

A new Paradigm of Dry Eye
Etiology, Diagnosis and Treatment

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My Relationships

- Tear Science
- Noble Vision

Introduction – Many Questions for Dry Eye Etiology, Diagnosis and Treatment

- Is there a need for a new approach?
- Is dry eye a single or multifactorial entity?
- Aqueous or lipid deficient?
- What are initiating factors?
- Role of inflammation?
- Diagnostic methods adequate?
- Is posterior blepharitis synonymous with MGD?
- Is Tx adequate?
- Do anomalous results force the adoption of a new paradigm?

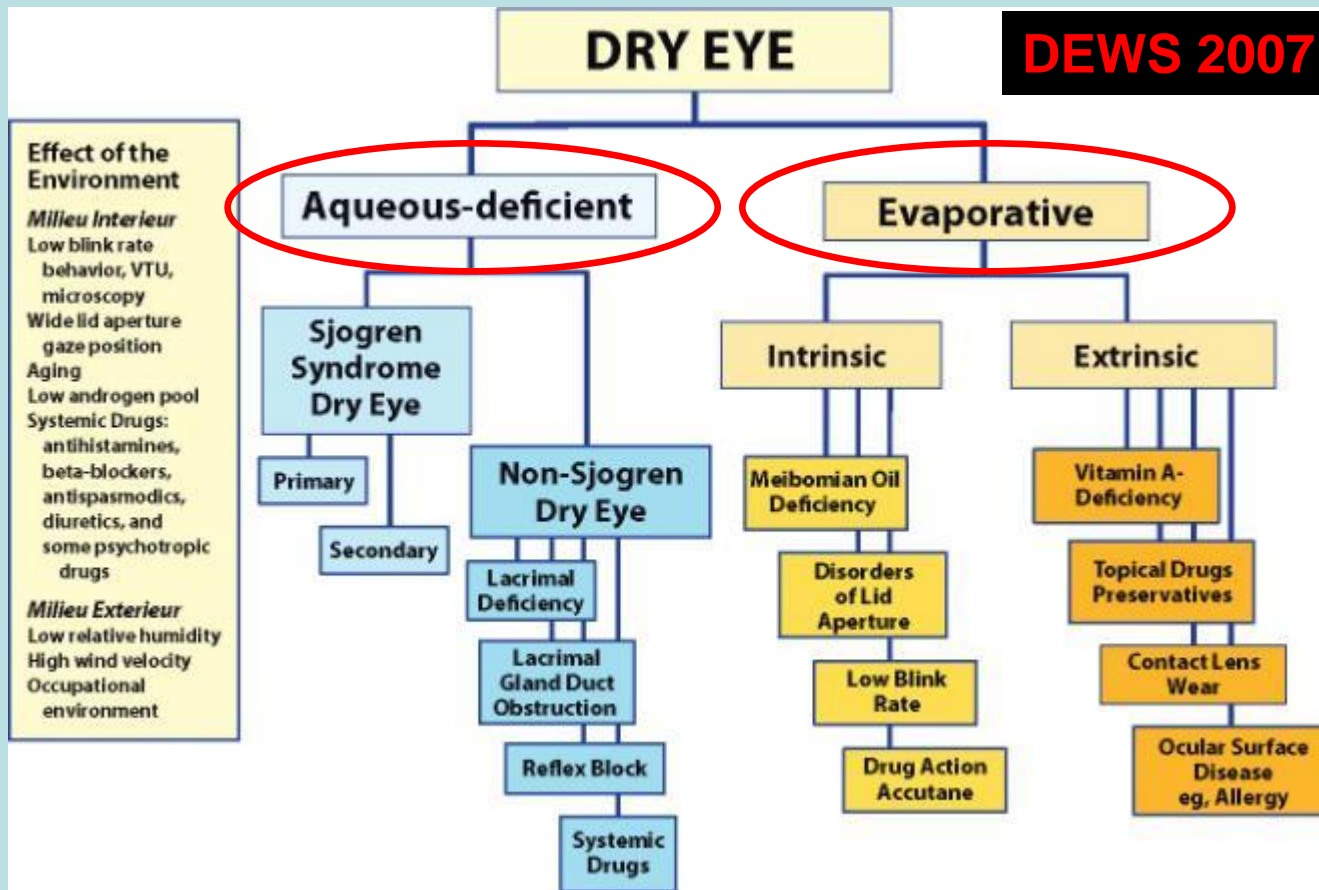


DRY EYE DEFINED – DEWS REPORTS

- 1995** “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.”
- 2007** “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 & increased inflammation of the ocular surface.”



Major Etiological Causes of Dry Eye – DEWS 2007



Mechanisms of Dry Eye – DEWS 2007

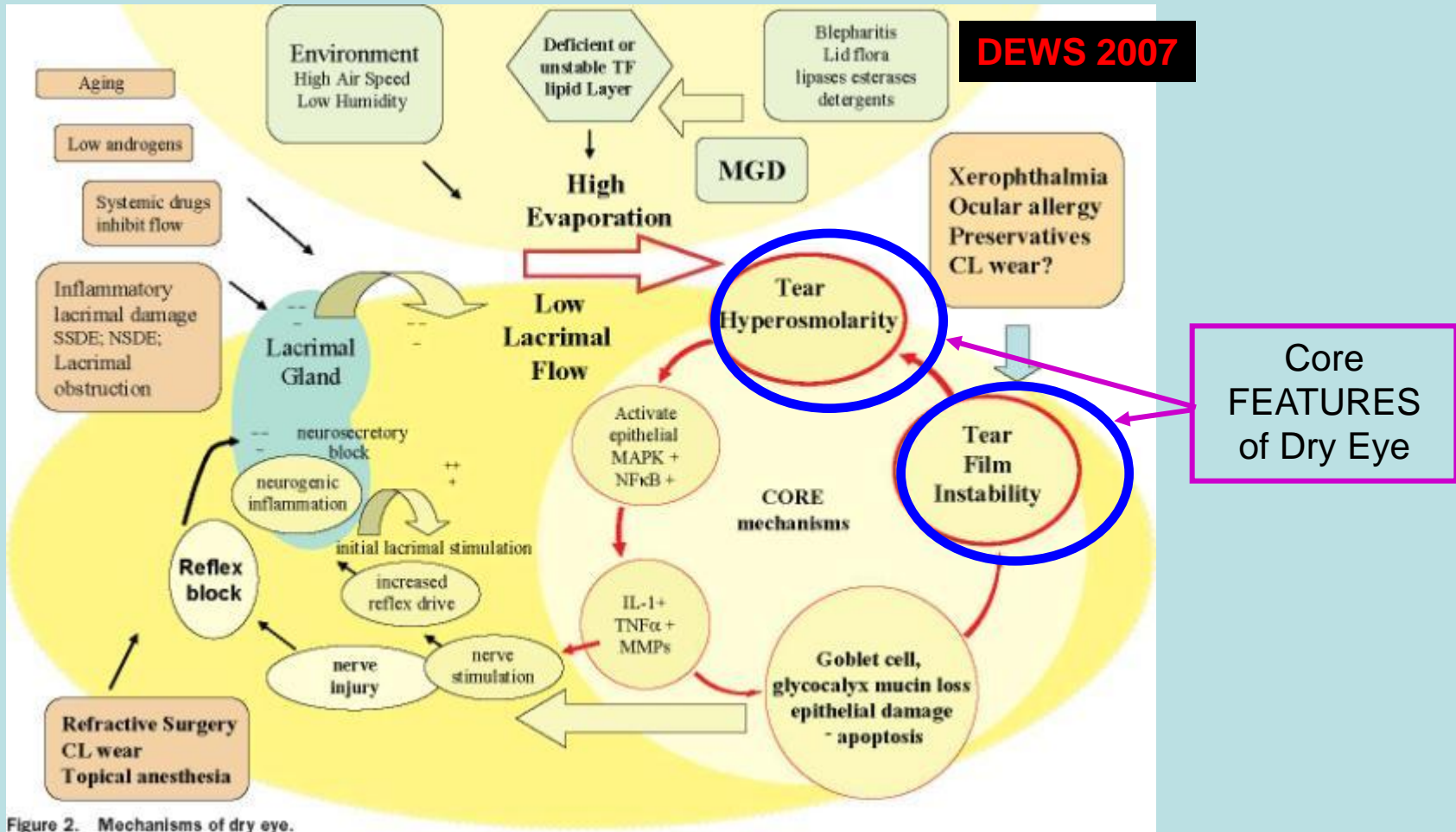


Figure 2. Mechanisms of dry eye.

Mechanisms of Dry Eye – DEWS 2007

EXPANDING ROLE OF MGD & INFLAMMATION

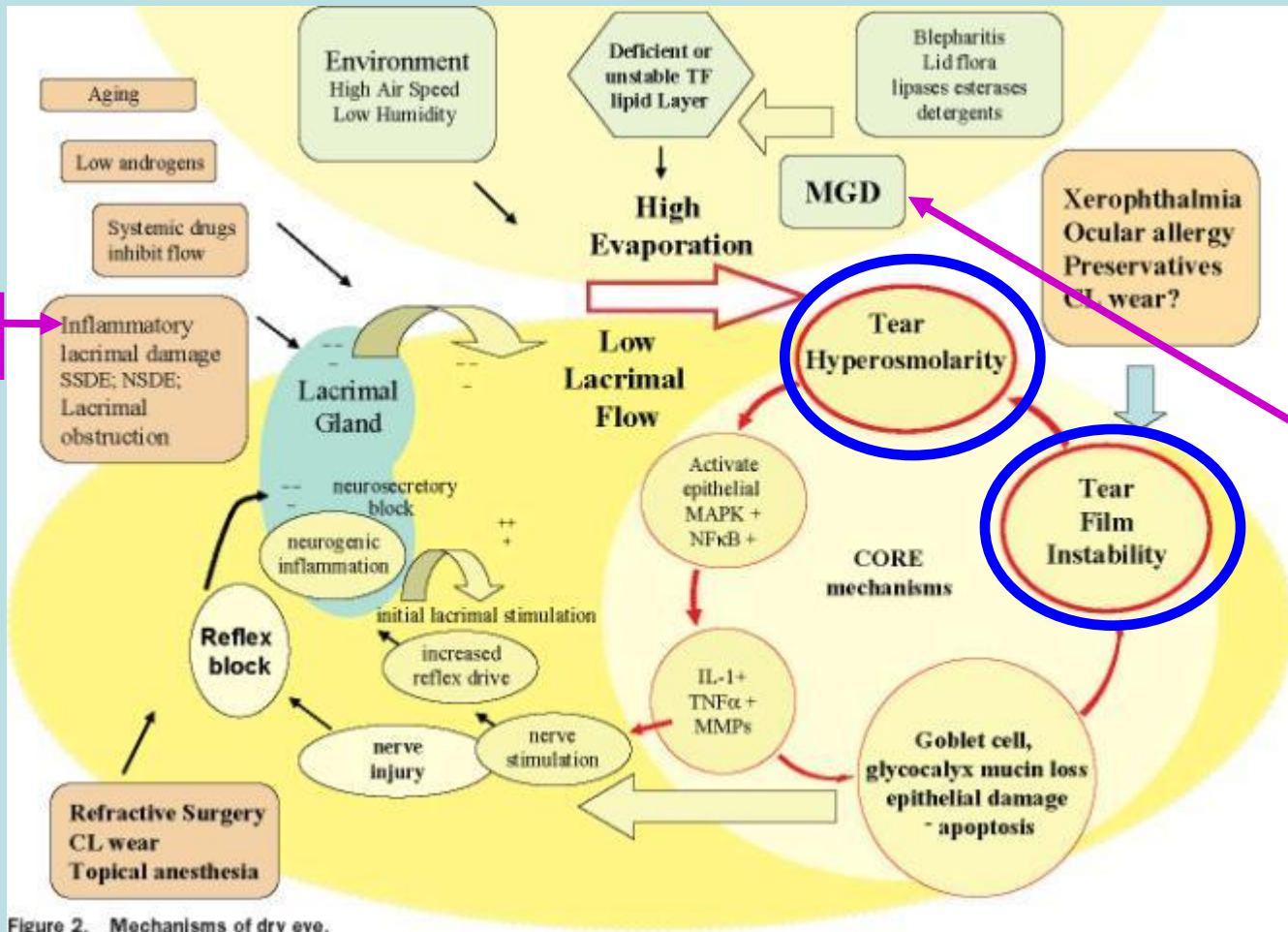


Figure 2. Mechanisms of dry eye.

QUESTIONS – WISH LIST

DEWS 2007 for Meibomian glands

- Number of MG for adequate tear layer
– Now answered
- Role of MG and lubrication
- Understand the obstruction process – particularly to keratinization of MG duct
- Analyze secretions – normal vs. dry eye
- Complex role of nutrition



EXPANDING & EVOLVING ROLE – INFLAMMATION

CURRENT CONCEPT: *Inflammation a critical feature of DED and results in significant tissue destruction*

QUESTION: *Where – When does inflammation enter the sequence – the cause, the result, or both ?*

- Literature past 20 years – animal models
- Proinflammatory cytokines in human tears
- Infiltration of inflammatory cells in to lacrimal glands



POST DEWS 2007 – A NEW PARADIGM FOR DRY EYE

September 2008 Update by Prestigious
Tear Film & Ocular Surface Society (TFOS)

***“It is important to note that
meibomian gland dysfunction
may be the leading cause of
dry eye syndrome throughout the world.”***

TFOS (DEWS) has held meeting of
~ 40 meibomian gland/tear film lipid experts
from around the world to develop
report to professions on MGD – 2010

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WHY A NEW PARADIGM?

“As anomalous results build up, science reaches a crisis, at which point a new paradigm, which subsumes the old results along with the anomalous results into one framework, is accepted.”

**Thomas S. Kuhn, 1962
The Structure of Scientific Revolutions**



This lecture will emphasize

1. *Etiology, Diagnosis, Pathogenesis, Prevention and Treatment of Dry Eye, MGD & MGO*
2. *NOMGD = non-obvious meibomian gland dysfunction*
3. *Maximizing the function of the meibomian glands, and thus the lipid layer, tear layer, lid wiper, and anterior segment*
4. *The insidious course of NOMGD and sequelae – inflammation and loss of secretory function*



DIAGNOSTIC TESTS FOR DRY EYE

Over 16 techniques reported by 68 World's experts

Rapid Review and explanation of key information

Multifactorial disease presents Dx dilemma

Multiple tests required for Dx

Survey for Preferred Tests for Dx of Tear Film and Dry Eye
Korb, 2000

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DIAGNOSTIC TESTS FOR DRY EYE

Over 16 techniques reported by 68 world's experts

FOUR PRIMARY TESTS RANKED

1. History – *Arguably the gold standard*

CONUNDRUM – SYMPTOMS BUT NO SIGNS

2. Break-up time

3. Corneal staining

4. Schirmer's test

**AUTHORS'
CLINICAL
COMMENTS**

*Survey for Preferred Tests for Dx of Tear Film and Dry Eye
Korb, 2000*

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History – Questionnaire – The Gold Standard

- Symptoms are a pillar of dry eye states but design of questionnaire critical
- Patient interpretation problematic
- **CONUNDRUM – SYMPTOMS BUT NO SIGNS**
- Requires ongoing verbal questioning

“ I thought my problem was normal ”

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HISTORY – QUESTIONNAIRES

- Plethora of questionnaires – Dry eye & CL
- Ocular Surface Disease Index (OSDI)
 - Allergan Research Questionnaire – validated

Schiffman et al, Arch. Ophthal, 2000

- NEI Visual Function Questionnaire (NEI-VFQ-25)

Clinician – Verbal questioning may suffice

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SPEED QUESTIONNAIRE

Name: _____, _____ **Date:** ___/___/___
 (Last) (First)

DOB: ___/___/___ **Sex:** M F (Circle)

Report the Type of **Symptoms** you Experience and when they have **occurred:**

Report the type of symptoms you experience and when they have occurred

SYMPTOMS	AT THE PRESENT TIME		WITHIN PAST 72 HOURS		WITHIN PAST 3 MONTHS	
	YES	NO	YES	NO	YES	NO
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye fatigue						

Report the frequency of the above-checked symptoms as Never, Sometimes, Often or Constant using the numbering system below:

Symptoms	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye fatigue				

Report the severity of your symptoms using the severity rating chart list :

Symptoms	0	1	2	3	4
Dryness, Grittiness or scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye fatigue					

Severity Rating List

- 0 = No problems
- 1 = Tolerable – not perfect but not uncomfortable
- 2 = Uncomfortable – irritation but does not interfere with my day
- 3 = Bothersome – irritating and interferes with my day
- 4 = Intolerable – unable to perform my daily tasks

Do you use drops? YES NO

(Standard Patient Evaluation of Eye Dryness = SPEED Form)

TEAR FILM BREAK-UP TIME (FBUT)

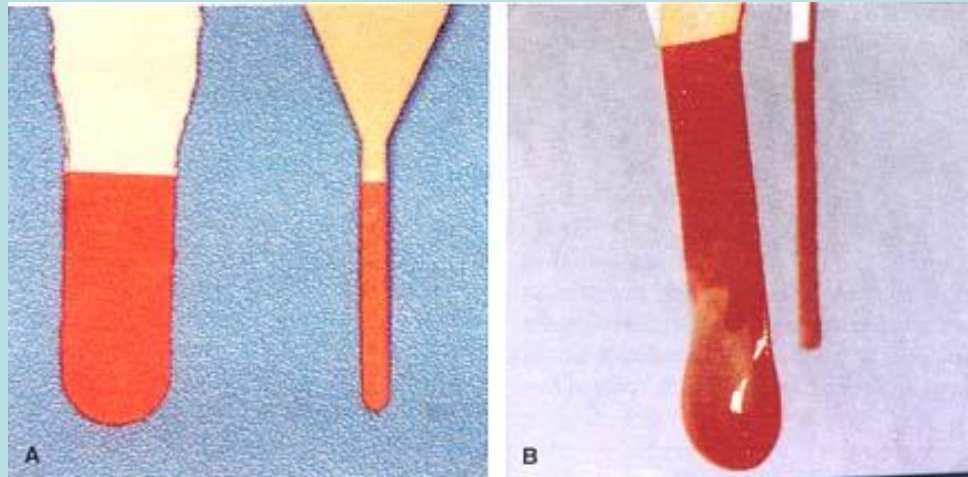
- Break-up time (1969) criticized as inaccurate, unscientific & not reproducible

Vanley et al., 1977; Mengher et al., 1985-86; Marquardt et al., 1986

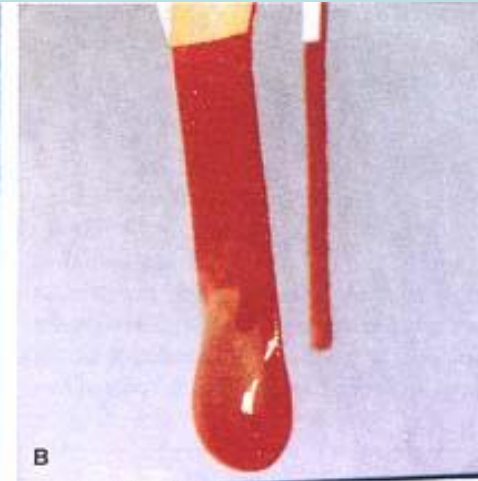
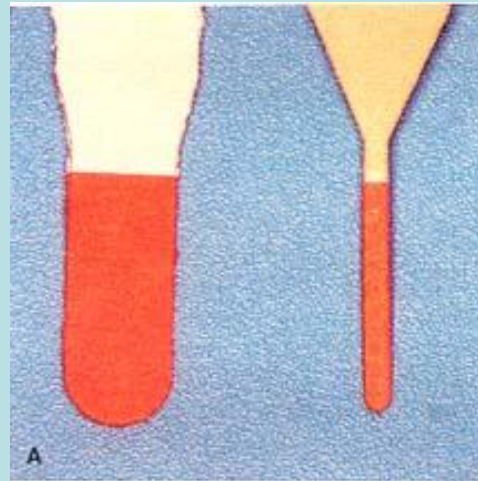
- Any volume of fluorescein over 2 μl instilled to conduct the FBUT test destabilizes the 7 μl tear film

Marquardt et al., 1986; Korb et al., 2001

- Volume cannot be controlled by the standard strip methodology

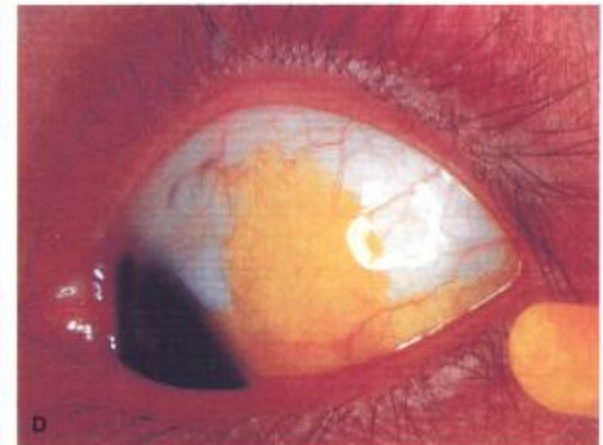
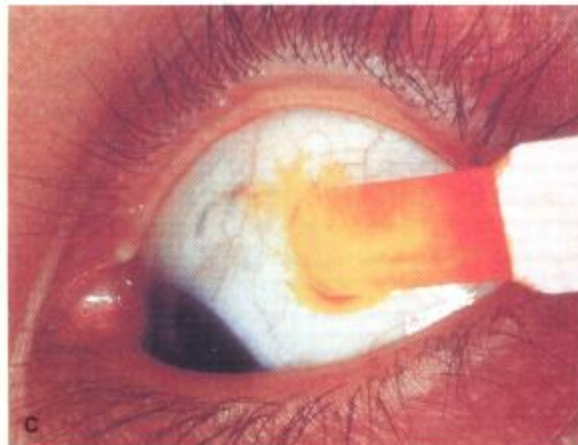
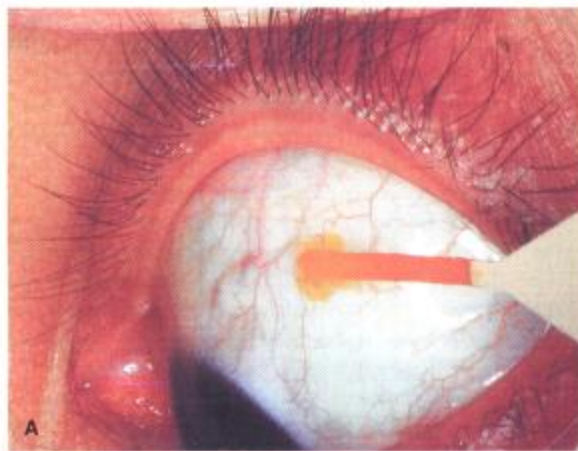


Meniscus and drop
on standard strip
NO meniscus on
DET strip



DET strip
Width = 0.9 mm
APPLIES DOSE
 $OF \leq 1 \mu l$

Standard strip
Width = 5.0 mm



***Korb is the inventor of
The DET Test***

TEAR FILM BREAK-UP TIME (FBUT)



CONCLUSION

A 1 μ l dose of NaFl can be applied with a special strip allowing reproducible FBUT measurements

Korb, Greiner & Herman; Cornea, 2001

Comparison of FBUT measurement reproducibility using standard fluorescein strips vs. the DET method

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OCULAR STAINING

*Complex subject
1 hour in 2 minutes*

DYE RECOMMENDATIONS

2008 STUDY

*An evaluation of the efficacy of fluorescein,
rose bengal, lissamine green and a new dye
mixture for ocular surface staining*

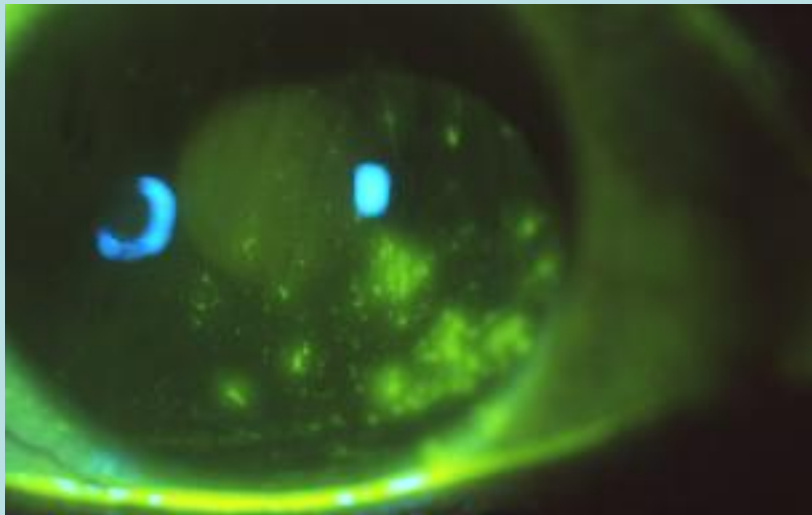
Korb, et al., Eye and Contact Lens, 2008

DYE RECOMMENDATIONS – 2008 STUDY

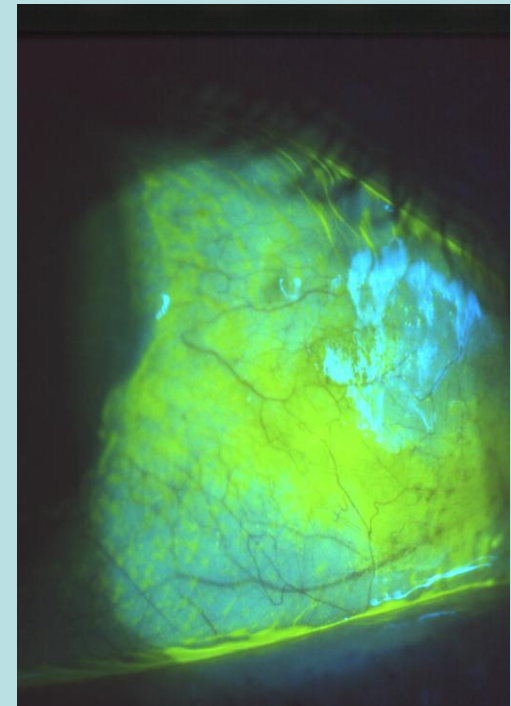
Korb et al., Eye and Contact Lens

FLUORESCEIN 2%

***Premiere dye for
corneal staining***



***Adequate dye for
conjunctival staining***



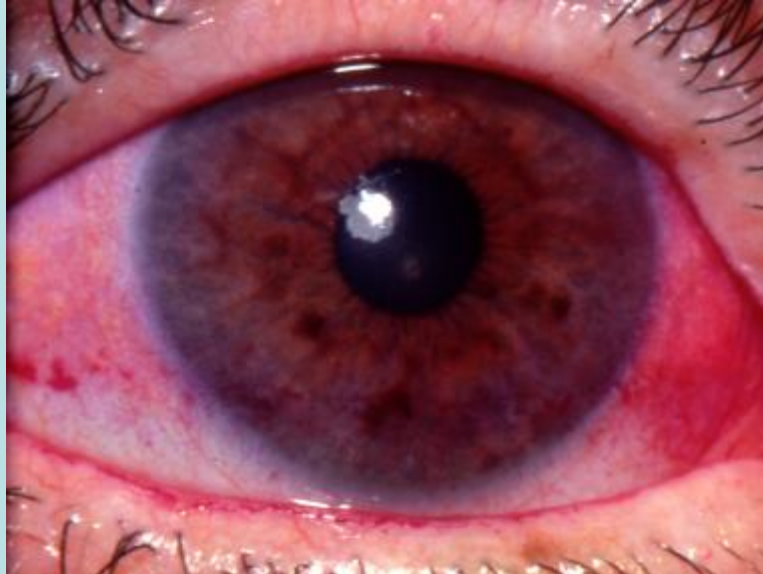
Thanks to Dr. John P. Herman

DYE RECOMMENDATIONS

ROSE BENGAL 1%

Premiere dye for conjunctival staining = Dx for KCS

**Perhaps the only test for
inadequate mucin layer**



Poor for corneal staining
Sting and toxicity limits use

KCS Grading, 1969
O. Paul van Bijsterveld

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DYE RECOMMENDATIONS

LISSAMINE GREEN 1%

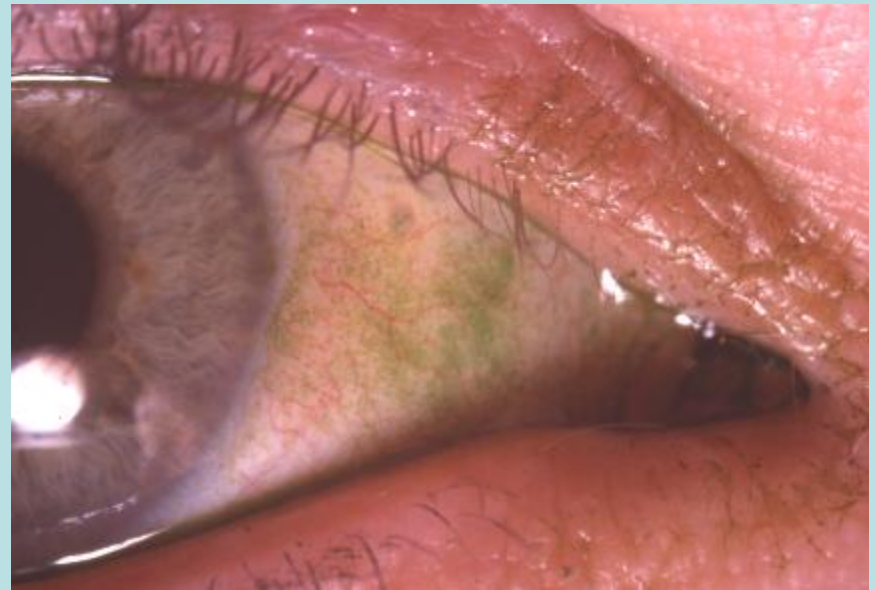
No sting at 1% concentration or from strips

Poor for corneal staining



Grade 1

Equal to RB for conjunctival staining



Grade 2

DYE RECOMMENDATIONS SUMMARY

- Use BOTH fluorescein & lissamine green
A mixture would be more efficacious
- Liquid optimal for staining
- Otherwise, use strips & avoid dilution for high concentration
- Rose bengal: reserve for when all else
STILL VALUABLE
- *Value of Sequential Staining*



SCHIRMER TEST – 1903

- Use anesthetic to standardize
- Higher readings not diagnostic
- ***Low readings***
 - zero to 5 mm in 5 minutes - ***diagnostic***
- Zone Quick 15 seconds
 - less sensation



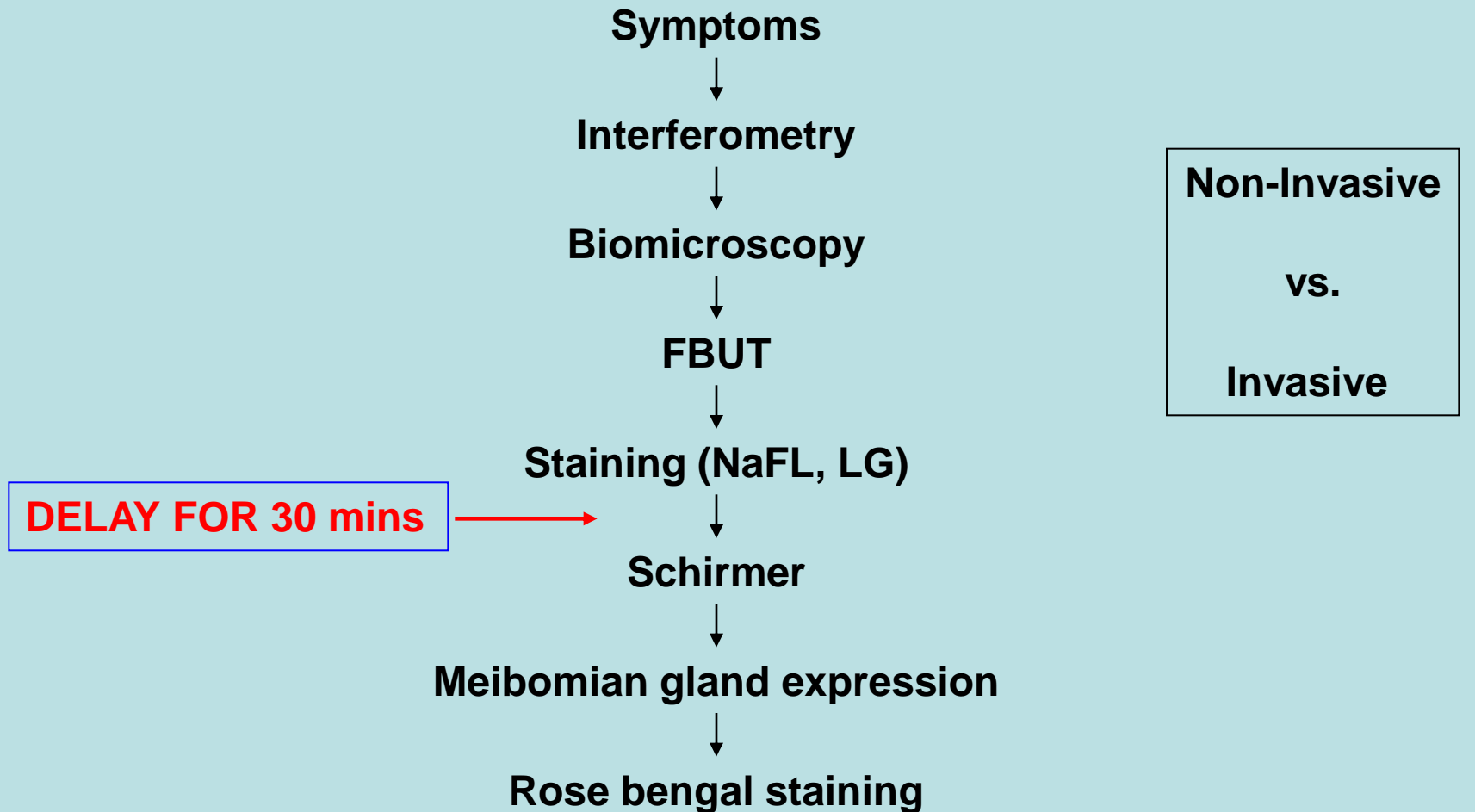
DIAGNOSIS – TESTS FOR DRY EYE

- Meibometry – developing area
- Osmolarity – available – validates decrease in aqueous
- Lipid Layer Thickness
- Lid Wiper Epitheliopathy
- The Line of Marx - not ready
- Meibomian Glands



SEQUENCE – DIAGNOSTIC TESTS FOR DRY EYE

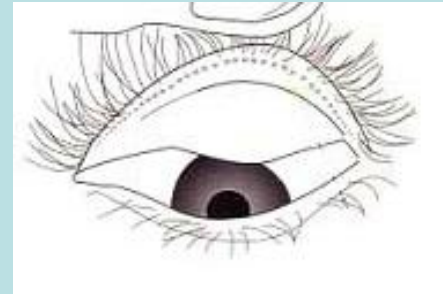
(Bron, Pflugfelder, Korb)



USUALLY NOT POSSIBLE TO PERFORM ALL TESTS IN ONE VISIT

LID WIPER EPITHELIOPATHY

***A possible missing link in dry eye
treatment and diagnosis***



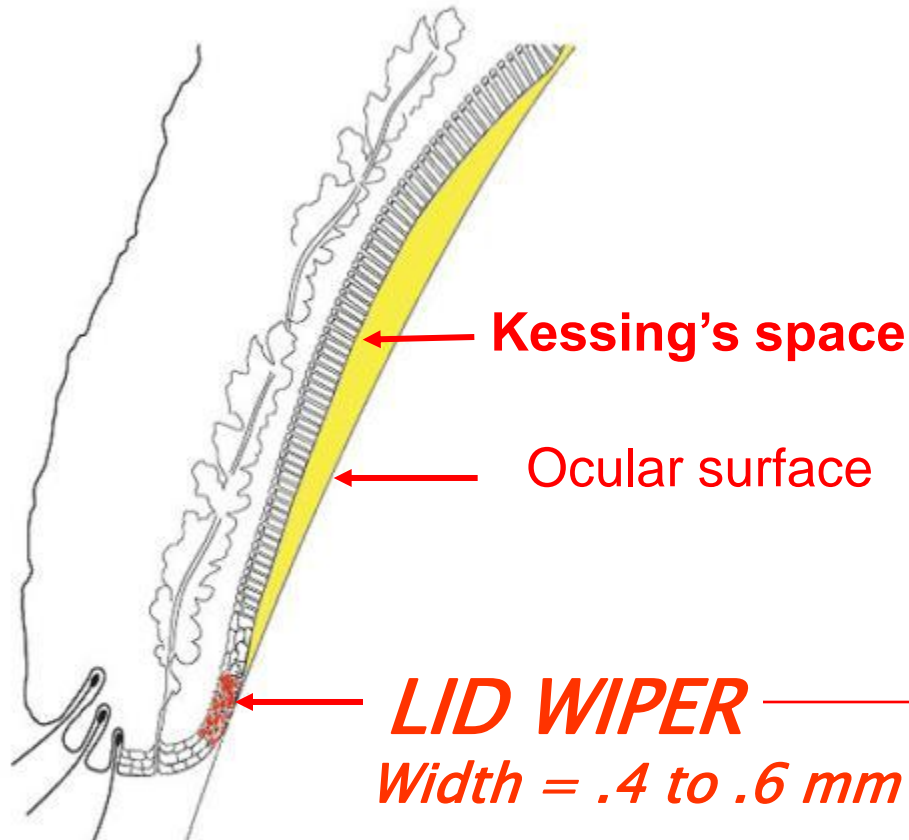
- **What is the Lid Wiper ?**
- **What is Lid Wiper Epitheliopathy ?**
- **How is Lid Wiper Epitheliopathy (LWE) diagnosed ?**
- **Line of Marx – Function and is it the Lid Wiper ?**
- **What is the “evidence based medicine” for LWE occurring with and without contact lenses ?**
- **What are the causes of LWE ?**
- **How is LWE treated ?**

25 M



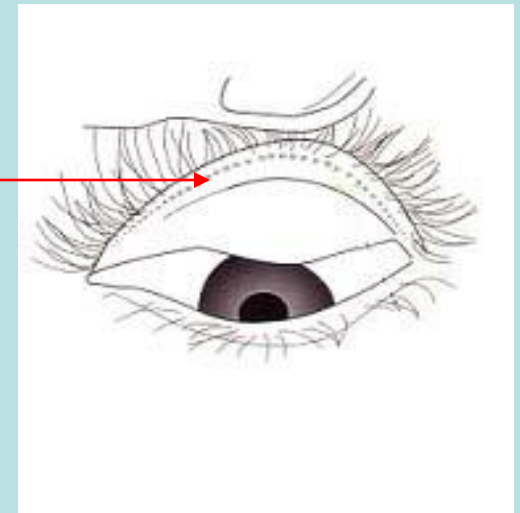
THE LID WIPER

Korb, et al., 2002-2009

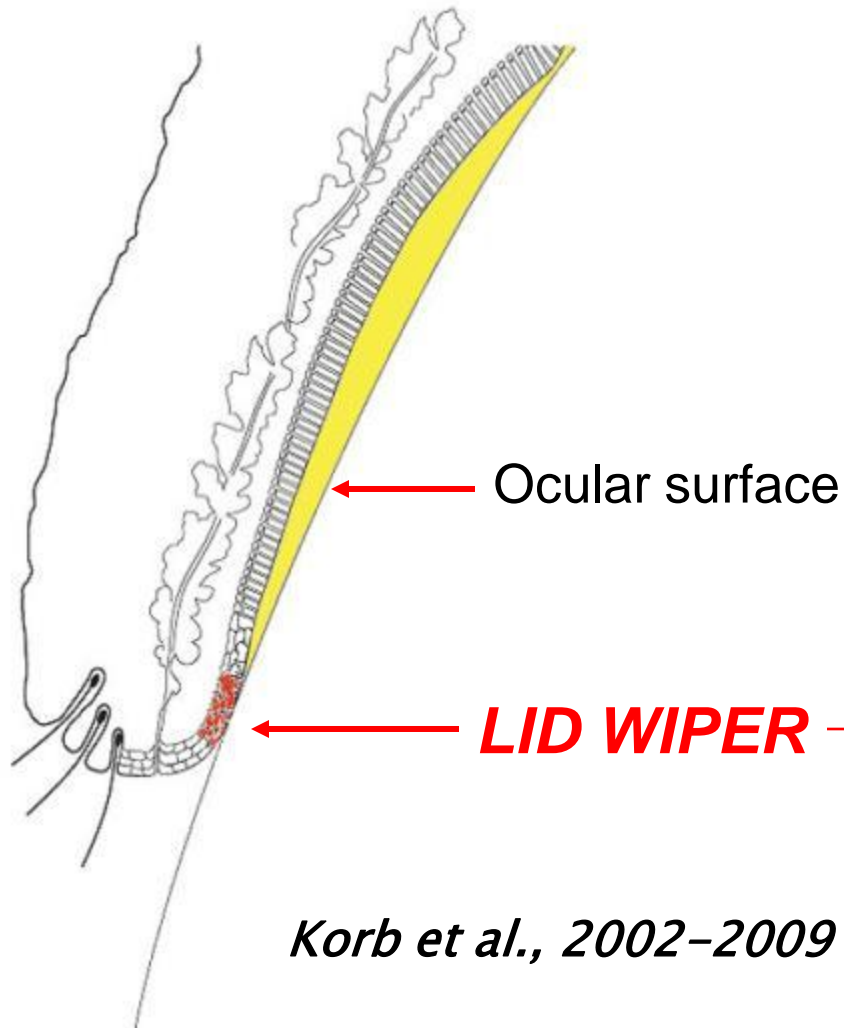


Parsons : Squamous epithelium indicates contact of that surface

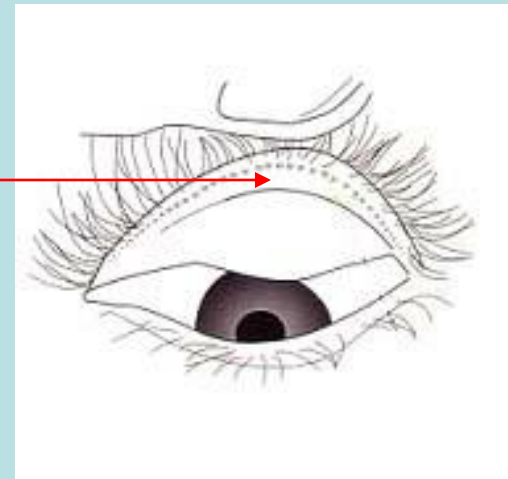
That aspect of the marginal conjunctiva of the upper eyelid that wipes the ocular surfaces during blinking



LID WIPER EPITHELIOPATHY DEFINED



Any compromise to the lid wiper's squamous epithelia and/or their protective coatings



DIAGNOSIS OF LWE REQUIRES DYES

Fluorescein – the premier dye for the cornea

Rose bengal or lissamine green – for the bulbar conjunctiva

DIFFERENT STAINING PROPERTIES

USE BOTH FOR THE LID WIPER

Fluorescein or lissamine green

One application - wait 60 seconds

Preferably 2 applications, 5 min apart

Rose bengal

One application - wait 30 to 60 seconds

*An Evaluation of Fluorescein, Rose Bengal,
Lissamine Green, and a New Dye Mixture
Korb et al., Eye & CL, 2008*



Same lid prior to
and after staining

- ***No evidence of LWE***
- **Minimal evidence of inflammation**

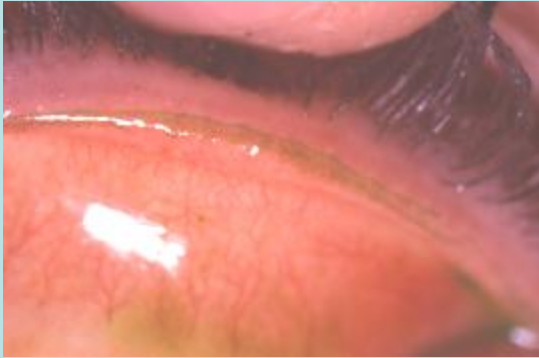


- ***Severe LWE***
- **100% of width**
- **Over 15 mm in length**
- **Severe staining**

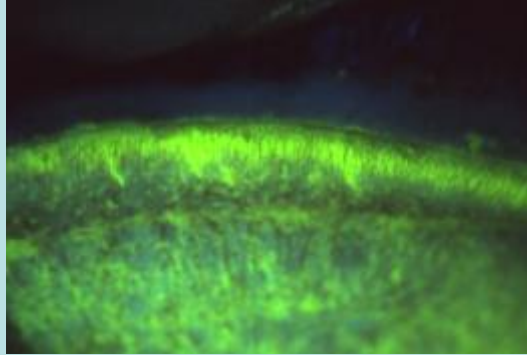
*(Vertical linear fluorescein staining
is evidence of inflammation)*

**Staining is necessary for the Dx of LWE
(fluorescein, rose bengal, lissamine green)**

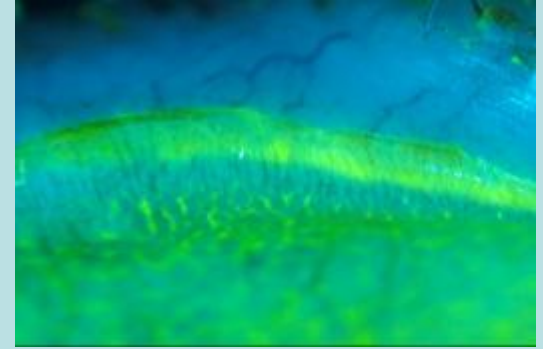
Grade 1.5



Grade 2



Grade 3



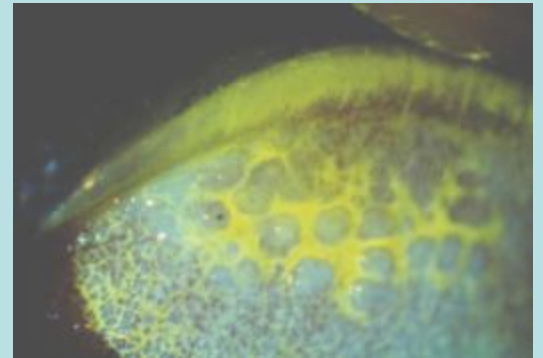
Grade 1.5



Grade 2



Grade 3



Recommend: SERIAL – SEQUENTIAL STAINING

2 drops – 5 minutes apart

Must conduct prior to lid eversion

- If lid everted, lid wiper becomes desiccated and will evidence iatrogenic staining when reexamined following staining and lid eversion.
- Summary – Clinical Procedure:
Stain → wait 5 mins → re-stain and evert for first time

In preparation – Blackie & Korb



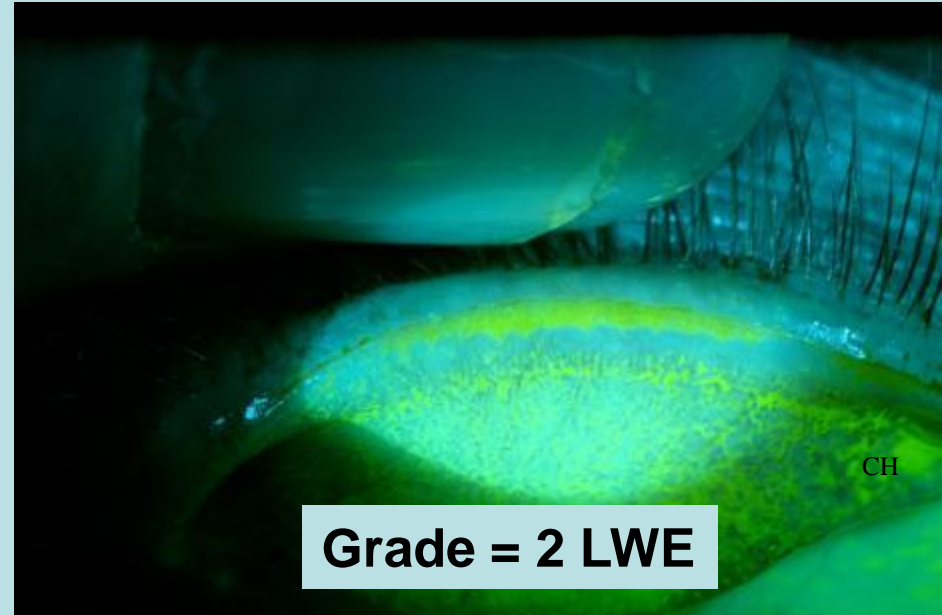
FLUORESCEIN SERIAL – SEQUENTIAL STAINING

One drop at 1 minute vs. 2 drops at 5 minutes apart

OD
DROP 1 – Wait 1 minute, then evert



OS
DROP 1 – DO NOT EVERT
DROP 2 at 5 minutes, wait 1 minute,
then evert



*If symptoms present,
sequential staining indicated for LWE Dx*

LISSAMINE GREEN SEQUENTIAL STAINING

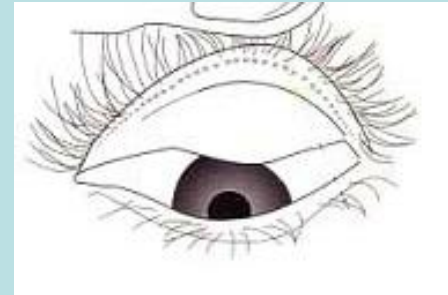
One drop at 1 minute vs. 2 drops at 5 minutes apart

OD
DROP 1 – Wait 1 minute, then evert



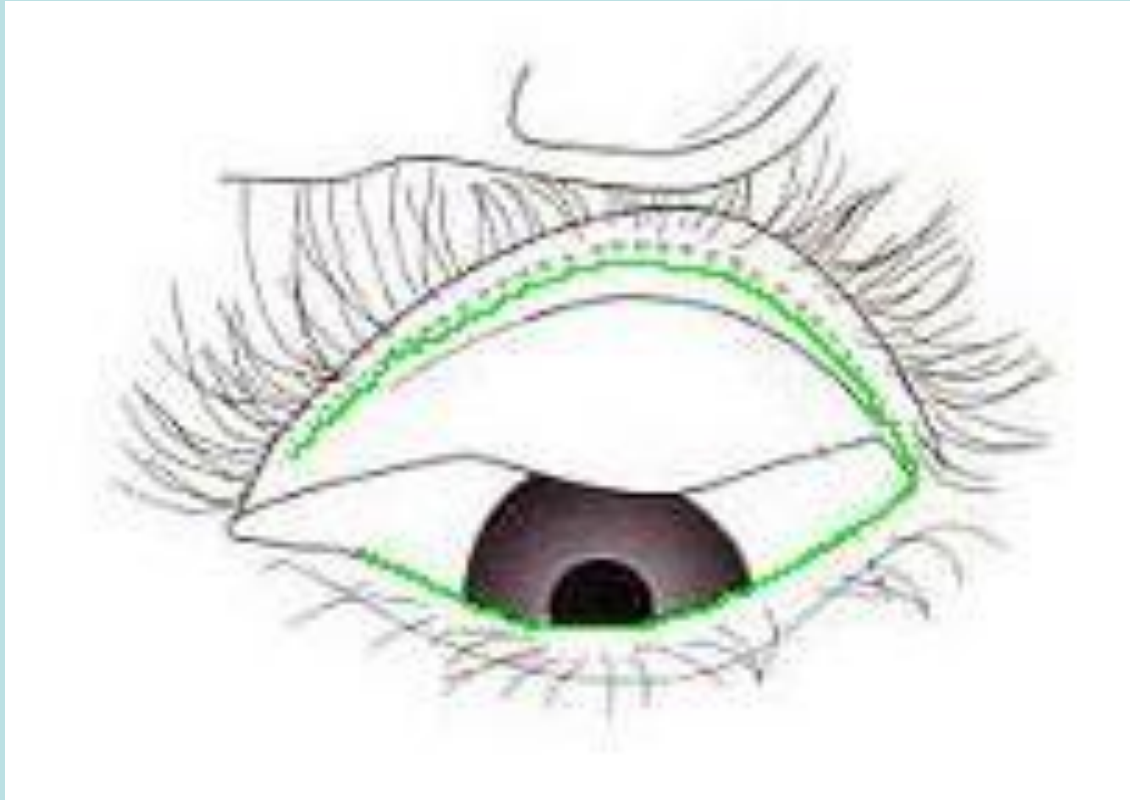
OS
DROP 1 – DO NOT EVERT
DROP 2 at 5 minutes, wait 1 minute,
then evert





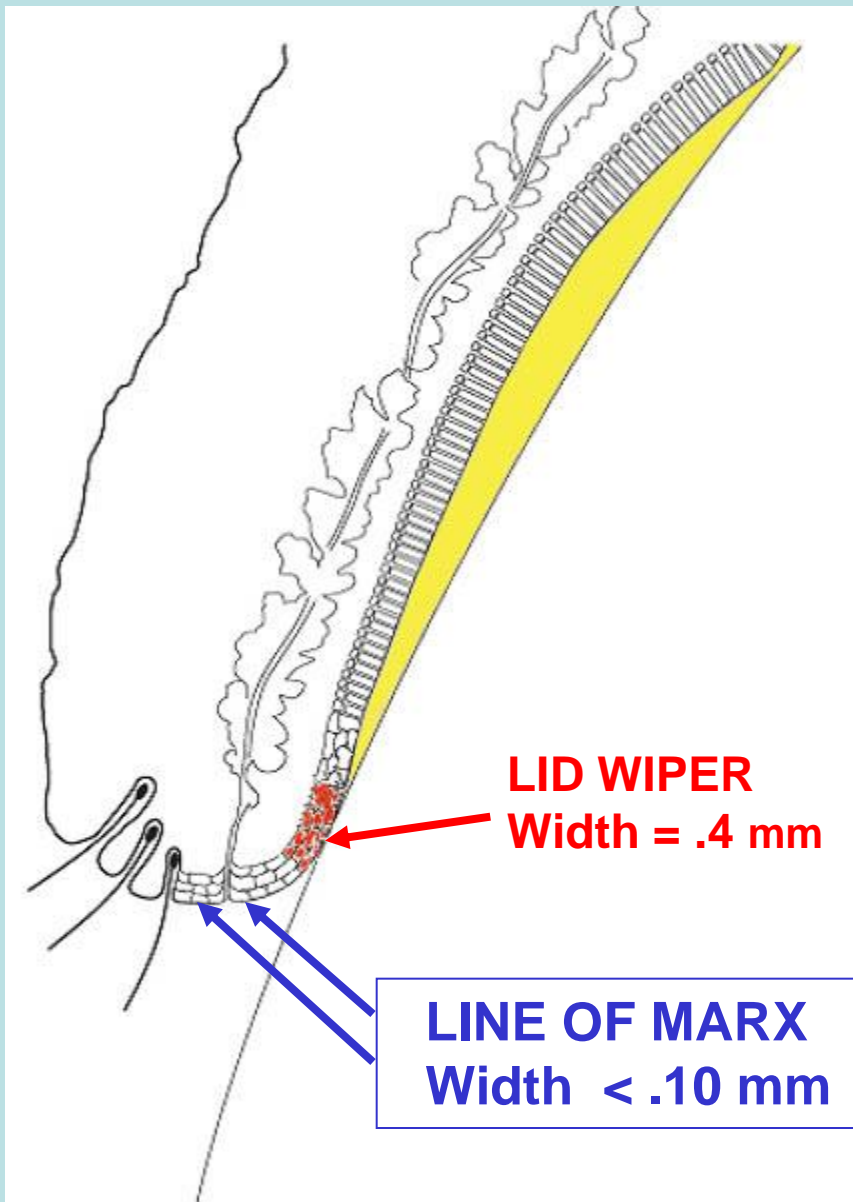
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- **Line of Marx – Function and is it the Lid Wiper ?**
- What is the “evidence based medicine” for the prevalence of LWE with and without contact lenses ?
- What are the causes of LWE ?
- How is LWE treated ?

Marx – Reported a fine line of staining of the entire length of both the upper and lower lids



Marx's research was confined to the lower lid

Heiko Pult, PhD, MSc, FAAO; Cardiff University, Germany



Line of Marx – 1924

***Used rose bengal
(mucocutaneous
junction)***

Studied only lower lid

***Marx did not explain
function***



The Line of Marx **IS** the Lid Wiper

- 2003 A Quantitative Assessment of the Location and Width of Marx's Line Along the Marginal Zone of the Human Eyelid.**
Hughes et al, OVS, 2003
- 2004 Visualization of Marx's line along the marginal eyelid conjunctiva of human subjects with lissamine green dye.**
Doughty et al, Ophthal Physiol Opt, 2004
- 2009 Eyelid Pressure: Inferences From Corneal Topographic Changes.**
Shaw et al, Cornea, 2009
-

The Line of Marx **IS NOT** the Lid Wiper

- 2008 Elastohydrodynamics of the eyelid wiper.**
Jones et al., Bulletin of Math Bio;70(2):323-43 2008
- 2008 Clinical tests for successful contact lens wear: relationship and predictive potential.**
Pult et al., Optom Vis Sci. 2008 Oct;85(10):924-9



***Marx's Line is not the Contact Area for the Wiping
of the Ocular Surfaces by the Upper Lid***

Korb and Blackie, review , 2009

Purpose: To determine if Marx's line is
the contact area of the upper lid



OBSERVATION OF MARX'S LINE WITHOUT EVERSION

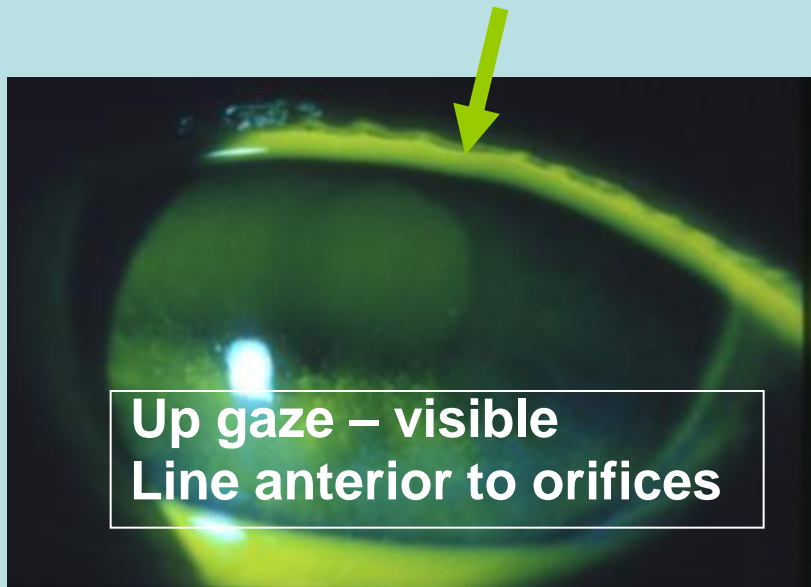


Originally used mirror

Up gaze

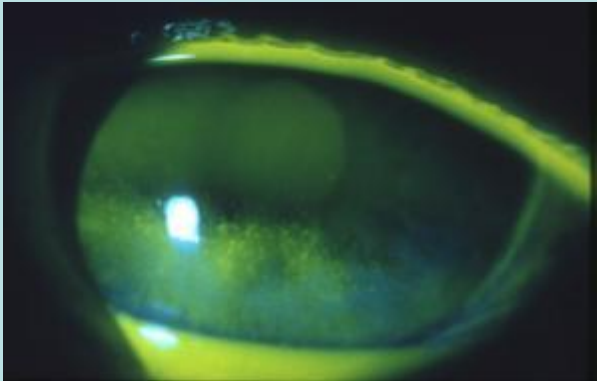
Wait for thinning of meniscus

Position of Marx's Line to orifice



RESULTS

N = 199



Marx's line visible for

93% of all subjects for entire width

97% of all subjects for partial width

03% not visible due to lid structure



CONCLUSION: MARX'S LINE IS NOT THE CONTACT AREA

*Marx's line **is not** the contact area for the wiping of the ocular surfaces by the upper lid, since it is impossible for the contact area to be visible and also be in contact with the ocular surface during blinking.*

The Lesson of The Meniscus

- A fluid layer cannot form on keratinized epithelium
- The epithelium under the meniscus must be wettable
- The histology of Marx's Line establishes it is the mucocutaneous junction and cannot be a wettable surface designed for wiping.



LWE PREVALENCE – EVIDENCE BASED - summary of 3 prevalence studies

1. In CL Wearers

- **80%** for Symptomatic Group
- **13%** for Asymptomatic (Controls)

Korb, Greiner, Herman, et al., CLAO 2002

2. In Dry Eye with Sx but no signs

- **76%** for Symptomatic ($P < 0.0001$)
- **12%** for Asymptomatic (Controls)

Korb, Herman, Greiner et al., Eye & Contact Lens, 2005

3. In Dry Eye with Sx & signs

- **88%** for Symptomatic
- **12%** for Asymptomatic (Controls)

Korb, Herman, Blackie et al., in press, Cornea, 2009

Prevalence of LWE

16 X greater for grade 2 Symptomatic vs. Controls

LWE Highly Correlated to:

Dry Eye Symptoms

Dry Eye Signs

Dry Eye States

Contact Lens Dry Eye Symptoms

***Staining technique is the tool
for diagnosis of LWE
fluorescein and lissamine green***

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CAUSATIVE FACTORS LID WIPER EPITHELIOPATHY

Inflammation

The primary cause
or a sequela of LW
and dry eye ?

Compromised lubrication of LW

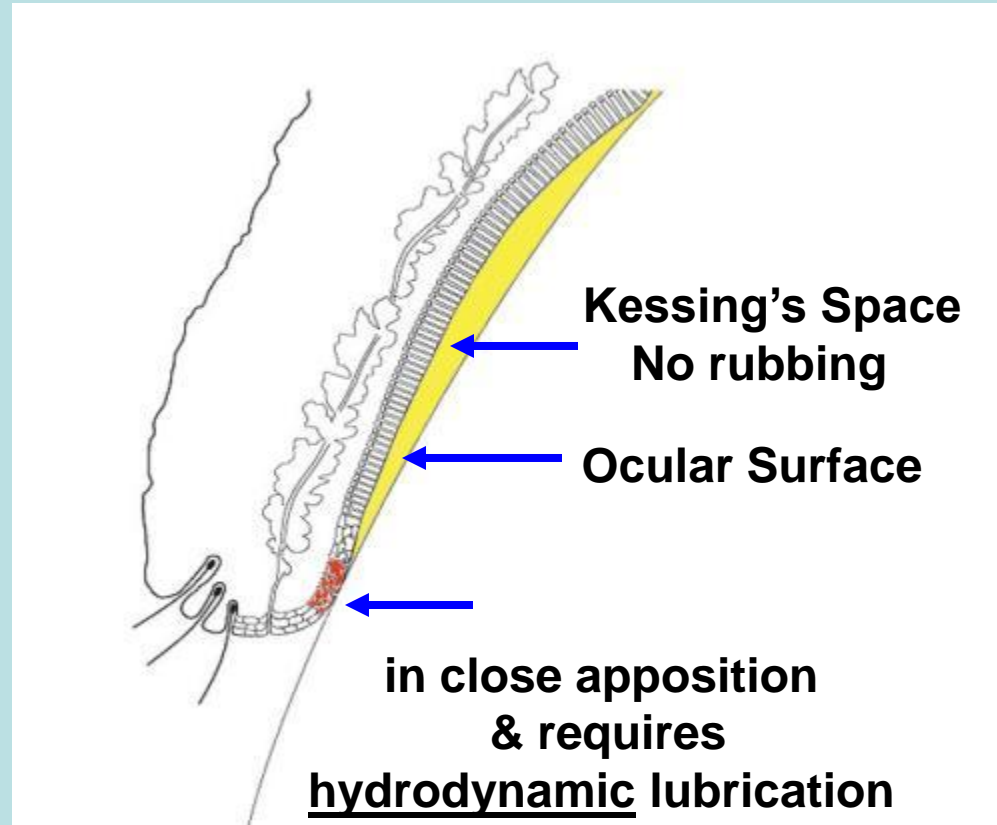


Microtrauma
3-5,000 blinks/day

leading to

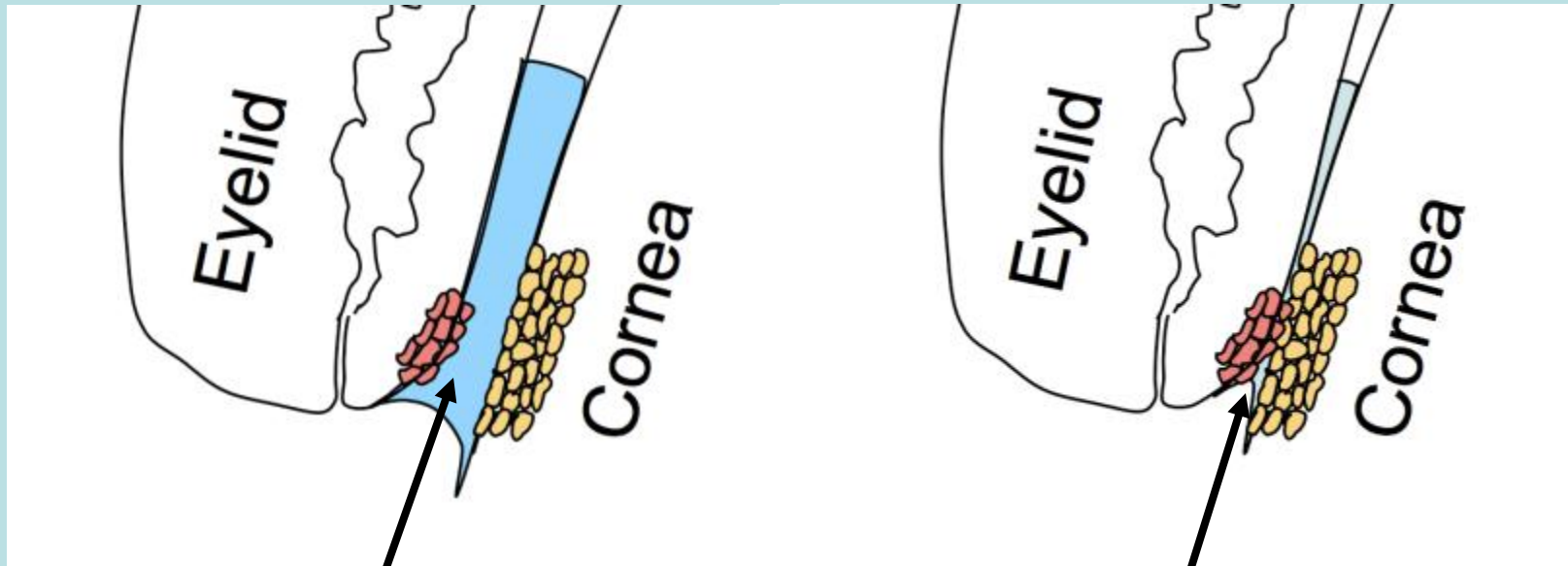


Inflammation
Trauma & LWE



THE LID WIPER

Requires hydrodynamic lubrication



**Sufficient
hydrodynamic lubrication**

**Insufficient
boundary lubrication
MICROTRAUMA**



PATHOGENESIS – LID WIPER EPITHELIOPATHY

Dry eye states and contact lens surfaces



Inadequate **lubrication**



Microtrauma & inflammation
to epithelium with every blink



Staining of epithelium of the lid wiper
& ocular surface



Triple Response of Lewis



Inflammatory cascade & sequelae





To understand ocular inflammation in dry eye
need to understand

Triple Response of Lewis – 1927

INFLAMMATORY RESPONSE
TO EXCESS TRAUMA



Firm Stroking of Skin

1. Sharply demarcated erythema
– release of histamine
2. Red flare
– extending beyond margins of pressure
3. Appearance of wheal

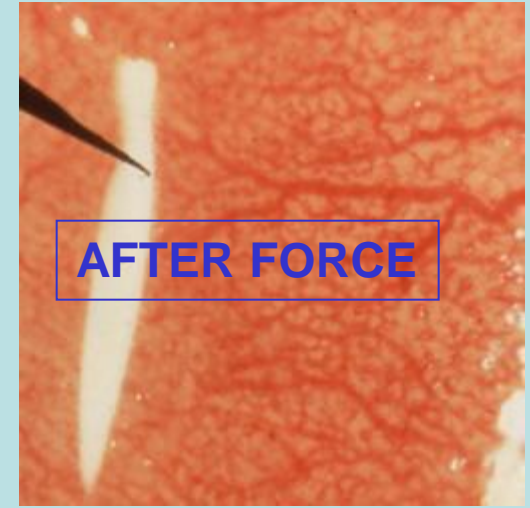
THE TRIPLE RESPONSE OF LEWIS ON PALPEBRAL CONJUNCTIVA

APPLICATION OF
15 GRAMS OF FORCE (4 GRAM/MM²)
WITH
CUSTOM INSTRUMENT



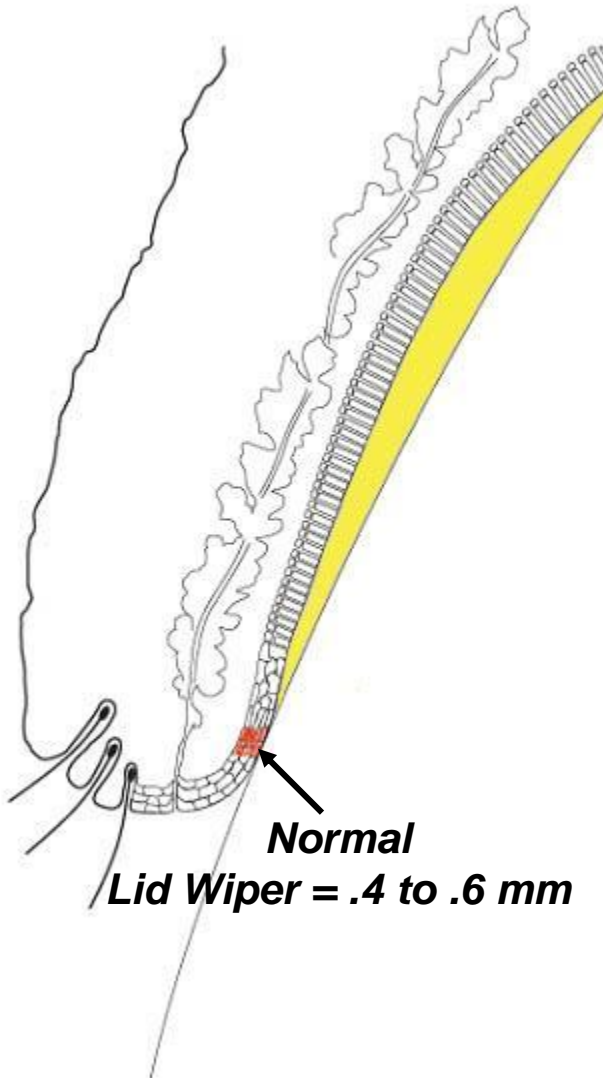
INFLAMMATORY RESPONSE
TO EXCESS TRAUMA
PALPEBRAL CONJUNCTIVA

INFLAMMATORY MARKERS
2009 POSSIBILITIES



LID WIPER WIDTH AND INFLAMMATION

LESSON OF LEWIS: MECHANICAL TRAUMA = INFLAMMATION

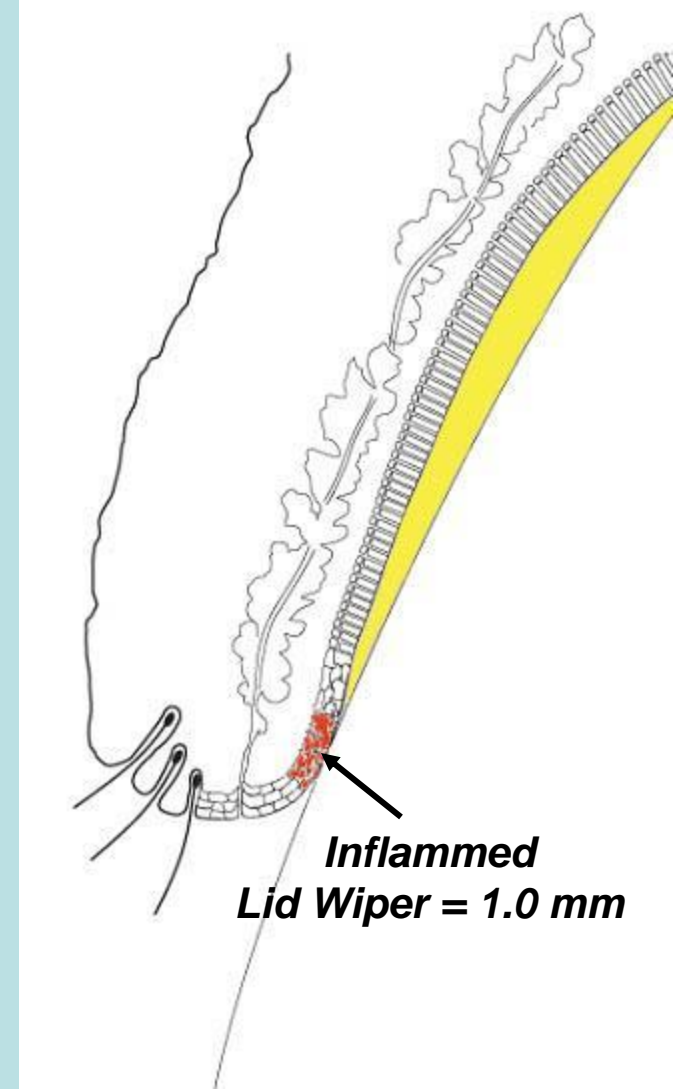


Effect of inflammation

**Normal LW width =
.4 to .6 mm**

**With epitheliopathy,
the width increases
(even > 1.0 mm)**

**Advance stages –
GPC analog of lid wiper**



PAIN AND INFLAMMATION

Pain is associated with inflammation and
increases
with continuing insult

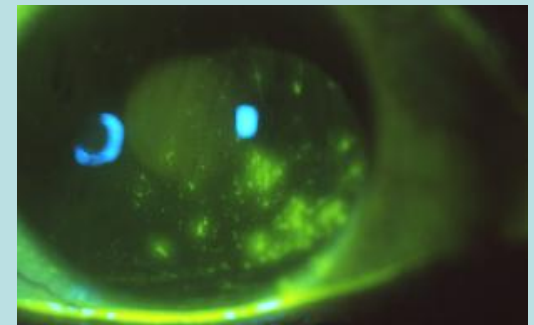
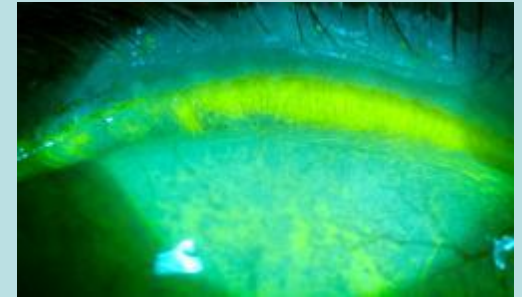
Explains correlation with symptoms



LID WIPER EPITHELIOPATHY TREATMENT

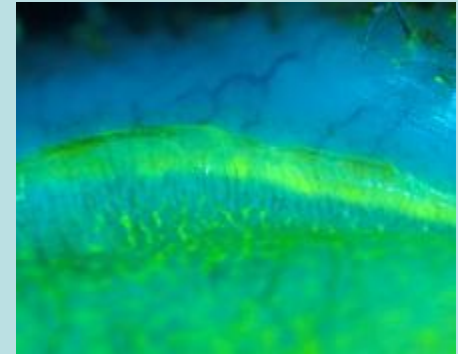
- LWE is a sequela of a dry eye state
- Treat the specific dry eye state
 - Must include treatment of MGD**
- Treat inflammation as required
- *With contact lenses, the problem is the front surface of the lens*
- **Conundrum – a bandage lens may be treatment of choice for acute LWE conditions**

INCREASE HYDRODYNAMIC LUBRICATION



TREATMENT – LWE

1. Lubrication – ointment
2. Steroids
3. Restasis
4. Other medications for dry eye
5. NSAIDS – not effective
6. Punctal occlusion
7. Meibomian gland treatment



LUBRICATION – TREATMENT LWE

- Days – liquids (oil important) – **Increase lipid layer thickness**
- **Night – ointment**

EBM – ARVO posters

Clinically helpful, but product dependent



CONTAIN LIPIDS



Korb has commercial interest

STEROID TREATMENT OF LWE

- Fluorometholone (0.1%), hyaluronic acid & tears for one month.
 - A new form of successful treatment is necessary to overcome LWE
Yamada et al., 2004, Int. Conf. - Dry Eye Syndromes
- Lotemax® and Soothe™ for one month
 - Both moderately successful as solo treatments
Herman, Korb et al., 2006 ARVO

A mechanical etiology with secondary inflammation is suggested

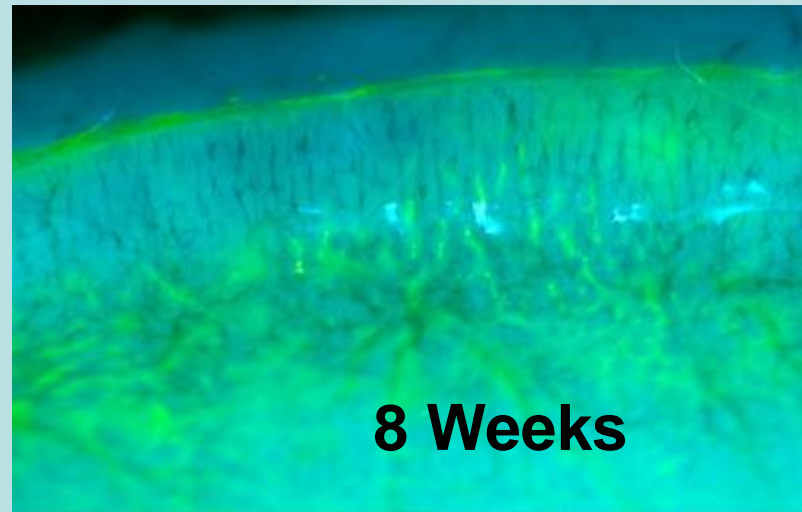
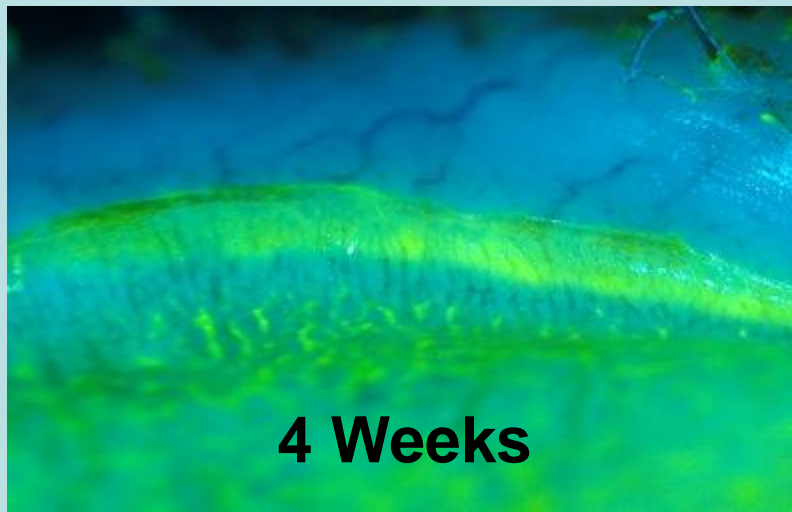
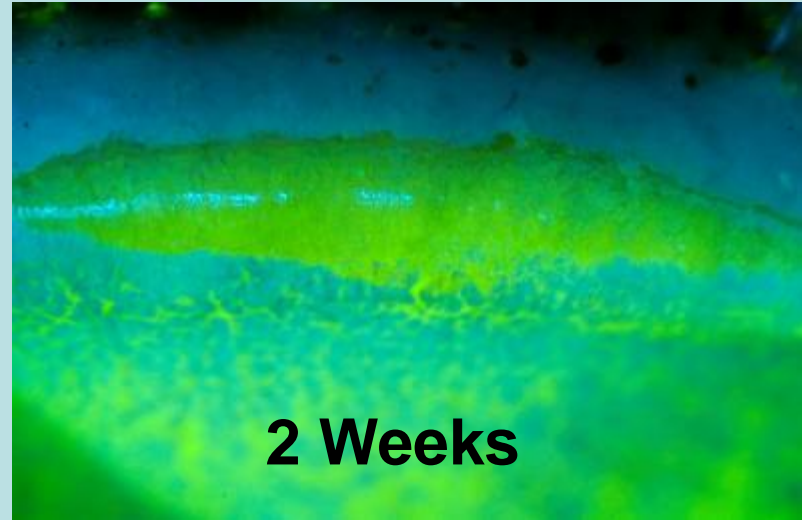
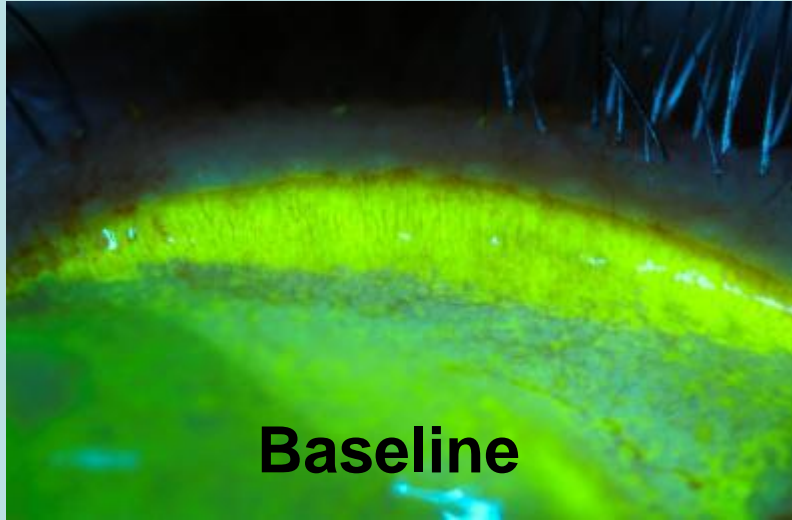
***Recommend steroid and lipid emulsion for one month
Taper steroid and continue lipid emulsion***

Palliative – not restorative – treat causative factors



TREATMENT

Lotemax QID 1 month, Soothe TID post 1 month



RESTASIS – CYCLOSPORINE A (0.05%)

The first and only dry eye Rx product !

Premise – Inflammation of lacrimal gland

If Restasis improves lacrimal secretion it will help LWE

Excellent vehicle (Endura = castor oil)

Evaluation of efficacy

An individual professional decision

MG TREATMENT TO IMPROVE MG FUNCTION

PATIENT therapy

- warm compresses (lid hyperthermia)
- massage – expression
- lid scrubs



If glands can be expressed, therapy likely successful
Bron, 2006

PROFESSIONAL OFFICE treatment

- Expression – forceful in office
- Add home therapy
- Study – improved Sx & LLT

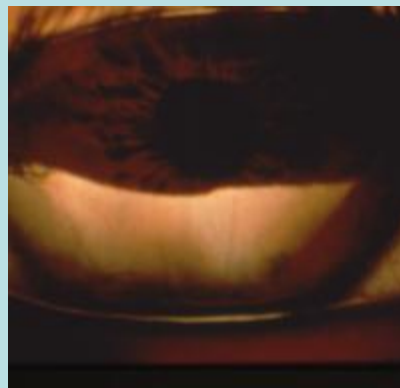
Korb & Greiner, Tx of MGD > LLT, 1994



CONTACT LENSES AND LWE

- All contact lenses may cause LWE
- The surface properties of CLs do not yet mimic those of the cornea
- The surfaces of all CLs do not allow a normal lipid layer – some are better than others

LWE is a lubrication problem



LWE SUMMARY – CONTACT LENSES

THE LENS – WET AND CLEAN

IMPROVE TEAR FILM

- Drugs, lacrimal gland, MG treatment, blink
- Adjuvant tear and rewetting products – palliative

IMPROVE CONTACT LENS

- CL materials – CLs must be wet and clean
- 1-Day lenses (packaging formulation for lubricity)
- CL design – thin membranes and designs for lids



LWE – TREATMENT SUMMARY

Restore lubrication
Eliminate excess trauma
Treat inflammation



EXPANDED ROLE FOR MEIBOMIAN GLANDS

DEFINITION – MEIBOMIAN GLAND DYSFUNCTION

2007 Report of the International Dry Eye Workshop (DEWS)

*“ Meibomian gland dysfunction, or **posterior blepharitis**, is a condition of meibomian gland **obstruction** and is the most common cause of evaporative dry eye.”*

Blepharitis = inflammation of the eyelids

MGD & posterior blepharitis unfortunately synonymous

These anomalies contributed to the new paradigm – Kuhn



POST DEWS 2007 – A NEW PARADIGM FOR DRY EYE

September 2008 Update by Prestigious
Tear Film & Ocular Surface Society (TFOS)

***“It is important to note that
meibomian gland dysfunction
may be the leading cause of
dry eye syndrome throughout the world.”***

TFOS (DEWS) has held meeting of
~ 40 meibomian gland/tear film lipid experts
from around the world to develop
report to professions on MGD – 2010

McDONALD EYE ASSOCIATES



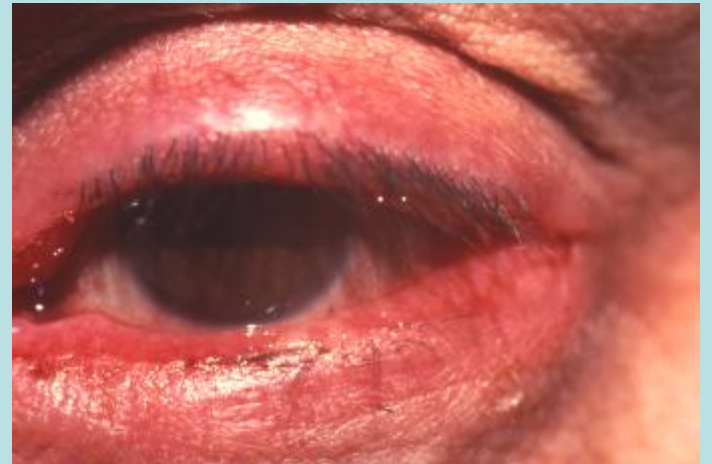
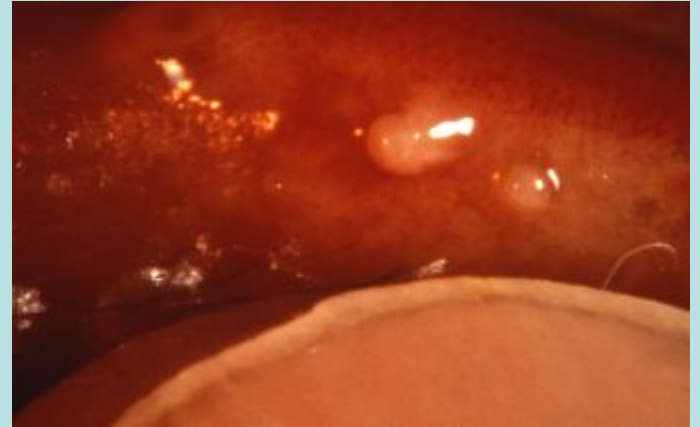
MGD CLASSIFICATION – 5 TYPES

1. Normal (glands open)
2. Obstructive — may **not** be **obvious** if without inflammation

Types of Obvious

1. Hypersecretion (seborrheic)
2. **Inflammatory** (pouting & plugging)
3. **Infective** (glands and/or lids)

Or combinations



McCauley et al., 1981; Mathers et al., 1991

WHAT IS MG DYSFUNCTION ?

DEFINED AS A CONDITION OF MG OBSTRUCTION

What is the normal for a meibomian gland ?

What is the abnormal for a meibomian gland ?

How are normal vs. abnormal MGs diagnosed ?

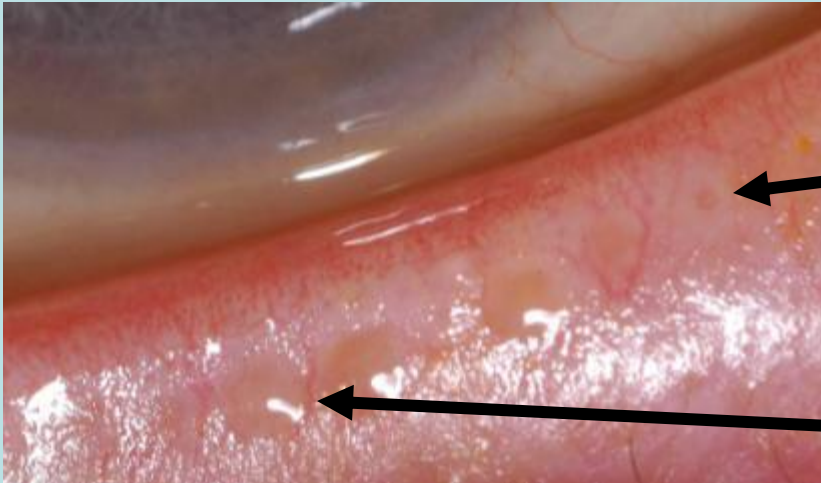


NORMAL – YIELDING CLEAR OIL



Orifice – no secretion
Why no secretion?

Considered Optimal
(expresses clear sebum)



Orifice – no secretion
Why no secretion?

Considered Optimal Plus
(expresses copious clear sebum)

A new concept

NON-OBVIOUS MG OBSTRUCTION (NOMGD)

WITHOUT

OBVIOUS INFLAMMATION

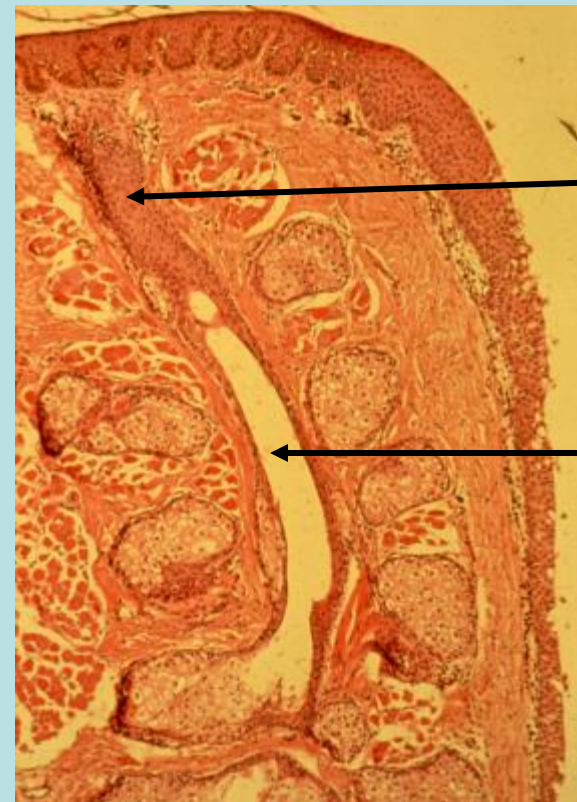
***Blackie, Korb et al.
Non-obvious Obstructive MGD – submitted***

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NON-OBVIOUS MG OBSTRUCTION & MGD WITHOUT OBVIOUS INFLAMMATION

REQUIRES EXPRESSION FOR DIAGNOSIS



Obstruction
of duct

Duct

May appear normal without expression

**Total obstruction –
NO SECRETIONS
despite extreme pressure**



OBSTRUCTIVE MGD DEFINED

Deficient or inadequate MG secretion
due to obstruction of the
meibomian gland ducts – orifices,
usually by keratinized epithelial plugs

*The most frequent form of MGD is
non-obvious obstruction without inflammation*

Requires expression for Dx

*Korb & Henriquez, J Am Opt Assoc, 1980
Meibomian gland dysfunction & contact lens intolerance*

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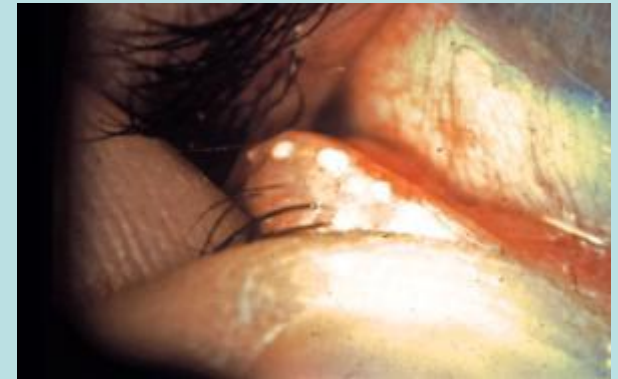
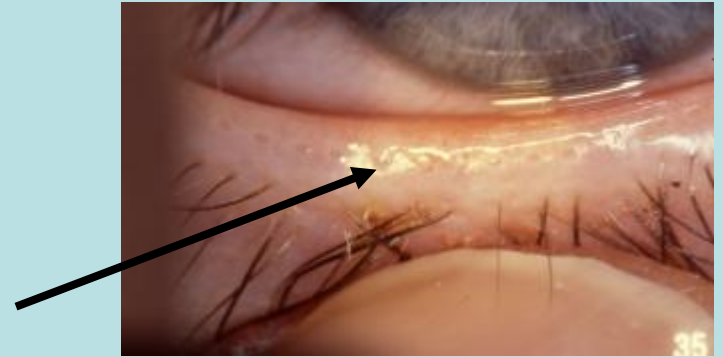


HOW IS MG FUNCTIONALITY DETERMINED ?

Currently by expression of secretion

- Manual expression on cutaneous surface overlying meibomian glands
- Massage – squeezing

*Problem – an art form
and difficult to quantify*



*Addario 1888; Gifford 1921; Korb 1980; Henriquez 1981;
Hamano 1982; Craig 1985; **Norn 1987**; Hom 1987;
Ong 1990; Driver 1996; Goto 2002; Bron 2004; Mastrota 2006*

DEVELOPING A SCIENTIFIC METRIC FOR MG FUNCTIONALITY

We need to know:

“ the minimum number of meibomian glands required to provide an adequate lipid layer for tear film function”
(DEWS, 2007)

We do know:

- Meibomian gland secretion appears to be dependent upon blinking

*Wolff, 1946; Linton 1961; many authors
LLT as a Function of Blinking. Korb et al, 1994*

- A blink exerts $\approx 1.0 \text{ gram/mm}^2 = .3 \text{ PSI}$

Pressure of the Lid on the Eye. Miller D, Arch Ophthal, 1967

- **If a MG secretes with a \leq force mimicking that of a forceful blink, the meibomian gland may be considered active & functional**

*Meibomian Gland Diagnostic Expressibility: Correlation with Dry Eye Symptoms and Gland Location
Korb & Blackie, Cornea, 2008*

If a MG secretes with a \leq force mimicking that of a forceful blink,
the meibomian gland may be considered active & functional

GOAL:

**To develop devices
to apply ≈ 1.0 gram/mm² to lid
to simulate a
forceful blink on meibomian glands**



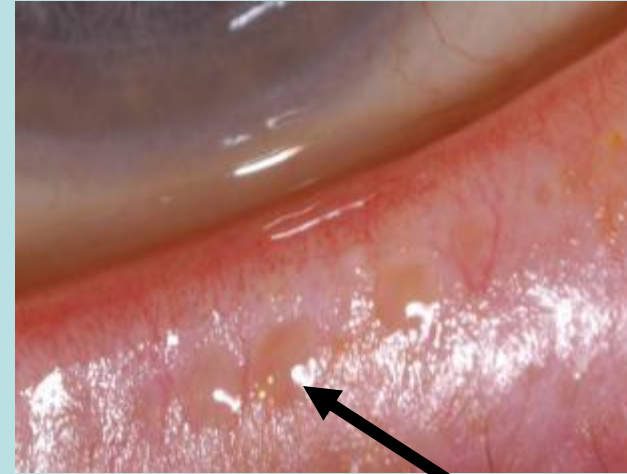
***In the absence of
an objective method of evaluation,
fact-gathering and development
are severely impeded.***

*Formulated from Thomas S. Kuhn, 1962
The Structure of Scientific Revolutions*



DIAGNOSTIC EXPRESSION FOR MG FUNCTIONALITY

Concept of an active/functional meibomian gland
yielding liquid secretion = MGYLS



THREE DIAGNOSTIC QUALIFIERS

1. Standard force for expression $\approx 1.0 \text{ gram/mm}^2$ (.3 PSI)
2. Application = ≤ 15 seconds
3. Secretion must be liquid

A new metric allowing standardized expression & quantification

What have we been able to answer with standardized meibomian gland expression?

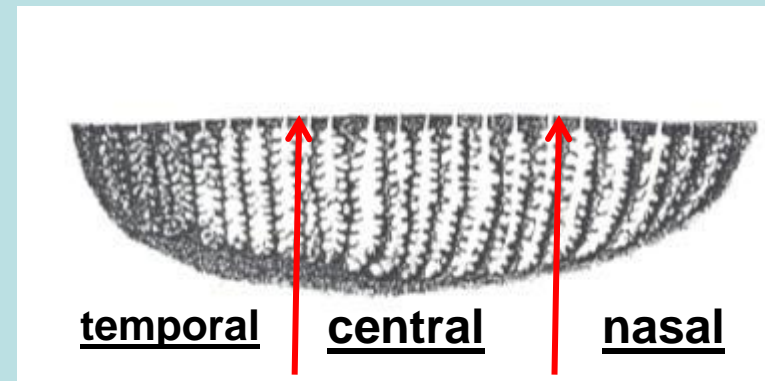
1. **The number of meibomian glands yielding liquid secretion (MGYLS) varies by location on the lower eyelid**
2. **The number of MGYLS is correlated with dry eye symptoms**
3. **Recovery time of an optimally secreting meibomian gland**
4. **The diurnal secretory behavior of individual meibomian glands**



Correlation of MG Diagnostic Expressibility to Dry Eye Symptoms & Gland Location

Korb & Blackie – Cornea 2008

Do the MG of nasal, central & temporal regions of the lower eyelids secrete equally ?



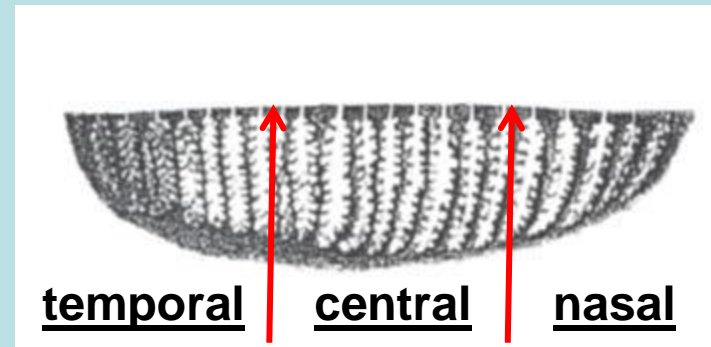
***Symptomatic
population***

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CORRELATION OF MG DIAGNOSTIC EXPRESSIBILITY TO GLAND LOCATION

SYMPTOMATIC POPULATION (n = 133)



NUMBER OF MGYLS BY REGION OF LOWER EYELID

Region of lower eyelid	Mean number of meibomian glands yielding liquid secretion (MGYLS) for all 3 symptom groups (n = 133)
Temporal Third	0.27 ± 0.06
Central Third	2.14 ± 0.13
Nasal Third	3.10 ± 0.15 (12X)

The mean numbers of MGYLS in each third of the lower eyelid were significantly different, $p \leq 0.0001$



What have we been able to answer with standardized meibomian gland expression?

1. The number of meibomian glands yielding liquid secretion (MGYLS) varies by location on the lower eyelid
2. **The number of MGYLS is correlated with dry eye symptoms**
3. Recovery time of an optimally secreting meibomian gland
4. The diurnal secretory behavior of individual meibomian glands

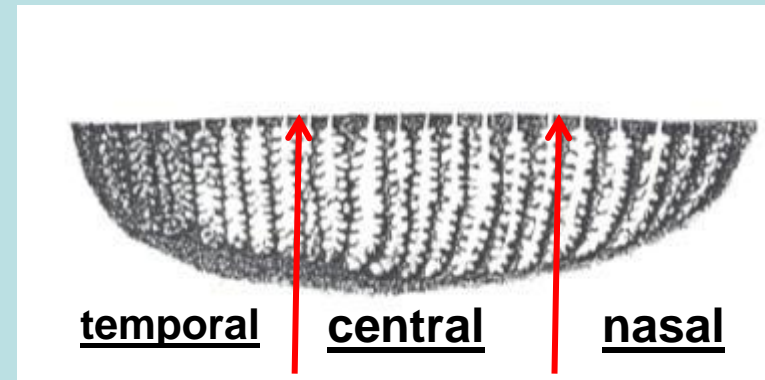


Correlation of MG Diagnostic Expressibility to Dry Eye Symptoms & Gland Location

Korb & Blackie – Cornea 2008

Purpose:

Is the number of MG yielding liquid secretion (MGYLS) correlated to dry eye symptoms?



***Symptomatic
population***

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CORRELATION OF FUNCTIONAL GLANDS (MGYLS) TO DRY EYE SYMPTOMS & SEVERITY

<i>Dry Eye Symptoms & Severity</i>	<i>Glands Open (MGYLS)</i>
Moderate to severe Sx	0 - 4
Minimal symptoms	5 - 7
Symptoms - unlikely	8 - 10
No symptoms	≥ 11

Maximizing function requires treatment of obstruction



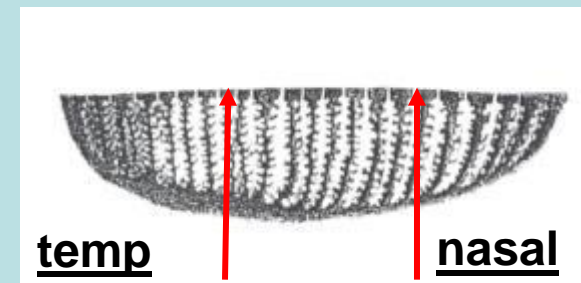
MEIBOMIAN GLAND DIAGNOSTIC EXPRESSIBILITY:

CONCLUSIONS

- 1) There is a correlation between the number of MGYLS in the lower eyelid and dry eye symptoms ($p = 0.0002$)
- 2) The highest number of MGYLS is in the nasal third and the lowest number of MGYLS in the temporal third of the lower eyelid – **a surprising finding**

MAXIMIZE DX AND TX

Evaluate the nasal MG
Nasal contribute over 60% of all secretion



What have we been able to answer with standardized meibomian gland expression?

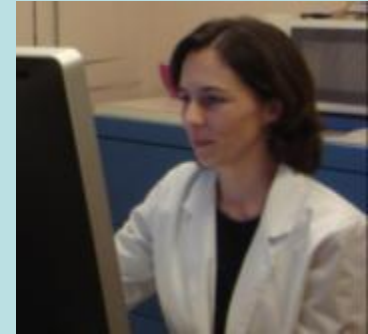
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3. **Recovery time of an optimally secreting meibomian gland**
4. The diurnal secretory behavior of individual meibomian glands

TIME REQUIRED FOR A SINGLE OPTIMALLY SECRETING MG TO RECOVER AFTER BEING DRAINED OF AVAILABLE OIL

Replenish rate of MG in an asymptomatic population

Blackie & Korb, Cornea, 2008

- **Asymptomatic population**
 - limited to 18-25 yrs (21.3 ± 1.9 yrs), $n = 12$
- Single gland identified and marked with Henna tattoo
- Diagnostic Expression Device used to drain the gland
- Re-evaluation – at 30 & then 60 min intervals until MG again released clear oil



***Personal acknowledgment to
Caroline Blackie, OD, PhD***

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TIME REQUIRED FOR A SINGLE OPTIMALLY SECRETING MG TO RECOVER AFTER BEING DRAINED OF AVAILABLE OIL
Replenish rate of MG in an asymptomatic population

Time to drain MG	11.9 sec 3.5	Range = 8-20 secs
Recovery time of drained MG	2.16 hours	Range = 1.5-2.5 hours
Time to re-drain MG after recovery	5.8 sec 1.9	Range = 5-10 secs

Conclusions:

- *MG will replenish during day – not usually considered*
- *Replenishment is limited in volume*

Clinical Implications: Self-expression or extended WC therapy in AM may lead to temporary dryness

What have we been able to answer with standardized meibomian gland expression?

1. The number of meibomian glands yielding liquid secretion (MGYLS) varies by location on the lower eyelid
2. The number of MGYLS is correlated with dry eye symptoms
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4. The diurnal secretory behavior of individual meibomian glands



A day in the life of a meibomian gland

***DO MEIBOMIAN GLANDS SECRETE
THROUGHOUT THE WAKING HOURS?***

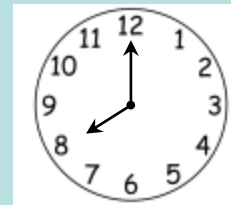
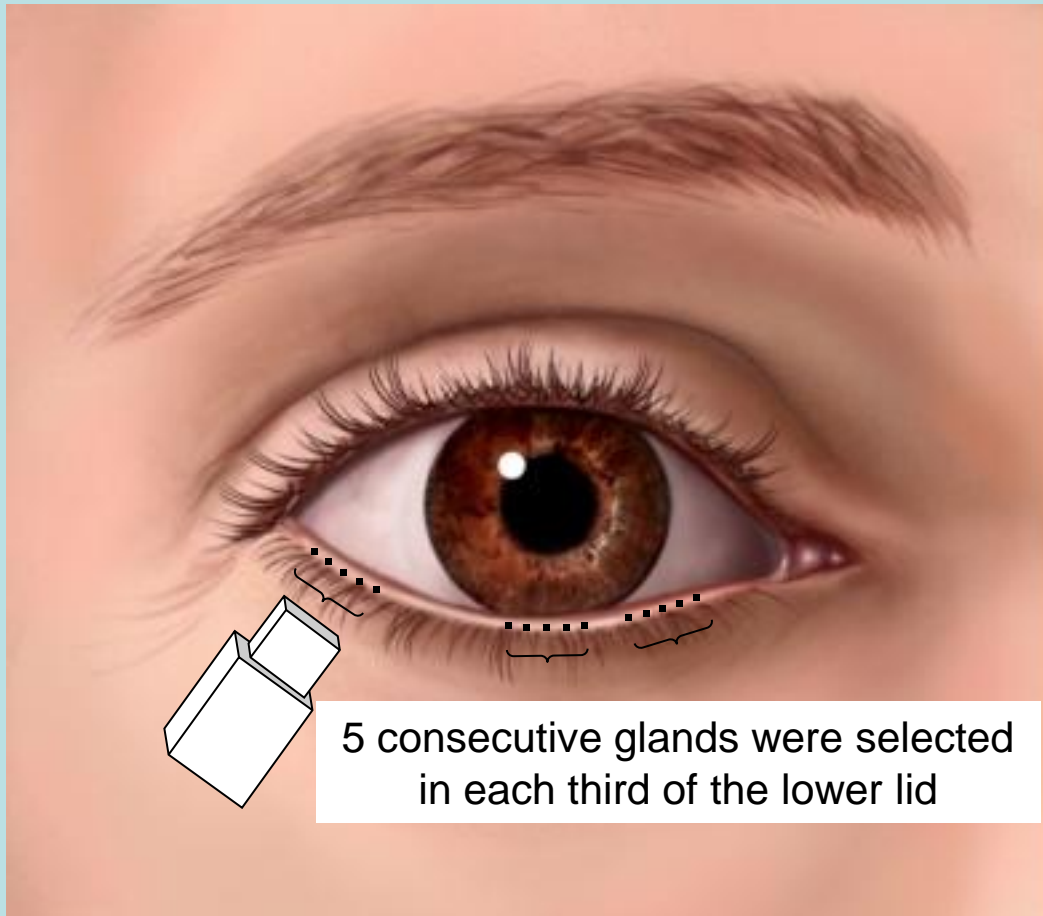
***Diurnal Characteristics of Meibomian Gland Secretion
Blackie & Korb, Cornea-in press 2009***

The Experiment: **ASYMPTOMATIC SUBJECTS**

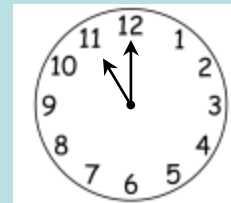
For each third of the lower eyelid 5 consecutive meibomian glands were diagnostically expressed 4 times in one day (3 hrs apart)

Demographics:
ASYMPTOMATIC
 n = 10; 4 males, 6 females
 mean age = 23.8 ± 1.8 yrs

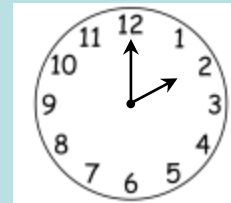
■ No liquid oil expressed
■ Liquid oil expressed



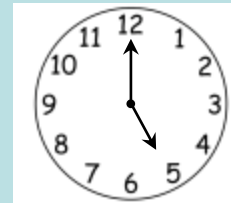
Gland #	1	2	3	4	5
Temporal					
Central1					
Nasal					



Gland #	1	2	3	4	5
Temporal					
Central					
Nasal					

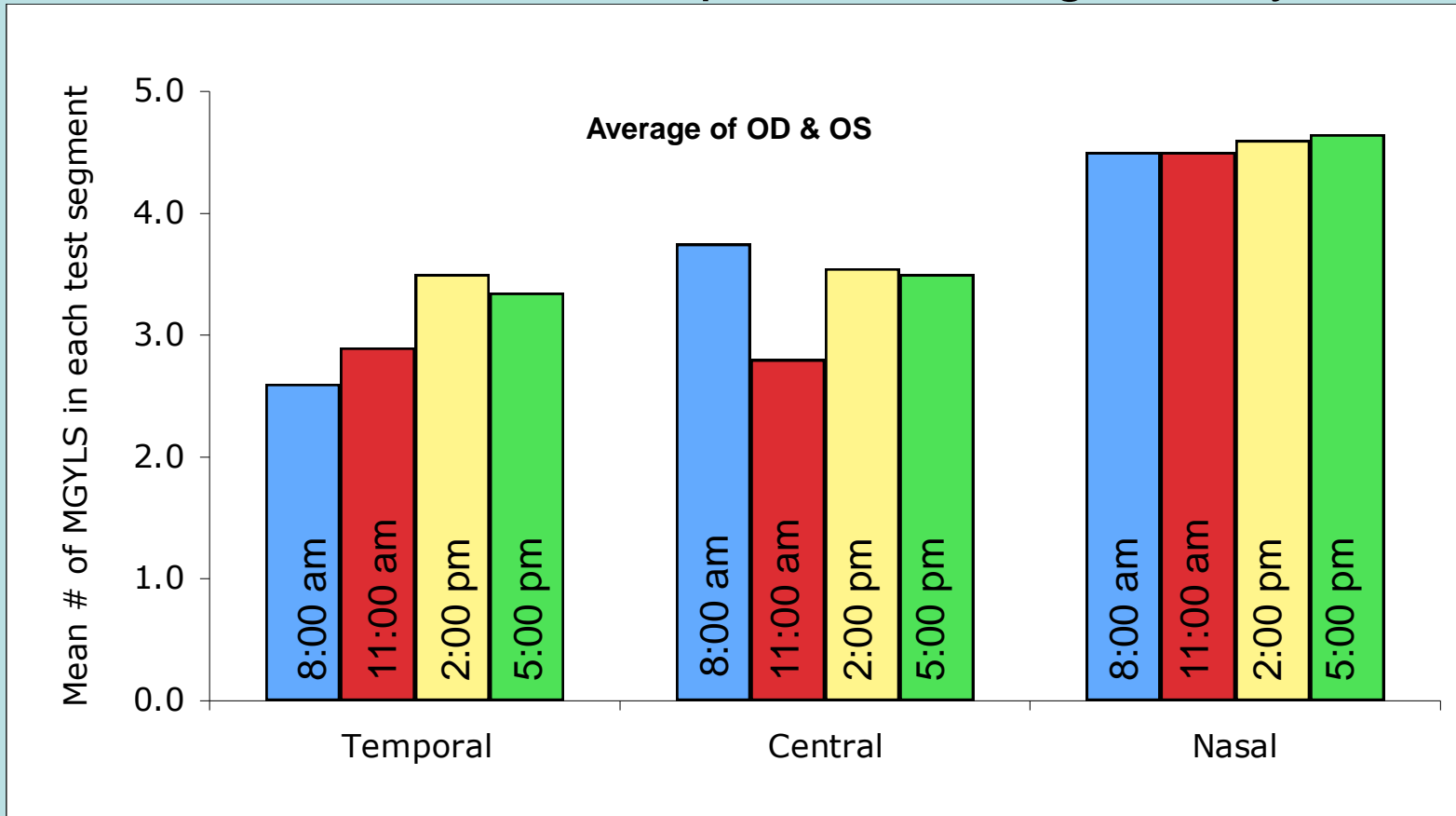


Gland #	1	2	3	4	5
Temporal					
Central					
Nasal					



Gland #	1	2	3	4	5
Temporal					
Central					
Nasal					

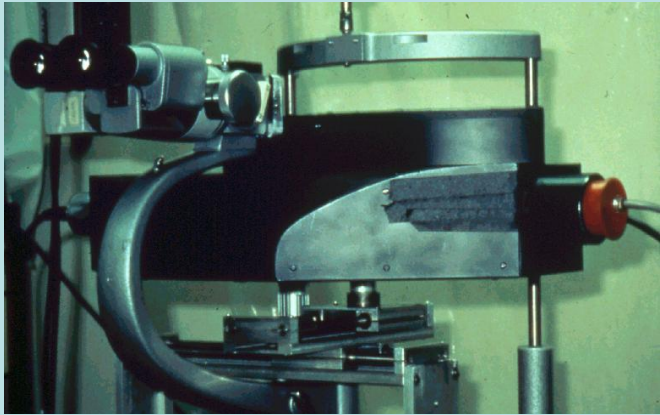
Mean number of MGYLS per lid test segment by time



The nasal glands show less variation between individuals relative to the central and temporal regions

Confirms gland secretory behavior varies according to location in lid





1993

***INTERFEROMETRY
THE OPHTHALMOSCOPE
OF THE LIPID LAYER***



2008

***Allows quantification of
Lipid Layer Thickness***

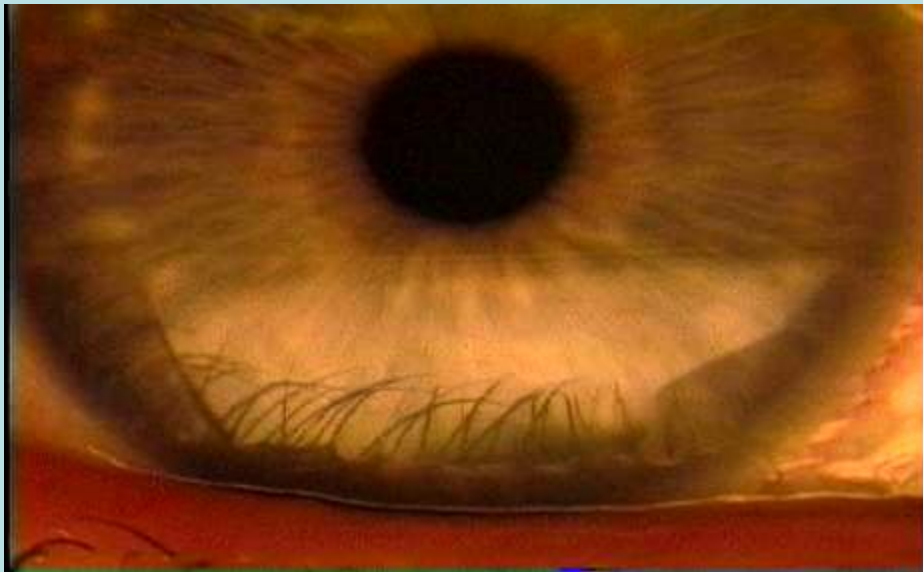
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INTERFEROMETRY – LIPID LAYER

Allows the measurement of LLT

Blue	Thick	180 nm
Yellow	Moderate	90 nm
White	Thin	≤ 60 nm



***IS THERE A RELATIONSHIP
BETWEEN LIPID LAYER THICKNESS
&
DRY EYE SYMPTOMS ?***



RELATIONSHIP BETWEEN LIPID LAYER THICKNESS & DRY EYE SYMPTOMS

Blackie, Korb et al., Cornea, 2009

Two Populations:

**Symptomatic
Asymptomatic**

n = 137

Age = 18 – 60

Mean = 41.7 ± 15.5 yrs

- 3 of 4 individuals with moderate to severe symptoms have thin lipid layers ≤ 60 nm
- 3 of 4 individuals without symptoms have thick lipid layers ≤ 60 nm

LLT & symptoms correlated (p = 0.0018)

**LLT CORRELATED TO SYMPTOMS BETTER
THAN ANY OTHER CLINICAL DRY EYE TEST**

TREATMENT OPTIONS

If lipid layer thickness is compromised

- Replace the meibomian gland secretions
- Increase efficacy of meibomian glands & meibomian gland secretions

GOALS

Stop evaporation
Provide lubrication



OPTION – REPLACE THE MG SECRETIONS

Korb is the inventor of Soothe & has a financial interest

SOOTHE XP™ vs. ARTIFICIAL TEARS & LLT

**Soothe™ more than doubled LLT
from 61 nm to 146 nm – others do not**



Soothe XP™ contains lipids

The best adjuvant cannot replace MG secretion

Maximize MG secretion

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WHY MG OBSTRUCTION? OFFICIAL POSITION – DO NOT KNOW

Blinking inhibition
Age
Drugs
Seborrhea
Eczema
Lipid Profiles
Surfactant
Phospholipids
Epithelial overgrowth

Ductal hyperkertinization

Sullivan 2009 – Androgens

**Dental Plaque
Analog**

Why no chalazia when gland obstructed ?



IMPLICATIONS – MGD

1. Decrease in lipid secretion and LLT

2. Evaporation increases

Mishima and Maurice, 1961 **16 X**

Craig and Tomlinson, 1997 **4 X**

3. Correlations of MGD to dry eye states

- Contact Lens Intolerance – *Korb et al., 1980, 1996*
- Dry Eye Signs – *Yokoi et al., 1996;*
Isreb et al., 2003; Goto et al., 2006
- Selected Dry Eye Symptom
Population – *Korb et al., 2004; Scaffidi et al., 2005;*
Blackie et al., 2007; Korb et al., 2008
- Symptoms – *Goto et al., 2006; Korb and Blackie, 2008_*

MG TREATMENT TO MAXIMIZE MG FUNCTION

PATIENT therapy

- **warm compresses**
(lid hyperthermia)
- **massage – expression**
- **lid scrubs**



If glands can be expressed therapy likely successful
Bron, 2006

Professional Tx

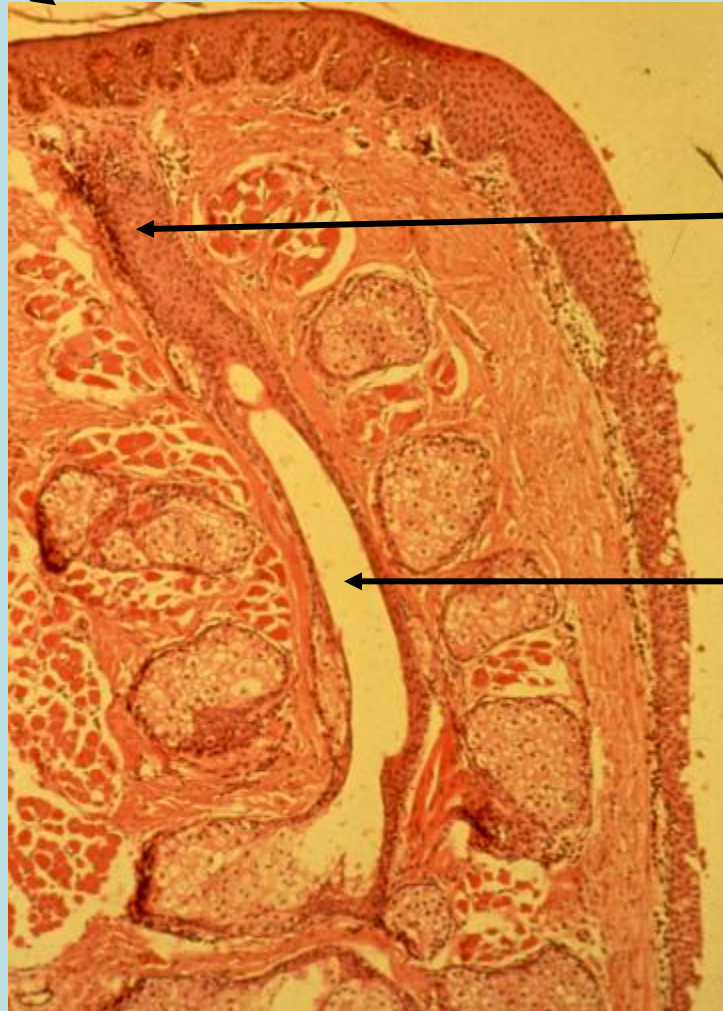
- Expression – forceful in office
- Add home therapy
- Study – improved Sx & LLT

Korb & Greiner, Tx of MGD > LLT, 1994



MEIBOMIAN GLAND SCRUBS – MAXIMIZE MG FUNCTION

Scrub epithelial overgrowth



warm compresses
(lid hyperthermia)

Obstruction
of duct

Duct

INNER EYELID SURFACE TEMPERATURE AS A FUNCTION OF WARM COMPRESS METHODOLOGY

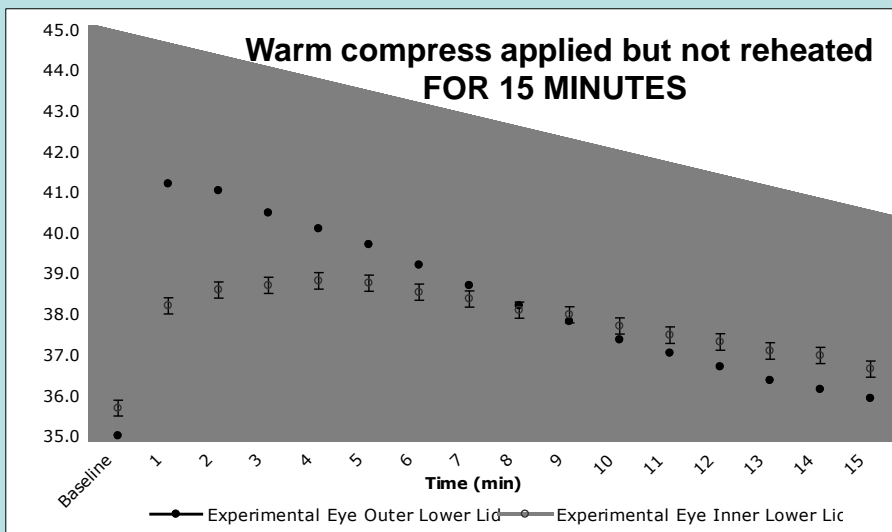
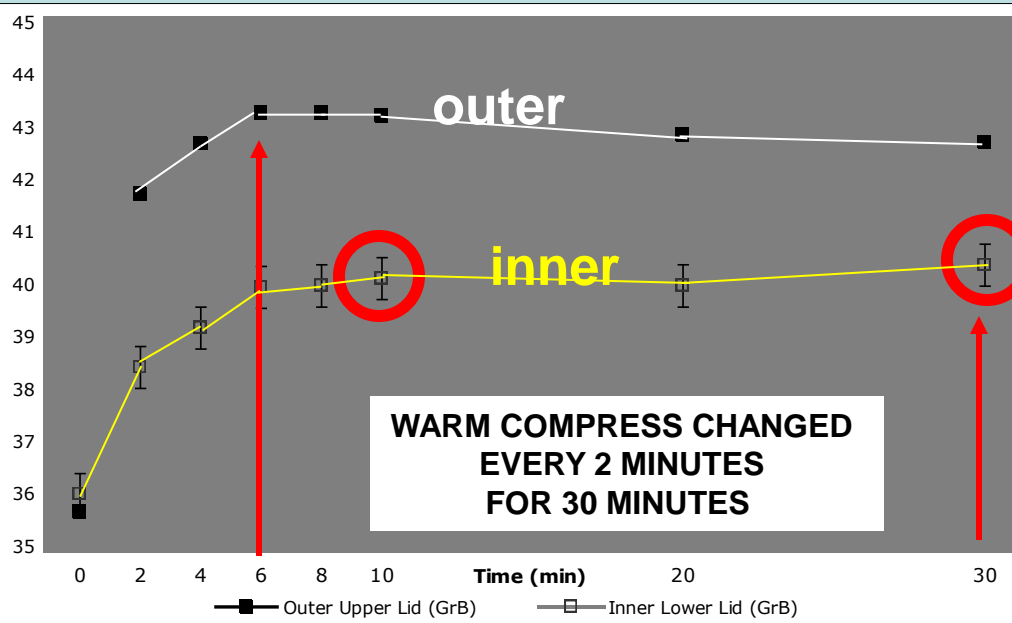
Blackie, Korb et al., OVS 4/2008

Warm compress at 45 C (113°F)

Temp measured with infrared pyrometer

outer lid: 35.5 to 43.3 C (6 mins)
inner lid: 36.0 to 40.4 C (10-30 mins)

Maximizing efficacy
Pressing upward on lower lid
increases efficiency



WARM COMPRESS TREATMENT

Increase in LLT Following Treatment with Warm Compresses in Patients with MGD

Olson, Korb, Greiner, Eye & CL, 2003

<i>Baseline LLT</i>	=	<i>60 nm</i>
<i>5 minutes</i>	=	<i>105 nm</i>
<i>15 minutes</i>	=	<i>117 nm</i>
<i>30 minutes</i>	=	<i>122 nm</i>

Maximizing MG Treatment

5 to 15 minutes required

Not published: 1 to 2 mins – minimal or no improvement



MG TREATMENT

- Primary problem is obstruction
- Addario in 1888 “described an ingenious method of **expression** with a modified Snellen’s forceps, by which pressure could be maintained on each lid for 15 to 45 minutes at a time”
(Reported by Gifford in 1921)
- Expression utilizing a hard surface against palpebral conjunctiva best available professional method

LIMITATION IS PAIN



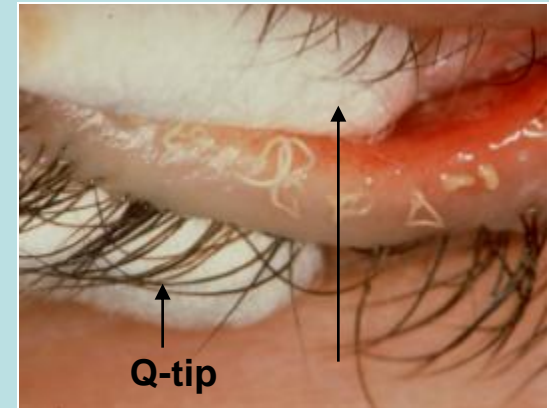
MG TREATMENT - EXPRESSION

Problems with forceful expression against a hard surface

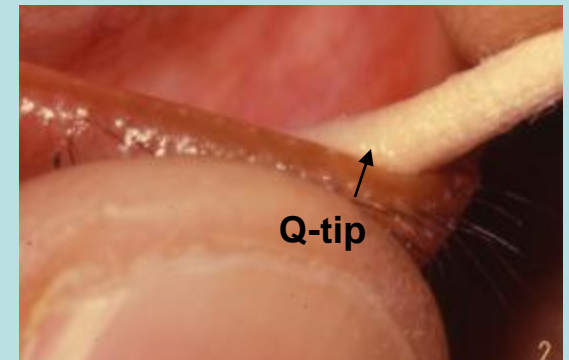
- Anesthesia not effective – **Painful**
- Requires multiple Tx: monthly - qtr - annual
- Trauma results in transient edema & inflammation (black and blue)
- Effective expression may require expression for 3 - 15 minutes each lid
- Elevated melting point of obstructive material
- Variable efficacy



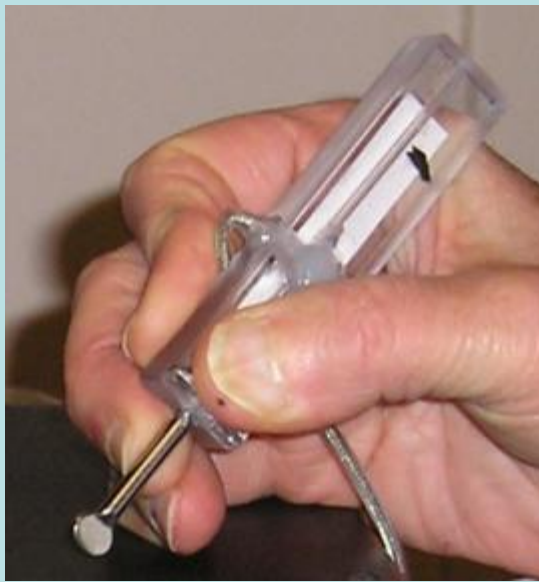
Mastrotta paddle



2 Q-tips

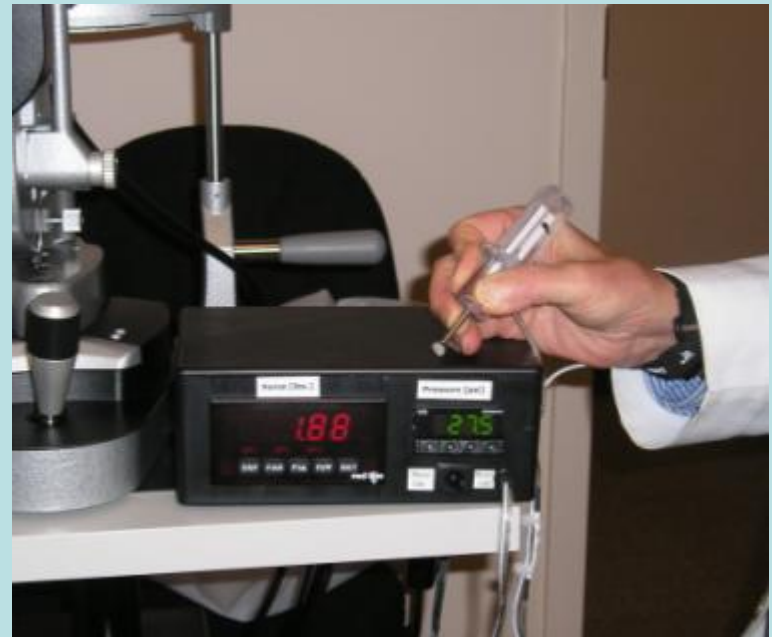


1 Q-tip



Pain level during MG expression with topical anesthesia

Pain Level	Force PSI
No pain	2-4 PSI
Mild to moderate	5- 9 PSI
Painful	10 – 20 PSI
Excruciating	> 20 PSI



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Pain level dependent upon individual responses

MG TREATMENT – EXPRESSION

Efficacy of expression treatment vs. pain level **with topical anesthesia during expression**



Force PSI	Pain Level	Efficacy of Expression	Expressed Material
2 – 4	None	Zero to minimal	Liquid oil to semi-fluid
5 – 9	Mild/Moderate	Minimal	Semi-fluid & inspissated
10 – 20	Painful	Moderate	Inspissated
> 20	Excruciating	Optimal	Inspissated

Pain level dependent upon individual and infective status

MG TREATMENT – SUMMARY

RECOGNIZE PROBLEM IS OBSTRUCTION

- New metrics - to evaluate MG functionality
- Express & meibomian glands will upregulate
- **Treatment by drugs:**
 - Requires penetration?
 - Topical (Azasite) vs. systemic (doxycycline)
 - Antibiotic-steroid combinations (tobradex-blephamide)
- Treat blepharitis – with drugs and hygiene
- Treat MGD – MGO with expression and warm compresses

The Future: Improve methods to treat obstruction

IMPLICATIONS – UNTREATED NON-OBVIOUS OBSTRUCTIVE MGD

Decrease in lipid secretions



Decrease in LLT



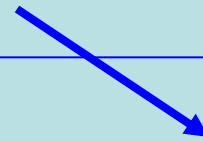
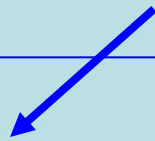
Evaporation increases – minimal to 4 - 16 x



Decrease in Aqueous layer thickness



Unstable tear film



Ocular surface compromised



Dry eye



Inflammation



Lubricity compromised



Lid Wiper Epitheliopathy



Inflammation



BLEPHARITIS

Do we have blepharitis backwards ?

Is lid inflammation or infection first ?

Is all blepharitis infectious ?

THE DEFINITION IS INFLAMMATION

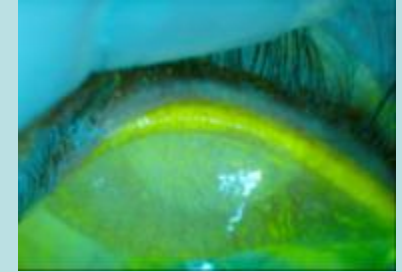


Do we have it backwards? Inflammation or infection first?

LWE includes an inflammatory response

Products of inflammation deposit in tear film

Secondary inflammation



Inflammatory material
resides in
Kessing's space
↓
Palpebral
conjunctivitis

Inflammatory material
resides in tear film
↓
Inferior meniscus
Inferior cul-de-sac
↓
Posterior blepharitis
Infection

*Inflammatory affections of
conjunctiva involve
lid margins as a result
of irritation from
conjunctival discharges*

Duke Elder, Vol. VIII, 1965 p. 78-79



**MGO RESULTS in
CASCADE to
posterior blepharitis**

McDONALD EYE ASSOCIATES



IMPLICATIONS – MGD - MGO

Decrease in lipid secretions



Evaporation increases – minimal to 4 - 16 x

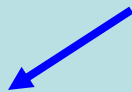


Decrease in Aqueous layer thickness



Unstable tear film

**Immune Disease
Sjögren's**



Ocular surface compromised

↓
Dry eye

↓
Inflammation



Lubricity compromised



Microtrauma



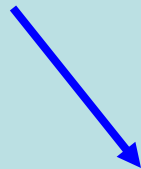
Lid Wiper Epitheliopathy



Triple Response of Lewis



Inflammation



**Palpebral and Bulbar conjunctivitis
Posterior blepharitis**



IMPLICATIONS – MGD

Decrease in lipid secretions



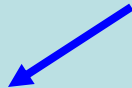
Evaporation increases – minimal to 4 - 16 x



Decrease in Aqueous layer thickness



Unstable tear film



Ocular surface compromised



Dry eye



Inflammation



Lubricity compromised



Microtrauma



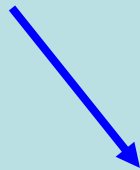
Lid Wiper Epitheliopathy



Triple Response of Lewis



Inflammation



Palpebral and Bulbar conjunctivitis
Posterior blepharitis

Does lacrimal gland
upregulate &
overwork?

Diabetic &
adrenal analogues



IMPLICATIONS – MGD

Decrease in lipid secretions



Evaporation increases – minimal to 4 - 16 x



Decrease in Aqueous layer thickness

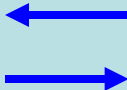


Unstable tear film



**Maximizing
Function**
**Treat MG early
to prevent
Inflammation
LWE
Dry eye**

Ocular surface compromised
↓
Dry eye Inflammation



Lubricity compromised
↓
Microtrauma
↓
Lid Wiper Epitheliopathy
↓
Triple Response of Lewis
↓
Inflammation

Palpebral and Bulbar conjunctivitis
Posterior blepharitis



SUMMARY

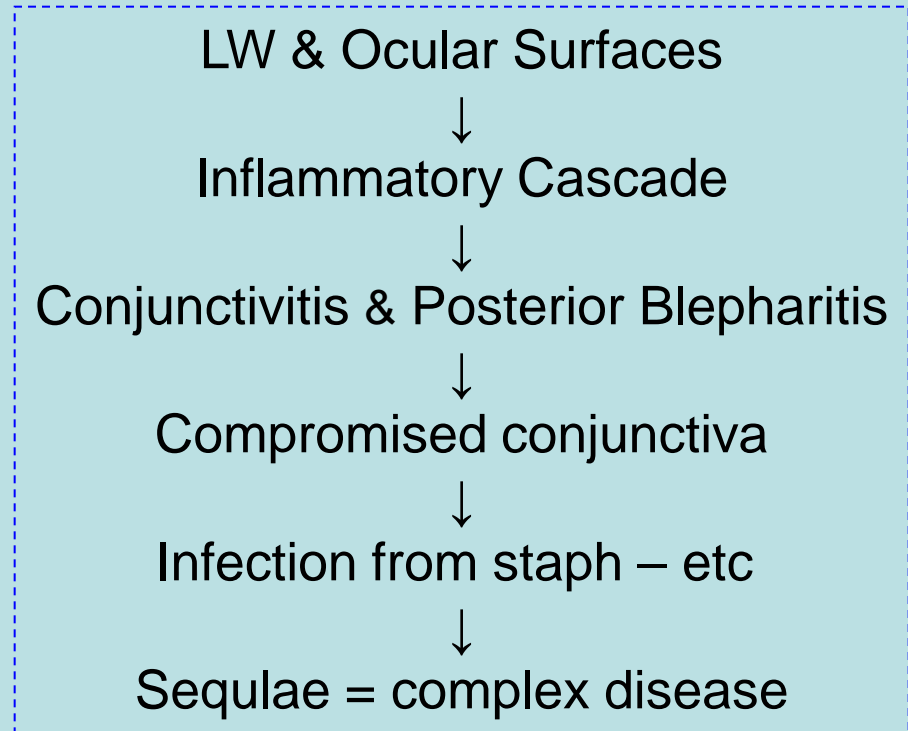
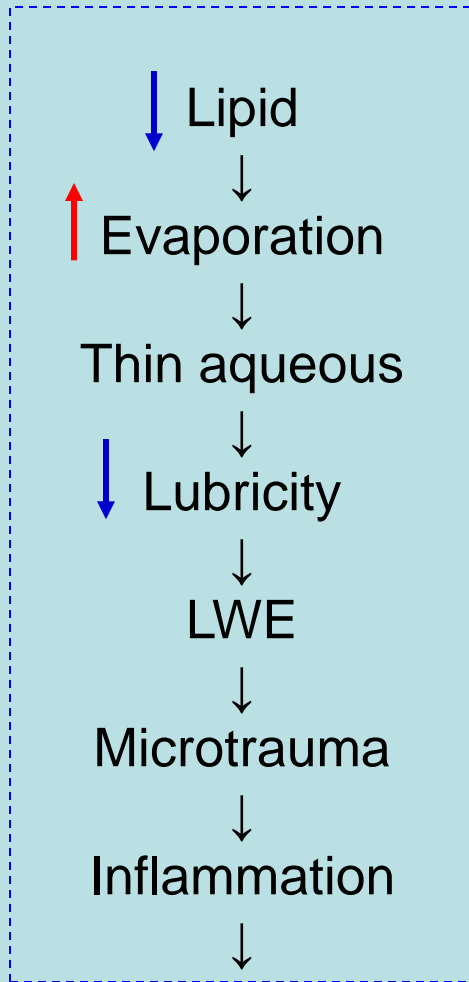
TFOS NEW PARADIGM

“It is important to note that MGD, a condition of MG obstruction, may be the leading cause of dry eye syndrome throughout the world”

- **Lipid deficiency & not aqueous deficiency** usually the catalyst for DRY EYE & inflammatory cascade
Backward to conventional models and treatment
- MGD and MG OBSTRUCTION may be obvious or non-obvious, **most frequently non-obvious**
- Dx of MG functionality **requires expression** – new metrics
- Interferometry will provide overview of adequacy of MG functionality



Sequae of MGD – MGO over years



Aqueous and lipid deficient dry eye may not be distinguishable

Low Schirmer score and thin-low lipid layer thicknesses coexist
Isreb, et al. (2003)

**The phenotypes of evaporative dry eye and aqueous dry eye
take on the form of each other**

Bron (2009)

**Next steps – The relationship of aqueous deficiency to meibomian
gland dysfunction – obstruction can now be studied with the new
metrics for determining MG functionality and lipid layer thickness**



SUMMARY

Maximizing the function of the meibomian glands

Treat all blepharitis – treat cause

Tx of MG & MGD should be started early – dental analogy

Heating – lid hyperthermia not ideal but mandatory Tx

Include expression

***Blinking is to ocular surface health
as exercise is to general health***



Conclusions

- Dry Eye is a multifactorial, frequently chronic disease with no simple cure
- Expanded role of MGD – MGO & new paradigm
- Patient education and symptom management are critical to success of therapy
- Multiple treatment approaches are likely necessary
- Must increase lubrication and decrease evaporation – therefore, **must treat MGD & inflammation**



Thank you to the over 200

Scientists

Optometrists

Ophthalmologists

Residents & Fellows

And all those in industry

Who have taught me unselfishly

& worked with me

for the past 40 years

McDONALD EYE ASSOCIATES



Thank You

- J.E. “Jay” McDonald, II, M.D.