

Don't Let *Demodex* Dog You

Woo University
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 Diplomate, American Board of Optometry
 June 12, 2022

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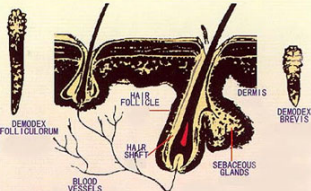
Demodex

- Mites of the genus *Demodex* were described as parasites of hair follicles and sebaceous glands in man 180 years ago.
- *Demodex* are the most common obligatory human ectoparasite.
- The hair follicle mite *Demodex folliculorum* (detected by Henle, 1841 and described by Simon 1842) and *Demodex brevis* (separated in 1963 by Akubulatova)

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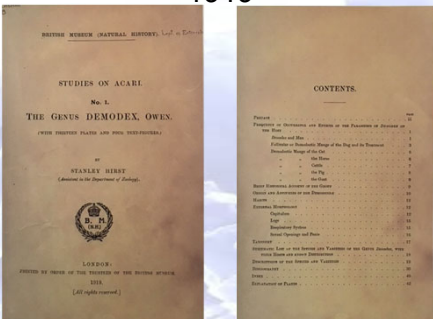
Demodex Folliculorum/Brevis

- Follicle cell mite *Demodex folliculorum*, in the eyelash/hair follicle.
- *Demodex brevis*, in oil glands



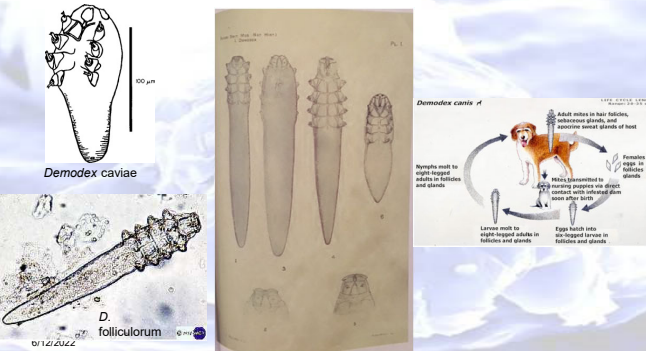
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>140 species of Demodex have been identified



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Demodex Has Been Linked to Rosacea and Blepharitis

Slide courtesy of Scheffer Tseng, MD
The Ocular Surface Center, Miami Florida

Skin Rosacea Ocular Rosacea, Blepharitis

Coston, 1967, English, 1971, English & Nutting, 1981, Heacock, 1986, Fulk & Clifford, 1990, Fulk et al, 1996, Kamoun et al. 1999, Morfin, 2003

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Rosacea and Blepharitis

- The pathophysiology of rosacea is complex and multifactorial.
- *Demodex* can live in the skin either as a harmless commensal organism or as a pathogenic agent.
- The clinical/molecular host's immunological interactions with *Demodex* mites are not fully understood.

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Acne Rosacea

- Ocular disease can precede cutaneous manifestations in 20% of cases.
- Approximately 60% of patients with rosacea develop ocular rosacea.



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Lid Telangiectasia in Ocular Rosacea



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Are *Demodex* mites principal, conspirator, accomplice, witness or bystander in the cause of rosacea?

- There a statistical association between *Demodex* mite density and rosacea, facial itching, and chronic blepharitis.
- Existence of more virulent form of mites with higher pathogenicity? *
- Endosymbiotic bacteria in certain life periods of the mites?
- Interactions between mites and human hosts?
- Interactions between mites and the environment?

* Elston DM. Demodex mites: facts and controversies. Clin Dermatol. 2010 Sep-Oct;28(5):502-4.
 Chen W, Plevig G. Are Demodex mites principal, conspirator, accomplice, witness or bystander in the cause of rosacea? Am J Clin Dermatol. 2016 Apr;16(2):107-12.

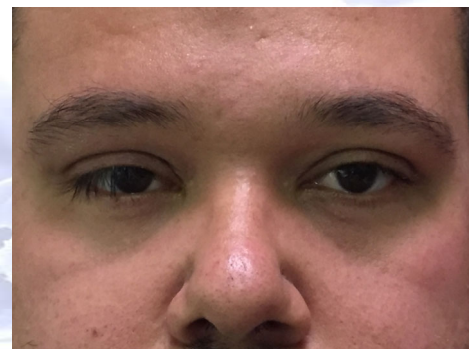
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Floppy Eyelid Syndrome: Associated with *Demodex Brevis*

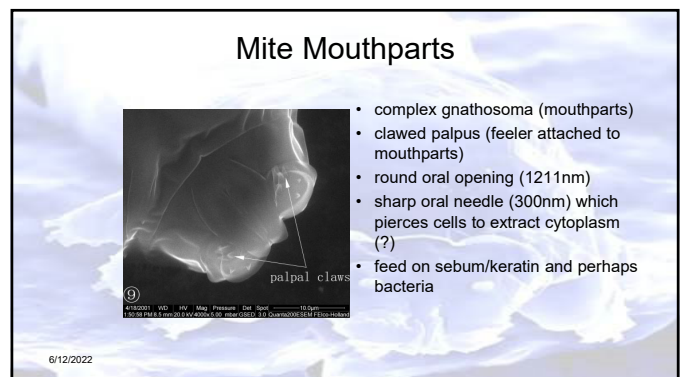
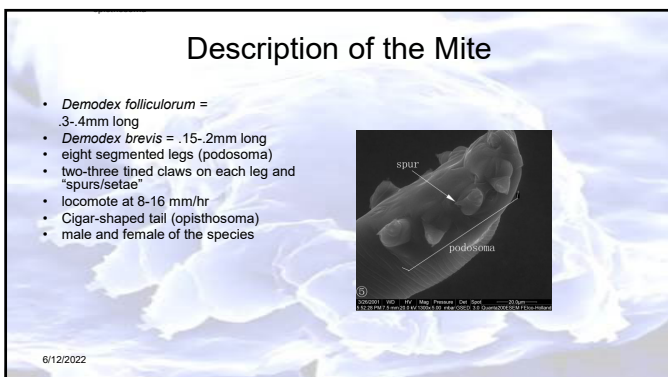
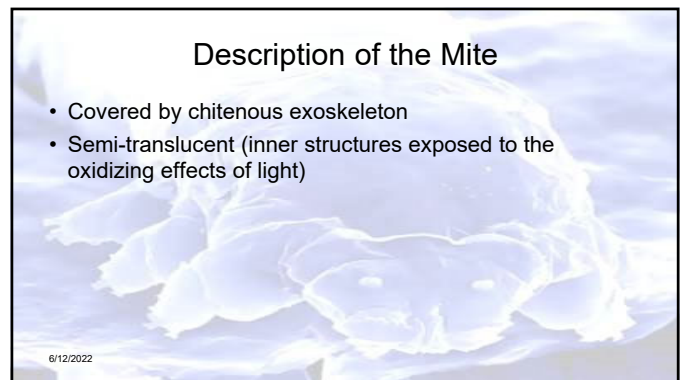
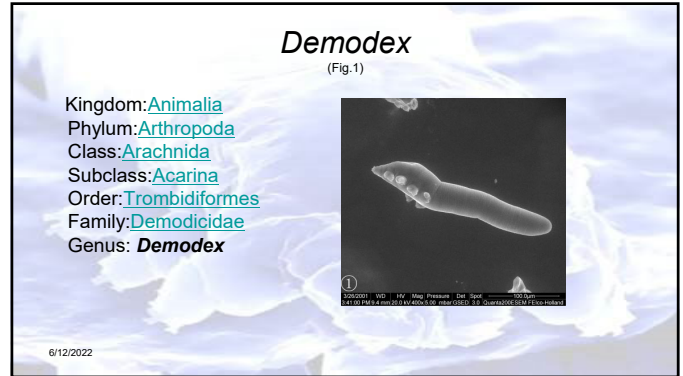
- floppy, rubbery and easily everted upper eyelids
- eye lid hyperpigmentation.
- ptosis/lash ptosis
- dematochalasis
- papillary conjunctivitis.
- lacrimal gland prolapse
- squamous metaplasia and keratinization in meibomian glands/gland dysfunction
- lax lids have diminished lipid production
- associated with obstructive sleep apnea

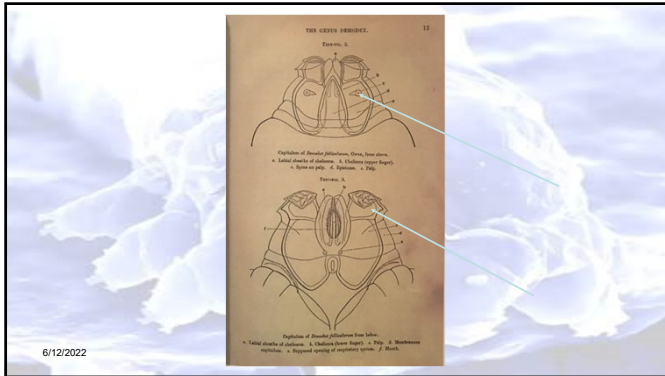


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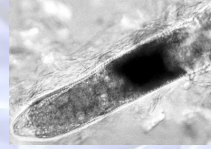


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Description of the Mite



- Digestive pouch
- No terminal excretory opening (digested material regurgitated and may contain proteases and lipases)

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Associated Bacteria

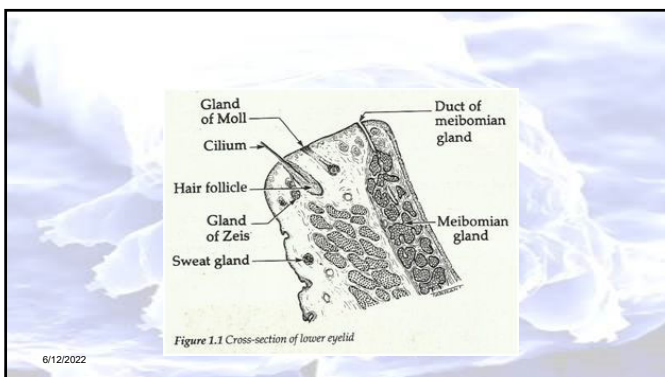
- *Demodex* flora include *Streptococcus* spp., *Staphylococcus* spp. and *Bacillus Oleronius*
- Patients with *Demodex* blepharitis have varying degrees of bacterial microbiota imbalance in the conjunctival sac.
- *Demodex* serve as bacterial vectors: role for lid hygiene

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Demodex

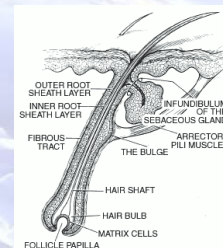
- *Demodex* populations are age dependent, increasing with age and reaching up to 100% in elderly patients.
- *Demodex folliculorum* is found in hair and eyelash follicles and elsewhere on the face and body.
- *Demodex brevis* is generally found in sebaceous glands of the body and in the meibomian and Zeiss glands of the eyelid.

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The Anatomy of Hair

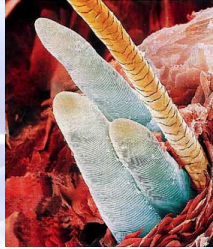
- *Demodex folliculorum* will nestle "head down" into a lash follicle.
- the bulge is the site of hair follicle stem cells; pluripotent stem cells proliferate and then elaborate the various portions of the hair shaft
- hair follicle stem cells are important contributors to the wound-healing process
- *Demodex* infestation may interfere with bulge stem cells



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Demodex folliculorum

- three mites buried "head-down" into a hair follicle with conical opisthosomas (tail ends/caudal portion) visible
- up to 25 mites per follicle have been demonstrated
- there is no consensus on what denotes "demodicosis" (over-infestation of the organism)



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HANDBOOK OF MEDICAL ENTOMOLOGY

Dr. WM. A. RILEY, Professor of Insect Morphology and Parasitology, Cornell University

Dr. O. A. JOHANNSEN, Professor of Biology, Cornell University

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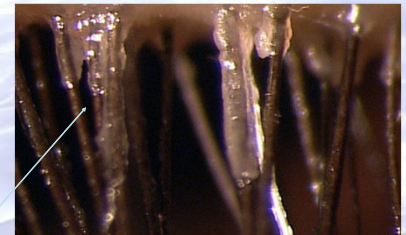
Mite/Claw Induced Eyelid/Eyelash Changes

- interrupts tissue integrity
- causes edema/inflammation/distention/hypertrophy/plugging of the lash follicle
- epithelial hyperplasia = "cuff"/ "sleeves"/ "cylindrical dandruff" formation
- eyelash deposits- mélange/mortar of eggs/digestive excretions/decomposed mites
- "spiney" blepharitis
- implicated in meibomian gland granulomas/pediatric chalazia (2022) and meibomian gland dysfunction
- TODAY: "In conclusion, low fluence IPL seems to be a safe and effective alternative for moderate-to-severe pediatric blepharitis, and MG dropout is prone to recover in younger patients." J Clin Med 2022(May); : 676-686.

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Mite/Claw Induced Eyelash Changes

- easier lash epilation
- madarosis
- brittle cilia
- poliosis/depigmented
- shorter, straighter cilia
- misdirected cilia
- trichiasis

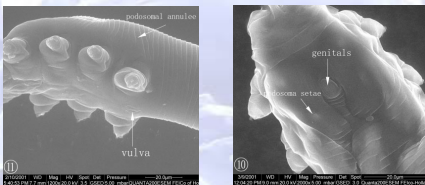


"Conical or volcanic" waxy peaking

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The Sexes

Fig. 3, Fig. 4



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Making More

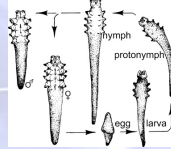
- copulation occurs at the mouth of the hair follicle
- the female burrows into the follicle and lays eggs (oviparous) or can sometimes be seen on lashes
- life span = 14.5-21 days with 120 adult hours



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Making More

- Copulation
- Egg deposition- on lashes and within the follicle
- Larval emergence
- Nymphs (six legs)
- Adulthood- feed, excrete (via mouth) and breed



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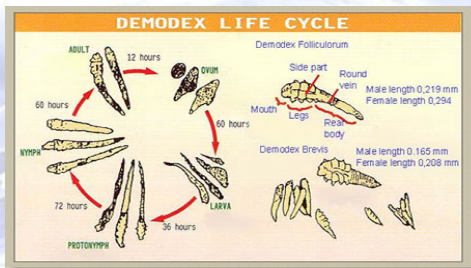
Demodex Life Cycle

- Moulting in intermediate stages
- Moults may excite an immunological response



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Demodex Life Cycle



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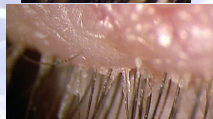
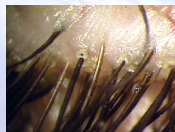
Demodex Life Cycle

- Death
- Female apoptosis (after egg delivery) ?
- Involution (males?)
- Coagulation/necrosis (cylindrical cuffs/biofilm)

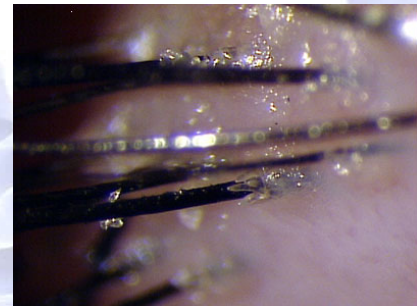
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Diagnosing Demodex Overpopulation

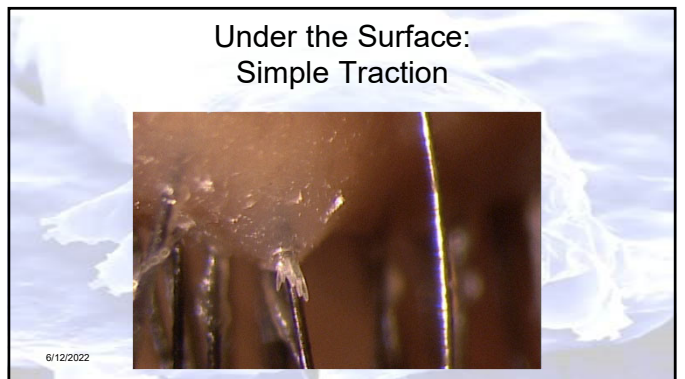
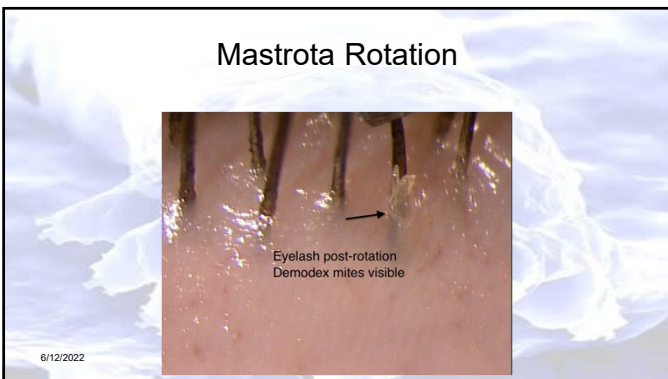
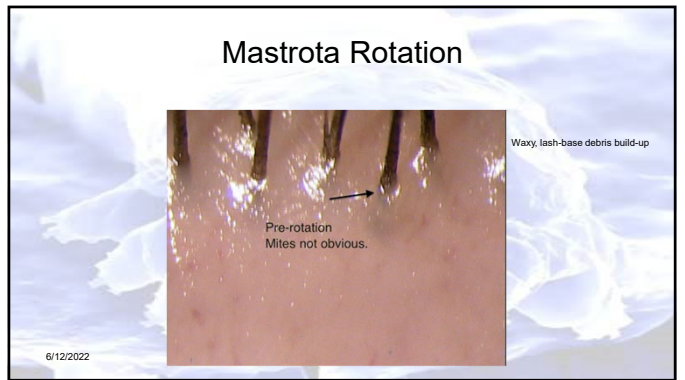
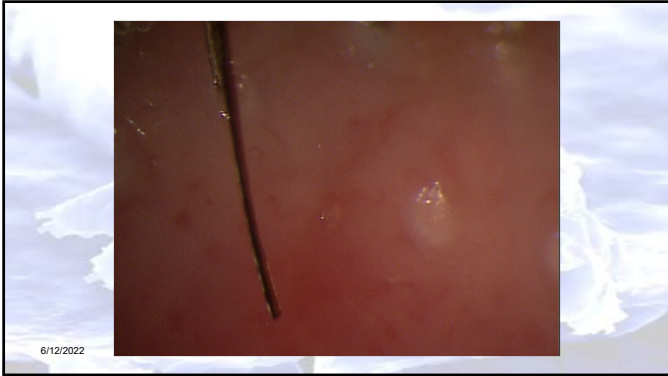
- complaints of eyelid itching
- slit lamp examination: "cylindrical cuffs/sleeves/dandruff" around base of eyelashes
- abnormal lash integrity/growth/misdirection
- in some cases corneal and conjunctival inflammation
- *Demodex folliculorum*: identified by microscopic evaluation (slit lamp/light)
- *Demodex brevis* is generally not isolated as it may be within the meibomian/Zeiss gland

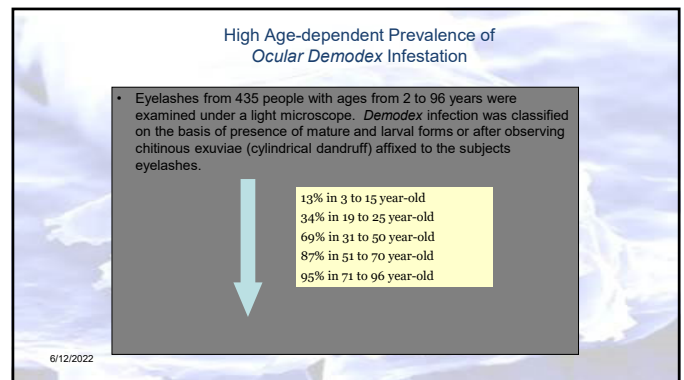
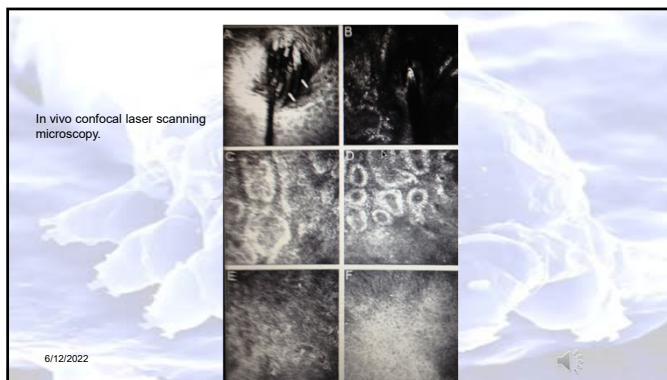
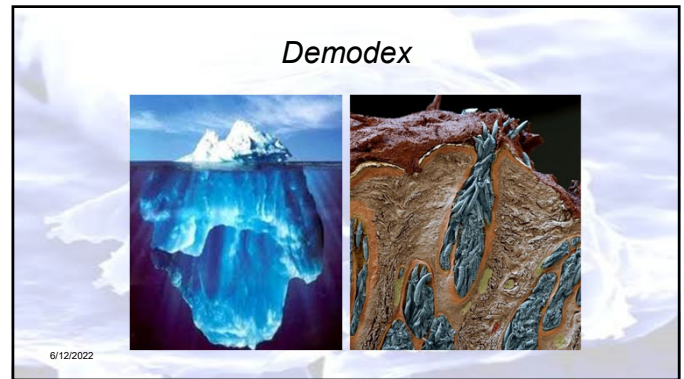
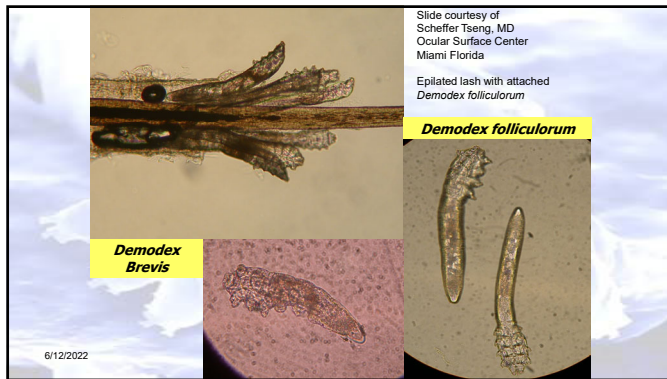


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Cytokine. 2011 Jan;53(1):94-9.
Tear cytokines and chemokines in patients with Demodex blepharitis.

- Infestation of *Demodex* mites induces change of tear cytokine levels, IL-17 especially, which cause inflammation of the lid margin and ocular surface.
- Host cytokine production is thought to play an important role in ocular discomfort.
- Demodex* blepharokeratitis: superficial punctate keratitis, peripheral neovascularization, marginal corneal infiltrates, central stromal infiltrates, corneal scars or opacities, nodules or phlyctenular lesions, limbitis

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Demodex and Inflammation

- Demodex* upregulates MMPs that are involved in inflammation, collagen lysis and angiogenesis.
- Possibly contributes to lid laxity and ectropion.
- Response to chitin?
- Mites contain immune-reactive lipases that can produce free fatty acids from sebum triglycerides.

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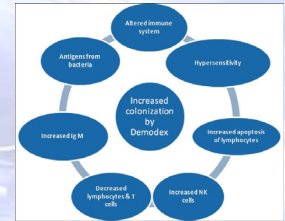
What is demodicosis?

- There is often poor correlation between symptoms experienced by patients and objective signs indicating demodicosis.

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Host Factors and *Demodex* Overpopulation

- Age (hormonal status)
- Reduced host immunity
- Essential fatty acid deficiency
- Diabetes
- Certain HLA haplotypes
- Down's Syndrome
- Vitamin D deficiency
- Poor sleep
- Psychological stress
- Chemical pollution



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Balance

- The aim of treatment is to address the ecological imbalance of the external ocular environment that is associated with *Demodex* overgrowth.
- Return normal balance of host immune system and *Demodex* counts.

“*Demodex* is an inhabitant of human hair follicles, and a mite which we live with in harmony.”

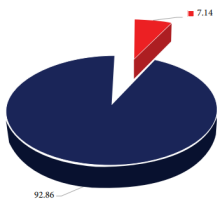
6/12/2022 M. Hallit Umar, The Netherlands

Any homeostatic imbalance caused by ocular surface conditions, such as dry eye or meibomian gland dysfunction can lead to **contact lens discomfort** or contact lens-induced dry eye.

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Demodex sp. as a Potential Cause of the Abandonment of Soft Contact Lenses by Their Existing Users. Tarkowski, Moneta-WielgołV, Bocicki BioMed Research International Volume 2015.

Percentage division of patients with intolerance to contact lenses based on the presence of *Demodex*



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ARVO 2022 Poster

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Treatment for Demodicosis

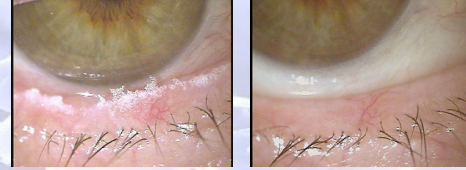
- lid hygiene with commercially prepared solutions can be helpful in removing cuffs, exposed mites and associated bacteria.

Treatment for Demodicosis

- bland ointments suffocate the mite (e.g., erythromycin and in the past, mercuric oxide ung. or pilocarpine gel).
- tea tree oil scrubs/shampoo: effective in reducing mite population (possible irritation, contact dermatitis, and allergy)
- sea buckthorn oil preparations (FaceDoctor TM products; Neal Bhatia, M.D., assistant clinical professor of dermatology at the UCSD, San Diego)
- ??Hedrin—Hedrin TM, a non-insecticide (combination of silicones) product for the treatment of head lice currently marketed in Europe and UK; disrupts the osmotic balance within the insect
- Permethrin cream- antiparasitic
- Oral Ivermectin-antiparasitic

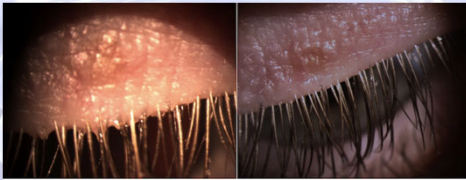
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Lid Hygiene



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Lid Margin TTO treatment



S. Schachter, OD

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*HMGECs

- T4O, even at levels 10-fold to 100-fold lower than mite-killing concentrations, is toxic to *HMGECs in vitro.

* human meibomian gland epithelial cells

[Effects of Terpinen-4-ol on Meibomian Gland Epithelial Cells In Vitro](#), Chen D, Wang J, Sullivan DA, Kam WR, Liu Y. *Cornea*. 2020 Dec;39(12):1541-1546.

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Microblepharoexfoliation ^{*4/22, Cornea}

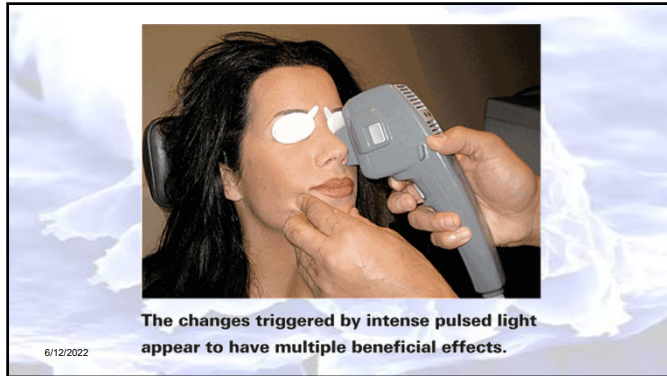


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At Home Hygiene



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Potential Mechanisms of IPL

- Modulating the secretion of pro- and anti-inflammatory molecules
- Suppressing MMPs
- Reducing intracellular oxidative stress*
- Thrombosis of abnormal blood vessels

*Kim J, Lee J, Choi H. Intense Pulsed Light Attenuates UV-Induced Hyperimmune Response and Pigmentation in Human Skin Cells. *Int J Med Sci*. 2021;20(6):3173.

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Potential Mechanisms of IPL

- Heating/liquefaction of meibum
- Reducing epithelial turnover/gland obstruction
- Photomodulation- activates fibroblasts/increasing collagen synthesis
- Killing *Demodex*: exoskeleton of *Demodex* contains chromophore that absorbs IPL energy. Histologic analysis demonstrated that IPL treatment induces coagulation and necrosis of *Demodex*.

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Manuka Honey

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Active Manuka Honey

- Antibacterial, including MRSA
- Antifungal, antiviral, anti-inflammatory
- Used in burn and trauma therapy
- Anti-cancer
- Stabilize blood sugar
- Treat GI problems (acid reflux, IBS, ulcers)
- Reduce cholesterol
- Skin-acne, excema, itch, moisturizer

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Novel Drug Designed to Treat *Demodex* Blepharitis by Eradicating Mites/ Collarette Reduction, Phase 3, Lotilaner

Product Form	Multi-dose eye drop solution bottle, preserved
Targeted Use	Treatment of <i>Demodex</i> blepharitis
MOA	Paralysis and death of <i>Demodex</i> mites
Diagnosis	Collarettes identified in standard eye examination
Dosing	BID* for 6 weeks
Efficacy Goal	1 st collarette cure, 2 nd mite eradication, 2 nd redness + collarette cure
Safety Goal	Well-tolerated safety profile

Lotilaner

* Patient non-competitive antagonist of insect and animal GABA-C₁ channels
* Highly lipophilic molecule

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*acts selectively on mite neurotransmitters

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