPY SUBCOMMITTEE

Goals of this committee were to identify appropriate therapeutic methods for the management of dry eye disease and recommend a sequence or strategy for their application, based on evidence-based review of the literature.

The quality of the evidence in the literature was graded according to a modification of the scheme used in the American Academy of Ophthalmology Preferred Practice Patterns series. When possible, peer-reviewed full publications, not abstracts, were used. The report was reviewed

Table 1. Evidence grading scheme

Clinical Studies	
Level 1.	Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches.
Level 2.	Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more center, or a well-designed study accessible to more rigorous statistical analysis.
Level 3.	Evidence obtained from one of the following: descriptive studies, case reports, reports of expert committees, expert opinion.
Basic Science Studies	
Level 1.	Well-performed studies confirming a hypothesis with adequate controls published in a high-impact journal.
Level 2.	Preliminary or limited published study.
Level 3.	Meeting abstracts or unpublished presentations.

This evidence grading scheme is based on that used in the American Academy of Ophthalmology Preferred Practice Pattern series.

OUTLINE

by all subcommittee members and by the entire Dry Eye WorkShop membership. Comments and suggested revisions were discussed by the subcommittee members and incorporated into the report where deemed appropriate by consensus.

III. ASSESSMENT OF CURRENT DRY EYE THERAPIES

A. Tear Supplementation: Lubricants

1. General Characteristics and Effects

The term “artificial tears” is a misnomer for most products that identify themselves as such, because they do not mimic the composition of human tears. Most function as lubricants, although some more recent formulations mimic the electrolyte composition of human tears (TheraTears® [Advanced Vision Research, Woburn, MA]).[1,2] The ocular lubricants presently available in the United States are approved based on the US Food and Drug Administration (**FDA**) monograph on over-the-counter (**OTC**) products (21 CFR 349) and are not based on clinical efficacy. The monograph specifies permitted active ingredients (eg, demulcents, emulsifiers, surfactants, and viscosity agents) and concentrations, but gives only limited guidance on inactive additives and solution parameters. Certain inactive ingredients that are used in artificial tears sold in the US (eg, castor oil in Endura™ [Allergan, Inc., Irvine, CA] and guar in Systane® [Alcon, Ft Worth, TX]) are not listed in the monograph.

It is difficult to prove that any ingredient in an ocular lubricant acts as an active agent. If there is an active ingredient, it is the polymeric base or viscosity agent, but this has proved difficult to demonstrate. This is either because it is not possible to detect the effects or differences in clinical trials with presently available clinical tests or because the currently available agents do not have any discernable clinical activity beyond a lubrication effect. Although certain artificial tears have demonstrated more success than others in reducing symptoms of irritation or decreasing ocular surface dye staining in head-to-head comparisons, there have been no large scale, masked, comparative clinical trials to evaluate the wide variety of ocular lubricants.

What is the clinical effect of ocular lubricants or artificial tears? Do they lubricate, replace missing tear constituents, reduce elevated tear film osmolarity, dilute or wash out inflammatory or inflammation-inducing agents? Do they, in some instances, actually wash out essential substances found in normal human tears? These questions remain to be answered as more sensitive clinical tests become available to detect changes in the ocular surface.

The foremost objectives in caring for patients with dry eye disease are to improve the patient’s ocular comfort and quality of life, and to return the ocular surface and tear film to the normal homeostatic state. Although symptoms can rarely be eliminated, they can often be improved, leading to an improvement in the quality of life. It is more difficult to demonstrate that topical lubricants improve the ocular surface and the tear film abnormalities associated with dry eye. Most clinical studies fail to demonstrate significant correlation between symptoms and clinical test values or between the clinical test values themselves.[3-5] It is not unusual for a dry eye with only mild symptoms to show significant rose bengal staining. Until agents are developed that can restore the ocular surface and tear film to their normal homeostatic state, the symptoms and signs of dry eye disease will continue.

Ocular lubricants are characterized by hypotonic or isotonic buffered solutions containing electrolytes, surfactants, and various types of viscosity agents. In theory, the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate, and other electrolytes and have a polymeric system to increase its retention time.[1,6-8] Physical properties should include a neutral to slightly alkaline pH. Osmolarities of artificial tears have been measured to range from about 181 to 354 mOsm/L.[9] The main variables in the formulation of ocular lubricants regard the concentration of and choice of electrolytes, the osmolarity and the type of viscosity/polymeric system, the presence or absence of preservative, and, if present, the type of preservative.

2. Preservatives

The single most critical advance in the treatment of dry eye came with the elimination of preservatives, such as benzalkonium chloride (**BAK**), from OTC lubricants. Because of the risk of contamination of multidose products, most either contain a preservative or employ some mechanism for minimizing contamination. The FDA has required that multidose artificial tears contain preservatives to prevent microbial growth.[10] Preservatives are not required in unit dose vials that are discarded after a single use. The widespread availability of nonpreserved preparations allows patients to administer lubricants more frequently without concern about the toxic effects of preservatives. For patients with moderate-to-severe dry eye disease, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants. The ocular surface inflammation associated with dry eye is exacerbated by preserved lubricants; however, nonpreserved solutions are inadequate in themselves to improve the surface inflammation and epithelial pathology seen in dry eye disease.[11]

Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations, as well as in topical lubricants. Its epithelial toxic effects have been well established.[12-17] The toxicity of BAK is related to its concentration, the frequency of dosing, the level or amount of tear secretion, and the severity of the ocular surface disease. In the patient with mild dry eye, BAK-preserved drops are usually well tolerated when used 4-6 times a day or less. In patients with moderate-to-severe dry eye, the potential for BAK toxicity is high, due to decreased tear secretion and decreased turnover.[17] Some patients may be using other topical preparations (eg, glaucoma medications) that contain BAK, increasing their exposure to the toxic effects of BAK. Also, the potential for toxicity exists with patient abuse of other OTC products that contain BAK, such as vasoconstrictors.

BAK can damage the corneal and conjunctival epithelium, affecting cell-to-cell junctions and cell shape and microvilli, eventually leading to cell necrosis with sloughing of 1-2 layers of epithelial cells.[17] Preservative-free formulations are absolutely necessary for patients with severe dry eye with ocular surface disease and impairment of lacrimal gland secretion, or for patients on multiple, preserved topical medications for chronic eye disease. Patients with severe dry eye, greatly reduced tear secretion, and punctal occlusion are at particular risk for preservative toxicity. In such patients, the instilled agent cannot be washed out; if this risk has not been appreciated by the clinician, preserved drops might be used at high frequency.

Another additive used in OTC formulations is disodium (**EDTA**). It augments the preservative efficacy of BAK and other preservatives, but, by itself, it is not a sufficient preservative. Used in some nonpreserved solutions, it may help limit microbial growth in opened unit-dose vials. Although use of EDTA may allow a lower concentration of preservative, EDTA may itself be toxic to the ocular surface epithelium. A study comparing two preservative-free solutions, Hypotears PF® (Novartis Ophthalmics, East Hanover, NJ) containing EDTA and Refresh® (Allergan, Inc., Irvine, CA) without EDTA, showed that both formulations had identical safety profiles and were completely nontoxic to the rabbit corneal epithelium.[18] Other studies found that EDTA-containing preparations increased corneal epithelial permeability.[19,20] The potential exists that patients with severe dry eye will find that EDTA-containing preparations increase irritation.

Nonpreserved, single unit-dose tear substitutes are more costly for the manufacturer to produce, more costly for the patients to purchase, and less convenient to use than bottled ocular lubricants. For these reasons, reclosable unit dose vials (eg, Refresh Free [Allergan Inc., Irvine, CA]; Tears Natural Free® [Alcon, Fort Worth, TX]) were introduced. Less toxic preservatives, such as polyquad (polyquaternium-1), sodium chlorite (Purite®), and sodium perborate were developed to allow the use of multidose bottled lubricants and to avoid the known toxicity of BAK-containing solutions.[21,22] The "vanishing" preservatives were sodium perborate and sodium chlorite (TheraTears® [Advanced Vision Research, Woburn, MA], Genteal® [Novartis, East Hanover, NJ], and Refresh Tears® [Allergan Inc., Irvine, CA]).

Sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation. Sodium perborate is converted to water and oxygen on contact with the tear film. For patients with severe dry eye, even vanishing preservatives may not totally degrade, due to a decrease in tear volume, and may be irritating. Patients prefer bottled preparations for reasons of both cost and ease of use. The ideal lubricant would come in a multidose, easy-to-use bottle that contains a preservative that completely dissipates before reaching the tear film, or is completely nontoxic and nonirritating and maintains absolute sterility with frequent use. One such multi-use, preservative-free product has been introduced to the market (Visine Pure-Tears® [Pfizer, Inc, NJ]).

Ocular ointments and gels are also used in treatment of dry eye disease. Ointments are formulated with a specific mixture of mineral oil and petrolatum. Some contain lanolin, which can be irritating to the eye and delay corneal wound healing.[23] Individuals with sensitivity to wool may also be sensitive to lanolin.[23] Some ointments contain parabens as preservatives, and these ointments are not well tolerated by patients with severe dry eye. In general, ointments do not support bacterial growth and, therefore, do not require preservatives. Gels containing high molecular weight cross-linked polymers of acrylic acid (carbomers) have longer retention times than artificial tear solutions, but have less visual blurring effect than petrolatum ointments.

3. Electrolyte Composition

Solutions containing electrolytes and or ions have been shown to be beneficial in treating ocular surface damage due to dry eye.[1,6,20,24,25] To date, potassium and bicarbonate seem to be the most critical. Potassium is important to maintain corneal thickness.[7] In a dry-eye rabbit model, a hypotonic tear-matched electrolyte solution (TheraTears® [Advanced Vision Research, Woburn, MA]) increased conjunctival goblet cell density and corneal glycogen content, and reduced tear osmolarity and rose bengal staining after 2 weeks of treatment.[25] The restoration of conjunctival goblet cells seen in the dry-eye rabbit model has been corroborated in patients with dry eye after LASIK.[26]

Bicarbonate-containing solutions promote the recovery of epithelial barrier function in damaged corneal epithelium and aid in maintaining normal epithelial ultrastructure. They may also be important for maintaining the mucin layer of the tear film.[6] Ocular lubricants are available that mimic the electrolyte composition of human tears, eg, TheraTears® (Advanced Vision Research, Woburn, MA) and BION Tears® (Alcon, Fort Worth, TX).[1,2] These also contain bicarbonate, which is critical for forming and maintaining the protective mucin gel in the stomach.[27] Bicarbonate may play a similar role for gel-forming mucins on the ocular surface. Because bicarbonate is converted to carbon dioxide when in contact with air and can diffuse through the plastic unit dose vials, foil packaging of the plastic vials is required to maintain stability.

4. Osmolarity

Tears of patients with dry eye have a higher tear film osmolarity (crystalloid osmolarity) than do those of normal patients.[28,29] Elevated tear film osmolarity causes morphological and biochemical changes to the corneal and conjunctival epithelium[18,30] and is pro-inflammatory.[31] This knowledge influenced the development of hypo-osmotic artificial tears such as Hypotears® (230 mOsm/L [Novartis Ophthalmics, East Hanover, NJ]) and subsequently TheraTears® (181 mOsm/L [Advance Vision Research, Woburn, MA]).[32]

Colloidal osmolality is another factor that varies in artificial tear formulations. While crystalloid osmolarity is related to the presence of ions, colloidal osmolality is dependent largely on macromolecule content. Colloidal osmolarity, also known as *oncotic pressure*, is involved in the control of water transport in tissues. Differences in colloidal osmolality affect the net water flow across membranes, and water flow is eliminated by applying hydrostatic pressure to the downside of the water flow. The magnitude of this osmotic pressure is determined by osmolality differences on the two sides of the membrane. Epithelial cells swell due to damage to their cellular membranes or due to a dysfunction in the pumping mechanism. Following the addition of a fluid with a high colloidal osmolality to the damaged cell surface, deturgescence occurs, leading to a return of normal cell physiology. Theoretically, an artificial tear formulation with a high colloidal osmolality may be of value. Holly and Esquivel evaluated many different artificial tear formulations and showed that Hypotears® (Novartis Ophthalmics, East Hanover, NJ) had the highest colloidal osmolality of all of the formulations tested.[33] Formulations with higher colloidal osmolality have since been marketed (Dwelle® [Dry Eye Company, Silverdale, WA]).

Protection against the adverse effects of increased osmolarity (osmoprotection) has led to development of OTC drops incorporating compatible solutes (such as glycerin, erythritol, and levocarnitine (Optive® [Allergan Inc., Irvine, CA]). It is thought that the compatible solutes distribute between the tears and the intracellular fluids to protect against potential cellular damage from hyperosmolar tears.[34]

5. Viscosity Agents

The stability of the tear film depends on the chemical-physical characteristics of that film interacting with the conjunctival and corneal epithelium via the membrane-spanning mucins (ie, MUC-16 and MUC-4). In the classical three-layered tear film model, the mucin layer is usually thought of as a surfactant or wetting agent, acting to lower the surface tension of the relatively hydrophobic ocular surface, rendering the corneal and conjunctival cells "wettable."[33] Currently, the tear film is probably best described as a hydrated, mucin gel whose mucin concentration decreases with distance from the epithelial cell surface. It may have a protective role similar to that of mucin in the stomach.[35] It may also serve as a "sink" or storage vehicle for substances secreted by the main and accessory lacrimal glands and the ocular surface cells. This may explain why most of the available water-containing lubricants are only minimally effective in restoring the normal homeostasis of the ocular surface. In addition to washing away and diluting out irritating or toxic substances in the tear film, artificial lubricants hydrate gel-forming mucin. While some patients with dry eye have decreased aqueous lacrimal gland secretion, alterations or deficiencies involving mucin also cause dry eye.

Macromolecular complexes added to artificial lubricants act as viscosity agents. The addition of a viscosity agent increases residence time, providing a longer interval of patient comfort. For example, when a viscous, anionic charged carboxymethyl-cellulose (CMC, 100,000 mw) solution was compared with a neutral hydroxymethylcellulose (HPMC) solution, CMC was shown to have a significantly slower rate of clearance from the eye.[36] Viscous agents in active drug formulations may also prolong ocular surface contact, increasing the duration of action and penetration of the drug.

Viscous agents may also protect the ocular surface epithelium. It is known that rose bengal stains abnormal corneal and conjunctival epithelial cells expressing an altered mucin glycocalyx.[37] Agents such as hydroxymethycellulose (**HMC**), which decrease rose bengal staining in dry eye subjects,[38] may either "coat and protect" the surface epithelium or help restore the protective effect of mucins.

In the US, carboxymethyl cellulose is the most commonly used polymeric viscosity agent (IRI Market Share Data, Chicago, IL), typically in concentrations from 0.25% to 1%, with differences in molecular weight also contributing to final product viscosity. Carboxymethyl cellulose has been found to bind to and be retained by human epithelial cells.[39] Other viscosity agents included in the FDA monograph (in various concentrations) include polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose and hydroxypropyl cellulose.

The blurring of vision and esthetic disadvantages of caking and drying on eyelashes are drawbacks of highly viscous agents that patients with mild to moderate dry eye will not tolerate. Lower molecular-weight viscous agents help to minimize these problems. Because patient compliance, comfort, and convenience are important considerations, a range of tear substitute formulations with varying viscosities are needed.

Hydroxypropyl-guar (HP-guar) has been used as a gelling agent in a solution containing glycol 400 and propylene glycol (Systane®, Alcon, Fort Worth, TX). It has been suggested that HP-guar preferentially binds to the more hydrophobic, desiccated or damaged areas of the surface epithelial cells, providing temporary protection for these cells.[40,41] Several commercial preparations containing oil in the form of castor oil (Endura™ [Allergan Inc., Irvine, CA]) or mineral oil (Soothe® [Bausch & Lomb, Rochester, NY]) are purported to aid in restoring or increasing the lipid layer of the tear film.[42,43] Hyaluronic acid is a viscosity agent that has been investigated for years as an "active" compound added to tear substitute formulations for the treatment of dry eye. Hyaluronic acid (0.2%) has significantly longer ocular surface residence times than 0.3 percent HPMC or 1.4 percent polyvinyl alcohol.[44] Some clinical studies reported improvement in [44-48] dry eye in patients treated with sodium hyaluronate-containing solutions compared to other lubricant solutions, whereas others did not.[48] Although lubricant preparations containing sodium hyaluronate have not been approved for use in the US, they are frequently used in some countries.

6. Summary

Although many topical lubricants, with various viscosity agents, may improve symptoms and objective findings, there is no evidence that any agent is superior to another. Most clinical trials involving topical lubricant preparations will document some improvement (but not resolution) of subjective symptoms and improvement in some objective parameters.[4] However, the improvements noted are not necessarily any better than those seen with the vehicle or other nonpreserved artificial lubricants. The elimination of preservatives and the development of newer, less toxic preservatives have made ocular lubricants better tolerated by dry eye patients. However, ocular lubricants, which have been shown to provide some protection of the ocular surface epithelium and some improvement in patient symptoms and objective findings, have not been demonstrated in controlled clinical trials to be sufficient to resolve the ocular surface disorder and inflammation seen in most dry eye sufferers.

B. Tear Retention

1. Punctal Occlusion

a. Rationale

While the concept of permanently occluding the lacrimal puncta with cautery to treat dry eye extends back 70 years,[49] and, although the first dissolvable implants were used 45 years ago,[50] the modern era of punctal plug use began in 1975 with the report by Freeman.[51] Freeman described the use of a dumbbell-shaped silicone plug, which rests on the opening of the punctum and extends into the canaliculus. His report established a concept of punctal occlusion, which opened the field for development of a variety of removable, long-lasting plugs to retard tear clearance in an attempt to treat the ocular surface of patients with deficient aqueous tear production. The Freeman style plug remains the prototype for most styles of punctal plugs.

b. Types

Punctal plugs are divided into two main types: absorbable and nonabsorbable. The former are made of collagen or polymers and last for variable periods of time (3 days to 6 months). The latter nonabsorbable "permanent" plugs include the Freeman style, which consists of a surface collar resting on the punctal opening, a neck, and a wider base. In contrast, the Herrick plug (Lacrimedics [Eastsound,WA]) is shaped like a golf tee and is designed to reside within the canaliculus. It is blue for visualization; other variations are radiopaque. A newly designed cylindrical Smartplug™ (Medennium Inc [Irvine, CA]) expands and increases in diameter in situ following insertion into the canaliculus due to thermodynamic properties of its hydrophilic acrylic composition.

c. Clinical Studies

A variety of clinical studies evaluating the efficacy of punctal plugs have been reported.[52-56] These series generally fall into Level II evidence. Their use has been associated with objective and subjective improvement in patients with both Sjogren and non-Sjogren aqueous tear deficient dry eye, filamentary keratitis, contact lens intolerance, Stevens-Johnson disease, severe trachoma, neurotrophic keratopathy, post-penetrating keratoplasty, diabetic keratopathy, and post-photorefractive keratectomy or laser in situ keratomileusis. Several studies have been performed to evaluate the effects of punctal plugs on the efficacy of glaucoma medications in reducing intraocular pressure, and these studies have reported conflicting results.[57,58] Beneficial outcome in dry eye symptoms has been reported in 74-86% of patients treated with punctal plugs. Objective indices of improvement reported with the use of punctal plugs include improved corneal staining, prolonged tear film breakup time (**TFBUT**), decrease in tear osmolarity, and increase in goblet cell density. Overall, the clinical utility of punctal plugs in the management of dry eye disease has been well documented.

d. Indications and Contraindications

In a recent review on punctal plugs, it was reported that in a major eye clinic, punctal plugs are considered indicated in patients who are symptomatic of dry eyes, have a Schirmer test (with anesthesia) result less than 5 mm at 5 minutes, and show evidence of ocular surface dye staining.[56]

Contraindications to the use of punctal plugs include allergy to the materials used in the plugs to be implanted, punctal ectropion, and pre-existing nasolacrimal duct obstruction, which would, presumably, negate the need for punctal occlusion. It has been suggested that plugs may be contraindicated in dry eye patients with clinical ocular surface inflammation, because occlusion of tear outflow would prolong contact of the abnormal tears containing proinflammatory cytokines with the ocular surface. Treatment of the ocular surface inflammation prior to plug insertion has been recommended. Acute or chronic infection of the lacrimal canaliculus or lacrimal sac is also a contraindication to use of a plug.

e. Complications

The most common complication of punctal plugs is spontaneous plug extrusion, which is particularly common with the Freeman-style plugs. Over time, an extrusion rate of 50% has been reported, but many of these extrusions took place after extensive periods of plug residence. Most extrusions are of small consequence, except for inconvenience and expense. More troublesome complications include internal migration of a plug, biofilm formation and infection,[59] and pyogenic granuloma formation. Removal of migrated canalicular plugs can be difficult and may require surgery to the nasolacrimal duct system.[60,61]

f. Summary

The extensive literature on the use of punctal plugs in the management of dry eye disease has documented their utility. Several recent reports, however, have suggested that absorption of tears by the nasolacrimal ducts into surrounding tissues and blood vessels may provide a feedback mechanism to the lacrimal gland regulating tear production.[62] In one study, placement of punctal plugs in patients with normal tear production caused a significant decrease in tear production for up to 2 weeks after plug insertion.[63] This cautionary note should be considered when deciding whether to incorporate punctal occlusion into a dry eye disease management plan.

2. Moisture Chamber Spectacles

The wearing of moisture-conserving spectacles has for many years been advocated to alleviate ocular discomfort associated with dry eye. However, the level of evidence supporting its efficacy for dry eye treatment has been relatively limited. Tsubota et al, using a sensitive moisture sensor, reported an increase in periocular humidity in subjects wearing such spectacles.[64] Addition of side panels to the spectacles was shown to further increase the humidity.[65] The clinical efficacy of moisture chamber spectacles has been reported in case reports.[66,67] Kurihashi proposed a related treatment for dry eye patients, in the form of a wet gauze eye mask.[68] Conversely, Nichols et al recently reported in their epidemiologic study that spectacle wearers were twice as likely as emmetropes to report dry eye disease.[69] The reason for this observation was not explained.

There have been several reports with relatively high level of evidence describing the relationship between environmental humidity and dry eye. Korb et al reported that increases in periocular humidity caused a significant increase in thickness of the tear film lipid layer.[70] Dry eye subjects wearing spectacles showed significantly longer interblink intervals than those who did not wear spectacles, and duration of blink (blinking time) was significantly longer in the latter subjects.[70] Instillation of artificial tears caused a significant increase in the interblink interval and a decrease in the blink rate.[71] Maruyama et al reported that dry eye symptoms worsened in soft contact lens wearers when environmental humidity decreased.[72]

3. Contact Lenses

Contact lenses may help to protect and hydrate the corneal surface in severe dry eye conditions. Several different contact lens materials and designs have been evaluated, including silicone rubber lenses and gas permeable scleral-bearing hard contact lenses with or without fenestration.[73-77] Improved visual acuity and comfort, decreased corneal epitheliopathy, and healing of persistent corneal epithelial defects have been reported.[73-77] Highly oxygen-permeable materials enable overnight wear in appropriate circumstances.[75] There is a small risk of corneal vascularization and possible corneal infection associated with the use of contact lenses by dry eye patients.

C. Tear Stimulation: Secretogogues

Several potential topical pharmacologic agents may stimulate aqueous secretion, mucous secretion, or both. The agents currently under investigation by pharmaceutical companies are diquafosol (one of the P2Y2 receptor agonists), rebamipide, gefarnate, ecabet sodium (mucous secretion stimulants), and 15(S)-HETE (MUC1 stimulant). Among them, a diquafosol eye drop has been favorably evaluated in clinical trials. 2% diquafosol (INS365, DE-089 [Santen, Osaka, Japan]; Inspire [Durham, NC]) proved to be effective in the treatment of dry eye in a randomized, double-masked trial in humans to reduce ocular surface staining.[78] A similar study demonstrated the ocular safety and tolerability of diquafosol in a double-masked, placebo-controlled, randomized study.[79] This agent is capable of stimulating both aqueous and mucous secretion in animals and humans.[80-83] Beneficial effects on corneal epithelial barrier function, as well as increased tear secretion, has been demonstrated in the rat dry eye model.[84] Diquafosol also has been shown to stimulate mucin release from goblet cells in a rabbit dry eye model.[85,86]

The effects of rebamipide (OPC-12759 [Otsuka, Rockville, MD]; Novartis [Basel, Switzerland]) have been evaluated in human clinical trials. In animal studies, rebamipide increased the mucin-like substances on the ocular surface of N-acetylcysteine-treated rabbit eyes.[87] It also had hydroxyl radical scavenging effects on UVB-induced corneal damage in mice.[88]

Ecabet sodium (Senju [Osaka, Japan]; ISTA [Irvine, CA]) is being evaluated in clinical trials internationally, but only limited results have yet been published. A single instillation of ecabet sodium ophthalmic solution elicited a statistically significant increase in tear mucin in dry eye patients.[89] Gefarnate (Santen [Osaka, Japan]) has been evaluated in animal studies. Gefarnate promoted mucin production after conjunctival injury in monkeys.[90] Gefarnate increased PAS-positive cell density in rabbit conjunctiva and stimulated mucin-like glycoprotein stimulation from rat cultured corneal epithelium.[91,92] An in vivo rabbit experiment showed a similar result.[93,94]

The agent 15(S)-HETE, a unique molecule, can stimulate MUC1 mucin expression on ocular surface epithelium.[95]15(S)-HETE protected the cornea in a rabbit model of desiccation-induced injury, probably because of mucin secretion.[96] It has been shown to have beneficial effects on secretion of mucin-like glycoprotein by the rabbit corneal epithelium.[97] Other laboratory studies confirm the stimulatory effect of 15(S)-HETE.[98-101] Some of these agents may become useful clinical therapeutic modalities in the near future.

Two orally administered cholinergic agonists, pilocarpine and cevilemine, have been evaluated in clinical trials for treatment of Sjogren syndrome associated keratoconjunctivitis sicca (**KCS**). Patients who were treated with pilocarpine at a dose of 5 mg QID experienced a significantly greater overall improvement than placebo-treated patients in “ocular problems” in their ability to focus their eyes during reading, and in symptoms of blurred vision compared with placebo-treated patients.[102] The most commonly reported side effect from this medication was excessive sweating, which occurred in over 40% of patients. Two percent of the patients taking pilocarpine withdrew from the study because of drug-related side effects. Other studies have reported efficacy of pilocarpine for ocular signs and symptoms of Sjogren syndrome KCS,[103-105] including an increase in conjunctival goblet cell density after 1 and 2 months of therapy.[106]

Cevilemine is another oral cholinergic agonist that was found to significantly improve symptoms of dryness and aqueous tear production and ocular surface disease compared to placebo when taken in doses of 15 or 30 mg TID.[107,108] This agent may have fewer adverse systemic side effects than oral pilocarpine.

D. Biological Tear Substitutes

Naturally occurring biological, ie, nonpharmaceutical fluids, can be used to substitute for natural tears. The use of serum or saliva for this purpose has been reported in humans. They are usually unpreserved. When of autologous origin, they lack antigenicity and contain various epitheliotrophic factors, such as growth factors, neurotrophins, vitamins, immunoglobulins, and extracellular matrix proteins involved in ocular surface maintenance. Biological tear substitutes maintain the morphology and support the proliferation of primary human corneal epithelial cells better than pharmaceutical tear substitutes.[109] However, despite biomechanical and biochemical similarities, relevant compositional differences compared with normal tears exist and are of clinical relevance.[110] Additional practical problems concern sterility and stability, and a labor-intensive production process or a surgical procedure (saliva) is required to provide the natural tear substitute to the ocular surface.

1. Serum

Serum is the fluid component of full blood that remains after clotting. Its topical use for ocular surface disease was much stimulated by Tsubota’s prolific work in the late 1990s.[111] The practicalities and published evidence of autologous serum application were recently reviewed.[112] The use of blood and its components as a pharmaceutical preparation in many countries is restricted by specific national laws. To produce serum eye drops and to use them for outpatients, a license by an appropriate national body may be required in certain countries. The protocol used for the production of serum eye drops determines their composition and efficacy. An optimized protocol for the production was recently published.[113] Concentrations between 20% and 100% of serum have been used. The efficacy seems to be dose-dependent.

Because of significant variations in patient populations, production and storage regimens, and treatment protocols, the efficacy of serum eye drops in dry eyes has varied substantially between studies.[113] Three published prospective randomized studies with similar patient populations (predominantly immune disease associated dry eye, ie, Sjogren syndrome) are available. When comparing 20% serum with 0.9% saline applied 6 times per day, Tananuvat et al found only a trend toward improvement of symptoms and signs of dry eyes,[114] whereas Kojima et al reported significant improvement of symptom scores, fluorescein-breakup time (**FBUT**), and fluorescein and rose bengal staining.[115]

A prospective clinical cross-over trial compared 50% serum eyedrops against the commercial lubricant previously used by each patient. Symptoms improved in 10 out 16 patients, and impression cytological findings improved in 12 out of 25 eyes.[116] Noda-Tsuruya and colleagues found that 20% autologous serum significantly improved TFBUT and decreased conjunctival rose bengal and cornea fluorescein staining 1-3 months postoperatively, compared to treatment with artificial tears, which did not change these parameters.[117] Additional reports of successful treatment of persistent epithelial defects—where success is more clearly defined as "healing of the defect"—with autologous serum substantiate the impression that this is a valuable therapeutic option for ocular surface disease.[118]

2. Salivary Gland Autotransplantation

Salivary submandibular gland transplantation is capable of replacing deficient mucin and the aqueous tear film phase. This procedure requires collaboration between an ophthalmologist and a maxillofacial surgeon. With appropriate microvascular anastomosis, 80% of grafts survive. In patients with absolute aqueous tear deficiency, viable submandibular gland grafts, in the long-term, provide significant improvement of Schirmer test FBUT, and rose bengal staining, as well as reduction of discomfort and the need for pharmaceutical tear substitutes. Due to the hypo-osmolarity of saliva, compared to tears, excessive salivary tearing can induce a microcystic corneal edema, which is temporary, but can lead to epithelial defects.[110] Hence, this operation is indicated only in end-stage dry eye disease with an absolute aqueous tear deficiency (Schirmer-test wetting of 1 mm or less), a conjunctivalized surface epithelium, and persistent severe pain despite punctal occlusion and at least hourly application of unpreserved tear substitutes. For this group of patients, such surgery is capable of substantially reducing discomfort, but often has no effect on vision.[119,120]

E. Anti-Inflammatory Therapy

Disease or dysfunction of the tear secretory glands leads to changes in tear composition, such as hyperosmolarity, that stimulate the production of inflammatory mediators on the ocular surface.[31,121] Inflammation may, in turn, cause dysfunction or disappearance of cells responsible for tear secretion or retention.[122] Inflammation can also be initiated by chronic irritative stress (eg, contact lenses) and systemic inflammatory/autoimmune disease (eg, rheumatoid arthritis). Regardless of the initiating cause, a vicious circle of inflammation can develop on the ocular surface in dry eye that leads to ocular surface disease. Based on the concept that inflammation is a key component of the pathogenesis of dry eye, the efficacy of a number of anti-inflammatory agents for treatment of dry eye disease has been evaluated in clinical trials and animal models.

1. Cyclosporine

The potential of cyclosporine-A (**CsA**) for treating dry eye disease was initially recognized in dogs that develop spontaneous KCS.[123] The therapeutic efficacy of CsA for human KCS was then documented in several small, single-center, randomized, double-masked clinical trials.[124,125] CsA emulsion for treatment of KCS was subsequently evaluated in several large multicenter, randomized, double-masked clinical trials.

In a Phase 2 clinical trial, four concentrations of CsA (0.05%, 0.1%, 0.2%, or 0.4%) administered twice daily to both eyes of 129 patients for 12 weeks was compared to vehicle treatment of 33 patients.[126] CsA was found to significantly decrease conjunctival rose bengal staining, superficial punctate keratitis, and ocular irritation symptoms (sandy or gritty feeling, dryness, and itching) in a subset of 90 patients with moderate-to-severe KCS. There was no clear dose response; CsA 0.1% produced the most consistent improvement in objective endpoints, whereas CsA 0.05% gave the most consistent improvement in patient symptoms (Level I).

Two independent Phase 3 clinical trials compared twice-daily treatment with 0.05% or 0.1% CsA or vehicle in 877 patients with moderate-to-severe dry eye disease.[127] When the results of the two Phase 3 trials were combined for statistical analysis, patients treated with CsA, 0.05% or 0.1%, showed significantly ($P < 0.05$) greater improvement in two objective signs of dry eye disease (corneal fluorescein staining and anesthetized Schirmer test values) compared to those treated with vehicle. An increased Schirmer test score was observed in 59% of patients treated with CsA, with 15% of patients having an increase of 10 mm or more. In contrast, only 4% of vehicle-treated patients had this magnitude of change in their Schirmer test scores ($P < 0.0001$).

CsA 0.05% treatment also produced significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision symptoms, need for concomitant artificial tears, and the global response to treatment). No dose-response effect was noted. Both doses of CSA exhibited an excellent safety profile with no significant systemic or ocular adverse events, except for transient burning symptoms after instillation in 17% of patients. Burning was reported in 7% of patients receiving the vehicle. No CsA was detected in the blood of patients treated with topical CsA for 12 months. Clinical improvement from CsA that was observed in these trials was accompanied by improvement in other disease parameters. Treated eyes had an approximately 200% increase in conjunctival goblet cell density.[128] Furthermore, there was decreased expression of immune activation markers (ie, HLA-DR), apoptosis markers (ie, Fas), and the inflammatory cytokine IL-6 by the conjunctival epithelial cells.[129,130]The numbers of CD3-, CD4-, and CD8-positive T lymphocytes in the conjunctiva decreased in cyclosporine-treated eyes, whereas vehicle-treated eyes showed an increased number of cells expressing these markers.[131] After treatment with 0.05% cyclosporine, there was a significant decrease in the number of cells expressing the lymphocyte activation markers CD11a and HLA-DR, indicating less activation of lymphocytes compared with vehicle-treated eyes.

Two additional immunophilins, pimecrolimus and tacrolimus, have been evaluated in clinical trials of KCS.

2. Corticosteroids

a. *Clinical Studies*

Corticosteroids are an effective anti-inflammatory therapy in dry eye disease. Level I evidence is published for a number of corticosteroid formulations. In a 4-week, double-masked, randomized study in 64 patients with KCS and delayed tear clearance, loteprednol etabonate 0.5% ophthalmic suspension (Lotemax [Bausch and Lomb, Rochester, NY]), q.i.d., was found to be more effective than its vehicle in improving some signs and symptoms.[132]

In a 4-week, open-label, randomized study in 32 patients with KCS, patients receiving fluorometholone plus artificial tear substitutes (**ATS**) experienced lower symptom severity scores and lower fluorescein and rose bengal staining than patients receiving either ATS alone or ATS plus flurbiprofen.[133]

A prospective, randomized clinical trial compared the severity of ocular irritation symptoms and corneal fluorescein staining in two groups of patients, one treated with topical nonpreserved methylprednisolone for 2 weeks, followed by punctal occlusion (Group 1), with a group that received punctal occlusion alone (Group 2).[134] After 2 months, 80% of patients in Group 1 and 33% of patients in Group 2 had complete relief of ocular irritation symptoms. Corneal fluorescein staining was negative in 80% of eyes in Group 1 and 60% of eyes in Group 2 after 2 months. No steroid-related complications were observed in this study.

Level III evidence is also available to support the efficacy of corticosteroids. In an open-label, non-comparative trial, extemporaneously formulated nonpreserved methylprednisolone 1% ophthalmic suspension was found to be clinically effective in 21 patients with Sjogren syndrome KCS.[135] In a review, it was stated that "…clinical improvement of KCS has been observed after therapy with anti-inflammatory agents, including corticosteroids."[136]

In the US Federal Regulations, ocular corticosteroids receiving "class labeling" are indicated for the treatment "…of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation." We interpret that KCS is included in this list of steroid-responsive inflammatory conditions.[137-140]

b. *Basic Research*

Corticosteroids are the standard anti-inflammatory agent for numerous basic research studies of inflammation, including the types that are involved in KCS. The corticosteroid methylprednisolone was noted to preserve corneal epithelial smoothness and barrier function in an experimental murine model of dry eye.[141] This was attributed to its ability to maintain the integrity of corneal epithelial tight junctions and decrease desquamation of apical corneal epithelial cells.[142] A concurrent study showed that methylprednislone prevented an increase in MMP-9 protein in the corneal epithelium, as well as gelatinase activity in the corneal epithelium and tears in response to experimental dry eye.[141]

Preparations of topically applied androgen and estrogen steroid hormones are currently being evaluated in randomized clinical trials. A trial of topically applied 0.03% testosterone was reported to increase the percentage of patients that had meibomian gland secretions with normal viscosity and to relieve discomfort symptoms after 6 months of treatment compared to vehicle.[143] TFBUT and lipid layer thickness were observed to increase in a patient with KCS who was treated with topical androgen for 3 months.[144] Tear production and ocular irritation symptoms were reported to increase following treatment with topical 17 beta-oestradiol solution for 4 months.[145]

3. Tetracyclines

a. *Properties of Tetracyclines and Their Derivatives*

1) Antibacterial Properties

The antimicrobial effect of oral tetracycline treatment analogues (eg, minocycline, doxycline) has previously been discussed by Shine et al,[146] Dougherty et al,[147] and Ta et al.[148] It is hypothesized that a decrease in bacterial flora producing lipolytic exoenzymes[146,148] and inhibition of lipase production[147] with resultant decrease in meibomian lipid breakdown products[146] may contribute to improvement in clinical parameters in dry eye-associated diseases.

2) Anti-Inflammatory Properties

The tetracyclines have anti-inflammatory as well as antibacterial properties that may make them useful for the management of chronic inflammatory diseases. These agents decrease the activity of collagenase, phospholipase A2, and several matrix metalloproteinases, and they decrease the production of interleukin (**IL**)-1 and tumor necrosis factor (**TNF**)-alpha in a wide range of tissues, including the corneal epithelium.[149-151] At high concentrations, tetracyclines inhibit staphylococcal exotoxin-induced cytokines and chemokines.[152,153]

3) Anti-angiogenic Properties

Angiogenesis, the formation of new blood vessels, occurs in many diseases. These include benign conditions (eg, rosacea) and malignant processes (eg, cancer). Minocycline and doxycycline inhibit angiogenesis induced by implanted tumors in rabbit cornea.[154] The anti-angiogenic effect of tetracycline may have therapeutic implications in inflammatory processes accompanied by new blood vessel formation. Well-controlled studies must be performed, at both the laboratory and clinical levels, to investigate this potential.[155]

b. *Clinical Applications of Tetracycline*

1) Acne Rosacea

Rosacea, including its ocular manifestations, is an inflammatory disorder, occurring mainly in adults, with peak severity in the third and fourth decades. Current recommendations are to treat rosacea with long-term doxycycline, minocycline, tetracycline, or erythromycin.[156] These recommendations may be tempered by certain recent reports that in women, the risk of developing breast cancer and of breast cancer morbidity increases cumulatively with duration of antibiotic use, including tetracyclines.[157,158] Another large study did not substantiate these findings.[159]

Tetracyclines and their analogues are effective in the treatment of ocular rosacea,[160,161] for which a single daily dose of doxycycline may be effective.[162] In addition to the anti-inflammatory effects of tetracyclines, their ability to inhibit angiogenesis may contribute to their effectiveness in rosacea-related disorders. Factors that promote angiogenesis include protease-triggered release of angiogenic factors stored in the extracellular matrix, inactivation of endothelial growth factor inhibitors, and release of angiogenic factors from activated macrophages.[155,163]

Tetracyclines are also known to inhibit matrix metalloproteinase expression, suggesting a rationale for their use in ocular rosacea.[164] Although tetracyclines have been used for management of this disease, no randomized, placebo-controlled, clinical trials have been performed to assess their efficacy.[153]

2) Chronic Posterior Blepharitis: Meibomianitis, Meibomian Gland Dysfunction

Chronic blepharitis is typically characterized by inflammation of the eyelids. There are multiple forms of chronic blepharitis, including staphylococcal, seborrheic (alone, mixed seborrheic/staphylococcal, seborrheic with meibomian seborrhea, seborrheic with secondary meibomitis), primary meibomitis, and others, like atopic, psoriatic, and fungal infections.[165] Meibomian gland dysfunction (**MGD**) has been associated with apparent aqueous-deficient dry eye. Use of tetracycline in patients with meibomianitis has been shown to decrease lipase production by tetracycline-sensitive as well as resistant strains of staphylococci. This decrease in lipase production was associated with clinical improvement.[147] Similarly, minocycline has been shown to decrease the production of diglycerides and free fatty acids in meibomian secretions. This may be due to lipase inhibition by the antibiotic or a direct effect on the ocular flora.[146] One randomized, controlled clinical trial of tetracycline in ocular rosacea compared symptom improvement in 24 patients treated with either tetracycline or doxycycline.[166] All but one patient reported an improvement in symptoms after 6 weeks of therapy. No placebo group was included in this trial.

A prospective, randomized, double-blind, placebo-controlled, partial crossover trial compared the effect of oxytetracycline to provide symptomatic relief of blepharitis with or without rosacea. Only 25% of the patients with blepharitis without rosacea responded to the antibiotic, whereas 50% responded when both diseases were present.[167] In another trial of 10 patients with both acne rosacea and concomitant meibomianitis, acne rosacea without concomitant ocular involvement, or seborrheic blepharitis, minocycline 50 mg daily for 2 weeks followed by 100 mg daily for a total of 3 months significantly decreased bacterial flora ($P = 0.0013$). Clinical improvement was seen in all patients with meibomianitis.[148]

Because of the improvement observed in small clinical trials of patients with meibomianitis, the American Academy of Ophthalmology recommends the chronic use of either doxycycline or tetracycline for the management of meibomianitis.[165] Larger randomized placebo-controlled trials assessing symptom improvement rather than surrogate markers are needed to clarify the role of this antibiotic in blepharitis treatment.[153] Tetracycline derivatives (eg, minocycline, doxycycline) have been recommended as treatment options for chronic blepharitis because of their high concentration in tissues, low renal clearance, long half-life, high level of binding to serum proteins, and decreased risk of photosensitization.[168]

Several studies have described the beneficial effects of minocycline and other tetracycline derivatives (eg, doxycycline) in the treatment of chronic blepharitis.[146,147,168,169] Studies have shown significant changes in the aqueous tear parameters, such as tear volume and tear flow, following treatment with tetracycline derivatives (eg, minocycline). One study also demonstrated a decrease in aqueous tear production that occurred along with clinical improvement.[170]

A recently published randomized, prospective study by Yoo Se et al compared different doxycycline doses in 150 patients (300 eyes) who had chronic meibomian gland dysfunction and who did not respond to lid hygiene and topical therapy for more than 2 months.[171] All topical therapy was stopped for at least 2 weeks prior to beginning the study. After determining the TFBUT and Schirmer test scores, patients were divided into three groups: a high dose group (doxycycline, 200 mg, twice a day), a low dose group (doxycycline, 20 mg, twice a day) and a control group (placebo). After one month, TFBUT, Schirmer scores, and symptoms improved. Both the high- and low-dose groups had statistically significant improvement in TFBUT after treatment. This implies that low-dose doxycycline (20 mg twice a day) therapy may be effective in patients with chronic meibomian gland dysfunction.

3) Dosage and Safety

Systemic administration of tetracyclines is widely recognized for the ability to suppress inflammation and improve symptoms of meibomianitis.[172,173] The optimal dosing schedule has not been established; however, a variety of dose regimens have been proposed including 50 or 100 mg doxycycline once a day,[174] or an initial dose of 50 mg a day for the first 2 weeks followed by 100 mg a day for a period of 2.5 months, in an intermittent fashion.[146-148,170] Others have proposed use of a low dose of doxycycline (20 mg) for treatment of chronic blepharitis on a long-term basis.[171] The safety issues associated with long-term oral tetracycline therapy, including minocycline, are well known. Many management approaches have been suggested for the use of tetracycline and its derivatives; however, a safe but adequate option in management needs to be considered because of

Table 2. Dry eye severity grading scheme

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

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

Reprinted with permission from Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. *Cornea* 2006;25:90-7

the new information regarding the potentially hazardous effects of prolonged use of oral antibiotics. A recent study suggested that a 3-month course of 100 mg of minocycline might be sufficient to bring significant meibomianitis under control, as continued control was maintained for at least 3 months after cessation of therapy.[170]

In an experimental murine model of dry eye, topically applied doxycycline was found to preserve corneal epithelial smoothness and barrier function.[141] It also preserved the integrity of corneal epithelial tight junctions in dry eyes, leading to a marked decrease in apical corneal epithelial cell desquamation.[142] This corresponded to a decrease in MMP-9 protein in the corneal epithelium and reduced gelatinase activity in the corneal epithelium and tears.[141]

F. Essential Fatty Acids

Essential fatty acids are necessary for complete health. They cannot be synthesized by vertebrates and must be obtained from dietary sources. Among the essential fatty acids are 18 carbon omega-6 and omega-3 fatty acids. In the typical western diet, 20-25 times more omega-6 than omega-3 fatty acids are consumed. Omega-6 fatty acids are precursors for arachidonic acid and certain proinflammatory lipid mediators (PGE2 and LTB4). In contrast, certain omega-3 fatty acids (eg, EPA found in fish oil) inhibit the synthesis of these lipid mediators and block production of IL-1 and TNF-alpha.[175,176]

A beneficial clinical effect of fish oil omega-3 fatty acids on rheumatoid arthritis has been observed in several double-masked, placebo-controlled clinical trials.[177,178] In a prospective, placebo-controlled clinical trial of the essential fatty acids, linoleic acid and gamma-linolenic acid administered orally twice daily produced significant improvement in ocular irritation symptoms and ocular surface lissamine green staining.[179] Decreased conjunctival HLA-DR staining also was observed.

G. Environmental Strategies

Factors that may decrease tear production or increase tear evaporation, such as the use of systemic anticholinergic medications (eg, antihistamines and antidepressants) and desiccating environmental stresses (eg, low humidity and air conditioning drafts) should be minimized or eliminated.[180-182] Video display terminals should be lowered below eye level to decrease the interpalpebral aperture, and patients should be encouraged to take periodic breaks with eye closure when reading or working on a computer.[183] A humidified environment is recommended to reduce tear evaporation. This is particularly beneficial in dry climates and high altitudes. Nocturnal lagophthalmos can be treated by wearing swim goggles, taping the eyelid closed, or tarsorrhapy.

IV. TREATMENT RECOMMENDATIONS

In addition to material presented above, the subcommittee members reviewed the Dry Eye Preferred Practice Patterns of the American Academy of Ophthalmology and the International Task Force (**ITF**) Delphi Panel on dry

Table 3. Dry eye menu of treatments

Artificial tears substitutes
Gels/Ointments
Moisture chamber spectacles
Anti-inflammatory agents (topical CsA and corticosteroids, omega-3 fatty acids)
Tetracyclines
Plugs
Secretogogues
Serum
Contact lenses
Systemic immunosuppressives
Surgery (AMT, lid surgery. tarsorrhaphy, MM & SG transplant)

AMT = amniotic membrane transplantation; MM = mucous membrane; SG = salivary gland

Table 4. Treatment recommendations by severity level

Level 1:
Education and environmental/dietary modifications
Elimination of offending systemic medications
Artificial tear substitutes, gels/ointments
Eye lid therapy

Level 2:
If Level 1 treatments are inadequate, add:
Anti-inflammatories
Tetracyclines (for meibomianitis, rosacea)
Punctal plugs
Secretogogues
Moisture chamber spectacles

Level 3:
If Level 2 treatments are inadequate, add:
Serum
Contact lenses
Permanent punctal occlusion

Level 4:
If Level 3 treatments are inadequate, add:
Systemic anti-inflammatory agents
Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

Modified from: International Task Force Guidelines for Dry Eye[185]

eye treatment prior to formulating their treatment guidelines.[184,185] The group favored the approach taken by the ITF, which based treatment recommendations on disease severity. A modification of the ITF severity grading scheme that contains 4 levels of disease severity based on signs and symptoms was formulated (Table 2). The subcommittee members chose treatments for each severity level from a menu of therapies for which evidence of therapeutic effect has been presented (Table 3). The treatment recommendations by severity level are presented in Table 4. It should be noted that these recommendations may be modified by practitioners based on individual patient profiles and clinical experience. The therapeutic recommendations for level 4 severity disease include surgical modalities to treat or prevent sight-threatening corneal complications. Discussion of these therapies is beyond the scope of this report.

V. UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

There have been tremendous advances in the treatment of dry eye and ocular surface disease in the last two decades, including FDA approval of cyclosporin emulsion as the first therapeutic agent for treatment of KCS in the United States. There has been a commensurate increase in knowledge regarding the pathophysiology of dry eye. This has led to a paradigm shift in dry eye management from simply lubricating and hydrating the ocular surface with artificial tears to strategies that stimulate natural production of tear constituents, maintain ocular surface epithelial health and barrier function, and inhibit the inflammatory factors that adversely impact the ability of ocular surface and glandular epithelia to produce tears. Preliminary experience using this new therapeutic approach suggests that quality of life can be improved for many patients with dry eye and that initiating these strategies early in the course of the disease may prevent potentially blinding complications of dry eye. It is likely that future therapies will focus on replacing specific tear factors that have an essential role in maintaining ocular surface homeostasis or inhibiting key inflammatory mediators that cause death or dysfunction of tear secreting cells. This will require additional research to identify these key factors and better diagnostic tests to accurately measure their concentrations in minute tear fluid samples. Furthermore, certain disease parameters may be identified that will identify whether a patient has a high probability of responding to a particular therapy. Based on the progress that has been made and the number of therapies in the pipeline, the future of dry eye therapy seems bright.

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(Parenthetical codes following references indicate level of evidence, as described in Table 1. CS = Clinical Study; BS = Basic Science.)

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Research in Dry Eye:
Report of the Research Subcommittee of the International Dry Eye WorkShop (2007)

ABSTRACT **Members of the DEWS Research Subcommittee reviewed research into the basic mechanisms underlying dry eye disease. Evidence was evaluated concerning the tear film, lacrimal gland and accessory lacrimal glands, ocular surface epithelia (including cornea and conjunctiva), meibomian glands, lacrimal duct system and the immune system. Consideration was given to both animal and human research data. Results are presented as a series of information matrices, identifying what is known and providing supporting references. An attempt is made to identify areas for further investigation.**

KEY WORDS **DEWS, dry eye, Dry Eye WorkShop, mechanisms of dry eye, pathology of dry eye**

I. INTRODUCTION

Members of the Research Subcommittee were grouped according to their particular areas of expertise and asked to review the evidence for the basic mechanisms of dry eye pathology within that area. To facilitate this, a standardized template was developed (the DEWS Research Committee Report Form—Appendix 1 [access at: www.tearfilm.org]), which members used to present their findings. Based on the information derived from the returned reports, information matrices were developed.

Evidence related to the tear film, lacrimal gland and accessory lacrimal glands, ocular surface epithelia (including cornea and conjunctiva), meibomian glands, lacrimal duct system, and the immune system was evaluated. Consideration was given to both animal and human research data. Results are presented in a matrix of information that identifies what is known, with supporting references, and identifies areas for further investigation.

II. GOALS OF THE RESEARCH SUBCOMMITTEE

Goals of the Research Subcommittee were as follows:

A. To consider whether there is sufficient evidence to define the basic mechanisms underlying dry eye disease.
   1. To summarize the state of knowledge about primary alterations and/or secondary responses of the following ocular and systemic components that contribute to tear film dysfunction.
      a. Tear film
      b. Lacrimal gland and accessory lacrimal glands
      c. Ocular surface epithelia, cornea, conjunctiva
      d. Meibomian gland
      e. Lacrimal duct system
      f. Immune system
   2. To construct an information matrix to identify areas where knowledge is insufficient and to determine if there are common pathologies across the syndrome.
   3. To identify areas where clinical information is available or lacking.

B. Based on data derived from Part A, to answer Question 2: Is the state of basic knowledge on mechanisms of dry eye sufficient to determine how these give rise to disease symptoms?

C. Develop, if possible, definitions of the mechanism of dry eye pathology or develop major hypotheses on the mechanism that can be tested.

III. THE TEARS AND TEAR FILM

A. Human Disease

The evidence presented at the last dry eye workshop report (National Eye Institute [**NEI**]/Industry Workshop of 1995, hereafter referred to as the "1995 Workshop") indicated that tear film osmolarity is increased in all forms of

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

Reprints are not available. Articles can be accessed at: www.tearfilm.org

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OUTLINE

dry eye (**DE**) and that tear volume and certain lacrimal tear proteins, such as lysozyme and lactoferrin, are decreased in aqueous-deficient dry eye.[1] An evaporative form of dry eye was also recognized, caused, for example, by a decreased integrity of the tear film lipid layer.

New evidence since the 1995 Workshop indicates that meibomian lipid composition and distribution is altered in DE and a number of bioactive tear proteins, including plasmin, matrix metalloproteinases (**MMPs**), defensive molecules, and phospholipase A2 IIa in DE are increased. There is also an increase in inflammatory cytokines in non-Sjogren syndrome (**NSS**) dry eye, as well as in Sjogren syndrome (**SS**) dry eye, and a decrease in goblet cell mucin MUC5AC in keratoconjunctivitis sicca (**KCS**) and SS (Table 1).

Given the sparsity of information available about the changes in the composition of the tear film listed above, it is unclear how the changes in human tear composition relate to tear dysfunction. To better understand the mechanism of dry eye disease, there is need for proteomic, lipidomic, and glycomic analyses of the tears from large, well-defined, staged, and age-matched patients or subject populations, to develop biomarkers specific to dry eye disease. Progress has been made in developing proteomic baseline studies of tear proteins, but studies comparing normal and dry eye tears are lacking.[41-44] Mass spectrometry is a powerful analytical tool for identification[45] of molecules and compounds, and it is being used to develop a standard lipid profile of normal tears and to identify specific component differences in the tears from DE models.

The application of mass spectrometry to the characterization and identification of the lipids of the meibomian gland secretions is demonstrating that the previously reported compositions are in need of revision. Complicating these efforts is the observation that the lipids are very diverse in class and functionality. Different analytical approaches for isolation and detection are needed to differentiate lipid classes.

High throughput mass spectroscopic and glycan array methodologies are now available for glycomic analysis, and these could be used to analyze tear glycans in normal and DE patients. Similarly, determination of ratios and amounts of membrane-associated and secreted mucins in tear film is necessary. It will also be important to determine the relationship between various measures of tear stability (eg, tear film breakup time [**TFBUT**]) and the mucin and lipid quantity and character of the tears.

Abbreviations used in text and tables

↑ = Increase in/increased
↓ = Decrease in/decreased
Δ = Change in/changes to
–/– = Homozygous null mouse
– = totally depleted
ACAT-1 = Acyl-CoA:cholesterol acyltransferase-1
Auto-AG = Autoantigen
BUT = Breakup time
CALT = Conjunctiva-associated lymphoid tissue
Chr Bleph = Chronic blepharitis
CIC = Cicatrizing disease
Conj = Conjunctiva/conjunctival
Cont lens = Contact lens
DE = Dry eye
DES = Dry eye syndrome
EDA = Ectodermal dysplasia
ENV STR = Environmental stress
epi = Epithelia/epithelial
Epi. Diff/sq metaplasia = Epithelial differentiation/squamous metaplasia
GVHD = Graft vs host disease
KCS = Keratoconjunctivitis sicca
Lac = Lacrimal
Meibom = Meibomian
↓MG = Loss of meibomian glands
MGD = Meibomian gland dysfunction
NSS = Non-Sjogren syndrome
NSS/ACQ = Aqueous-deficient non-Sjogren syndrome
Nasolac = Nasolacrimal
NLD = Nasolacrimal duct
RA-MGD = Retinoic acid induced MGD
SCOP = Scopolamine
siRNA = Small interfering RNA
Spont DE = Spontaneous dry eye
SS = Sjogren syndrome
TALT = Tear duct-associated lymphoid tissue
TBUT = Tear breakup time
Undif KCS = undifferentiated keratoconjunctivitis sicca
↓Vit A = Vitamin A deficient
–Vit A = Vitamin A totally depleted

Table 1. Information matrix: human tear film

	KCS*	NSS	SS	MGD	Androgen Deficiency	Contact Lens/DE	Refs Refs
Tear Volume/Osmolarity:							
↑ Osmolarity, ↓ Volume	✓	✓	✓	✓	✓	✓	2-6
↑ Evaporation	✓			✓			1, 7-9
↓ Meniscus	✓	✓	✓	✓	✓	✓	5, 10-13
Correlation: Evaporation to osmolarity & lipid layer	✓						14, 15
↓ BUT, ↑ Surface tension	✓	✓	✓	✓	✓	✓	5, 12, 16-20
Mucins:							
↓ Glycoproteins, MUC5AC	✓		✓	✓			21-23
Lipids:							
Δ Lipid patterns, Distribution			✓	✓			24, 25
↓ Polar lipids	✓						26
↓ Lipid layer, ↑ Evaporation	✓						14
Proteins:							
Δ Proteins	✓						27, 28
↑ Plasmin levels	✓						29
↑ MMPs				✓			30, 31
↑ Inflammation markers, PRPs	✓			✓			32
↓ Lactoferrin							33
↑ Nine defensive molecules				✓			34
↓ Lysozyme, Lactoferrin							35
↑ Phospholipase A2 IIa	✓					✓	36, 37
Inflammatory Mediators:							
Proinflammatory cytokines: IL-1, IL-6, IL-8, TNF-α			✓	✓			38-40

*Type not defined

B. Animal Models of Dry Eye

Animal models discussed at the 1995 Workshop included a rabbit model in which the meibomian and lacrimal glands and the nictitans were ablated, which caused tear hyperosmolarity and ocular surface damage, mimicking the features of human DE.

New models and findings since the 1995 Workshop include: 1) mouse models of DE that employ scopolamine and environmental, dessicating stress that show increases in inflammatory cytokines and osmolarity in their tears; 2) neurturin-deficient mice that develop DE and have increased inflammatory mediators in their tear film; 3) a rabbit lacrimal gland ablation model that shows that treatment with dexamethasone reverses the decreased TFBUT and ocular surface damage; and 4) rabbit lacrimal gland denervation models that produce altered tear protein and lipid profiles (Table 2).

One critical area of investigation with respect to the existing evidence presented regards the need to correlate tear osmolarity, tear breakup, and the inflammatory stress

Table 2. Information matrix: animal tear film

	Rabbit	Mouse	Refs
Tear Vol/Osmolarity			
↑ Osmolarity + ↓ Tear volume	–Meibomian glands	Scop & Env Str	48-49
↑ Osmolarity, ↑ surface injury	–Lacrimal gland		50
↓ BUT, ↓ surface injury with dexamethasone	–Lacrimal gland		51
Lipids			
↑ Acylglycerols	–Lacrimal gland/nictitans		45
Lipids in rabbit/human match	–Lacrimal gland/nictitans		45
Proteins			
↓ Protein	–Nerves		52
↑ IL-1β		–Neurturin	53

response. To that end, immortalized human corneal and conjunctival epithelial cell lines are now available that have differentiation characteristics of native epithelia.[46,47] They will be useful to study effects of tear osmolarity, inflammatory mediators, and DE tears on surface epithelia.

Mass spectrometry, lipidomics, and proteomics in animal models of dry eye should be done to provide insight into the DE condition. Comparison of animal tear proteomes, lipidomes, and glycomes will help ascertain the most appropriate human-relevant models (eg, total chloroform extractables of rabbit tears match closely those of human tears).[45]

IV. OCULAR SURFACE

A. Human Disease

Aspects of dry eye surface pathology discussed at the 1995 Workshop included the lack of epithelial barrier function as demonstrated by increased dye uptake (with no data available on mechanism), an increased tear film osmolarity causing ocular surface damage, a loss of conjunctival goblet cells, and an increased squamous metaplasia of the surface epithelial cells (morphological observations).

New evidence since that report indicates that there are alterations in cell-surface and secreted mucins and in keratinization-related proteins expressed by epithelial cells. There also are alterations in corneal innervation density and sensitivity. Studies document increased conjunctival epithelial cell turnover. Evidence indicates that conjunctival epithelial cells are active in the immune response and are a source of inflammatory mediators[85] (Table 3).

Despite what is known, information about the tear film and ocular surface in dry eye disease is still deficient. It would be of value to determine the conjunctival epithelial proteome and glycome in a well-defined, staged, dry eye population compared to age- and sex-matched controls to identify common changes in apical surface components with disease. It is desirable to determine if age and sex, or a combination thereof, influence the effects of environmental stress on ocular surface epithelia. It is important to determine any genetic predictors of susceptibility to DE. Finally, a comparison of early intermittent stages of the disease to chronic disease may distinguish primary pathways causing DE from secondary responses associated with the disease.

B. In Vitro and Animal Models

Information gathered from in vitro and animal models as of the 1995 Workshop identified lack of barrier function as demonstrated by dye uptake in several animal models of dry eye, loss of goblet cells in several animal models of dry eye, and keratinization of ocular surface epithelium in vitamin A deficiency.

Since the 1995 Workshop, investigations have identified the role of membrane-associated mucins as a protective barrier (human epithelial cells in vitro), increased cell turnover (mouse experimental dry eye), and increased expression

Table 3. Information matrix: human ocular surface

	Undif KCS	NSS/ACQ	SS	CIC	↓ Vit A	Cont Lens	LASIK	Refs
Corneal and conj. epi. cell damage as indicated by dye penetrance — Fluorescein, lissamine green, rose bengal	✓	✓	✓	✓	✓	✓	✓	Well established
Mucins:								
↓ Goblet cells	✓	✓	✓	✓	✓	↑	✓	54-61
↓ MUC5AC	✓		✓					22, 23
Mucin glycosylation altered	✓					✓		62-65
Δ Glycosyltransferases				✓				66
Δ Membrane-associated mucins		✓	✓					22, 57, 65, 67
Δ Conj. Cell-Epithelial:								
↓ Microplicae			✓					68
Filamentary keratitis	✓							69
↑ Stratification	✓			✓				66, 70
Epi proliferation			✓					71
Δ Nuclear/chromatin structure	✓		✓					72-74
↑ Apoptosis	✓	✓	✓					75
Δ Innervation		✓	✓				✓	76-80
↑ Infection	✓							35, 81
↑ Keratinization related proteins			✓		✓			82-84
Inflammatory markers on conj. epi. cells	✓	✓	✓					75, 85

Table 4. Information matrix: animal ocular surface epithelium

	In vitro/human oc surf epi	Rabbit	Mouse	Rat	Dog	Refs
Goblet cells; mucins/glycoproteins:						
Rose bengal penetrance	–MUC16					86
↓ Goblet cells, MUC5AC		–Vit A –Meibomian gland –Neurotrophic keratitis	Scop & env str –/– Neurturin –/– I κβ–ζ	–Vit A		48, 53, 87-91
Δ Mucin glycosylation					Spont. DE	92
↓ Membrane associated mucins	–Vit A –Serum		–/– Neurturin	–Vit A		53, 89, 93, 94
↓ Glycogen		–Meibomian gland –Lacrimal gland –Neurotrophic keratitis				48, 50, 88
Epi. Diff/sq. Metaplasia:						
↑ Keratinization		–Vit A		–Vit A	Spont. DE	95-97
↑ Conj epi proliferation			Scop & env str			90
↑ Apoptosis			Scop & env str			98
↑ Inflammatory cytokines/MMPs:						
	+Hyperosmolar str		–/– Neurturin Scop & env str + Hyperosmolar str			49, 53, 99-101
Reversal of ocular surface defects/inflammation without meibomian gland:						
			EDA knockin			102

of inflammatory cytokines (mouse experimental dry eye). New mouse models have been developed as useful tools to study molecular mechanisms of ocular surface damage. Mouse models in which the lacrimal and/or meibomian glands are dysfunctional have allowed better characterization of ocular surface pathology (staining, goblet cell density, etc [Table 4]).

Given what is now known, additional research is needed to determine the role of ocular surface disease in the mechanism of tear dysfunction. A comparison of human and mouse tear and apical epithelial surface proteomes/glycomes would identify common components for validation of the animal models and facilitate interpretation of dry eye model data. Inducible models of specific dry eye diseases and models of chronic disease should be further developed. Importantly, mechanisms of goblet cell differentiation from epithelial stem cells and mechanisms of goblet cell loss need to be characterized, as goblet cell loss characterizes all forms of DE. It would be helpful to develop functional tests in vitro using siRNA techniques to elucidate the contribution of different cell surface molecules to the maintenance of corneal epithelial barrier function. Advanced genetic manipulation techniques using knockout, knockin, and knockdown animals to perform functional tests in standardized animal models of dry eye should be explored. Determination of the basis of fluorescein, lissamine green, and rose bengal staining is needed. It would be worthwhile to determine if epithelial-stromal interactions influence development of DE.

V. IMMUNE SYSTEM

A. Human Disease

Evidence from the 1995 Workshop indicated that SSDE is the result of an autoimmune disease in which response to autoantigens causes inflammatory destruction of the lacrimal tissue. The new evidence since the 1995 report indicates that proinflammatory cytokines and T-cell populations are increased in conjunctival tissue and lacrimal tissue in NSSDE as well as in SSDE. Chemokines and their receptors are increased in dry eye. Dry eye in graft vs host disease (**GVHD**) is associated with inflammation and immune cell infiltration of the lacrimal gland and ocular surface epithelia. The disease is also characterized by fibrosis associated with fibroblast and bone marrow-derived cell infiltration. It is clear that ocular surface epithelial cells can modulate inflammatory responses (Table 5).

Information is still lacking about the role played by the immune system in human tear dysfunction in DE. There is little or no information about the changes in cornea (vs tear film or conjunctiva) or the early changes in and role of immune factors causing disease. It is not known which changes are primary and which are secondary, information that is required in order to determine "cause and effect."

There is a need to determine more precisely the role of immunomodulatory proteins and peptides present in cornea and tear film (TGF-β, α-MSH, IL-1Ra, etc) and to delineate the role of innate immunity in dry eye disease (including lactoferrin, lysozyme, toll-like receptors, complement, kinin-kininogen, arachidonic acd metabolites, neuropeptides).

Table 5. Information matrix: human immune system/dry eye

	Undifferentiated KCS	NSS	Rosacea DE	SS	GVHD	Refs
Conjunctiva:						
↑ CD3, CD8 cells				✓	✓	103
↑ CD4 and T cells		✓		✓	✓	104-108
↑ Chemokine CCR5 receptor	✓	✓		✓	✓	109, 110
↑ Fas		✓				75
↑ ICAM-1					✓	111
Conjunctiva and Tears:						
↑ IL-1, TNF-α and IL-8, IL-6			✓	✓		38-40
Conjunctiva and Lacrimal Gland:						
↑ MHC class II, HLA-DR	✓	✓		✓	✓	75, 105, 107, 110-113
↑ CD40, CD40 ligand, CD80, CD86	✓	✓		✓	✓	75, 107
Fibrosis					✓	107, 108, 114
Lacrimal Gland:						
Lacrimal gland: ↑ CD4, T & B cells	✓			✓	✓	108, 115-117
↑ ICAM-1	✓				✓	107, 118
Inflammatory infiltrate		✓		✓		119, 120
Shared autoantigens, lacrimal & salivary gland		✓				115
↑ Fas-Fas ligand, IL-1β, IL-6, IFN-γ, vascular cell adhesion molecule-1 & intercellular adhesion molecule-1 Infiltrating lymphocytes, apoptosis		✓				121-123

B. In Vitro/Animal Models of Dry Eye—Immune System

The models and findings of the 1995 Workshop confirmed that cyclosporine A is effective in the treatment of a spontaneous canine dry eye model. New evidence available since the 1995 report indicates that IFN-γ can upregulate HLA-DR and ICAM-1 in human conjunctival cells, indicating that ocular surface cells can respond to and modulate inflammation. Mouse models of dry eye that employ either scopolamine and environmental stress or environmental stress alone show that ocular surface stress can induce the inflammatory/T-cell alterations seen in human dry eye. Evidence suggests that inflammation induced by desiccating stress is mediated by T-cells[126] (Table 6).

What questions can be answered or what promising types of basic research need to be done in model systems to determine the role of the immune system in the mechanism of tear dysfunction in DE? There is a dearth of information regarding understanding the role of T cells in the early immunopathogenesis of the ocular surface (vs lacrimal gland) disease in DE. The extent to which the ocular surface disease is T-cell-mediated needs to be clarified. It is also necessary to determine the role of autoimmunity in this disorder and the nature of the autoantigens. Studies are needed to characterize the effect of inflammatory cytokines on mucin genes and proteins. Delineation of the role of the innate immune system in dry eye syndrome is also needed (including

Table 6. Information matrix: animal immune system

	In vitro Animal	Rabbit	Mouse	Dog	Refs
IFN-γ ↑ HLA-DR, ICAM-1	Conj Primary Culture				124
Inflammation ↑ Conj, lacrimal gland apoptosis			Scop & Env Str	Spont. DE	96, 98
IFN-γ in TH1-type inflammations and DE			Scop & Env Str, Env Str		118, 125
T cells mediate local inflammation to eye drying			Scop & Env Str		126
Lac Inflammation & DE					
↑ T cells, CD4 especially			Autoimmune dacryoadenitis		127
↑ CD3 T cells; CD8, CD4			GVHD Model		128
↑ ICAM-1			MRL/lpr mice		118
↑ MHC class II		DE			129

lactoferrin, lysozyme, complement, kinin/kininogen, arachidonic acid metabolites, neuropeptides, toll-like receptors, and surfactant protein-D).

VI. HYPOTHESIS OF THE MECHANISM OF ACUTE AND CHRONIC INFLAMMATION IN DRY EYE DISEASE

The Cullen Symposium on Corneal & Ocular Surface Inflammation (Baylor College of Medicine, Houston. TX, January, 2005, *The Ocular Surface*, Vol. 3, Supplement) attempted to provide a unified mechanistic view of acute and chronic ocular surface inflammation (Figure 1), including that seen in DE.[130]

1) *Acute:* Irritation of the ocular surface (viral, bacterial, environmental) leads to rapid vascular endothelial selectin expression and diapedesis of non-primed (non-targeted) T-cells into the conjunctiva.

2) *Chronic:* Challenge to the ocular surface (over time) leads to activation and drainage of antigen-presenting (including dendritic) cells to lymphoid organs permitting T-cells to be primed and capable of targeting the ocular surface.

3) Symptoms correlate primarily with corneal epithelial damage, thought to be due to cumulative damage mediated by cytotoxic effects of inflammatory and pro-apoptotic stimuli, and hyperosmolarity. Concomitant with epithelial loss/devitalization is the stimulation of corneal nociceptive nerve endings

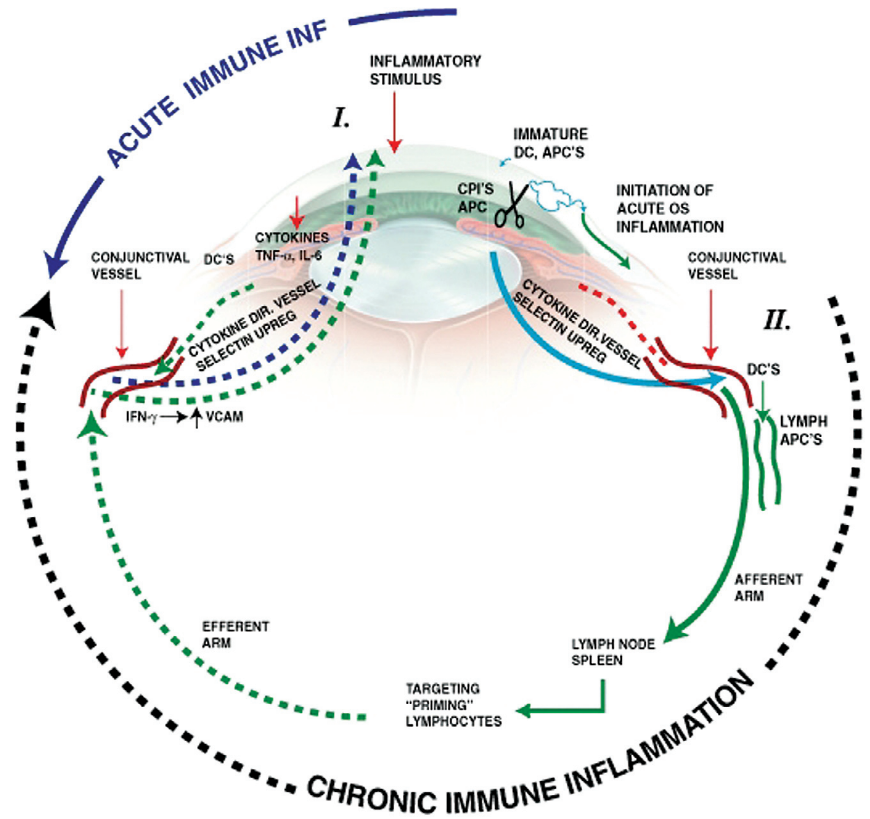

Figure 1. Hypothesis of the mechanism of acute and chronic immune inflammation.

I. Inflammatory stimuli (microbial antigens, trauma, UV light, hyperosmolar stress) initiate acute immune inflammation by stimulating production and release of inflammatory cytokines (eg, IL-1, TNF-α, and IL-6) by the ocular surface epithelial cells, which activate immature antigen presenting cells (APCs) and increased expression of adhesion molecules (eg, ICAM-1) and selectins by the conjunctival vascular endothelium, which facilitates recruitment of inflammatory cells to the ocular surface.

II. Chronic immune inflammation, which involves procurement and processing of antigens by ocular APCs that migrate to the regional lymph nodes and spleen via conjunctival lymphatics and veins, respectively, and prime naive T-cells. Primed CD4 T-cells travel to the conjunctiva, where they adhere to activated vascular endothelium and enter the tissue through diapedesis. Cytokines produced by activated T-cells, such as IFN-γ, amplify the immune response by increasing adhesion molecules (eg, VCAM) expression by conjunctival blood vessels.

APCs = antigen presenting cells; CPIs = corneal proteases; DC = dendritic cell; TNF-α = tumor necrosis factor alpha; IL-6 = interleukin 6; IFN-γ = interferon gamma. (Reprinted from McDermott AM et al. Pathways of corneal and ocular surface inflammation: a perspective from the Cullen Symposium. *Ocul Surf* 2005;3(4):S131-S138.)

VII. LACRIMAL/ACCESSORY LACRIMAL GLANDS/NASOLACRIMAL DUCT

A. Human Disease

Evidence from the 1995 Workshop indicated that the lacrimal glands of SSDE patients are infiltrated by lymphocytes and that tear secretion is decreased in volume. Some evidence suggested a potential Epstein-Barr virus infection link to dry eye, although this area was controversial. It was known that occluding the nasolacrimal duct improves ocular surface staining in DE.

Evidence accumulated since the 1995 Workshop has identified the lymphocyte types, Fas-Fas ligand expression, and apoptotic markers in lacrimal glands of SS patients. There is some evidence to suggest a link between hepatitis C and HIV infection with NSDE and SSDE. An autoantibody to the M3 muscarinic acetylcholine receptor has been identified, and increased serum levels correlate with decreased nasally stimulated Schirmer value and increased rose bengal staining score. There is an increase in lacrimal mucin in DE (Tables 7 and 8).

Questions remain to be answered about the role of the lacrimal gland, the accessory lacrimal glands, and the nasolacrimal duct in dry eye. Based on the current level of information, it would be useful to compare the lacrimal proteome in a population of well-characterized age/sex-matched normals to that of DE patients, as well as to compare the lacrimal proteomes of different KCS in order to identify potential biomarkers of the disease types.

Information is particularly lacking about the accessory lacrimal glands and the nasolacrimal duct in humans with dry eye disease. All histologic and immunohistochemical data on accessory lacrimal glands are from normal tissue;

no information is available regarding the glands in dry eye of any type. We do not know the extent to which they are affected in DE; because they are embedded in subconjunctival tissue at the ocular surface, they are an important therapeutic target for topical, lacrimal secretagogues. Gene expression in accessory glands, compared to the main lacrimal glands, is not defined. The relative contributions of accessory and main lacrimal glands to basal tear secretion or impairment of tear secretion are not known, and there is need for comparison of accessory and lacrimal gland gene expression.

Table 7. Information matrix: human lacrimal gland/nasolacrimal duct

	KCS	SS	GVHD	Aging	Refs
Lacrimal Gland					
Inflammatory infiltrate		✓	✓		107, 108, 119, 120
Shared autoantigens, lacrimal and salivary gland		✓			115
↑ FAS-FAS ligand, IL-1β, IL-6, IFN-γ, VCAM-1, ICAM-1, Infiltrating lymphocytes, apoptosis		✓			121-123
Viral etiology of hepatitis C, HIV, Epstein Barr	✓	✓			131-135
Autoantibodies to M3 muscarinic acetylcholine receptors		✓			136
Correlation: Serum autoantibody levels to Schirmer with nasal stimulation and rose bengal/ fluorescein staining		✓			137
↑ MUCs 4, 5AC & 5B in human lacrimal gland (4 cadavers with dry eye)				✓	138
↓ Innervation in lacrimal glands	✓	✓			139
↑ Fibrosis				✓	140
Nasolacrimal Ducts (NLD)					
Occluding nasolac. syst. (puntum plugs, etc.) improves oc. surf. DE	✓	✓			>100 refs.
DE & nasolac diseases occur frequently in middle to advanced-age women	✓	✓			141

Likewise, information is lacking on the nasolacrimal duct function in dry eye disease. Long-term studies of the benefit of punctal occlusion are lacking. Yen et al[150] found that ocular surface sensation and tear production decreased after temporary punctal occlusion in normal subjects. However, in normal subjects, there appears to be an autoregulatory mechanism that returns tear production and tear clearance to preocclusion levels 14 to 17 days after punctal occlusion, a mechanism that seems to be lacking in DE patients.[150] Thus, it could be suggested that the absorption of tear fluid components into the blood vessels of the surrounding cavernous body[151,152] could provide a signal for tear fluid production that ceases when tears are lacking. Studies are needed to characterize feedback systems in the nasolacrimal duct epithelia and blood vessels and their connections to the ocular surface system.

B. In Vitro/Animal Models

In the 1995 Workshop report, mouse models of SS had been identified, in which lacrimal inflammation was shown to be reduced by androgens.

Since the 1995 report, studies have been done with microarray analysis, showing dramatic changes in lacrimal gland gene expression after acute corneal injury in the mouse. Cytokines and chemokines have been identified in a mouse model of SS, as well as altered cholinergic function and neurotransmitter release. Alpha-fodrin has been identified as an autoantigen in the NFS mouse model of SS, and ICA69 is the autoantigen identified in the NOD mouse model of SS. Muscarinic receptors are autoantigens for SS in a rat model. It has also been demonstrated that nasolacrimal ducts can absorb labeled cortisol, an indication that absorption of tear components can occur within the duct (Table 9).

To validate animal models of dry eye, it may be important to characterize and compare the lacrimal gland transcriptome and proteome in both human and mouse. Comparing the proteomes of lacrimal glands from normal and DE mice could also be informative. It is also important to determine which signaling pathways are altered to cause the decrease in lacrimal gland secretion that occurs in aging mouse or rat models. Yet to be determined in animal models

Table 8. Information matrix: human accessory lacrimal gland (not DE relevant)

	Refs.
Acinar structure similar in accessory and main glands	142, 143
Secretory immune system of accessory and main gland similar	142, 144, 145
Innervation of accessory and main gland similar	146, 147
Protein secretion and signaling pathways similar in accessory and main glands	145, 148, 149

Table 9. Information matrix: animal lacrimal gland/nasolacrimal duct

	In Vitro	Rabbit	Mouse	Rat	Dog	Refs
Lacrimal Gland:						
Coculture of lacrimal acinar cells/ lymphocytes activates lymphocytes and cause inflammation in host lacrimal gland	Lacrimal gland	✓				153-157
↑ Lymphocytic infiltration, CD4, CD8; ↑ Fas, Fas-Ligand & cytokine			MRL/lpr mouse NOD mouse model of SS			158-166
Androgens ↓ inflammation, are immunosuppressive & decrease androgen receptors			MRL/Mp-lpr/ lpr mice; NZB/NZW F1 Mouse	Exp. autoimmune dacryoadenitis	Dog DE	161, 167-176
Lacrimal gland autoantigen or extract causes lymphocytic infiltration in lacrimal gland			Mouse in vivo	Rat in vivo		172, 173, 177, 178
Cholinergic function altered Sjögren's syndrome ICA69 is autoantigen			NOD mouse model of SS			179, 180
Lymphocytic infiltration blocks lacrimal gland secretion by preventing nerve release of neurotransmitters in Sjögren's syndrome			MRL/lpr mouse model of SS			181
α-fodrin is an autoantigen for the lacrimal gland and causes Sjögren's syndrome			NFS Mouse model of SS			182
↑ vulnerability to herpes infection				Cells of female lacrimal gland		174
Δ Lacrimal gland gene express. in corneal injury			Normal mouse			183
Nasolacrimal duct (NLD):						
^{3}H-cortisol incorporated from NLDs into rabbit blood		Absorpt. of lipophillic substances fr. tear fluid by epi. of NLDs		No absorption of lipophillic substance from tears by epi. of NLDs		184, 185
Anatomy useful for investigating NLDs		Comparative studies			Comparative studies	184-186
↓ Secretion ↓ Innervation ↑ Lipofusci			Aging model			187

is the role of myoepithelial cells in lacrimal gland dysfunction. It may be useful to determine, using the autologous lymphocyte rabbit model, if exposure of cryptic antigens through errors in recycling initiates SS. Determination of the cellular mechanisms used to induce autoimmune disease in the lacrimal gland could also employ the autologous lymphocyte rabbit model. This model could also be used to determine if the exocytotic process for protein secretion is a target for lacrimal gland dysfunction and to determine the role of lacrimal gland duct cells in lacrimal gland dysfunction through laser capture microdissection.

With regard to the nasolacrimal ducts, information is lacking regarding cells of the ducts, and cell lines of nasolacrimal duct epithelium are not currently available. Questions to be answered in animal models include whether the absorption of tear fluid components into the blood vessels of the cavernous body surrounding the nasolacrimal ducts changes or ceases in dry eye models, and what happens to drained tear fluid in the nasolacrimal passage.

VIII. MEIBOMIAN GLAND

A. Human Disease

The 1995 Workshop report documented decreased and/or altered meibomian lipids in DE, as well as morphologic abnormalities of the gland acini and tubules.

New evidence since the 1995 report identifies keratinization of ductal epithelium, orifice metaplasia, and reduced quality of meibomian gland secretions in people during aging, in patients taking antiandrogen therapy, and/or in women with Complete Androgen Insensitivity Syndrome (Androgen Deficiency). Correlations have been made between nutrient intake (eg, omega 3 fatty acids, vitamin B6, vitamin D) and the polar lipid profiles of meibomian gland secretions in women with SS. It has been determined that meibomian gland disease may be a contributing factor in over 60% of all dry eye patients (Table 10).

Information is still lacking about the role of the human meibomian gland in the tear dysfunction of dry eye. Factors influencing meibomian duct keratinization should be explored further, with the hypothesis (not new) that duct hyperkeratinization is a common factor and key event leading to meibomian gland disease (**MGD**) in both primary and secondary MGD.

Some clues may derive from the literature concerning epinephrine toxicity in the rabbit and, perhaps more relevantly, retinoid toxicity in humans. Clues may also be derived from an insubstantial but interesting literature suggesting that conjunctivitis (eg, allergic, chronic) or SS dry eye are associated with MGD, with the implication that mediators (proinflammatory or otherwise) might be transferred across the conjunctiva to the meibomian glands and ducts.

Investigative approaches could include:

1) A review of the literature of keratinization processes in multiple epithelia;
2) A review of the mechanism of retinoid action and genetically regulated processes involved with keratinization, in mucosae, transitional epithelia (like the meibomian ductal epithelium) and in skin;
3) A comparative review of potential points of interaction of signaling pathways under retinoid control and pathways under adrenergic, particularly alpha adrenergic, control, with respect to the keratinization process;
4) Attention to the histochemistry and electronhistochemistry of keratinization at the cellular levels, markers of keratinization;
5) A search for retinoids or other compounds capable of blocking or reversing the action of anti-acne retinoid compounds;
6) Clinical studies of the comparative frequency of MGD in eyes treated with adrenergic agonists for glaucoma, particularly where agonists are used unilaterally.

We need to know the minimum number of glands required to provide an adequate lipid layer for tear film function and the molecular mechanisms leading to loss or to morphologic abnormalities of the meibomian gland. Determining how the lipid layer is attached to the aqueous layer and whether this changes in DE is important, as is defining the role of lipocalin and other lipid carriers in tear film stability. We need a comprehensive qualitative and quantitative evaluation of the meibomian gland secretions of normal subjects and DE patients, obtained with modern analytical techniques, in particular, using liquid chromatography/mass spectrometry to determine if the molar ratio of the critical lipid species that are present in the meibomian gland secretions changes with the development of DE. It would be helpful to create an artificial model of the tear film lipid layer that mimics the lipid composition of the meibomian gland secretions collected from normal subjects and has similar biophysical properties. Questions exist as to the etiology of meibomian gland obstruction, eg, why doesn't a chalazion form with every obstruction?

Additionally, we need to know more about age-related changes in meibomian gland function and the relationship between meibomian gland obstruction and nutrition. The role of lipids in lubricity of the lid and ocular surfaces should be clarified. Is there a role of the lid wiper and lid wiper epitheliopathy within MGD?

B. In Vitro/Animal Models

Relatively little was known about animal models for MGD at the time of the 1995 Workshop other than that keratinization of the duct epithelium existed in the epinephrine rabbit models. Since then, new models and findings have provided the knowledge that androgen deficiency, which in humans is associated with meibomian gland dysfunction, alters the lipid profiles of meibomian gland secretions, and causes tear film instability and evaporative dry eye. Androgen deficiency in mice and

Table 10. Information matrix: human meibomian gland

	KCS	Chr Bleph	MGD	NSS	SS	Androgen Deficiency	Aging	Cont Lens	Refs
Meibomian gland loss/ obstruction/distortion decreased secretions		✓	✓	✓18.5%	✓60%		✓	✓	6, 188-195
Δ Lipid profiles						✓	✓	✓	36, 196-198
Keratinization, orifice metaplasia						✓	✓		5, 10
Melting pt. of lipid 3° higher than normal			✓						199
Bacterial strains associated with Chr Bleph		✓							200
↑ Fluorescein, rose bengal			✓						195
Δ Lipid layer; ↑ Thickness	✓					✓	✓	✓	36, 197, 198, 201, 202

Table 11. Information matrix: animal meibomian gland

	Rabbit	Mouse	Hamster	Refs
↓ MG, Conj. erythema	RA-MGD model	–/– EDA	RA-MGD model	102, 203, 204
↑ Ductal keratinization	MGD/epinephrine model			205
↑ Sterols and ceramides	MGD/epinephrine model			206
Atrophic MG with ocular surface damage		–/– ACAT-1		207
↓ Androgens Δs Lipids, gene expression in meibomian gland	castrated male model	castrated male model		208-210

rabbits is associated with altered lipid profiles and gene expression in meibomian glands (Table 11).

A number of questions remain to be answered, and basic research using model systems is needed to determine the role of the meibomian gland in various forms of DE and in the mechanism of tear dysfunction. Most importantly, we need to determine the structure and composition of the lipid layer and its change in experimental MGD. It is necessary to determine which components of the meibomian secretion actually spread on the tear film and what change in composition is required to effect a significant change in the melting point and expressibility of oil. Finally, we need to understand the structure of the lipid layer and how it changes in MGD.

IX. MECHANISMS UNDERLYING DRY EYE PATHOLOGY

Based on data derived from the information accumulated in the preceding reports, it was the opinion of the group that insufficient information was available to define the basic mechanism underlying dry eye, but that a hypothesis as to the mechanisms might be advanced. The evidence suggests that dry eye is multifactorial: factors such as age, hormonal status, genetics, sex, immune status, innervation status, nutrition, pathogens, and environmental stress alter the cellular and molecular structure/function of components of the ocular surface system. The term and concept of the *Ocular Surface System* was adopted by consensus agreement at the DEWS Meeting, Miami, Florida, May 2006.

The "ocular surface system" is defined as *the wet-surfaced and glandular epithelia of the cornea, conjunctiva, lacrimal gland, accessory lacrimal glands, nasolacrimal duct and meibomian gland, and their apical and basal matrices, linked as a functional system by both continuity of epithelia, by innervation, and the endocrine and immune systems* (For further explanation see Gipson, 2007[211]). Also included in the ocular surface system are portions of the eye lids. The rationale for the description of the unit as the *Ocular Surface System* is several-fold. First, the primary functions of the system are to provide a smooth refractive surface to the cornea (the ocular surface) and to protect and maintain that surface. Thus, the name *Ocular Surface System* is linked to its primary function at the ocular surface. Second, all the epithelia of the ocular surface are in continuity and derived embryologically from surface ectoderm. The corneal and conjunctival epithelium are in continuity through the ductal epithelium, with the lacrimal gland, glandular epithelium, as is the case with the accessory lacrimal glands, the meibomian gland, and the nasolacrimal system. The glandular systems are essentially invaginations from and specializations of the ocular surface epithelium. Thirdly, all regions of the epithelia produce components of the tear film. The functions of the various regions of the continuous epithelia are integrated by the nervous system, endocrine system, immune system, and vascular system, and are supported by the connective tissue with its resident cells. Finally, dry eye disease affects and is detected on the ocular surface.

*The term *Ocular Surface System* represents an elaboration of the *Lacrimal Functional Unit*, which has been previously described by Stern, Pflugfelder, and Beuerman[212-215] and is discussed in detail elsewhere in this supplement (Chapter 1: Definition and Classification).[216] Alterations in one or several components of the ocular surface system or its secretions results in changes in the tear film or corneal epithelial surface composition (eg, tear osmolarity, volume), leading to susceptibility to desiccation and epithelial damage (as evidenced by dye penetrance). Epithelial damage leads to release of inflammatory mediators. Attendant inflammation amplifies and sustains further damage by chronic deregulation of the ocular surface system.

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*Note added by writing committee

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*Index compiled by Marilyn Rowland.

f = figure; *t* = table

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DEWS Disclosures

Disclosures of financial/proprietary relationships of DEWS participants with companies with products or interests related to dry eye

STEERING COMMITTEE MEMBERS

Christophe Baudouin has received financial support from Alcon, Allergan, Pfizer, Santen, and Thea. He has been a consultant to Alcon, Allergan, Bausch & Lomb, Novagali, Pfizer, Santen, and Laboratoires Théa and is currently consulting for Allergan, Novartis, Pfizer and Novagali.

Anthony J. Bron has a personal financial interest in OcuSense. He has been a consultant to Acucela, Alcon, Novartis, OcuSense, Proctor and Gamble, Senju, and Takeda, and he has received gifts from Alcon, Allergan, and Takeda. Currently, Professor Bron is a consultant for Actelion, Acucela, Canfite Novagali, OcuSense, Proctor and Gamble and Takeda. He receives meeting support from Alcon, and Allergan.

Murat Dogru has no proprietary interest in any company with products or interests related to dry eye.

Gary N. Foulks has received financial support from Alacrity, Allergan, Inspire, Lantibio, Novartis, and Otsuka and he has a personal financial interest in Inspire. He is, or has been, a consultant to Alacrity, Alcon, Alimera Sciences, Allergan, Bausch & Lomb, Fovea, Inspire, ISTA, Lantibio, Nascent, Novagali, Novartis, OcuSense, Otsuka, and Pfizer, Santen, Sarcode and XTL Biopharmaceuticals. He has received gifts from Alacrity, Alcon, Bausch & Lomb, Inspire, Otsuka, and Pfizer.

Ilene K. Gipson has received financial support from Alcon.

Michael A. Lemp has received financial support from Addition Technologies, Alcon, Allergan, Bausch & Lomb, Inspire, Novagali, Novartis, Pfizer, OcuSense, and Santen. He is a consultant for Otsuka Research Corp. and Fovea Pharmaceuticals. He has a personal financial interest in Inspire and OcuSense, and he is Chief Medical Officer of OcuSense.

J. Daniel Nelson has no proprietary interest in any company with products or interests related to dry eye. He is listed on a patent for dry eye that is held by the University of Illinois.

Kelly K. Nichols has a personal financial interest in Inspire, and she is a consultant to Alcon, Allergan, and Inspire.

Stephen C. Pflugfelder has received support from Allergan, and he is a consultant to Allergan. He is listed on two patents held by the University of Miami that relate to dry eye disease.

Debra A. Schaumberg has received financial support from DSM Pharmaceuticals, Daiichi, and Pfizer Consumer Healthcare, Inc. She has a personal financial interest in OcuSense, and she is a consultant to OcuSense.

Janine A. Smith is named on a patent held by the US government.

David A. Sullivan has received financial support from Allergan, and has serverd as a consultant to Allergan and Novartis. He is named as the inventor on patents for Sjogren Syndrome and Keratoconjunctivitis Sicca treatments held by the Schepens Eye Research Institute.

Alan Tomlinson has received financial support from Allergan, Renaissance Pharmaceuticals, and Pfizer. He has a personal financial interest in Bausch & Lomb.

Kazuo Tsubota has received financial support from Etech and Santen, and he is a consultant to Nidek and Rainbow. He is named on multiple patents both in the U.S. and Japan that relate to dry eye disease.

SUBCOMMITTEE MEMBERS

Mark Abelson is president of Ophthalmic Research Associates, a company that provides consulting and research services to many ophthalmic industries.

Julie Albietz has no proprietary interest in any company with products or interests related to dry eye.

Pablo Argüeso has received financial support from Alcon.

Penny Asbell serves as a Speaker Bureau consultant to Alcon, Allergan, Bausch & Lomb, Inspire, Novagali, Novartis, Otsuka, Pfizer, Santen, and Vistakon Pharma.

Jules Baum has no proprietary interest in any company with products or interests related to dry eye.

Carolyn Begley has received financial support from Alcon Research, Allergan, and Vistakon. She is a consultant to Alcon and Novartis.

Roger Beuerman has received financial support from Advanced Ocular Systems and Allergan, and he is a consultant to both companies.

Stefano Bonini has received financial support from Alcon, Allergan, Bausch & Lomb, Novartis, SIFI and SOOFT. He is a member of the Anabasis Society, SrL, which holds rights to a patent for the use of NGF as it relates to the treatment dry eye disease.

Ig**or Butovich** has no proprietary interest in any company with products or interests related to dry eye.

Barbara Caffery has no proprietary interest in any company with products or interests related to dry eye.

Margarita Calonge is a consultant to Allergan.

Reza Dana has received financial support from Allergan, Biogen-Idec, and Johnson & Johnson. He is a consultant to Johnson & Johnson.

Darlene Dartt has received financial support from Johnson & Johnson and Otsuka. She is a consultant to Johnson & Johnson, and holds a patent with that company. She has received gifts from Johnson & Johnson and Alcon.

Desmond Fonn has received financial support from Advanced Medical Optics, Alcon, Allergan, Bausch & Lomb, Ciba Vision, CooperVision, and Johnson & Johnson Vision Care. He is a consultant to Ciba Vision, and he has received gifts from Ciba Vision and CooperVision.

Daniel Gamache is employed by Alcon and is named on many of its patents related to dry eye disease.

Gerd Geerling is a consultant to Pfizer Health Care and Novartis Pharma. He holds a patent application for a dry eye product. The patent has not been assigned.

Eiki Goto has no proprietary interest in any company with products or interests related to dry eye.

Franz Grus has no proprietary interest in any company with products or interests related to dry eye.

Bryan Ham has no proprietary interest in any company with products or interests related to dry eye.

Marcia Jumblatt has no proprietary interest in any company with products or interests related to dry eye.

Shigeru Kinoshita has received financial support from Alcon Japan, Alblast Ltd, Otsuka, Senju, and Santen. He is a consultant to Advanced Medical Optics, Otsuka and Senju.

Donald Korb has a personal financial interest in Ocular Research of Boston and Kolis Scientific. He is an employee of and holds patents with both companies.

Friedrich Kruse has no proprietary interest in any company with products or interests related to dry eye.

Peter Laibson has no proprietary interest in any company with products or interests related to dry eye. He is on the Speakers Bureau for Bausch & Lomb.

James McCulley is a consultant for Alcon Laboratories.

Juan Murube has no proprietary interest in any company with products or interests related to dry eye disease.

Gary Novack owns and operates PharmaLogic, which provides editorial and consulting services to industry.

George Ousler is employed by Ophthalmic Research Associates, a company that provides consulting and research services to many ophthalmic industries.

Jerry Paugh's employing institution has received financial support from Alcon, Allergan, and Bausch & Lomb.

Friedrich Paulsen has no proprietary interest in any company with products or interests related to dry eye.

Ian E. Pearce has received support from Allergan, Pfizer, and Sequani, Ltd. He is a consultant to Pfizer, and he has received gifts from Pfizer.

Maurizio Rolando has received gifts from Alcon and Pfizer.

Oliver Schein has received financial support from Bausch & Lomb, Novartis, and he has received financial support from CIBA (inactive). He is a consultant to Bausch & Lomb.

Jun Shimazaki has no proprietary interest in any company with products or interests related to dry eye.

Michael Stern is employed by Allergan.

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Deborah Sweeney has no proprietary interest in any company with products or interests related to dry eye.

John Tiffany is a consultant to Pfizer Consumer Healthcare. He holds a patent for lipid-containing eyedrops (no longer active).

Ikuko Toda has no proprietary interest in any company with products or interests related to dry eye.

John Ubels has no proprietary interest in any company with products or interests related to dry eye. He is a consultant for Alcon Research, Ltd.

Hitoshi Watanabe has no proprietary interest in any company with products or interests related to dry eye.

Mark Willcox has received financial support from CIBA, Alcon, Allergan, Clearlab International Pte, and Ocular Sciences (CooperVision). He currently receives funding from Alcon, Allergan, Bausch & Lomb, and CIBA Vision.

Clive G. Wilson has received financial support from industries in the fields of gastroenterology and ocular drug delivery unrelated to dry eye. He is a consultant to Allergan (retinal drug delivery) and to GlaxoSmithKline (biopharamaceutics).

Norihiko Yokoi has no proprietary interest in any company with products or interests related to dry eye.

INDUSTRY LIAISON COMMITTEE

Fouad Amer is employed by Novartis.

Michael J. Brubaker is employed by Alcon.

Timothy Comstock is employed by Bausch & Lomb.

David Eveleth is employed by Pfizer.

William Florida formerly employed by Novartis.

Fulvio Foschini is employed by SOOFT.

Sherryl Frisch formerly employed by Pfizer, now Johnson & Johnson, McNeil Consumer Health Care Group

Jeff Gilbard is employed by Advanced Vision Research and is a consultant to that company.

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Ami Shah formerly of Bausch & Lomb

Masatsugu Nakamura is employed by Santen.

Ian Vessey is employed by Novartis.

NON-MEMBER ATTENDEES

Piero Biondi is employed by SOOFT.

Elizabeth Fini is employed by Bascom-Palmer Eye Institute.

Sebastiano Giuffrida is employed by Bausch & Lomb.

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Kevin Stanley formerly of Alcon Laboratories.