International Workshop on Meibomian Gland Dysfunction: The Report

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

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Membership

Steering Committee

- Kelly K. Nichols, OD, PhD (chair)
- Gary N. Foulks, MD (vice-chair)
- David A. Sullivan, PhD (organizer)
- Anthony J. Bron, FRCS (consultant)
- Murat Dogru, MD
- Michael A. Lemp, MD
- Kazuo Tsubota, MD
- Ben J. Glasgow, MD

Subcommittee Chairs

- J. Daniel Nelson, MD, & Jun Shimazaki, MD (definition)
- Erich Knop, MD, PhD (anatomy)
- Kari Green-Church, PhD (lipid)
- Debra A. Schaumberg, ScD, OD, MPH (epidemiology)
- Alan Tomlinson, MCOpt, PhD (diagnosis)
- Gerd Geerling, M (management)
- Penny A. Asbell, MD (clinical trials)
- David A. Sullivan, PhD (industry liaison)

Objectives

- Conduct an evidence-based evaluation of meibomian gland structure and function in health and disease
- Develop a contemporary understanding of the definition and classification of MGD
- Assess methods of diagnosis, evaluation and grading of severity of MGD
- Develop appropriate norms of clinical trial design to evaluate pharmaceutical interventions for the treatment of MGD
- Develop recommendations for the management and therapy of MGD
- Create an executive summary of recommendations for future research in MGD

Timeline

- Late 2008 - Early 2009: Steering Committee and Subcommittee meetings begin
- March 2009: First outlines due
- May 2009: A plenary session of all Workshop participants post-ARVO
- September 15: Rough draft reports due
- January 2010: Final Workshop reports due, review/ comment period begins
- April – Nov. 2010: Manuscript revision/ preparation
- Planned publication of full report in IOVS early 2011
- Workshop Symposia: ARVO, BCLA, EVER, WOC, TFOS Conference, AAOptom, AOA, ISOPT, APAO and others

A Grateful Thanks to Our Sponsors

Meibomian Gland Dysfunction Definition & Classification

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J. Daniel Nelson, M.D. (Co-Chair)
Jun Shimazaki, M.D., Ph.D. (Co-Chair)
Jose M. Benitez-del-Castillo, M.D., Ph.D.
Jennifer Craig, Ph.D., MCOptom
James P. McCulley, M.D.
Seika Den, M.D., Ph.D. & Gary N. Foulks, M.D.

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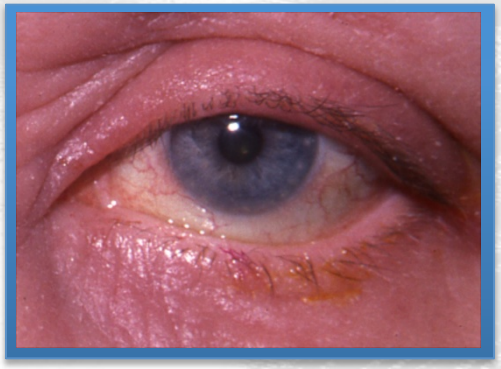
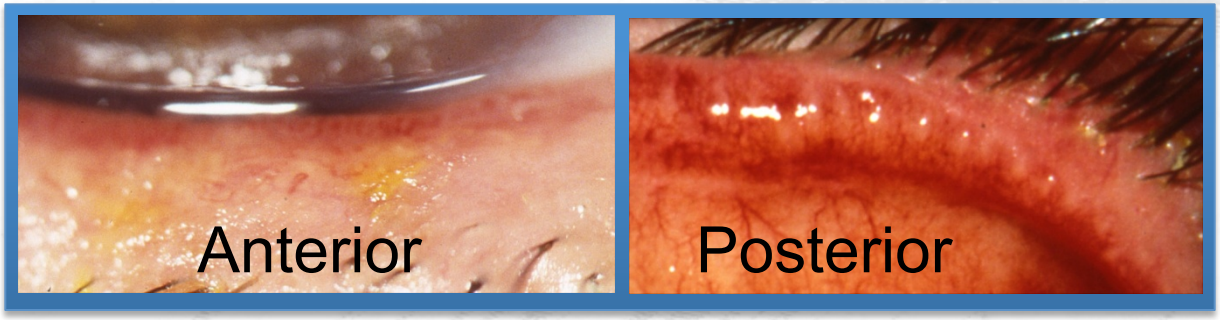
Definitions

Blepharitis

- *Blepharitis*: inflammation of the whole lid



- *Marginal blepharitis*



Posterior Blepharitis

- Inflammation of the posterior lid margin

Meibomian Gland Dysfunction (MGD)

- Functional abnormalities of the MG
- Emphasizes the important role of MG
- Meibomian gland disease
  - Broader range of meibomian gland disorders
  - Neoplasia and congenital disease

Meibomitis/Meibomianitis

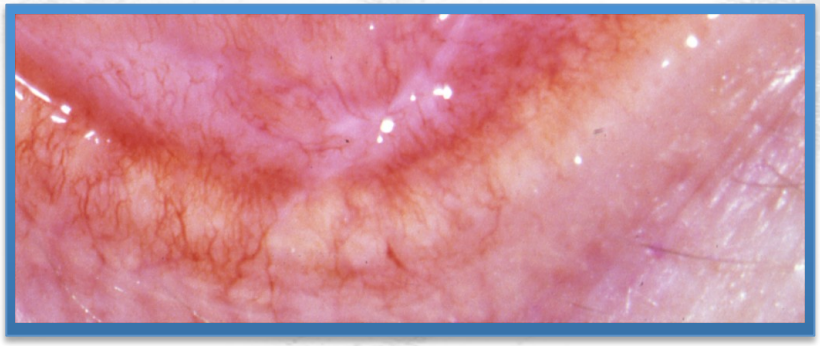
- Subset of disorders of MGD
- Infection associated with MG inflammation
- Terms not general enough

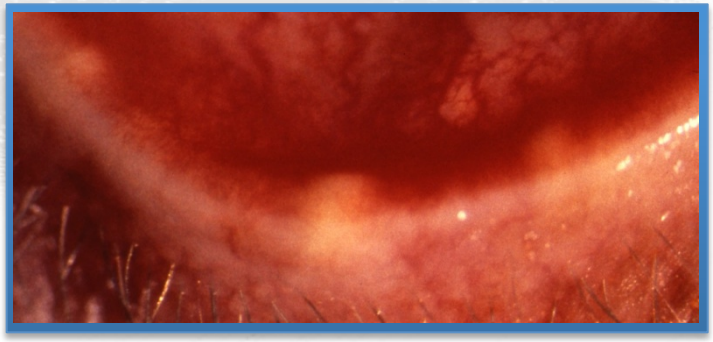
Hypersecretory MGD

- *Hypersecretory MGD vs Seborrheic MGD*
- Confusion with *seborrheic dermatitis*
- More appropriate, clinically understandable

Obstructive MGD

- Obstruction of meibomian ducts & orifices
- Cicatricial and Non-Cicatricial





Hyposecretory MGD

- Decreased MG secretions
- With and without duct or orifice obstruction
- Glandular atrophy

Definition of MGD

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.

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Previous Classification Systems

- Gifford (1921)- Blepharoconjunctivitis
- McCulley (1982)- Blepharitis
- Mathers (1991)- Chronic Blepharitis
- Bron (1991)- MG Disease
- Foulks and Bron (2003)- Chronic MG Disease
- Japan MGD WG* (2010)- Obstructive MGD

*In Press

Recommended Classification 2010

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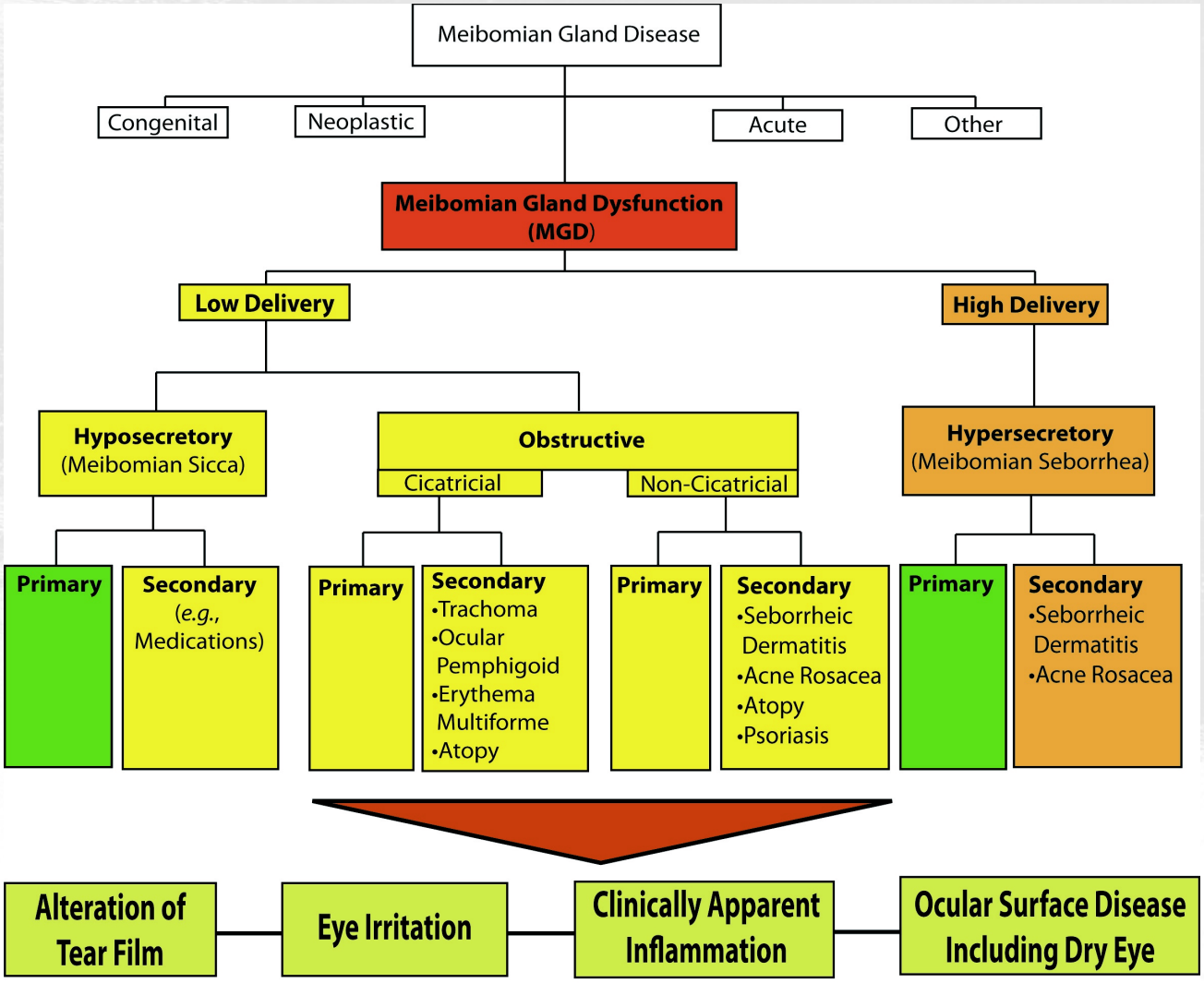

QUESTIONS?

Anatomy, Physiology and Pathophysiology of the Meibomian Gland

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A Report from the International Workshop on Meibomian Gland Dysfunction

Erich Knop, M.D., Ph.D. (Chair)
Nadja Knop, M.D., Ph.D.
Thomas J. Millar, Ph.D.
Hiroto Obata, M.D.
David A. Sullivan, Ph.D.

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Meibomian Gland - ANATOMY

- **Meibomian Glands**

  (tarsal glands)

  –first mentioned:

  - **Galen** (200 AD)

    –Greek physician and anatomist

  –more precisely described

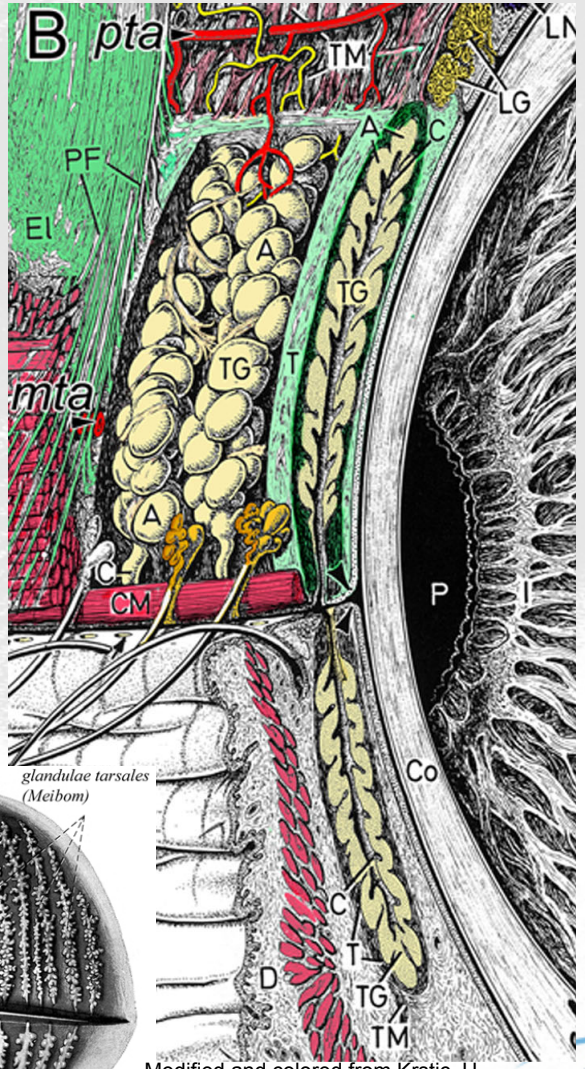
  - **Heinrich Meibom** (around 1666)

    –German physician and anatomist in Helmstedt, Germany

From Herzog August Bibliothek, Wolfenbüttel, Germany ,
(reproduced from Knop N & Knop E
Ophthalmologe 2009; 106:872–883)

Meibomian Gland - ANATOMY

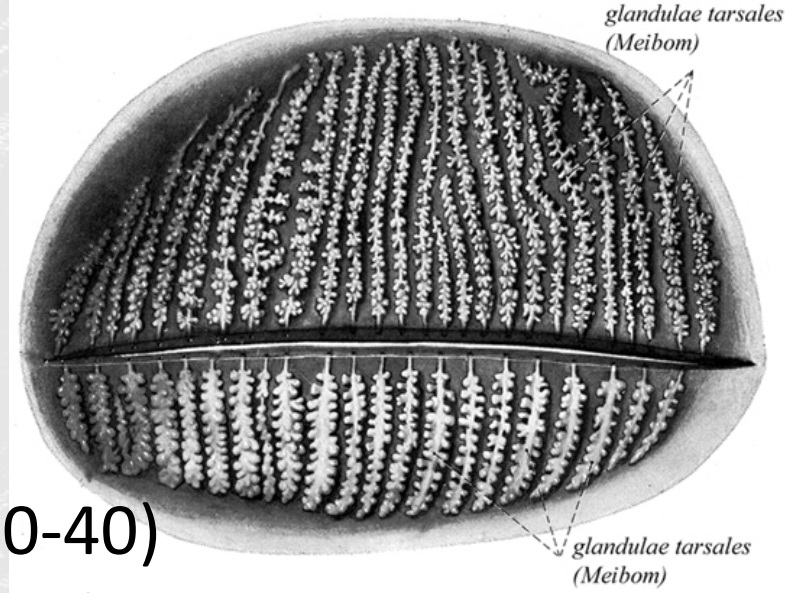
- **Large sebaceous glands**
- without direct contact to hair follicles
- located in the tarsal plates
  - of the upper and lower eye lids



Modified and colored from Krstic H. Human microscopic anatomy. Springer Medizin Verlag 1991, (reproduced from Knop N & Knop E Ophthalmologe 2009; 106:872–883)

Meibomian Gland - ANATOMY

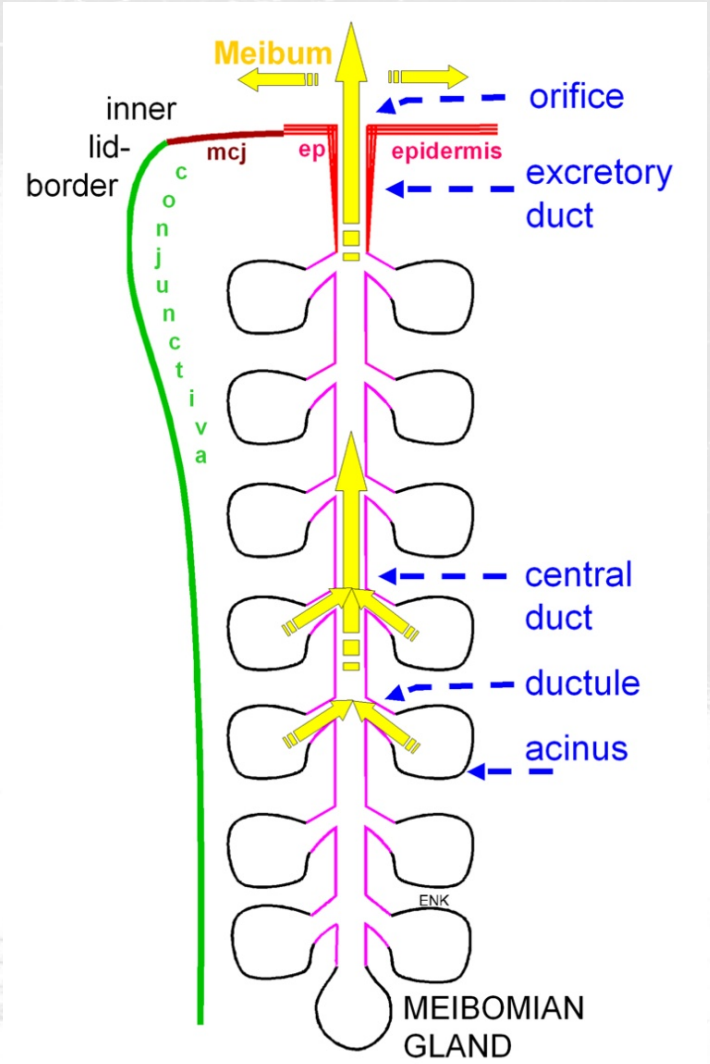
- **Dimensions**
  - **Length**
    - follows the tarsus
  - **Number**
    - more in upper lid (30-40)
    - less in lower lid (20-30)
  - **Volume**
    - higher in upper lid (26µl vs. 13µl)
  - Relative functional contribution (upper vs. lower) to the tear film lipid layer is unknown



Modified from Sobotta Atlas der Anatomie des Menschen. Urban & Schwarzenberg Verlag 1982, (reproduced from Knop N & Knop E. Ophthalmologe 2009; 106:872–883)

Meibomian Gland - ANATOMY

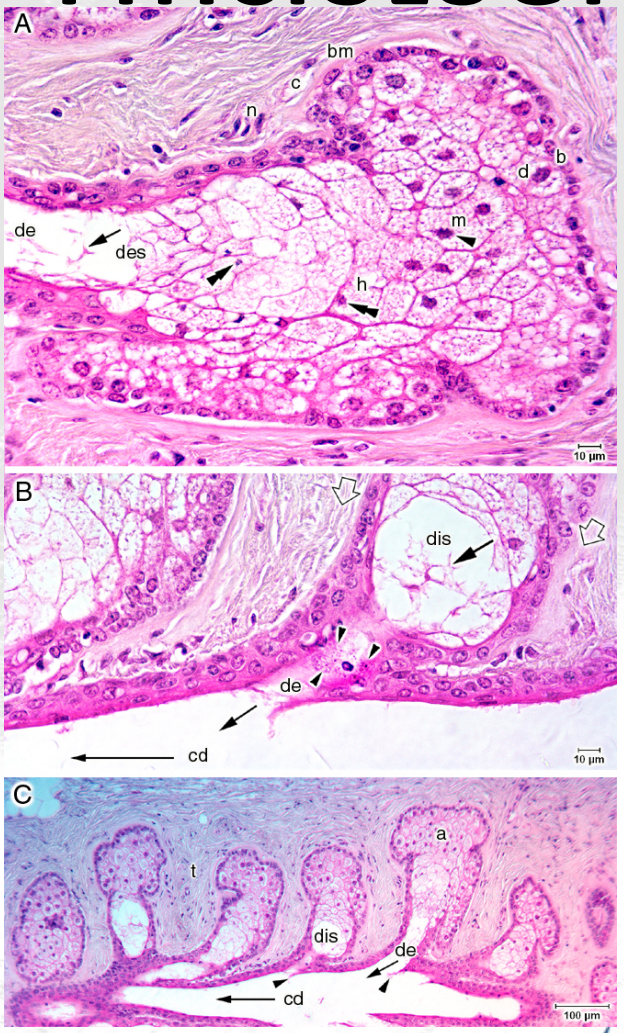
- **Separate straight tubular glands**
- Complex arrangement of
  - Excretory duct
    - opens at posterior lid margin
    - in-growth of epidermis
  - Central duct
  - Lateral ductules
  - Secretory acini



From Knop N & Knop E. Meibom-Drüsen,Teil I Anatomie, Embryologie und Histologie der Meibom-Drüsen. Ophthalmologe.2009;106:872–88

Meibomian Gland - PHYSIOLOGY

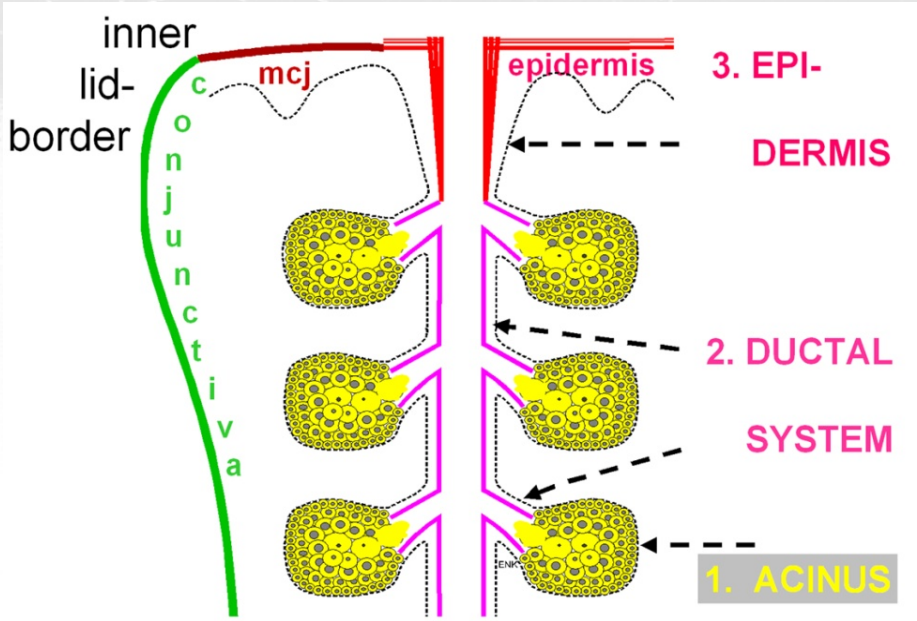
- **Holocrine glands**
  - Acini filled by secretory cell (meibocytes)
- Basal cells divide
  - mature by synthesis and accumulation of lipids
- Eventually the whole cells disintegrate and form the oily product (meibum)

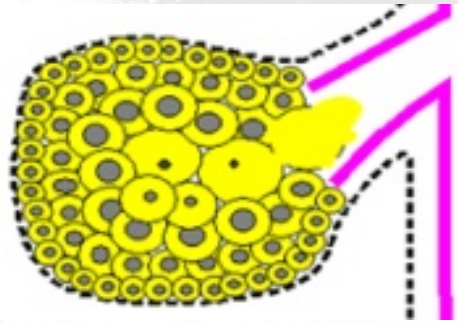


From Knop N & Knop E. Meibom-Drüsen,Teil I Anatomie, Embryologie und Histologie der Meibom-Drüsen. Ophthalmologe 2009;106:872–88

Meibomian Gland – CELL DYNAMICS

- **Progenitor cells**
  - are constantly dividing in the basal layer (every 4d)
  - migrate towards the center of the acinus (within 9d)
- The stem cell source is presently unknown

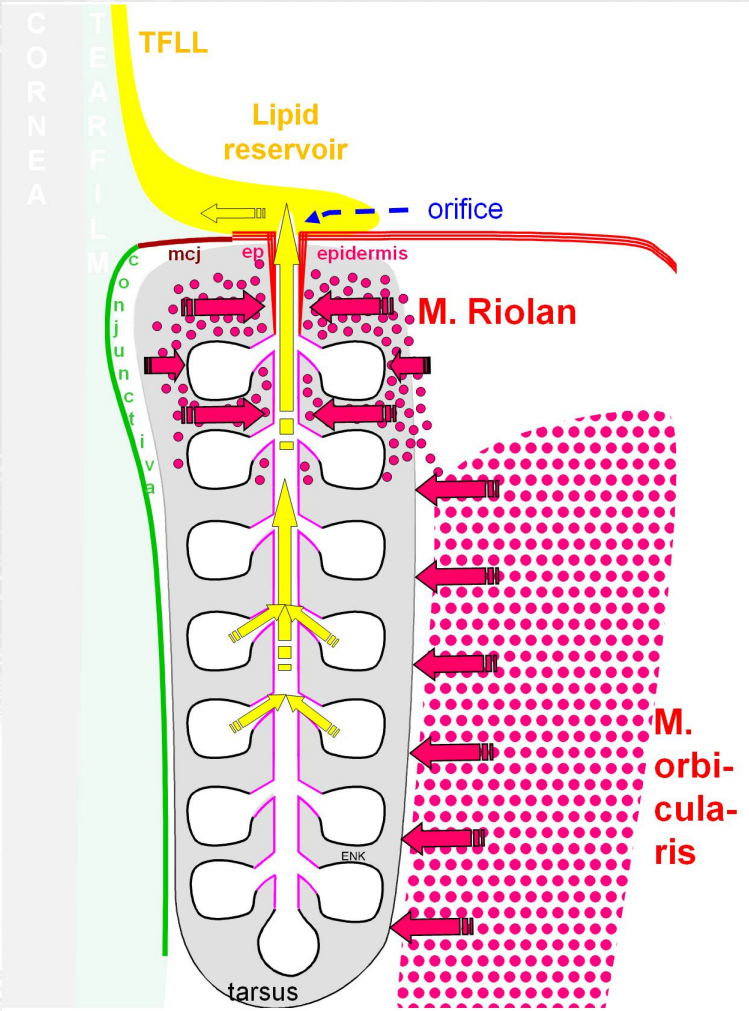




From Knop N & Knop E. Meibom-Drüsen,Teil I Anatomie, Embryologie und Histologie der Meibom-Drüsen. Ophthalmologe 2009;106:872–88

Meibomian Gland - PHYSIOLOGY

- **Delivery**
  - occurs with **muscular contraction** during lid movement
    - Riolans muscle
    - Orbicularis
- **Secretion**
  - generates a **secretory force** by a constant cell biological process of holocrine secretion

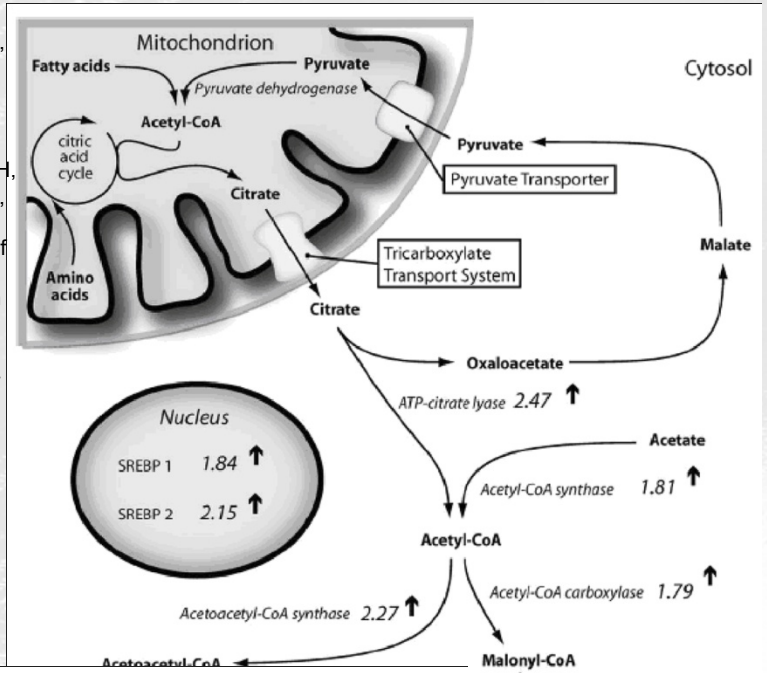


From Knop E, Knop N, Schirra F. Meibom-Drüsen Teil II. Physiologie, Eigenschaften, Verteilung und Funktion des Meibom-Öls. Ophthalmologe 2009;106:884–892

Meibomian Gland – LIPIDOGENESIS

- **Meibomian lipids** are produced by the cellular machinery of the meibocytes
- important cell organelles are
  - Mitochondria
  - Peroxisomes
- produce Polar and Non-polar lipids

From Exp Eye Res 83, Schirra F, Richards SM, Liu M, Suzuki T, Yamagami H, Sullivan DA, Androgen regulation of lipogenic pathways in the mouse meibomian gland, 291–296, 2006



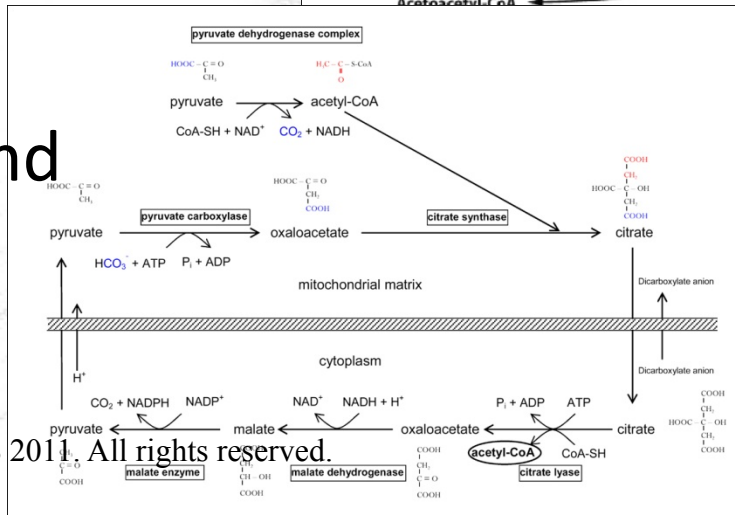


Figure courtesy of Tom Millar

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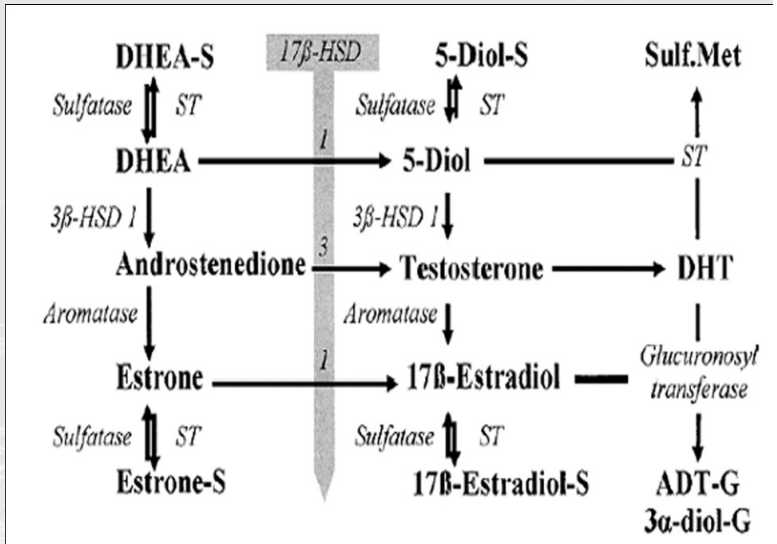
Meibomian Gland – REGULATION

- Meibomian glands have a distinct **innervation**
  - in contrast to ordinary sebaceous glands
- They are also prominently regulated
  - by **hormones**
    - **Androgens** act positive
    - **Estrogens** act negative on gland function
    - Hormonal metabolism is performed locally inside the glands
  - and by other soluble factors



From Schirra F, Suzuki T, Dickinson DP, Townsend DJ, Gipson IK, Sullivan DA. Identification of steroidogenic enzyme mRNAs in the human lacrimal gland, meibomian gland, cornea, and conjunctiva. Cornea.2006;25:438–442

Meibomian Gland – PATHOLOGY

- **In MGD the meibomian orifices are obstructed** by plugs of thickened opaque secretum with keratinized cell material (pouting)
- this is frequently non-obvious (underestimated)

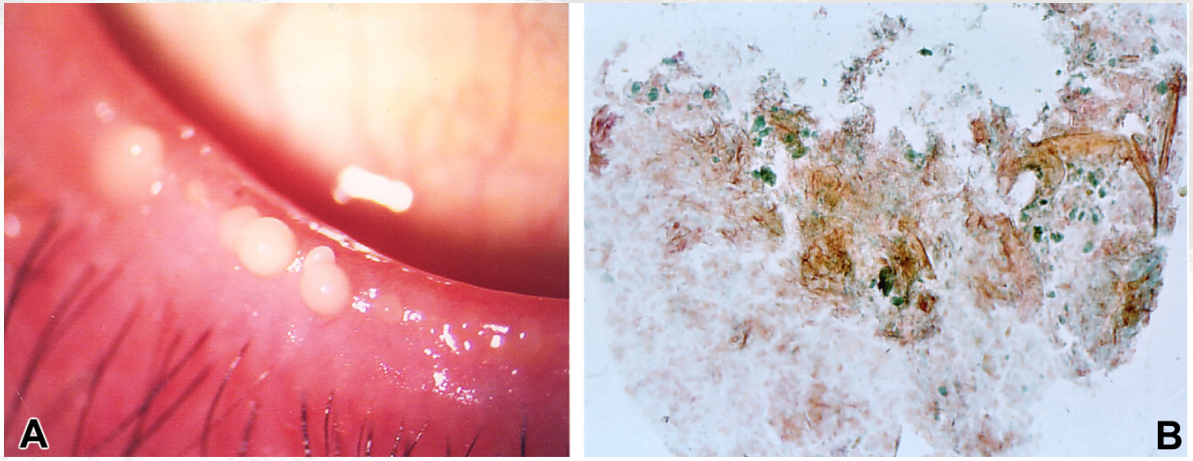
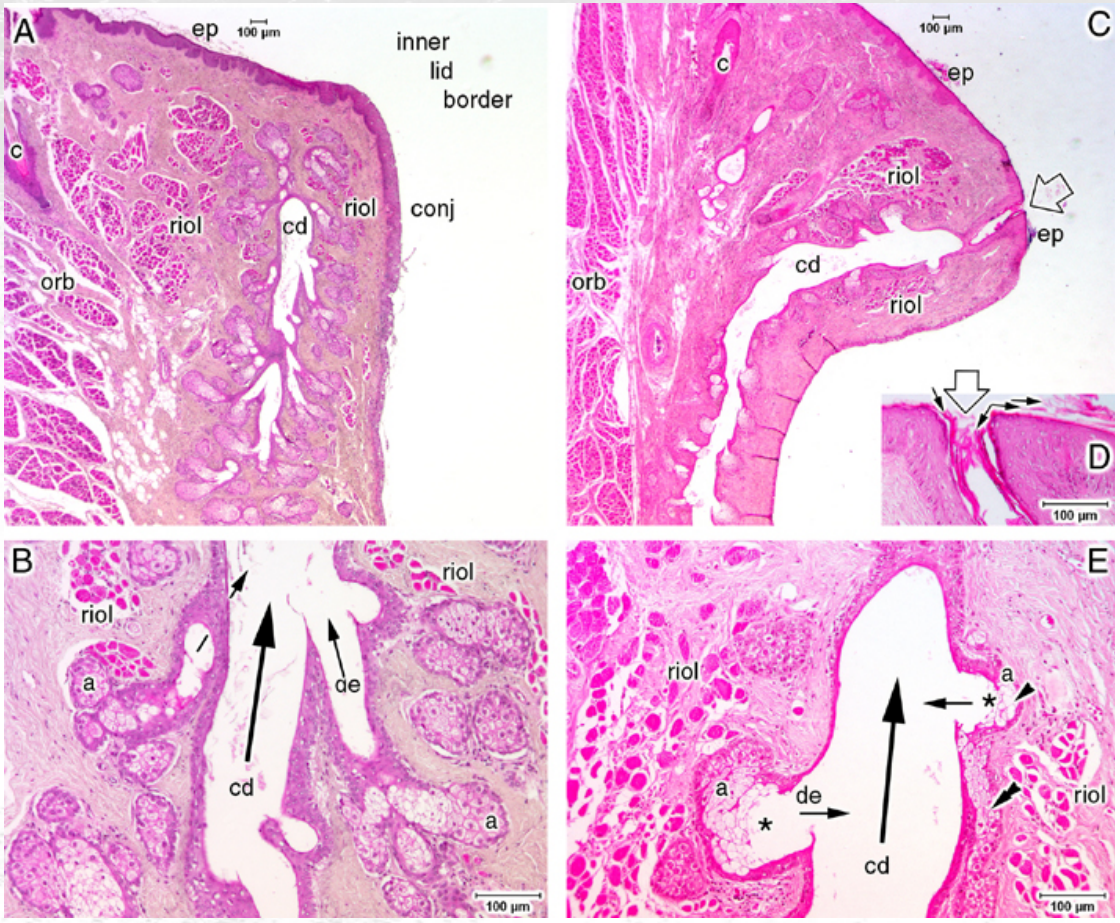


Figure courtesy of Hiroto Obata

- => reduced delivery of meibum onto lid margin
- => deficiency of the tear film lipid layer

Meibomian Gland – PATHOLOGY

- Obstruction of orifices
- Mainly by Hyper-keratinization of the ductal epithelium
- Together with a thickening of the secretum



normal **obstructed**

From Knop E, Knop N, Brewitt H, Rieck P, Seitz B, Schirra F. Meibom-Drüsen Teil III. Meibomdrüsen Dysfunktionen (MGD) – Plädoyer für ein eigenständiges Krankheitsbild und wichtige Ursache für das Trockene Auge. Ophthalmologe.2009;106:966–979

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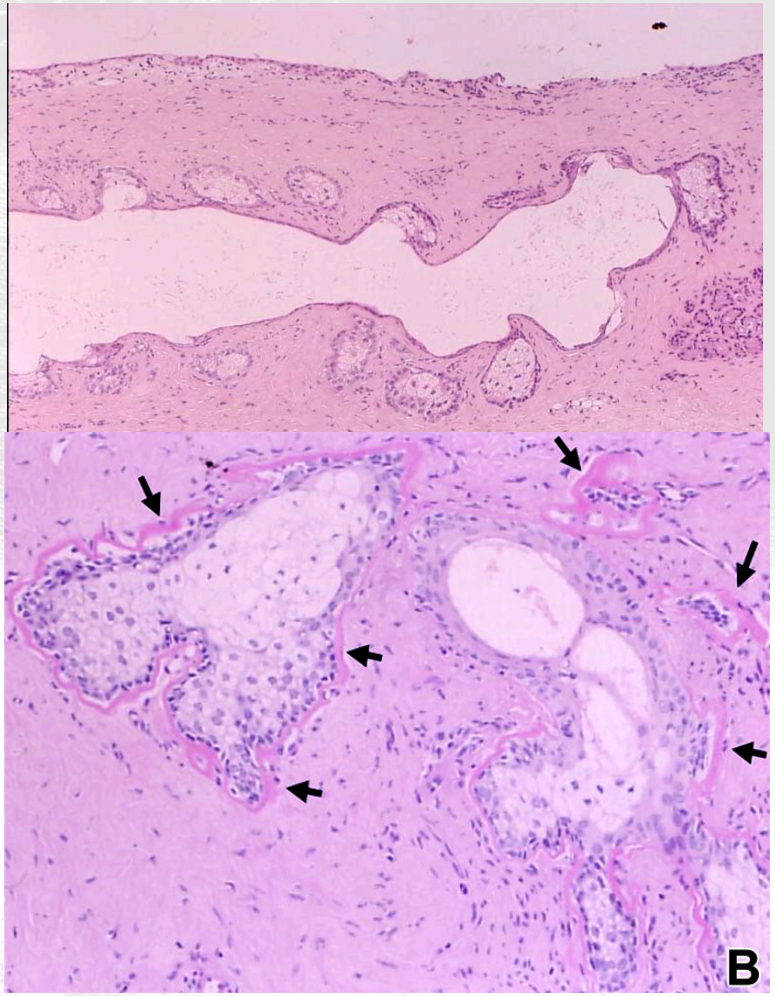
Meibomian Gland – PATHOLOGY

- Prolonged stasis can lead to a **progressive destruction** of the glandular structure

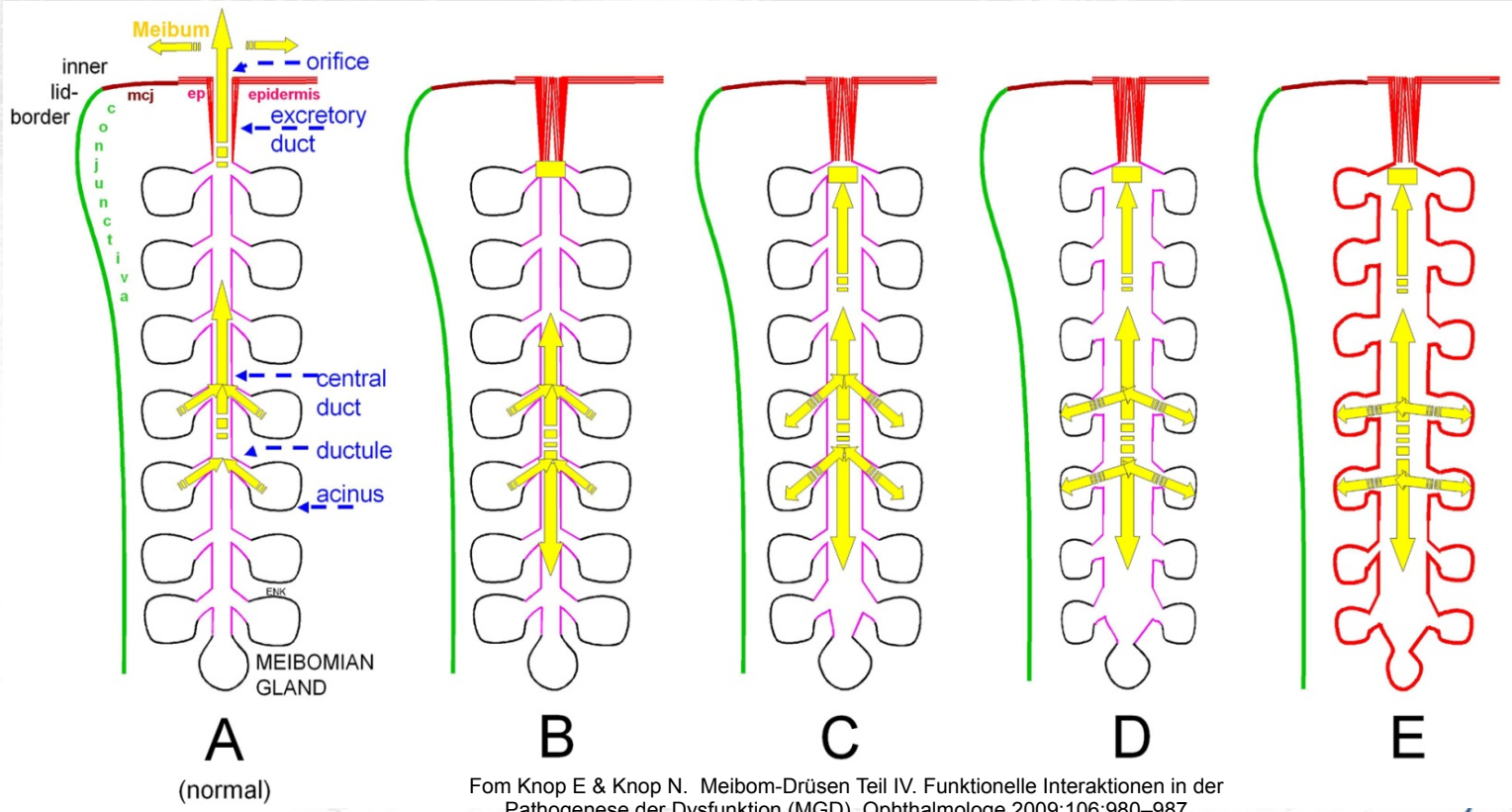
- This occurs apparently without prominent involvement of inflammatory cells



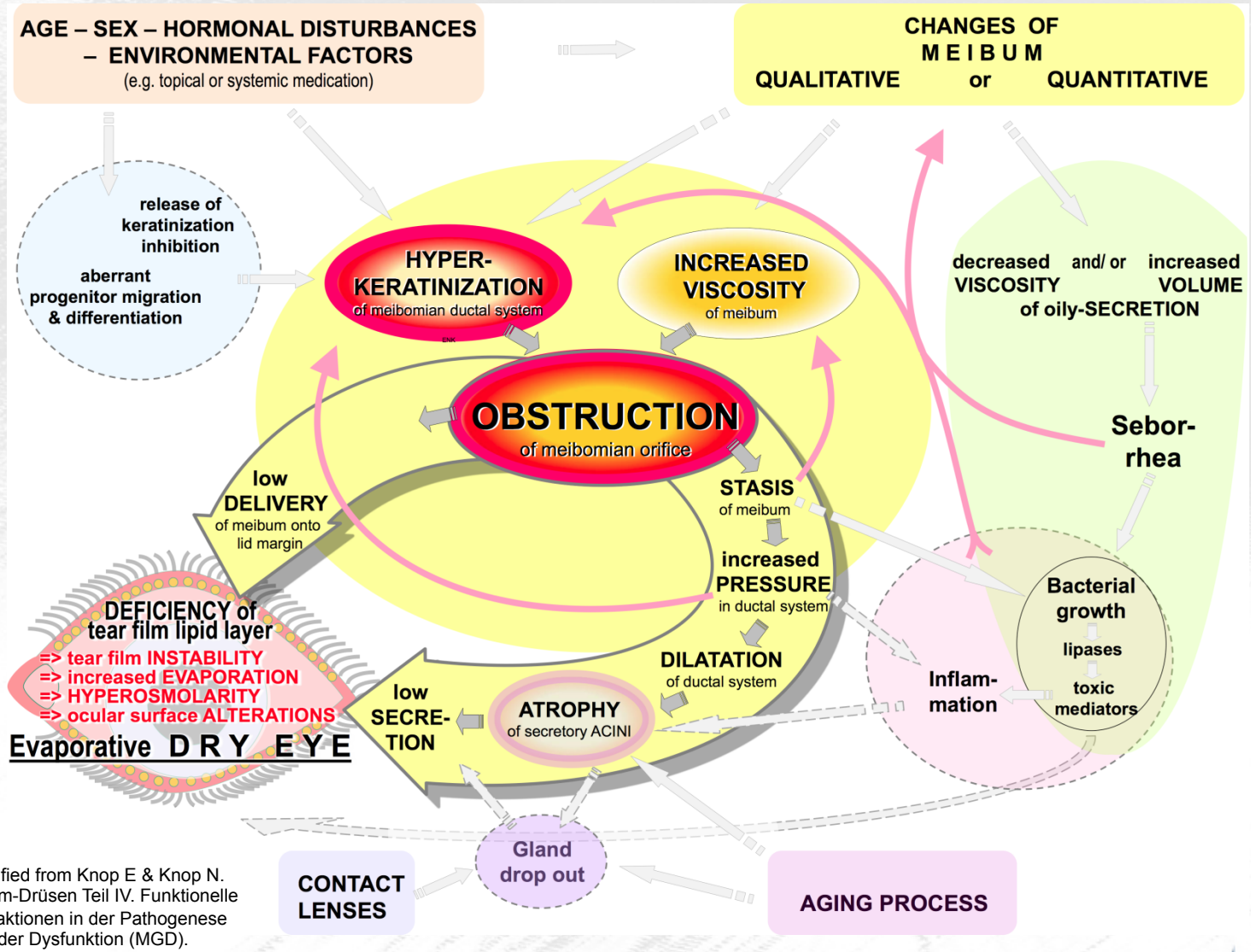
From Obata H, Horiuchi H, Miyata K, Tsuru T, Machinami R. Histopathological study of the meibomian glands in 72 autopsy cases. Nippon Ganka Gakkai Zasshi.1994;98:765–771

Meibomian Gland – PATHOLOGY

- **Obstructive MGD leads to a progressive ductal DILATATION and acinar ATROPHY**



Fom Knop E & Knop N. Meibom-Drüsen Teil IV. Funktionelle Interaktionen in der Pathogenese der Dysfunktion (MGD). Ophthalmologe.2009;106:980–987



Modified from Knop E & Knop N. Meibom-Drüsen Teil IV. Funktionelle Interaktionen in der Pathogenese der Dysfunktion (MGD). Ophthalmologe.2009;106:980–987

Interacting Pathways in MGD

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QUESTIONS?

Tear Film Lipids, and Lipid-Protein Interactions, in Health and Disease

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Kari B. Green-Church, Ph.D. (chair)
Igor Butovich, Ph.D.
Mark Willcox, Ph.D.
Douglas Borchman, Ph.D.
Friedrich P. Paulsen, M.D., Ph.D.
Stefano Barabino, M.D., Ph.D.
Ben J. Glasgow, M.D.

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- Analytical Methods for Lipids
- Chemical Properties of Lipids
- Lipids in Human Meibum
- Lipids of Human Tears
- Lipids of Animal Tears and Meibum
- Lipid Changes of Disease
- Bacterial Influence- Tear Film Lipids
- Lipids on Contact Lens
- Tear Lipid Protein Interactions
- Tear Film Lipid Layer- the model

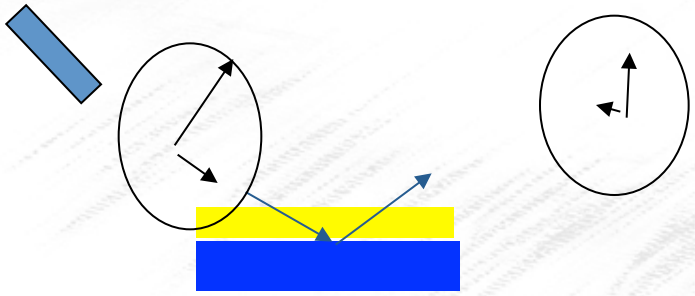
Tear film Thickness

Confocal Microscopy

Optical Coherence Tomography

Reflectometry

Ellipsometry- potential for Å resolution



Tear Film Thickness

- Ehlers 1965 8 µm
- Benedetto 1975 4 µm
- Green 1975 4 µm
- Danjo 1994 10 µm
- King-Smith 2000 2.7 µm
- Wang 2003 3.3 µm

- OVERALL 5 µm

- Prydal 1992 34-46 um

Lipid Layer Thickness

- MacDonald 1968- 100-370nm
- Norn 1979- 102 nm
- Olsen 1985- 40 nm
- Korb 2002- 87 nm
- Goto 2003- 74 nm
- King-Smith 2010- 42 nm (15-157)
- Contribution of lipid layer to tear thickness 0.3-7%

Analytical Methods- Lipids

- IR/Raman Spectroscopy- overview lipids
- Thin layer chromatography- lipid classes
- NMR- major lipid classes
- HPLC (High Pressure Liquid Chromatography)
- Mass Spectrometry-

  HPLC-MS, GC-MS, ESI, APCI, MALDI, MS/MS

Infrared Spectroscopy

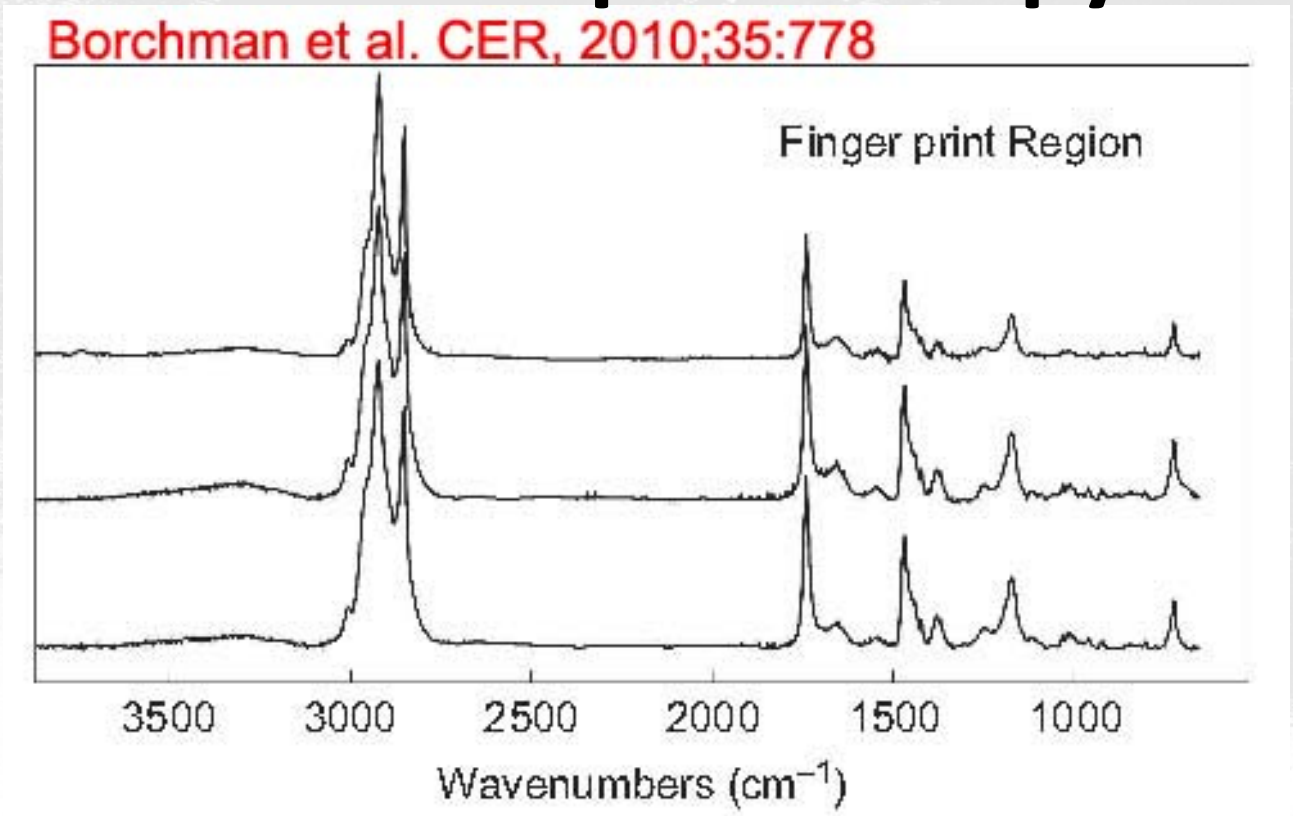


FIGURE 1 Average infrared spectra of normal human meibum from (top) under 13 years old; (middle) 13 to 50 years old; (bottom) over 50 years old.

Greiner et al, Arch Dermatol Res 1998;290:298-305

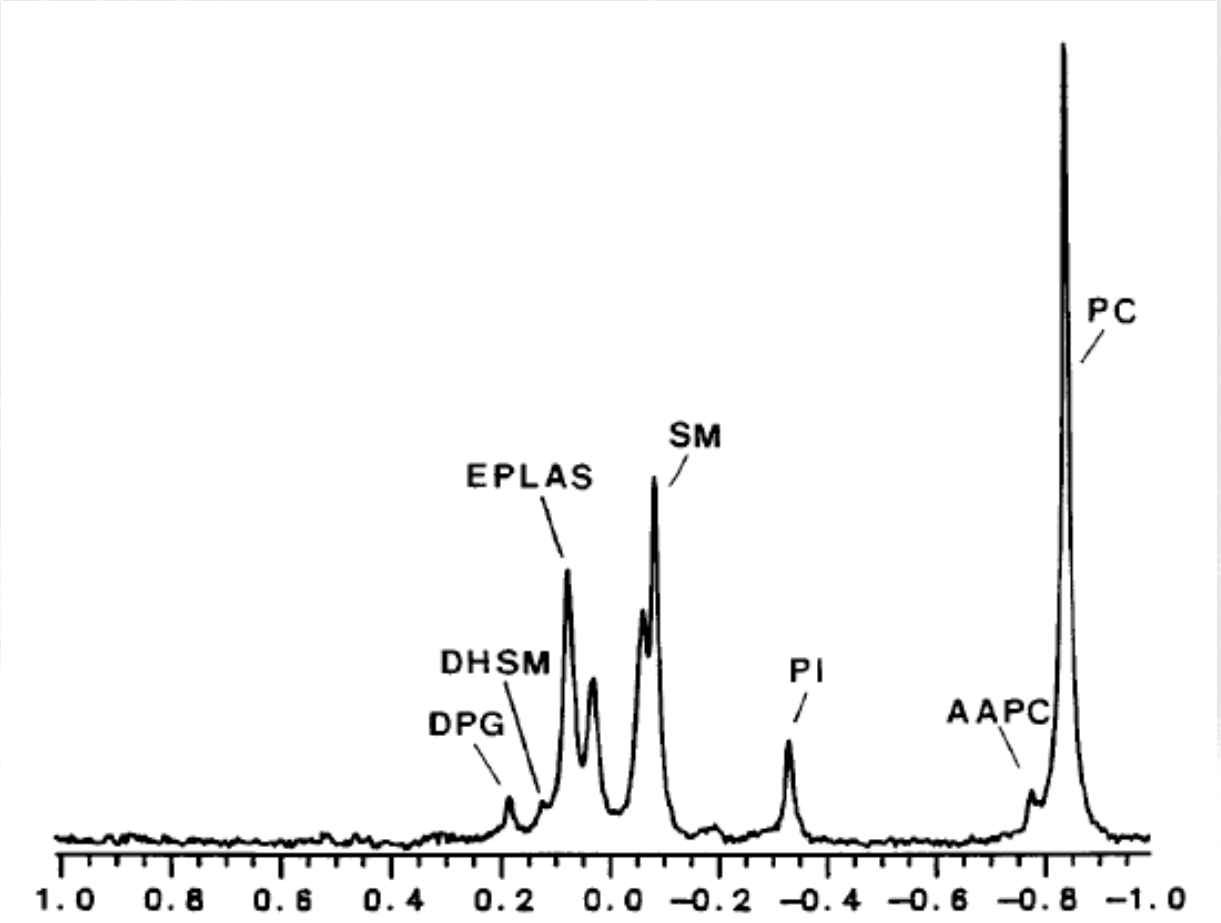
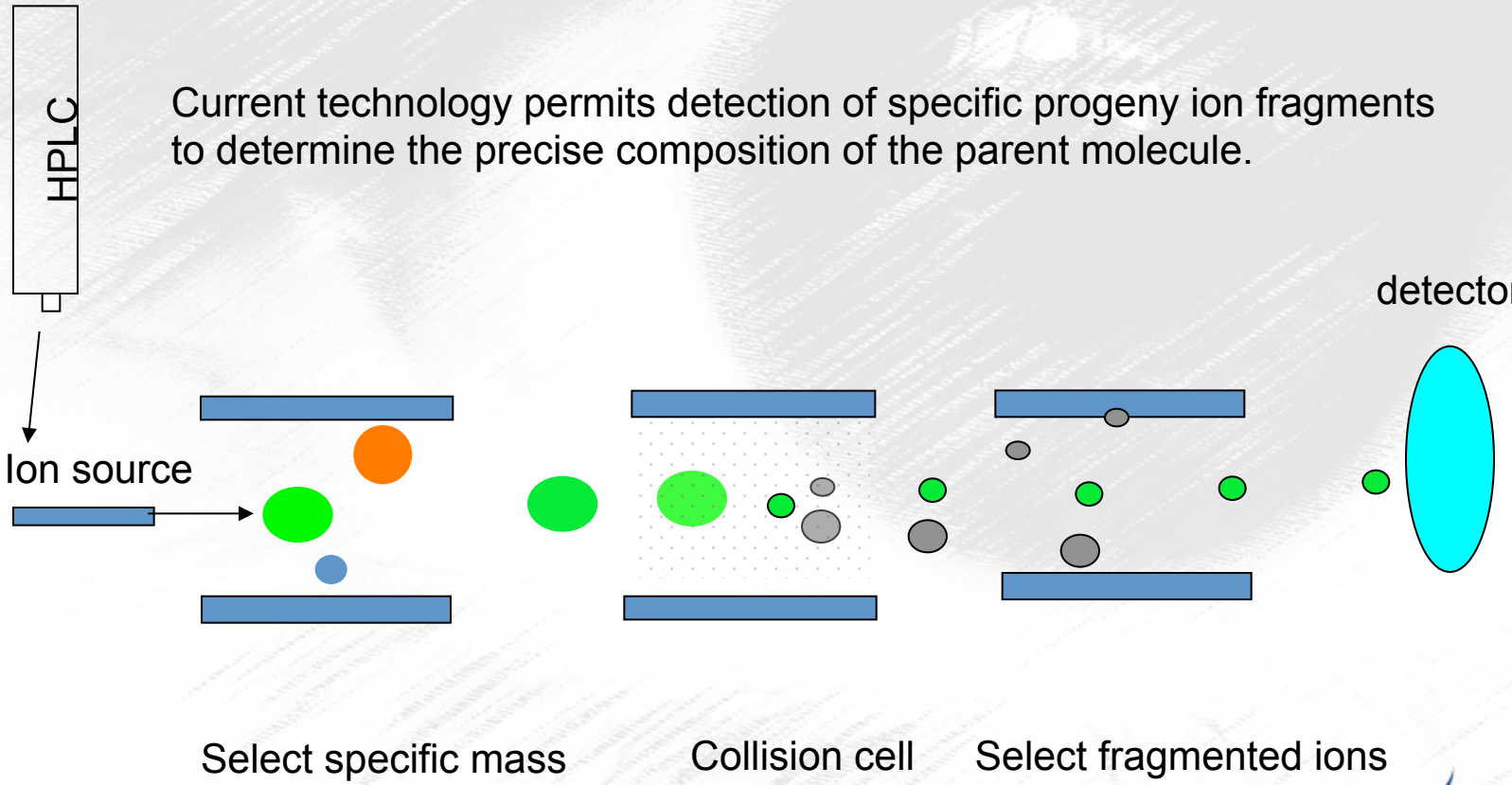


Fig. 1 ^{31}P NMR spectral phospholipid profiles of healthy human eyelid epidermis (*top spectrum*) and dermis (*bottom spectrum*)

Mass Spectrometry

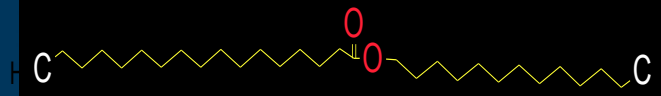
Current technology permits detection of specific progeny ion fragments to determine the precise composition of the parent molecule.



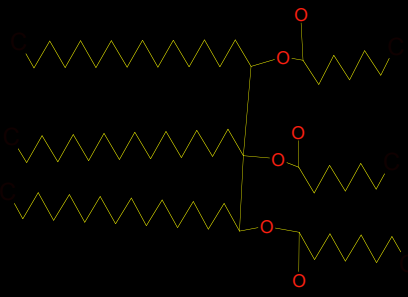
TYPES OF LIPIDS IN MEIBUM (%) of TOTAL

Non-polar Lipids

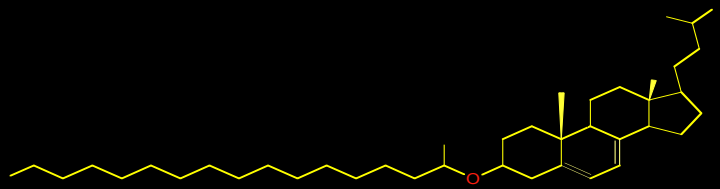
- Wax esters 13-68%



- Triacylglycerols 2-43%



- Cholesteryl esters 8-39%

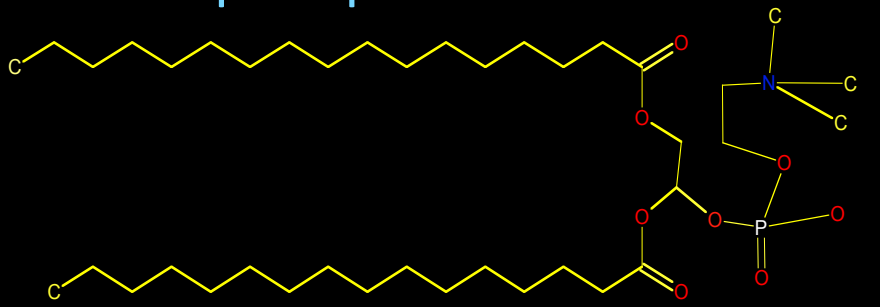


- Hydrocarbons 7.5-36%

Polar lipids

- Fatty acids 0-24%

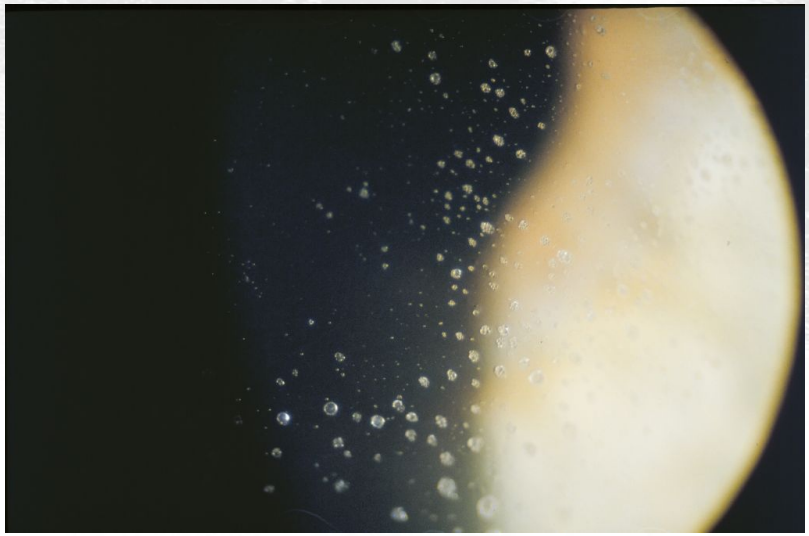
- Phospholipids 0-5%

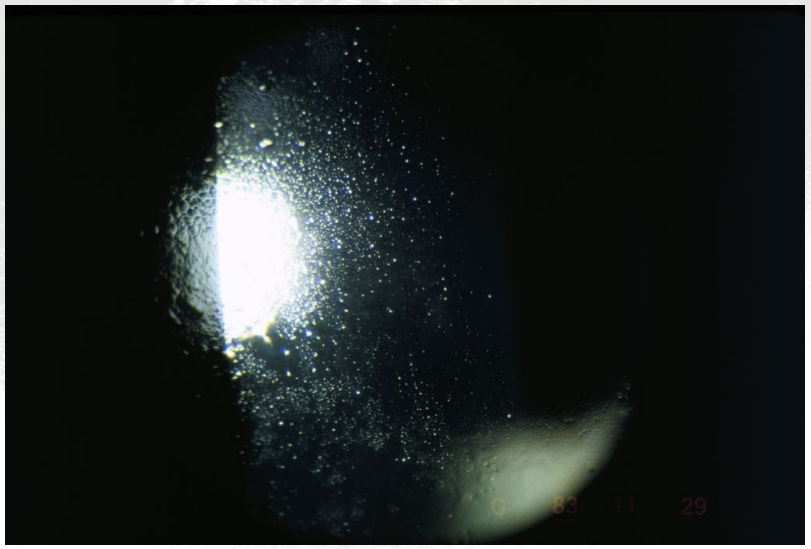


- Glycolipids ?

TEAR LIPIDS	DAG	TAG	Wax Esther	Steryl Ester	Cholesteryl Ester	Cholesterol	Free Fatty Alcohol	Free Fatty Acid	Glyco-lipid	Phospho-lipid
Andrews 70	+	+	+	+		+	+	+		+
Young 73						5 mM/L				
VanHaeringer 75						.8 mM/L				
Stuchell 84		6.9			9.7	7.1		18.3	55	0.9
Saatci 90						1.45 mM/L				
Wallensak 90		+	45			15	+	<15	+	15
Glasgow 95		+		+		+	+	+	+	+
Khyshiktuev 05								+		
Butovich 08	+	+	+	+	+	.5-1%				

Tear lipids and contact lenses





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Tear lipids and contact lenses

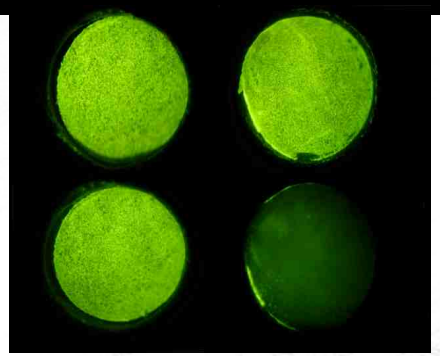
Soft lens polymer type	Polymer name	Amount of lipid adsorbed in vivo (µg/lens)				
		Total lipid	Phospho-lipids	Cholesterol	Oleic acid	Oleic methyl ester
Group I	Polymacon	62-66	2.1			
Group IV	Etafilcon A	44	1.8			
Group Va	Balafilcon A		0.019 (SM) 0.019 (PC)	3.9-15.6	1.0	0.2
Group Vb	Lotrafilcon B			0.1-0.5	0.7	0
Group Vd	Senofilcon A/ Galyfilcon A		0.059 (SM) 0.195 (PC)	0.3-9.9	0.7	0.1

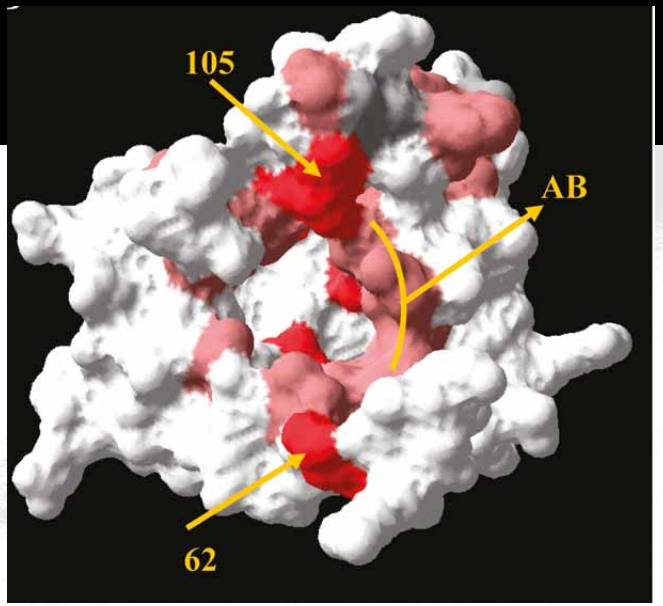
Lipid Protein Interactions

- Lysozyme (4.6 mg/ml) 300 µM
- Tear Lipocalin (1.5 mg/ml) 74 µM
- Phospholipase A2 (54 ug/ml) 3.8 µM
- Phospholipid Transfer Protein (10.9 ug/ml) 0.07 µM
- Surfactant Proteins (2-5 µg/ml, D) 0.08 µM
- Apolipoprotein D (.026 ug/ml) 0.00092 µM
- Mucins

Tear Lipocalin

Phospholipid Ki= 1.2 µM
Stearic acid Ki= 1.3
Palmitic acid Ki= 3.2
Lauric acid Ki= 9.1
Cholesterol Ki= 15.9





CER 2000;21;824
IOVS 2005;46:3589
Biochemistry 2009;48:7219

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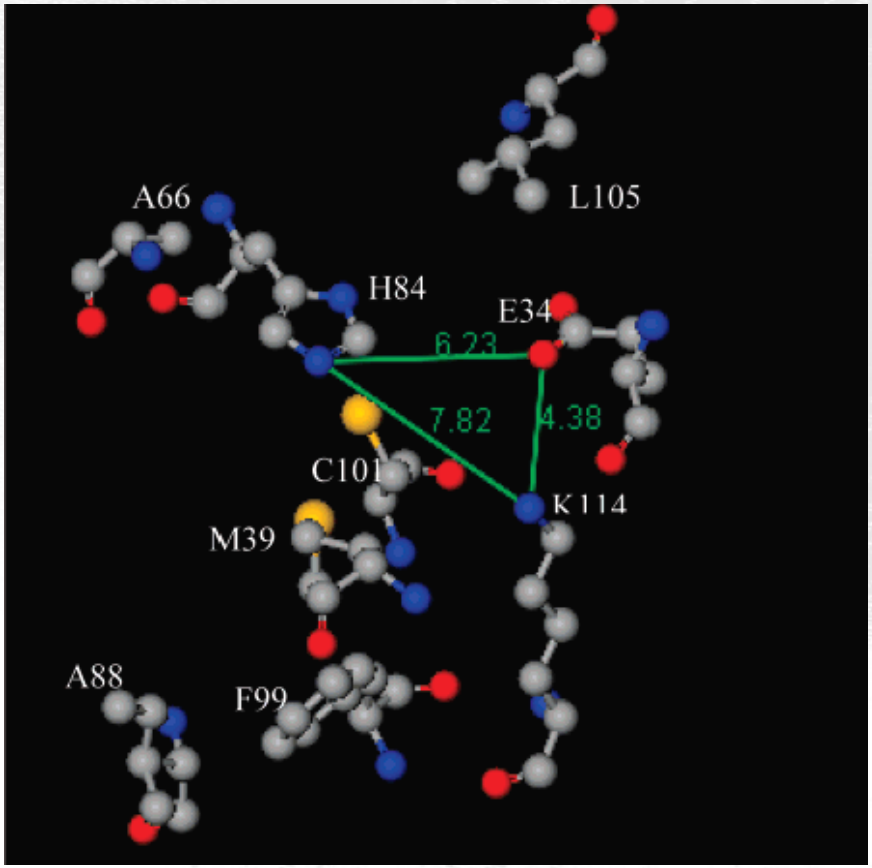
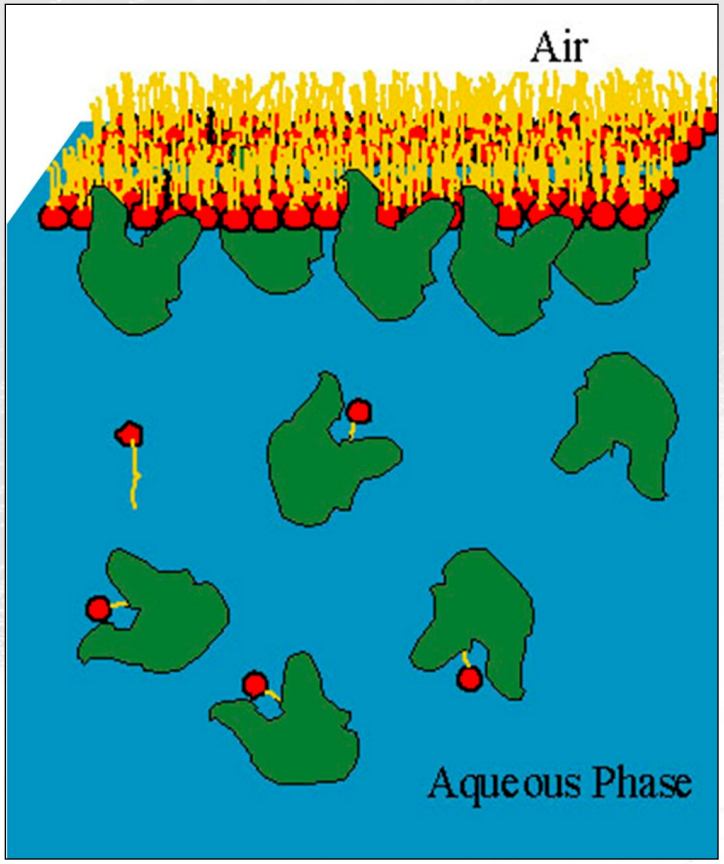
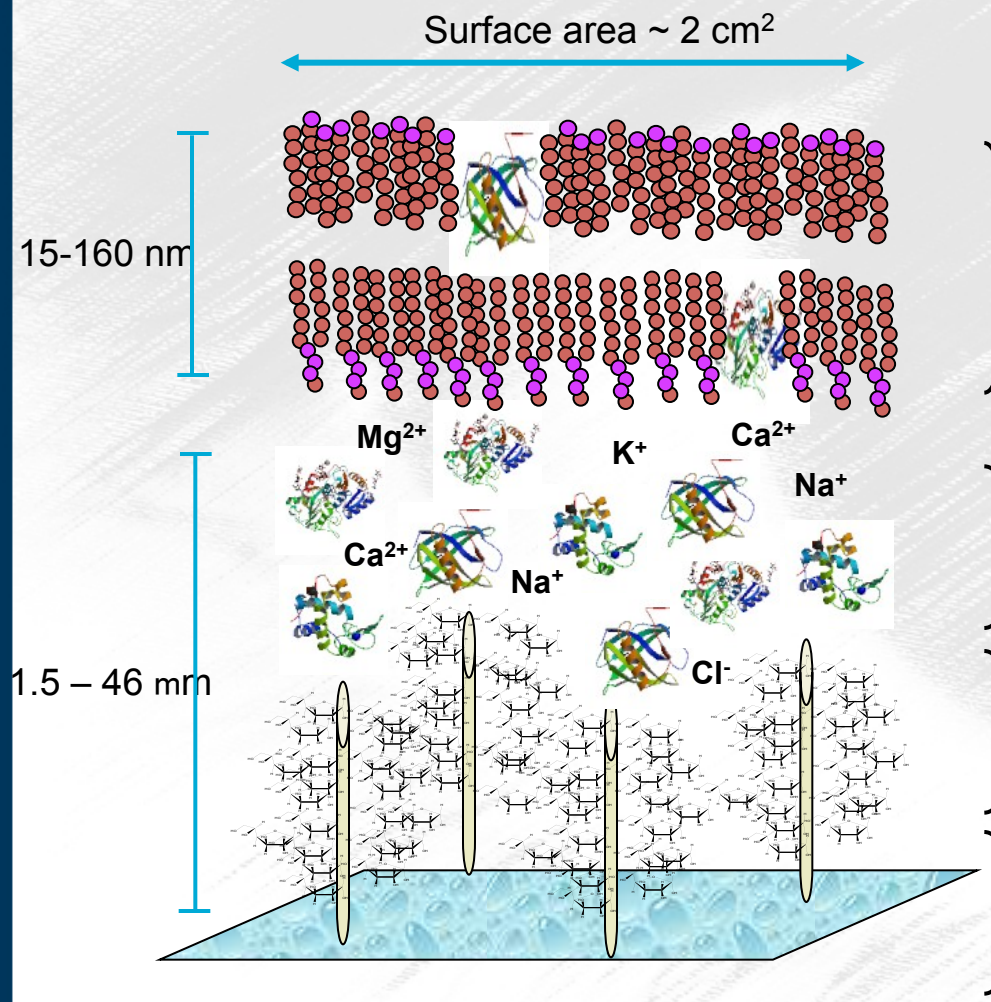
Trigonal Cluster-Tear Lipocalin to Intercalate into Lipid Layer





Biochemistry 2008:47:1414

A Model of the Tear Film



QUESTIONS?

Epidemiology and Associated Risk Factors of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

Debra A. Schaumberg, Sc.D., O.D., M.P.H. (Chair)
Jason J. Nichols, O.D., M.P.H., Ph.D.
Eric B. Papas, M.Sc., O.D., Ph.D.
Louis Tong, F.R.C.S., M.B.B.S.
Miki Uchino, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

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Challenges

- Epidemiological investigation limited by lack of agreed definition or standardized clinical assessment to characterize MGD
- Paucity of evidence on:
  - Natural history
  - Actual processes that cause MGD
  - When do symptoms actually develop in the disease process?
    - At onset of meibomian gland damage or altered meibum secretion
    - After a certain level of damage or alteration has occurred

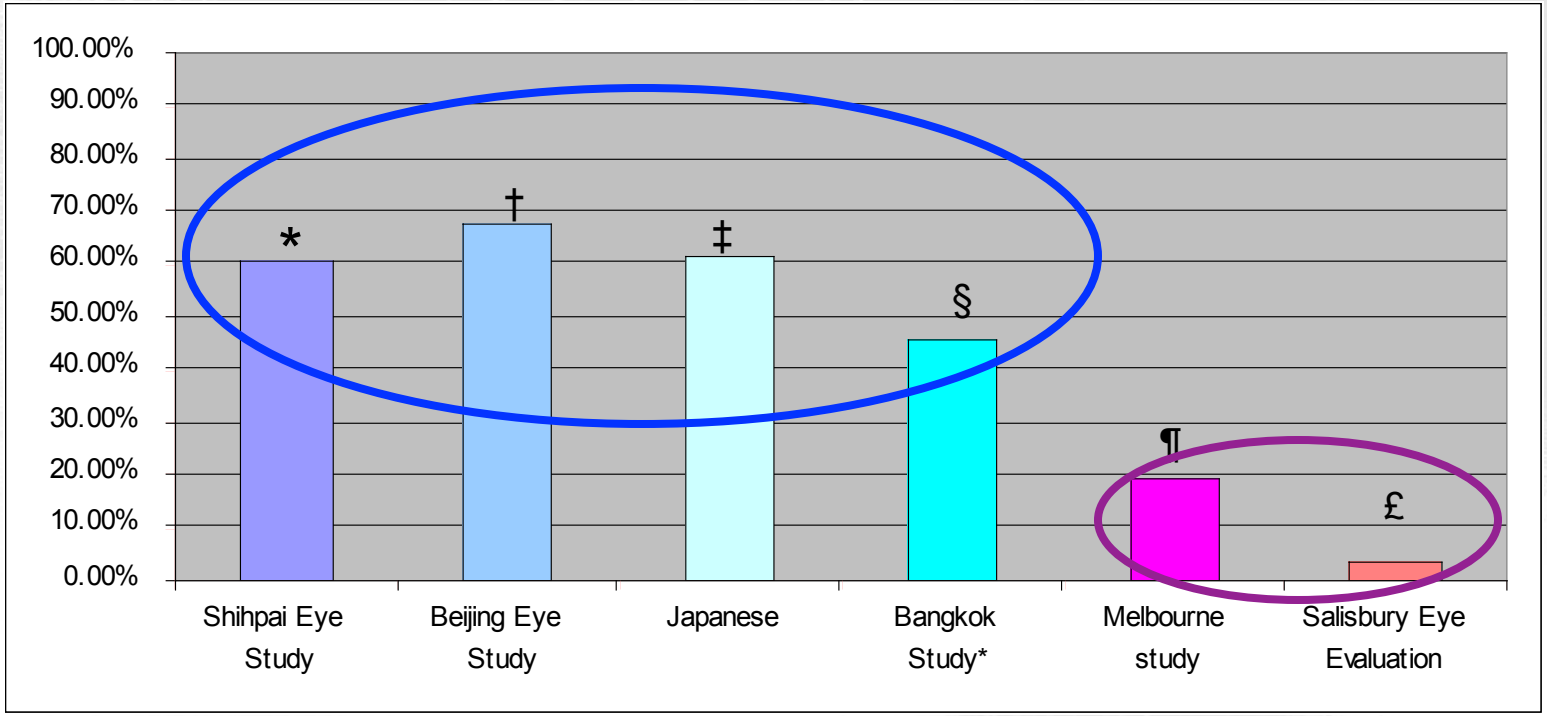
Challenges

- Symptoms may not be due to actual meibomian gland damage or altered meibum secretion at all, but instead arise from subsequent damage to other ocular surface tissues associated with secondary alterations in physiological processes

Methods of Assessment

- Objective
  - obtained without the influence of the examining clinician or the patient's perceptions
- Subjective
  - measures assessed by a clinician or patient each have components of subjectivity
- The most valuable outcomes demonstrate:
  - validity
  - reliability (low variability)
  - sensitivity (to differences between patient groups)
  - responsiveness (to change in disease status over time)
  - feasibility
  - practicality

Prevalence of MGD



* Telangiectasia or Meibomian gland orifice plugging

† Telangiectasia

‡ Gland dropout, expressibility and nature of Meibum secretion

§ Telangiectasia or Meibomian gland orifice plugging OR collarettes

¶ Tear break up time < 1SD (10 sec)

£ Meibomian gland plugging OR collarettes (grade 2-3)

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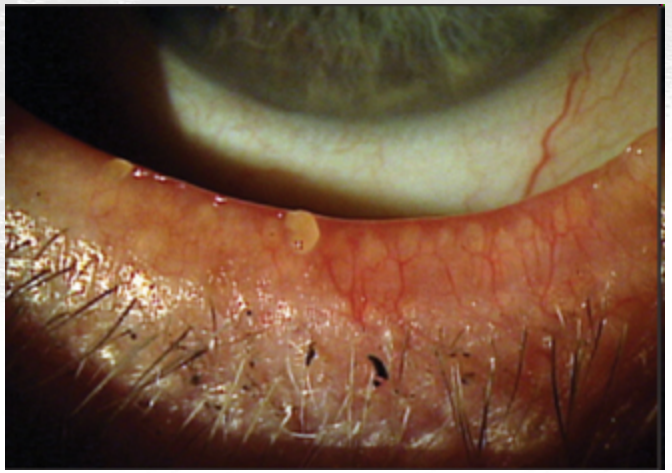
Overlap of DED Symptoms and Clinical Signs of MGD

Study	Symptoms Assessed (all frequency)	Clinical Evaluations/ MGD Definition	% with Dry Eye Symptoms who also had MGD
Shihpai Eye Study (Lin, 2003)	Eye dryness Gritty/sandy Burning Sticky Watery/tearing Redness Lash crusting Eyes stuck shut (am)	Telangiectasis or gland plugging ≥ G1	61.7% (p = NR)
Bangkok Study (Lekhanont, 2006)*	Eye dryness Foreign body sensation Burning Discomfort Sticky Tearing	Telangiectasis, Collarettes, and Plugging	63.6% (p = 0.006)

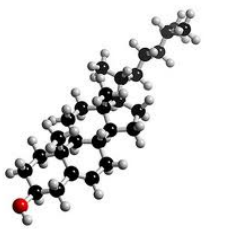
Clinical Correlates and Risk Factors

- Little epidemiological research available
- Suggested associations need further study
- Ocular Factors
  - Anterior Blepharitis
  - Contact Lens Wear
  - Demodex folliculorum
  - Dry eye disease



Systemic Factors

- Androgen deficiency
- Complete androgen insensitivity syndrome
- Menopause
- Aging
- Sjogren syndrome
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Haematopoietic stem cell transplantation
- Ectodermal dysplasia syndrome
- Pemphigoid
- Cholesterol levels



- Psoriasis vulgaris
- Parkinson's disease
- Psoriasis
- Atopy
- Rosacea

- Cicatrical pemphigoid
- Polycyctic ovary syndrome
- Discoid lupus erythematosus
- Turner syndrome
- Benign prostatic hyperplasia
- Hypertension

Medications

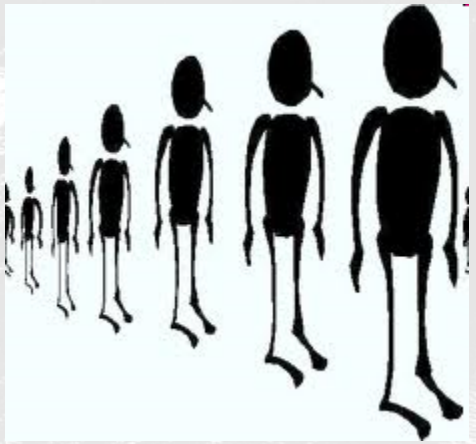
- Postmenopausal hormone therapy
- Anti-androgens
- Medications used to treat BPH
- Antihistamines
- Antidepressants
- Omega-3 fatty acids (possibly protective)
- Accutane (isotretinoin)

Meta-analysis of MGD in CL wear

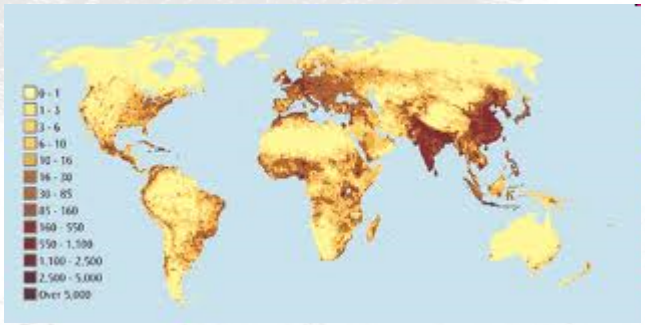
Study	N	N w/ CL	N w/o CL	CL + MGD	Non CL + MGD	% CL + MGD	% Non CL + MGD	Diff in % MGD CL vs Non CL
Ong & Larke (1990)	140	70	70	21	14	30.0	20.0	10.0
Marren (1994)	50	20	30	12	17	60.0	56.7	3.3
Ong (1996)	181	53	128	16	29	30.2	22.7	7.5
Hom et al (1990)	398	162	236	66	89	40.7	37.7	3.0
Aggregate	**769**	**305**	**464**	**115**	**149**	**37.7**	**32.1**	**5.6**
				Upper 95% CI		*43.1*	*36.4*	
				Lower 95% CI		*32.3*	*27.9*	
				Two-tailed p value		***0.11***		

Future Directions

- Population-based studies using standardized classification criteria to better delineate the frequency of MGD, including both prevalence and incidence



- Possible demographic differences in MGD rates such as by age, gender, and race/ethnicity



Future Directions

- Better delineation of the effects of contact lens wear on:
  - Health of meibomian glands (atrophy)
  - Meibomian excretions
  - Function of the lipid layer

Future Directions

- Describe the relation between meibomian gland status (e.g. through meibography) and other clinical correlates and symptoms
- Establish and validate specific subjective outcome measures for MGD
- Develop a better understanding of potential biomarkers that may help diagnostically, or in tracking changes in MGD
- Describe role MGD has in quality of life

Future Directions

- Establish the natural history of MGD
- Many questions:
  - Time course for progression
  - Relation between true etiological factors and the development of symptoms
  - Relation between MG atrophy and symptom development
  - Source of the symptoms of MGD is not known
    - E.g. do they derive from the meibomian glands or the ocular surface?
  - Once atrophy is present and the patient develops symptoms, is it possible for the glands to return to their normal state?
  - Associated morbidities

Summary

- MGD is prevalent with potentially important detriments to well being
- MGD prevalence, demographic and geographic distribution, risk factors, and impact on ocular health and quality of life are only beginning to emerge
- We are confident that the time has now arisen to embark upon the systematic study of MGD as was done for dry eye
- Through such efforts a better understanding of MGD will be gained, and strategies for prevention and treatment will be developed

QUESTIONS?

Evaluation, Diagnosis and Grading of Severity of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

Alan Tomlinson, MCOpt, Ph.D. (Chair)
Anthony J. Bron, F.R.C.S.
Donald R. Korb, O.D.
Shiro Amano, M.D., Ph.D.
Jerry R. Paugh, O.D.
E. Ian Pearce, Ph.D.
Richard Yee, M.D.
Norihiko Yokoi, M.D., Ph.D.
Reiko Arita, M.D., Ph.D.
Murat Dogru, M.D.

tfos

A Report from the TFOS International Workshop on Meibomian Gland Dysfunction

AlanTomlinson, Ph.D. (Chair)
Anthony Bron, M.D. (Consultant)
Shiro Amano, M.D., Ph.D.
Norihiko Yokoi, M.D., Ph.D.
Don Korb, O.D.
Richard Yee, M.D.
Ian Pearce, Ph.D.
Jerry Paugh, O.D. PhD.
Murat Dogru , M.D. (Steering Committee Liaison)

tfos

Evaluation, diagnosis and grading of severity of MGD

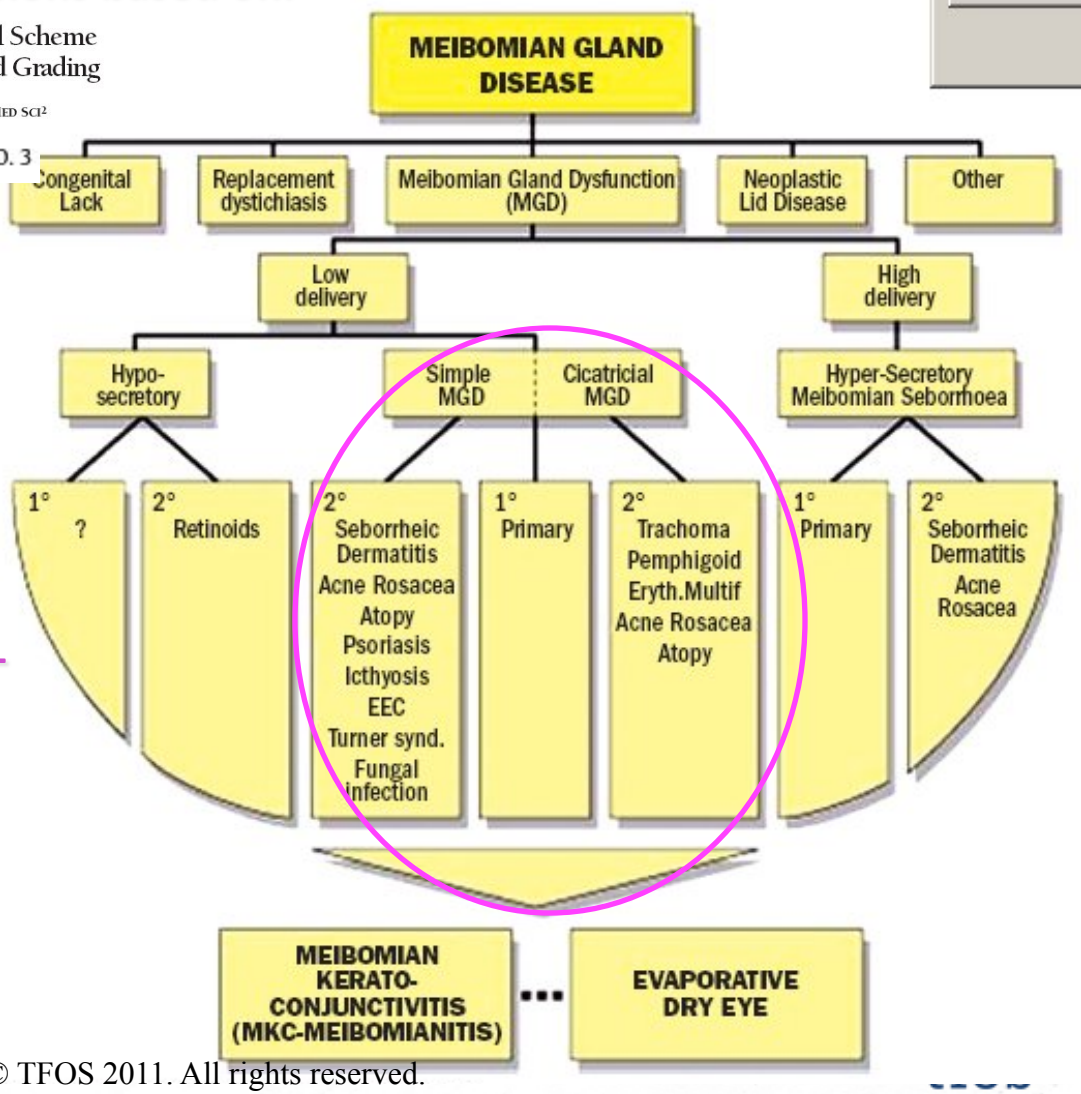
Committee discussions based on:

Meibomian Gland Dysfunction: A Clinical Scheme for Description, Diagnosis, Classification, and Grading

GARY N. FOULKS, MD, FACS,[1] AND ANTHONY J. BRON, FCOPHTH, F MED SCI[2]

THE OCULAR SURFACE / JULY 2003, VOL. 1, NO. 3

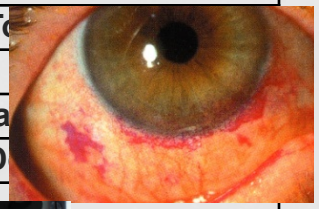
Diagnosis focused on-

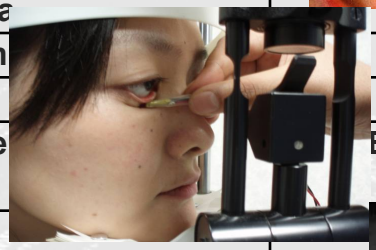
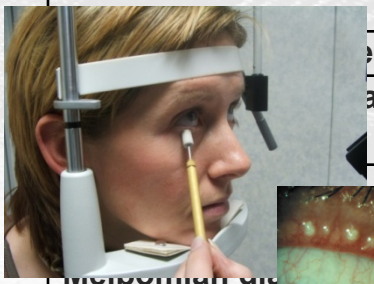


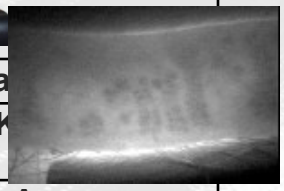
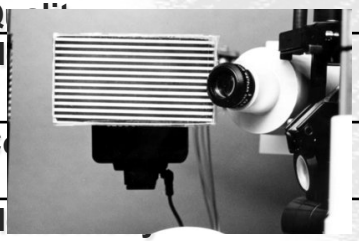
Committee members undertook reviews of tests for MGD

A	Technique	Reviewer
M		T
T	ine-	
H	eye)	la
T		D
T		
		Dogru
		Dogru
		Bron
		Richa
	MG expression- Expressibility/ Volume/ Q	Don K
Meibomian tissue mass	M	Shiro Amano
MG alcinar unit density/ diameter	C	Murat Dogru
Casual lid margin oil level	M	Norihiko Yokoi
Tear lipid film	Interferometry	Norihiko Yokoi
Evaporation rate	Evaporimetry	Tomlinson
	che	
Tear Osmolarity	Osmo	Alan
Tear Dynamics	Total Tear Flow/ Ratio: Evap/TTR	Alan Tomlinson

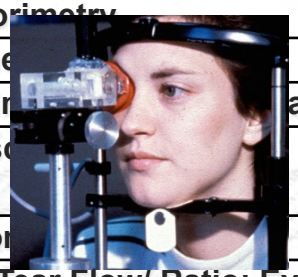
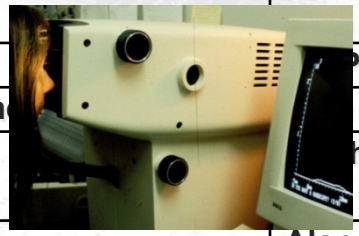


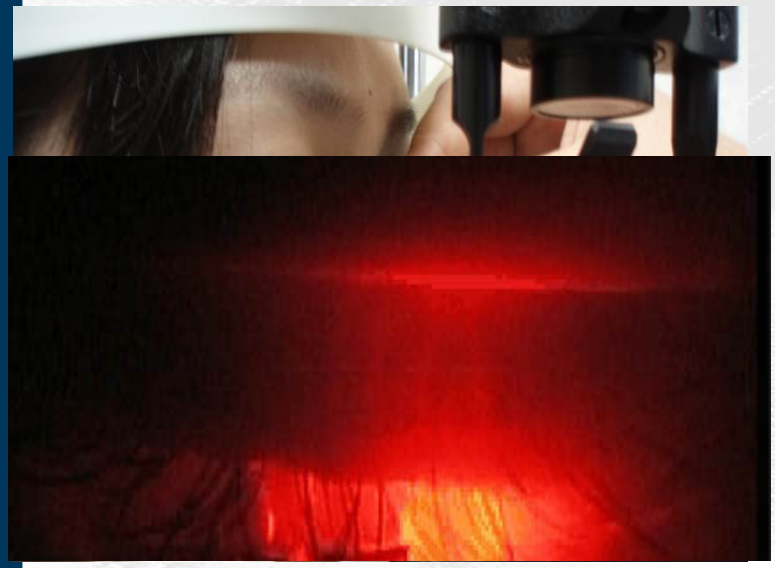



Committee members undertook reviews of tests for MGD - example

Assessment	Technique	Reviewer
MGD Classification		Tony Bron
Tests for a Clinical Routine-		
History- Symptoms (dry eye)	Interview/Symptom questionnaire	Ian Pearce
Tear stability	Fluorescein /Noninvasive BUT	Don Korb
Tear secretion	Schirmer I with anaesthesia	
	Schirmer II (with nasal stimulation)	Murat Dogru
Index of tear volume	Phenol red thread test	Murat Dogru
Ocular surface damage	Graded staining: Fluorescein/ lissamine green/ Rose Bengal	Tony Bron
Additional Tests-		
Signs of MGD	Lid (meibomian morphology)	Richard Yee
Meibomian gland function	MG expression- Expressibility/ Volume/ Quality	Don Korb
Meibomian tissue mass	Meibography	Shiro Amano
MG alcinar unit density/ diameter	Confocal microscopy	Murat Dogru
Casual lid margin oil level	Meibometry	Norihiko Yokoi
Tear lipid film	Interferometry	Norihiko Yokoi
Evaporation rate	Evaporimetry	Alan Tomlinson
Meibomian physiochemistry	Oil chemistry analysis	Ian Pearce
Tear secretion /volume	Fluorimetry (TTR) / Clearance (TFI)	Alan Tomlinson
Tear meniscus height, radius/ volume	Meniscometry	Norihiko Yokoi
Tear Osmolarity	Osmometry	Alan Tomlinson
Tear Dynamics	Total Tear Flow/ Ratio: Evap/TTR	Alan Tomlinson

Meibography

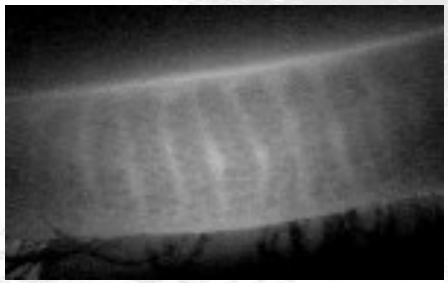


Technique described by Yokoi et al

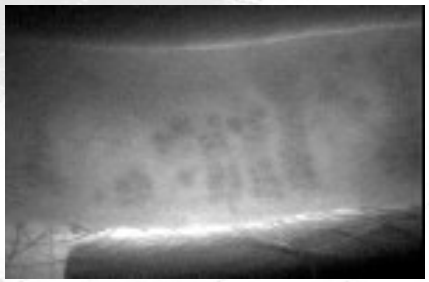
Yokoi, Exp Eye Res 2003 78 (3): 399-407

- **Fibre optic light transilluminator**
- **Gland drop out assessed from central one third upper and lower lids**

Mathers, Ophthalmol 1993, 100 (3): 347-351



Normal



MG Drop out

tfos

Meibography Relevent literature

Cornea 10(4): 277–285, 1991.

Meibomian Gland Dysfunction in Chronic Blepharitis

William D. Mathers, M.D., William J. Shields, B.A., Mahipal S. Sachdev, M.D., W. Matthew Petroll, Ph.D., and James V. Jester, Ph.D.

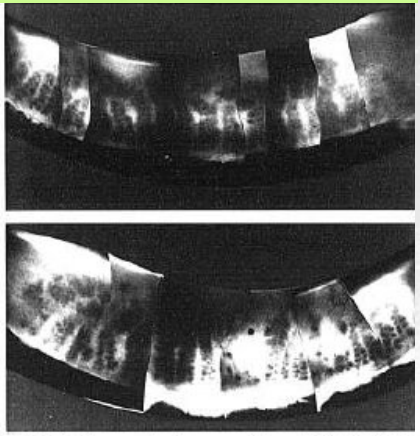


FIG. 2. Meibography of a normal lower lid (A) and meibography showing gland dropout in chronic blepharitis (B).

1: Cornea. 1996 Mar;15(2):110-9.

Model for ocular tear film function.

Mathers WD, Lane JA, Sutphin JE, Zimmerman MB.

	Drop Out
Normal (n = 72)	1.12 ± 3.41
Dry Eye (n = 37)	0.27 ± 0.82
All MGD Patients (n= 109)	3.79 ± 5.17
MGD obst and DE	4.78 ± 5.05
MGD seb. and DE	0.41 ± 1.05
MGD roseacea and DE	7.94 ± 8.7
MGD seb. obst. and DE	2.43 ± 1.44

Noncontact Infrared Meibography to Document Age-Related Changes of the Meibomian Glands in a Normal Population

Reiko Arita MD, PhD[1, 2], Kouzo Itoh MD, PhD[1], Kenji Inoue MD, PhD[3] and Shiro Amano MD, PhD[2]

Ophthalmology
Volume 115, Issue 5, May 2008, Pages 911-915

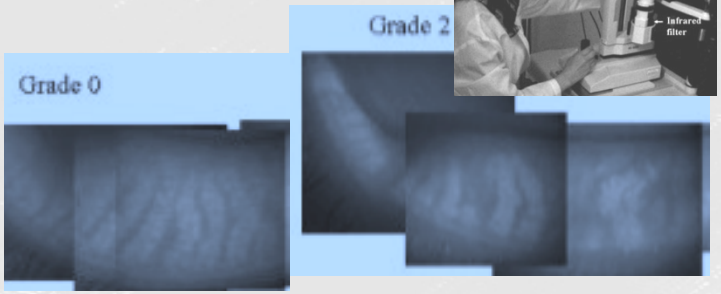


TABLE 3. *Table of cluster analysis and diagnostic groups using osmolarity (OSM), dropout (Schirmer's test (SCHIR); group values for volume (VOLUME) and thickness (THICK) of excreta a*

Group	N	OSMOL	DROPOUT	SCHIRM	VOLUME
Seborrheic MGD	29	301 ± 9	0.84 ± 0.9	11.3 ± 4.6	2.3 ± 0.9
Obstructive MGD	12	319 ± 10	3.67 ± 1.7	24.2 ± 4.7	1.2 ± 0.4
Obstructive with sicca	7	322 ± 7.1	5.5 ± 1.3	6.9 ± 5.0	1.0 ± 0.5
Sicca	9	327 ± 8.2	0.61 ± 0.8	7.78 ± 4.2	1.8 ± 0.8

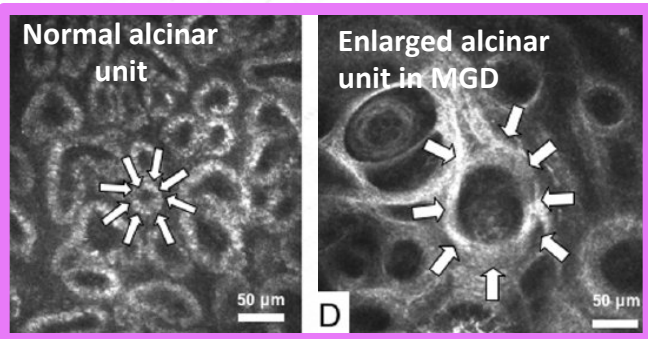
MV Molecular Vision 2008; 14:1263-1271 <http://www.molvis.org/molvis/v14/a149>
Received 12 May 2008 | Accepted 22 June 2008 | Published 9 July 2008

The application of in vivo laser confocal microscopy to the diagnosis and evaluation of meibomian gland dysfunction

Yukihiro Matsumoto,[1] Enrique Adan Sato,[1] Osama M.A. Ibrahim,[1] Murat Dogru,[1] Kazuo Tsubota[2]

TABLE 2. COMPARISON OF ACINAR UNIT DENSITY AND DIAMETER OF MEIBOMIAN GLANDS IN NORMAL CONTRO

	Controls	MGDs	p valu
Acinar unit density (/mm²)	101.3±33.8	47.6±26.6	p=0.0(
Acinar unit diameter (μm)	41.6±11.9	98.2±53.3	p=0.0(



Meibography: Committee Report includes

Table 4 Techniques for imaging the Meibomian glands

Technique	Lid region	Grading Scheme	Ref
Meiboscopy	##	0 = no d	
		1 ☒ 33	
		2 34 - 6	
		3 ☒ 67	
		Percent dropout the nasa lower li	
Meibography (contact; retro-illumination)	#LL	Total nu central was giv	
		1 = norr 2 = glan	
microscopy	&/or UL	(based Mean acinar diameter	

Table 5: Validation of Meib

Test reliability	
Gestalt method:	
-within observer	
-between observer	
Intact gland counting	
-within observer	
-between observer	
☒ statistic: **<0.00 poor reliability** **0.00-0.20, slight reliability**	

Table 10
Assessment of Meibomian Gland Function

Based on Meibomian gland dropout. Meibography:	
The technique of meibography offers a big opportunity to refine the quantification of gland loss by digitising the images. It should be noted that estimates of 'gland loss' are based on an assumption of the original size of each gland. Therefore estimates of residual gland area will be more accurate, although relevant to a particular individual. There is a need for detailed age/sex stratified infomation about gland area	Precise description of any technique proposed must be given. For example, if the term 'partial gland loss is used, this must be defined. An estimate of loss is based on the presumed, intact length of each gland. Training would be enhanced by the use of videos showing both the performance of the technique of method of scoring in use.
Either contact or non-contact meibography can be used.	
Method C: LL 15 glands: A partial gland is >10% of the assumed gland length. [4] [4] 1 = no partial glands (PGs) 2 = < 25% PGs 3 = 25-75% PGs 4 = > 75% PGs	An aggregate score from the combined LL/UL would expand the scale
Method D: (nasal half, lower eyelid) [5] [5]	
De Paiva 2003 has also devised a composite score including lids signs and expressibility, with a scale range of 0-11. 0 = no dropout 1 = £ 25% 2 = £ 50% 3 = £ 75% 4 = £ 100%	
Assessment by meibography	
☒ 20 years. Method C. Normal is zero	
> 20 years. Method C. 1= ☒ 25% is acceptable as normal. >1 is abnormal.	

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Information for

- Name of diagnostic technique/ grading
- Rationale for use in
- Description of technique-

References to published work

Information contained in Appendices to the main committee report

Appendix 7 (Amano)

Meibography.

Classifies: Meibomian tissue mass

Method/ Description: Meibography is a technique to observe and document the morphology of meibomian glands in vivo. In the first report of meibography, white light from an illuminator was applied onto conjunctival side of the everted eyelid and the images were documented on black-and-white films.[1] The most basic version uses white light from a transilluminator. This is applied onto the cutaneous side of the everted eyelid and allows observation and documentation of morphological changes in meibomian glands from the conjunctival side. The images are documented using black-and-white films,[1,2] infrared films,[3-5] near infrared CCD video camera,[6] or infrared CCD video-camera.[7,8] A recent variation of the technique is a usage of near infrared[6] or infrared light source.[7,8] In a recent study[8] using an infrared filter and an infrared CCD video-camera, meibomian glands can be observed without a light source applied onto the cutaneous side of the everted eyelid, which makes meibography a patient-friendly examination.

The observable morphological changes include gland loss and gland shortening, which is quantified using scoring systems. Different authors used different scoring scales as follows. Mathers WD et al[9] scored gland dropout by the number of whole or partial glands missing from central two thirds of lower lid. Shimazaki J et al[10] scored loss of the meibomian glands in the lower eyelid using subsequent grades: grade 0 (no loss of meibomian glands), grade 1 (lost area is 50% or less than the observed area), and grade 2 (lost area is over 50% of the observed area). Pflughelder SC et al[11] scored partial or complete loss of the meibomian glands in the lower eyelid using the following grades: grade 0 (no loss of meibomian glands), grade 1 (lost area is less than 1/3 of the observed area), grade 2 (lost area is between 1/3 and 2/3), and grade 3 (lost area is over 2/3). Nichols JJ et al[6] scored the gland dropout using subsequent grades: grade 1 (no partial glands), grade 2 (less than 25% of the image contains partial meibomian glands), grade 3 (between 25% and 75% of the image contains partial meibomian glands), and grade 4 (more than 75% of the image contains partial meibomian glands). Arita R et al[7] scored partial or complete loss of the meibomian glands using the following grades for each eyelid (meibo-score): grade 0

Cut- off for: (Sensitivity/ specificity)	Normal vs obstructive MGD
	ADDE >= 3 (83.0 / 90.0)

(no loss of meibomian glands), grade 1 (lost area is less than 1/3 of the total area of meibomian glands), grade 2 (lost area is between 1/3 and 2/3), grade 3 (lost area is over 2/3). Meibo-scores for the upper and lower eyelids were summed to obtain a score from 0 through 6 for each eye.

As shown below, diagnostic cut-off values for meibo-score offer promising sensitivity and specificity when normal eyes are compared with eyes with obstructive meibomian gland dysfunction in a recent study.

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- **Nichols JJ, Berntsen DA, Mitchell GL, Nichols KK. An assessment of grading scales for meibography images. Cornea. 2005;24:382-8.**
- **Yokoi N, Komuro A, Yamada H, et al. A newly developed video-meibography system featuring a newly designed probe. Jpn J Ophthalmol. 2007; 51: 53-56.**
- **Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the Meibomian glands in a normal population. Ophthalmology 2008; 115:911-915**
- **Mathers WD, Billborough M. Meibomian gland function and giant papillary conjunctivitis. Am J Ophthalmol 1992; 114:188-192.**

Selecting tests for evaluation and diagnosis of MGD

Assessment	Technique	Reviewer
MGD Classification		Tony Bron
Tests for a Clinical Routine-		
History- Symptoms (dry eye)	Interview/Symptom questionnaire	Ian Pearce
Tear stability	Fluorescein /Noninvasive BUT	Don Korb
Tear secretion	Schirmer I with anaesthesia	
	Sch	
Index of tear volume	Phe	
Ocular surface damage	Gra gre	
Additional Tests-		
Signs of MGD	Lid	
Meibomian gland function	MG Qua	
Meibomian tissue mass	Mei	
MG alcinar unit density/ diameter	Cor	
Casual lid margin oil level	Mei	
Tear lipid film	Inte	
Evaporation rate	Eva	
Meibomian physiochemistry	Oil	
Tear secretion /volume	Flu	
Tear meniscus height, radius/ volume	Mer	
Tear Osmolarity	Osmometry	Alan Tomlinson
Tear Dynamics	Total Tear Flow/ Ratio: Evap/TTR	Alan Tomlinson

Content and order of tests, on the bases of:

-Opinion on the clinical relevance

-Underlying physiological

-Evidence base– level of evidence

-Diagnostic efficacy of test cut-off (sensitivity and specificity)

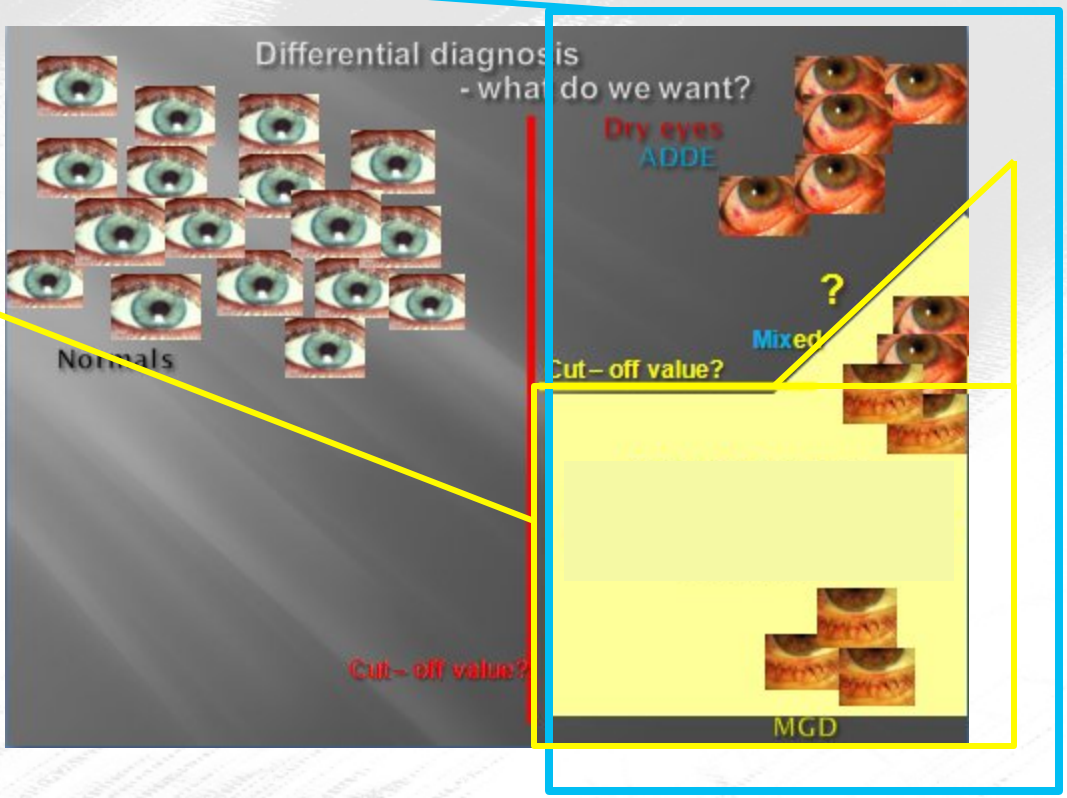
-Series order - least to most invasive.

- Severity grading of MGD

Assessment of MGD:
2 –Stage

Tear Assessment

MGD Assessment



Disease /etiological based and/or evidence based approach to diagnosis

Test efficacy in diagnosis- summary from reviews

Sens/Spec)>70%

Evidence based approach

E fficacy in differential diagnosis Test measure	N v DE: Cut-off (Sens%/Spec %)	N v EDE: Cut-off (Sens%/Spec %)	EDE v ADDE: Cut-off (Sens%/Spec %)
Symptoms questions	DE > 14.5-McMon[1] (82/36-v RB,SCH,TBUT) DE >15- OSDI[4] (80/79- v Lissamine,Sch, Symp) (80/83- Dr. diagnosis)		
Tear stability	FBUT< 10s[27] (82/86)		
Tear secretion Schirmer I Schirmer II	<5.5mm/5min[15] (85/83)		
Index of tear volume- PRT	PRT<12mm [14] (56/69) PRT< 20mm [17] (86/83)		
Ocular surface damage	RB Stain >3.5[12] (95% v 96%) RB Stain >4[13] (63/84)		
Lid (meibomian morphology)	NA		
MG expression- Expressibility/ Volume/ Quality	Expression grade>1.0[19] 86/73		
Meibography		EDE >= 3 (83.0 / 90.0)[8]	
Acinar unit density/diameter		Unit density <70/mm [2, 16] (81/81) Long diameter <65um (90/81) Short diameter<25um (86/96)	
Meibometry	NA		
Interferometry	NA		
Evaporation rate	DE<22 [29](51.1/89.9)	EDE>22.3(61.2/90.6)	EDE>27.5(45.5/79.8)
Meibomian physiochemistry			
Tear secretion- Fluorimetry Fluorescein clearance	DE<12.9 (74.5/73.6)[29]	EDE<15.1(80.2/58.7)	ADDE<9.6(69.5/96.8)
Tear volume- Fluorimetry	NA		
Tear meniscus height, radius/ volume	DE<0.25 [7](74.5/73.6)-R DE<0.18[9] (72.8/66.6)-TMH DE<9.6[2] (93.3/66.7)		
Tear Osmolarity	DE>316[11] (69%/92.8%)	EDE>315[10] (73%/72%/)	ADDE> 325[10] (60%/39%)
Tear Dynamics- Indices- Evap/ Total flow	DE>15[29] (na)	EDE>15[29] (na)	EDE> na (NA)
Tear Dynamics- Indices- Evap/ TTR	DE>20[29] (na)	EDE>20[29] (na)	EDE>na (na)
Tear Dynamics- Indices- TFI	DE<196 [3] (64.7/60) DE<240 [6] (83%/40%)	NA	

EDE >= 3 (83.0 / 90.0)

EDE>315 (73%/72%/)

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Test efficacy in diagnosis- summary from reviews

Sens/Spec)>70%

Evidence based approach

E fficacy in differential diagnosis Test measure	N v DE: Cut-off (Sens%/Spec %)	N v EDE: Cut-off (Sens%/Spec %)	EDE v ADDE: Cut-off (Sens%/Spec %)
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EDE >= 3 (83.0 / 90.0)

EDE>315 (73%/72%/)

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A Report from the TFOS International Workshop on Meibomian Gland Dysfunction

Recommended tests for evaluation and diagnosis of MGD

Area	Tests	General clinic	Specialised unit
SYMPTOMS	Questionnaires	McMonnies; Schein; OSDI; DEQ; OCI;SPEEDetc	McMonnies; Schein; OSDI; DEQ; OCI; SPEED etc
SIGNS - MGD			
Meibomian Function	Lid morphology	Slit-lamp microscopy	Slit-lamp Confocal microscopy
	Meibomian gland mass	-	Meibography
	MG expressibility Expressed oil-quality,volume?	Slit-lamp microscopy	Slit-lamp microscopy
	Lid margin reservoir	-	Meibometry
	Tear Film Lipid Layer Thickness Spread time/rate	Intererferometry Slit-lamp -	Interferometry SL.Video interferometry
Evaporative loss	Evaporimetry	-	Evaporimetry
Tears			
Osmolarity	Osmolarity	TearLab device, other	TearLab device, other
Stability	Tear film	TFBUT; OPI	TFBUT; OPI
	TFLL	Spread time	Interferometry; spread rate; pattern
Indices	Tear secretion	Schirmer 1	Fluorophotometry/FCR
	Tear volume	Meniscus height	Volume by fluorophotometry
	Tear volume	Not available	Meniscus radius of curvature-meniscometry
	Tear clearance	TFI	
Ocular Surface	Ocular surface staining	Oxford scheme; NEI/Industry scheme	
Inflammation	Biomarkers		Flow cytometry; bead arrays; cytokines; interleukins; MMPs

Severity Grading and Treatment of MGD

Severity Grading and Treatment of MGD-related ocular surface disease and dry eye

Severity Grading and Treatment of MGD

SEVERITY LEVEL	Level Zero	Level 1	Level 2	Level 3	Level 4	Level 5
MGD		Subclinical	Symptomatic Minimal	Symptomatic Mild	Symptomatic Moderate	Symptomatic Severe
Symptom frequency & severity	No symptoms	Asymptomatic or occasional symptoms	Some of the time. Precipitated by environmental factors	Half of the time Some limitation of activity	Most of the time Frequent limitation of activity	All of the time Severe/disabling/ constant
OSDI grade Range (0-100)	0	0-12	0-12	13-22	23-32	33-100
MGD Grade	clear	Subclinical, non-obvious MGD; Altered quality, only on expression; No gland loss	Minimally altered quality of expressed meibum from scattered glands; None to minor gland loss	Mildly altered meibum quality. Occasional lid margin signs; Mild gland loss	Moderately increased opacity and viscosity of meibum, Plugging; increased marginal vascularity; Loss of orifice definition; Moderate gland loss	Marked, diffuse MGD: cicatricial or non-cicatricial. Multiple lid margin signs. Lid deformity and marked lid margin hyperaemia; Severe gland loss
Quality of expressed meibum – grade range 0-3, LL, 8 glands * Range (0-24)	0	1-5	6-10	11-15	16-20	21-24

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Quality of expressed meibum – grade range 0-3, LL, 8 glands * Range (0-24)	0	1-5	6-10	11-15	16-20	21-24
TREATMENT OF MGD Based on symptom and gland status.		+ general advice about MGD, the potential influence of diet, home and work environment ☒ hygienic measures	+ hygienic measures, heat and massage	☒ topical ATs ☒ emollient lubricant or liposomal spray ☒ topical azithromycin ☒ oral tetracycline derivatives	+ oral tetracycline derivatives	☒ anti-inflammatories

Severity Grading and Treatment of MGD-related ocular surface disease and dry eye

SEVERITY LEVEL	Level Zero	Level 1	Level 2	Level 3	Level 4	Level 5
Disease Stage		Subclinical	Symptomatic Minimal	Symptomatic Mild	Symptomatic Moderate	Symptomatic Severe
Symptom frequency & severity	None	Asymptomatic or occasional symptoms	Some of the time. Precipitated by environmental factors	Half of the time Some limitation of activity	Most of the time Frequent limitation of activity	All of the time Severe/disabling/ constant
OSDI Range (0-100)	0	0-12	0-12	13-22	23-32	33-100
TFBUT seconds	☒10s	< 10 - ☒ 7s	< 7 - ☒ 5s	< 5 - ☒3	< 3 - ☒1	< 1 or instant breakup
Tear Osmolarity mOsm/L	< 308	< 308	< 308	Mildly increased > 308 - ☒ 313	Moderately Increased > 314 - ☒ 317	Markedly increased > 317
Conjunctival Hyperaemia		Nil	minimal	mild	moderate	marked
CCLRU	Nil	Nil	CCLRU 1	CCLRU 2	CCLRU 3	CCLRU 4
Ocular Surface Staining	0	Nil	Minimal	Mild	Moderate	Severe
Scale (0-15)	0	Nil	0-3	4-6	7-10	11-15
NEI Industry (0-33)	0	Nil	0-7	8-14	15-23	24-33
Schirmer Score mm	☒ 10 mm	☒ 10 mm	< 10 - ☒ 7 mm	< 7 - ☒ 5 mm	< 5 - ☒ 3 mm	< 3 mm

Severity Grading and Treatment of MGD-related ocular surface disease and dry eye

SEVERITY LEVEL	Level Zero	Level 1	Level 2	Level 3	Level 4	Level 5
Disease Stage		Subclinical	Symptomatic Minimal	Symptomatic Mild	Symptomatic Moderate	Symptomatic Severe
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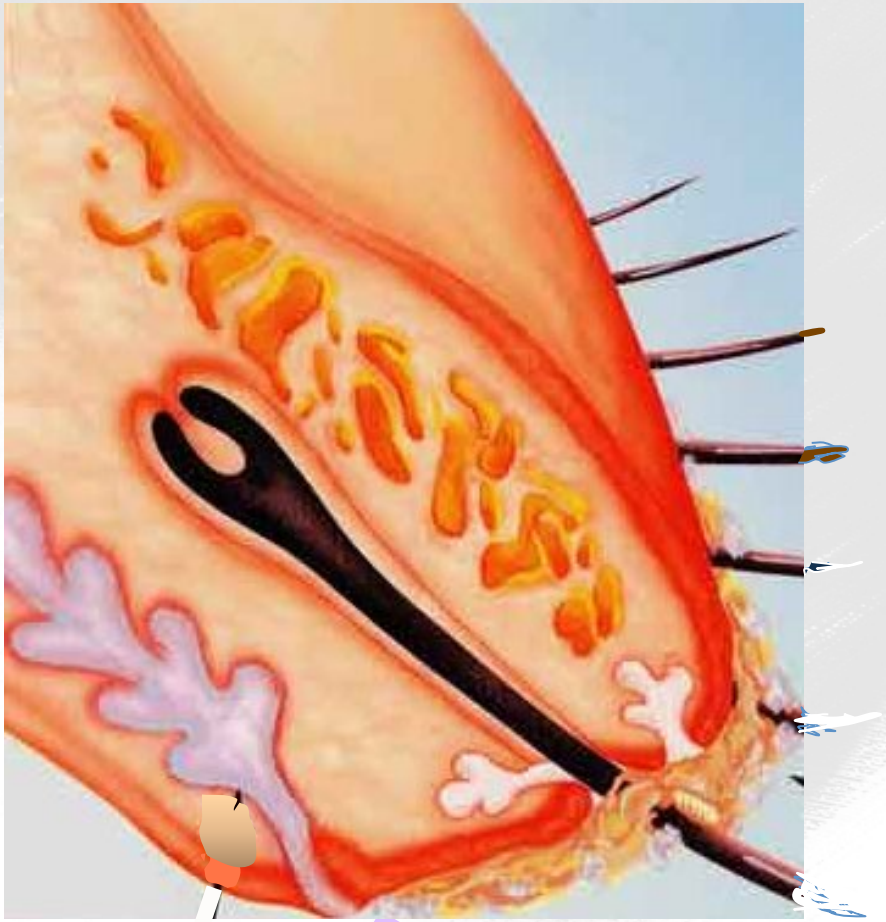
NEI Industry (0-33)	0	Nil	0-7	8-14	15-23	24-33
Schirmer Score mm	☒ 10 mm	☒ 10 mm	< 10 - ☒ 7 mm	< 7 - ☒ 5 mm	< 5 - ☒ 3 mm	< 3 mm
TREATMENT OF MGD –RELATED OCULAR SURFACE DISEASE	No treatment	No treatment	+ artificial tear substitutes + simple viscosity agents (preservatives allowable at low frequency of use)	+ alternative AT selection + immune modulation	+ alternative AT selection + gels and ointments ☒ punctal plugs ☒ moisture conserving spectacles	+ alternative AT selection + autologous serum + conserving spectacles + surgical procedures

Committee on
Evaluation, diagnosis and
grading of severity of MGD



QUESTIONS?

Thank you

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Management and Therapy of Meibomian Gland Dysfunction

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

Gerd Geerling, M.D. (Chair)
Joseph Tauber, M.D.
Christophe Baudouin, M.D., Ph.D.
Eiki Goto, M.D.
Yukihiro Matsumoto, M.D.
Terrence O'Brien, M.D.
Maurizio Rolando, M.D.
Kazuo Tsubota, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

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Goals

- To review current practice / published evidence of treatments for MGD
- To identify areas with conflicting or lack of evidence, observations or concepts where further research is required
- Comprehensive review of clinical textbooks and scientific literature
- Quality of published evidence graded according to objective criteria for clinical and basic research studies

Current Practice Patterns*

- Lid hygiene, warm compresses and lid massage
  - Cleaning of the lid margin with baby shampoo, cotton buds or wet towels, daily for 5-15 minutes
- Lubricants in cases with additional dry eye
- Topical antibiotic oint (moderate to severe)
- Systemic tetracyclines/ derivatives in recurrence
- Incision and curettage with optional steroid injection in chalazion

*Excerpted from Moorfields Manual, Wills Eye Manual (Guidelines for posterior blepharitis and meibomitis)

Current Practice Patterns

- World-wide variation
  - Underreporting → difficult to assess patterns
  - Underdiagnosis common, clinical follow-up irregular
- Lid warming and hygiene common
- Many use artificial lubricants
- Most Common Rx: Systemic tetracycline or derivatives (less frequent in EU/Japan)
  - 2nd most common Rx: topical antibiotic or antibiotic-steroid combination

American Academy of Ophthalmology Preferred Practice Pattern and DEWS report, The Ocular Surface, 2007 (5)163).

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

Over 140 Papers Reviewed

Evidence for Current Treatment Options

1. Artificial Lubricants
2. Topical Lipid Supplements
3. Lid hygiene, warming, manual expresssion
4. Anti-infective treatments (local)
5. Treatment of Demodex
6. Tetracycline and Derivatives (systemic)
7. Steroids
8. Calcineurin Inhibitors (topical)
9. Sex Hormones
10. Essential Fatty Acids
11. Surgical Options

Artificial Lubricant Therapy

References n=16
None in MGD

Rationale

- Issue of ATD vs. specific for MGD

Evidence-based options

- ↑ efficacy with higher viscosity AT for DE (Level II)

Other issues (discussed in DEWS report)

- Preservative toxicity issues
- Role of osmolarity / "osmoprotection"
- Interplay between residence time and blur

Topical Emollient Lubricant or Liposomal Spray

References n = 11
Clinical level II

- Evidence improve signs and symptoms of MGD
- Action may be by improving tear film stability/ slowing evaporation

Eye Lid Warming: References n=11

Mechanical Lid Hygiene: References n=13

Basic level I

Clinical level II

- Widely considered effective for MGD
  - Despite lack of standard technique and uncertainty of compliance
  - Studies comparing specific techniques missing
  - Patients should be advised in techniques
  - Follow-up examinations to ensure compliance

Topical Antibiotics:

References n=34
Basic / Clinical level II

Uncertain pathophysiologic role

- Causal, non-pathophysiologic colonization or secondary with/without pathophysiologic contribution (MMP, cytokine, lipases, other)

Antibiotic Selection Issues:

- By coverage spectrum (gm +)
- By anti-inflammatory co-actions (azithromycin)

Published evidence:

- Metronidazole (C.Level II), Azithromycin (B.Level II)
- RCTs missing

Treatment of Demodex:

References n=8
Clinical level III

- Understanding of *Demodex* in MGD incomplete
  - Symbiosis between mites and microbes part of the pathogenesis of MGD?

- Lid scrub with tea tree oil eradicates Demodex
  - May have antibacterial, antifungal and anti-inflammatory action
  - Reduces symptoms of surface inflammation

Tetracyclines / Derivatives: References n=26
Clinical level I

Various complementary mechanisms of action:

- Antibiotic effects, lipase inhibition, decreased FFA, ↓ of MMPs, anti-inflammatory, -oxidative, -apoptotic properties

Lots of evidence, BUT…Few placebo-controlled clinical trials:

- Improvement of signs and biological criteria (MMPs, FFA, inflammatory cytokines, etc.)

Steroids:

References n=5
Clinical level II

- Acute inflammation present / absent in MGD?
- Steroids controversial / potential complications

- CL II: Use of intralesional steroids for chalazia
- CL III: Lid hygiene ± with topical antibiotics
  ± topical steroids in MGD

Calcineurin Inhibitors (topical)

Topical Cyclosporine A: References n=3
Clinical level I-II

- Mostly studied in ATD dry eye or rosacea/MGD
  - Signs and symptoms improved with treatment
- Little data in MGD alone

Sex Hormones:

References n=5
Clinical level III

- Androgens influence gene expression for keratinization and lipogenesis in mouse MG
- Androgen receptor dysfunction / systemic anti-androgen medication associated with MGD
- Androgen eye drops in a 54-year-old male with dry eye restored lipid phase of tear film

Essential Fatty Acids:

References n=4
Clinical level II

- Omega-3 fatty acids gained popularity
- Anti-inflammatory (prostaglandin pathway)
- Oral O-3 reduces symptoms of ATD dry eye
- MGD: Little evidence of O-3 use to date

Surgical Treatment:

References n=3
Clinical level III

of 1° MGD:

- Probing of MG (Clin. level III, n=25) => Symptoms ↓

of complications of 1°MGD (+ disease):

(Chalazion, trichiasis, lid margin keratinization)

- Surgical procedures => Symptoms ↓, vision ↑
- Effect on MGD undetermined

of MGD-associated conditions (+ disease):

(Conj. chalasis, entropion, ectropion, lid laxity)

- Treatment may improve control of MGD

Table 2. Clinical summary of MGD staging used to guide treatment.

DISEASE STAGING			
Stage	**MGD grade**	**Symptoms**	**Corneal Staining**
1	+ (minimally altered expressibility and secretion quality)	Asymptomatic	None
2	++ (mildly altered expressibility and secretion quality)	Minimal to Mild	None to limited
3	+++ (moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severely altered expressibility and secretion quality)	Marked	Marked; central in addition
"PLUS DISEASE"	**Co-existing or accompanying disorders of the ocular surface and/ or eyelids**		

Recommended Staged Therapy

Stage = **I** **2** **3** **4** **Plus-Disease**

+Inform patient (about dietary / environmental / medication effects)
± Eyelid hygiene (warming / expression)

+Eyelid hygiene (warming / expression),
Advise re: potential benefits of ambient humidity / O3 fatty acid,
± Lubricant/lipid, topical azithromycin, tetracycl. derivatives

+ Oral tetracyclines
± Ointment (pm), cyclosporine/steroid for DE

+ Anti-inflammatory therapy for DE

+ Steroids, CL, Surgery

Future : Address Lack of Evidence

MORE RCTs…
Dietary:
- Omega 3 fatty acids
- Anti-oxidant therapy

Surgical, Mechanical or Physical Treatment:
- Surgical duct probing
- Therapeutic MG expression
- MG Warming, Pulse laser MG therapy

Pharmacological treatments:
- Improved understanding of pathophysiology of MGD and enthusiasm must drive development

QUESTIONS?

Design and Conduct of Clinical Trials

Tear Film & Ocular Surface Society presents MGD Workshop 2010

A Report from the International Workshop on Meibomian Gland Dysfunction

Penny A. Asbell, M.D.(Chair)
Fiona Stapleton, M.Sc., O.D., Ph.D.
Kerstin Wickström, Ph.D.
Esen Akpek, M.D.
Pasquale Aragona, M.D., Ph.D.
Reza Dana, M.D., M.Sc., M.P.H.
Michael A.Lemp, M.D. & Kelly K. Nichols, O.D., M.P.H., Ph.D.

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Clinical Trials - Goal

- Summarize the evidence in clinical trials of meibomian gland dysfunction (MGD)
- Utilize this information to make recommendations for best practice clinical trial design for this condition

Clinical Trials: Methodology

- Search for peer reviewed publications on observational/clinical trials
- 26 publications identified
- Studies ranked according to AAO classification
- Noted key trial characteristics
- Review of registration trials

Evidence Level for Eligible Trials (American Academy of Ophthalmology, 2008)

Evidence level	No. of publications	References
I	3	Yoo SE 2005, Perry HD 2006, Schechter 2009
I-II	2	Goto E., Shimazaki J. 2002, Rubin M 2006
II	8	Paugh JR 1990, Yalcin E 2002, Olson MC. 2003, Romero JM 2004, Pinna A 2007, Luchs J.. 2008, Matsumoto Y 2008, Souchier M. 2008
II-III	1	Mori A. 2003
III	9	Epstein GA 1988, Meisler DM 2000, Goto E., Endo K. 2002, Goto E., Monden Y. 2002, Shine WE 2003, Matsumoto Y 2006, Albietz JM 2006, Cetinkaya A 2006, Ishida 2008

Level I : at least one properly conducted, well-designed, randomized controlled trial. It could include meta-analyses of randomized controlled trials.

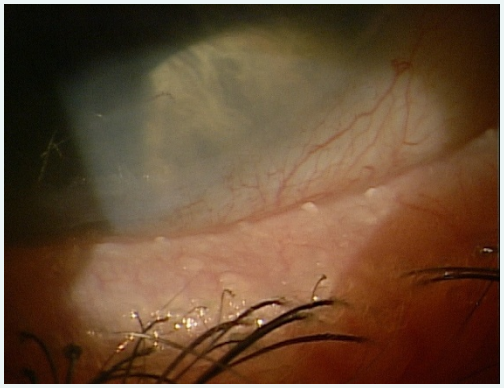
Level II : well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, preferably from more than one center or from multiple-time series with or without the intervention.

Level III : descriptive studies, case reports, or from reports of expert committees/ organizations (e.g., PPP panel consensus with external peer review)

Findings

Key Issues	Findings
Trial objective	Majority interventional treatment trials. 1/3 comparative (hot compresses or artificial tears)
Trial design / Methodology	Primarily small trials (<40 subjects) of short (<3 months) duration. Most prospective, 3 randomized controlled design, & 2 were double masked
Study population	Chronic disease but selection criteria not uniformly defined; lid changes & symptoms most common clinical characteristics,
Inclusion criteria	No specific and consistent criteria; most common are lid margin signs (80%), dry eye findings (50%), symptoms of discomfort/foreign body sensation (46%)
Exclusion criteria	Classification of exclusion criteria in three different categories: 1) Ocular disease related/CL wear (most common); 2) Iatrogenic (e.g surgery, 1/3 studies); 3) Systemic disease related/pregnancy (15%)

Findings

Issue	Findings
Outcome measures	1. Symptoms 2. TBUT 3. MG secretion/expression 4. Schirmer 5. Corneal staining 6. MG obstruction 7. Eyelids 8. Lipid layer 
Treatment	Most lacked washout period & did not check for relapse; 50% allowed concurrent use of other treatment & 30% treatment in the control group; large variability between tx duration but pharmacological trials tended to be longer with follow up
Statistics	Limited number of RCTs available; difficult to calculate effect size, power or required sample size. Limited information on how missing data e.g. loss to follow up, exclusion due to non-compliance, were handled.

Registration Trials

Condition	Interventions	Outcome
MGD	Testosterone ophthalmic solution vs. vehicle	**Primary:** MG secretion **Secondary:** Comfort
MGD	0.05% cyclosporine eye drop	**Primary:** NTBUT **Secondary:** OSDI score, TBUT, fluorescein/ rose bengal staining, MG grade
Blepharitis	Doxycycline; essential fatty acid; azithromycin	**Primary:** Inflammation of eyelid **Secondary:** Characteristics of MG secretions
Blepharitis Meibomianitis; Dry Eye	Doxycycline vs. placebo	**Primary:** Change in OSDI, bulbar conjunctival hyperemia **Secondary:** Change in Schirmer, TBUT, meibum character/ fluidity, MG inspissation
Blepharitis	Essential fatty acid supplement	**Primary:** Lipid biochemistry changes **Secondary:** Evaporimetry and Fluorophometry
Posterior blepharitis	2.5% IL-1Ra, Placebo; 5% IL -1Ra	**Primary:** MG secretion, quality, TBUT, corneal & conjunctival staining **Secondary:** MG occlusion, Schirmer with/without

Summary

Main priorities in future clinical trials

- RCTs in treatment trials with clearly defined objectives & relevant outcome measures
- Inclusion & exclusion criteria based on clear understanding of disease associations
- Determine natural history of disease
- Distinguish or determine associations with dry eye disease
- Develop specific /validated symptoms questionnaire for MGD

Summary

Main priorities in future clinical trials

- Develop standardised grading/evaluation system for signs aligned with outcome measures & agreement with standard of care
  - Objective, subjective???
  - Accessible for multi-centre trials?
  - Training program for investigators
  - Reading centres

- Determine the feasibility & clinical value of laboratory tear measures
- Establish surrogate outcomes/biomarkers

QUESTIONS?

A Report from the TFOS International Workshop on Meibomian Gland Dysfunction

Definition
J. Daniel Nelson, M.D. (Co-Chair)
Jun Shimazaki, M.D., Ph.D. (Co-Chair)
Jose M. Benitez-del-Castillo, M.D., Ph.D.
Jennifer P. Craig, Ph.D., MCOptom
James P. McCulley, M.D.
Seika Den, M.D., Ph.D.
Gary Foulks, M.D.

Clinical Trials
Penny A. Asbell, M.D.(Chair)
Fiona Stapleton, MScOD, Ph.D.
Kerstin Wickström, Ph.D.
Esen Akpek, M.D.
Pasquale Aragona, M.D., Ph.D.
Reza Dana, M.D., M.Sc., M.P.H.
Michael A. Lemp, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

Diagnosis
AlanTomlinson, MCOpt, Ph.D. (Chair)
Anthony J. Bron, F.R.C.S.
Donald R. Korb, O.D.
Shiro Amano, M.D., Ph.D.
Jerry R. Paugh, O.D.
E. Ian Pearce, Ph.D.
Richard Yee, M.D.
Norihiko Yokoi, M.D., Ph.D.
Reiko Arita, M.D., Ph.D.
Murat Dogru , M.D.

Anatomy
Erich Knop, M.D., Ph.D. (Chair)
Nadja Knop, M.D., Ph.D.
Thomas J. Millar, Ph.D.
Hiroto Obata, M.D.
David A. Sullivan, Ph.D.

Team
Michelle Dalton
Cathy Frey
Amy Gallant Sullivan
Rose M. Sullivan, R.N.
Sabrina Zappia

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Industry Liaison
David A. Sullivan, Ph.D. (Chair)
Marco Betancourt
Kim Brazzell, Ph.D.
Amy Brill
Michael J. Brubaker, Ph.D.
Timothy L. Comstock, O.D., M.S.
Neil D. Donnenfeld, M.B.A.
Marie Laure Dupuy Perard, Pharm.D.
David Eveleth, Ph.D.
Fulvio Foschini
Sherryl Frisch, M.S., M.B.A.
Manal Gabriel, D.D.S., Ph.D.
Kazuto Masuda, M.Sc.
Katsuhiko Nakata, Ph.D.

Epidemiology
Debra A. Schaumberg, Sc.D., O.D., M.P.H. (Chair)
Jason J. Nichols, O.D., M.P.H., Ph.D.
Eric B. Papas, M.Sc., O.D., Ph.D.
Louis Tong, F.R.C.S., M.B.B.S.
Miki Uchino, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

Management
Gerd Geerling, M.D. (Chair)
Joseph Tauber, M.D.
Christophe Baudouin, M.D., Ph.D.
Eiki Goto, M.D.
Yukihiro Matsumoto, M.D.
Terrence O'Brien, M.D.
Maurizio Rolando, M.D.
Kazuo Tsubota, M.D.
Kelly K. Nichols, O.D., M.P.H., Ph.D.

Lipid
Kari B. Green-Church, Ph.D. (Chair)
Igor Butovich, Ph.D.
Mark Willcox, Ph.D.
Douglas Borchman, Ph.D.
Friedrich P. Paulsen, M.D., Ph.D.
Stefano Barabino, M.D., Ph.D.
Ben J. Glasgow, M.D.

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