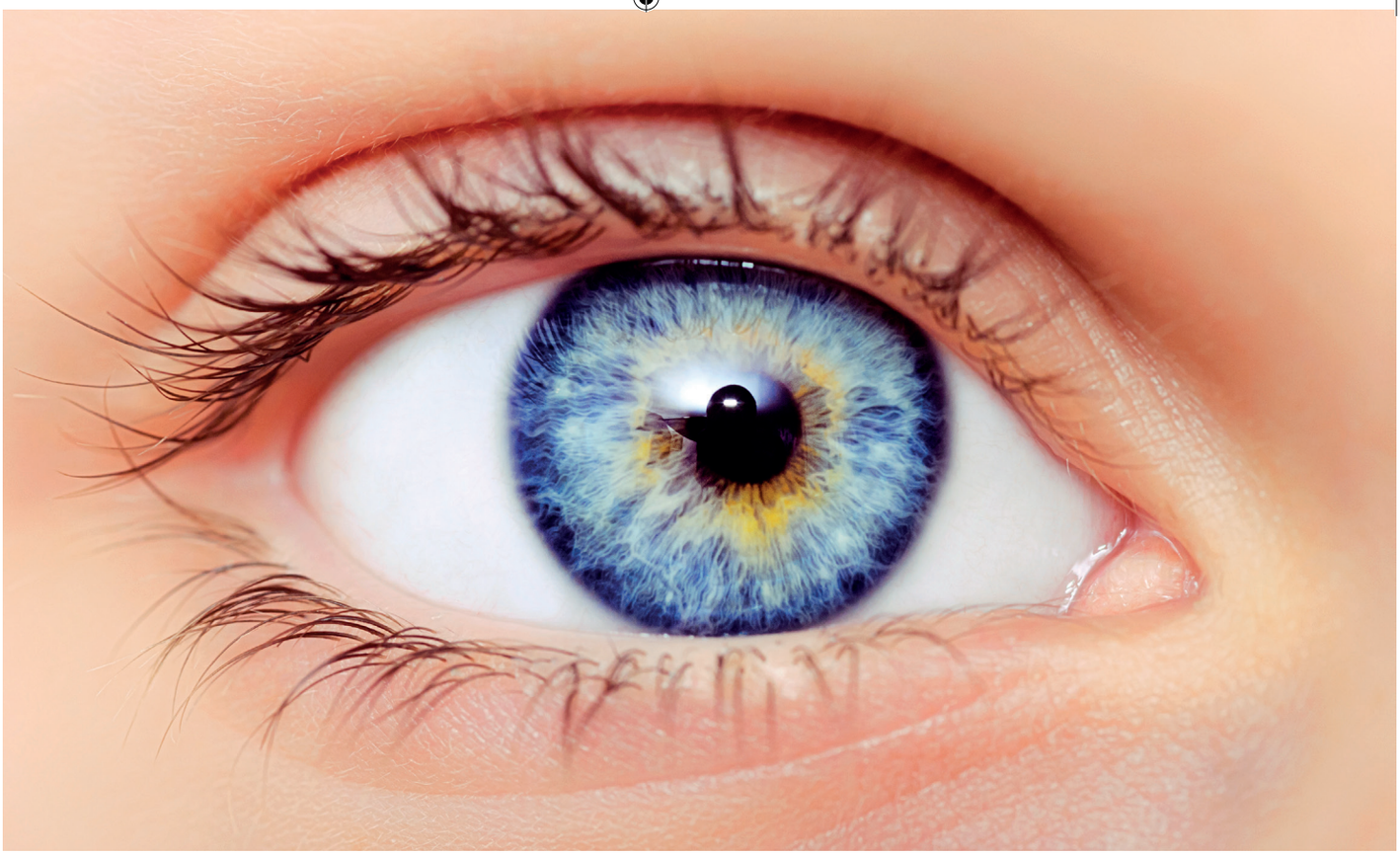

Know your enemy:

Rich snippet on Demodex

Unless recently qualified, it is unlikely that information regarding Demodex was included in your optometric training. And, until recently, the subject has even remained absent from post-graduate diploma courses in Ocular Therapeutics.

by David Crystal

It has been estimated that Demodex mites are the most common, but often overlooked, cause of ocular surface inflammation from blepharitis and meibomian gland dysfunction, which account for 37% and 47% respectively[1] of the patients seen in clinical practices by ophthalmologists and optometrists. A higher incidence is witnessed in elderly patients: Demodex are present in 84% of the population at age 60, rising to 100% of those older than 70 years[2].

It is perhaps surprising the first case of Demodex mites was reported in 1842, yet it is only in the last three years that an evidenced-based method for eradicating them has begun to form[3]. Blepharitis is still widely understood to be a chronic, incurable staphylococcal based condition, the symptoms of which can only be managed. Consequently, an entire product industry has arisen and practitioners have had to choose from a multitude of lid hygiene and dry eye products that are not miticidal.

Recent press and media attention has increased public awareness by suggesting that Demodex are simply endemic[4]. For the majority of people the presence of Demodex will be low-grade and asymptomatic[5], but herein lies the professional conundrum – there is compelling evidence that links the presence of Demodex to the chronic lid margin disease blepharitis[6], meibomian gland dysfunction and ocular surface inflammation from blepharo-keratitis[7], which can be sight threatening[8]. Collectively this group of conditions, when associated with Demodex, is known as 'Ocular Demodecosis'.

Ocular Demodecosis causes itching, soreness, redness and crusting of the lid margins, and blurred vision. It is the major cause of evaporative dry eye which is the most common condition presenting to optometrists. There is also an association with facial rosacea[9] and pterygia[10].

Transmission occurs by direct contact with an individual who has a Demodex infestation, or from pillows and towels. Since Demodex multiply with time the risk to vision also increases with age, especially for individuals with a depressed immune system such as steroid users.

Understanding Demodex

Demodex mites are microscopic parasites that live inside eyelids. One of the two human species, Demodex folliculorum, buries itself face down, next to the shaft of the eyelash and feasts on the cells and sebum that line the follicle. The other species, Demodex Brevis, burrows deeper towards the base of the eyelash to depths of up to 2.3mm, where the follicle's sebaceous gland is located. Brevis also burrows deep into the meibomian gland orifices (Fig. 1).

The mites have eight claws at the front, which they use for locomotion. Every night male Demodex folliculorum leave the hair follicles to mate by reversing out along the eyelash shaft, which is not smooth but has a layered, slated, texture. In doing so the mite's claws push out a mixture of keratinized skin cells and sebum[11], in the same way a mole pushes up earth when surfacing. This quickly accumulates around the base of the lashes as cylindrical dandruff (CD). CD is the new term for lash collarets and its observation is pathognomic for Demodex (Fig. 2).

Moving slowly at 6-8mm/ hour, the folliculorum mites leave a trail of Staphylococci bacteria in their effort to find a female and copulate. Eggs are laid just inside the eyelash follicle. Nymphs hatch 3-4 days later and they take about a week to develop into adults. The total lifespan of a Demodex is no more than 18 days. At the end of their life, a Demodex's entire internal contents are expulsed in a single event as waste products. Outside of the body, a Demodex can survive up to 56 hours in a drop of oil.

The activity and life cycle of Demodex Brevis within the meibomian glands is believed to cause obstruction resulting in meibomian gland disease (MGD), with associated lipid tear deficiency. Clinical and histopathologic studies have revealed that terminal duct occlusion due to hyperkeratinization of the ductal epithelium within the glands is the most significant factor in the pathogenesis of MGD[12]. Micro-abrasions caused by the mite's claws can induce epithelial hyperplasia and reactive hyperkeratinization[13], so Demodex Brevis is a prime candidate for causing MGD.

It is thought that bacteria from Demodex can either convert neutral meibomian gland oils into irritating fatty acids or cause release of exotoxins into the tear film. Either way, if the tear lipid layer is not perfectly formed, further disruption may lead to evaporative dry eye symptoms.

Treatment is based on waiting for eggs to hatch, killing the mites, and preventing them from reproducing. Demodex folliculorum are the easiest to destroy as they reside in the hair follicles and regularly surface to mate. In contrast, Demodex brevis live deeper and, being solitary in nature, do not surface as often; they are much more difficult to reach, and hence are much harder to eliminate.

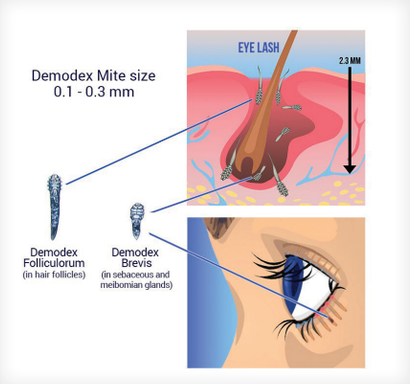

Figure 1 - Original artwork commissioned by David Crystal

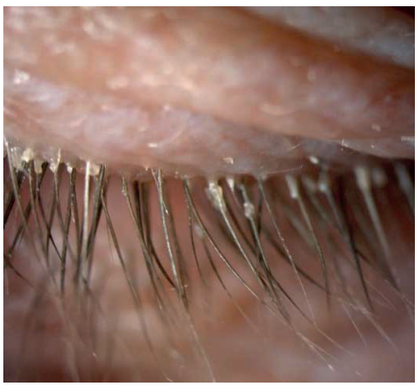

Figure 2 – Cylindrical dandruff is attached to base of lashes – loose "flakes" are not CD

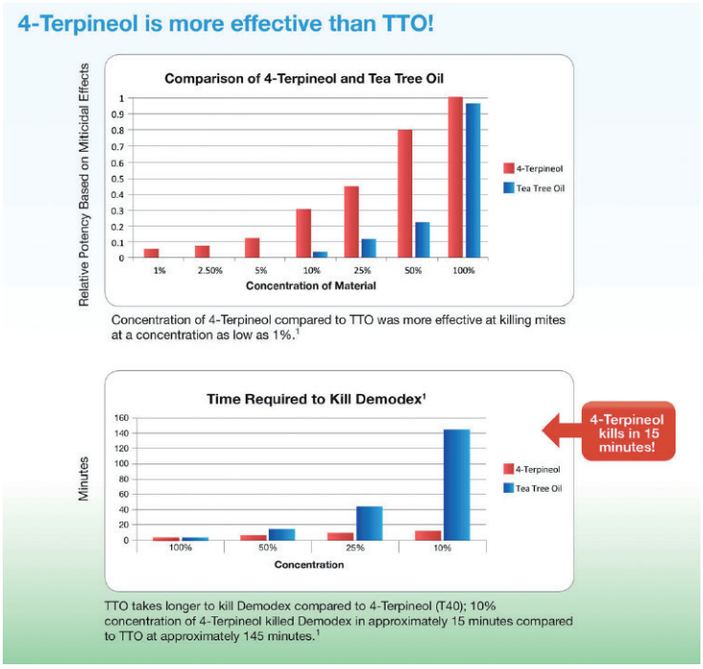

Figure 3 - With kind permission from Biotissue

In trying to deliver miticidal agents to the deepest Brevis at a 2.3mm depth from the lid margin, follicular penetration researchers have found, using Optical Coherence Tomography, the presence of CD acts as a physical plug barrier to follicular penetration. The follicle needs to be "opened" by removal of the dried sebum by mild peeling or dissolving to render the lash follicle receptive for penetration.

The phrase "like dissolves like" predicts that a solute will dissolve best in a solvent that has a similar chemical structure to it. The follicular canal is a lipoidal environment and sebum is primarily composed of triglycerides (~41%), wax esters (~26%), squalene (~12%), and free fatty acids (~16%). Jojoba oil (which is actually a liquid wax) is assessed to most closely resemble human sebum.

In tests, the deepest follicular penetration occurred by applying formulations containing nano-particles of around 600nm in size, which, in conjunction with digital massage, recorded a maximum penetration depth of only 1.2mm. Formulations with both smaller or larger particle sizes penetrated less, proving that size matters. As such, the deepest Brevis are out of reach.

Continued overleaf »

T40: *the facts*

- > T4O has a greater miticidal effect than TTO alone with less irritation.
- > 10% T4O kills mites on a microscope slide in 15 minutes compared to 145 minutes for 10% TTO.
- > Concentrations of T4O as low as 1% have been observed to be effective at killing the Demodex mites.
- > Although 100% pure TTO should contain around 38% T4O, batches and products vary and the T4O content can be as low as 30% (this is the minimum Australian Industry Standard). This means that a product that contains a lower-quality 5% TTO component has just enough T4O to be miticidal (30% of 5% = 1.5% T4O).

Evidence based treatments
Research has shown that 50% Tea Tree Oil (TTO), 100% Caraway Oil and 100% Dill Weed Oil exerted effective in vitro killing of mites within 15 minutes. Unfortunately these latter two agents are not amenable for clinical use because of their intrinsic toxicity and irritation to the eye. Whilst 50% TTO is also capable of delivering a chemical burn to the cornea, its careful application to the lid margins represents the current paradigm in treatment for Demodex.

Tighe *et al*. 2013[14] found that the most active ingredient in TTO to kill Demodex mites is Terpinen 4-ol (T4O) (Figure 3)

Figure 4
In the above picture (Fig. 4) the tea tree oil quality is high having > 38% Terpinen 4-ol but the TTO content is actually around 2%. These are excellent cleaning wipes but they are unlikely to have sufficient miticidal effect to kill significant numbers of Demodex.

Occlusive creams or ointments containing 5% TTO have been successful in treating Demodex however when this was tried[15], allergic reactions were observed[16]. TTO suffers from aerial oxidation causing a dramatic rise in irritating substances such as p-cymene and epoxides (which also greatly reduces the active terpinen-4-ol). Furthermore, ointments, creams and gels commonly contain one or more of the known mucosal eye irritants: Benzyl Alcohol, Phenoxyethanol, Benzoic acid, Isopropyl myristate and Ethylhexyl Stearate. This is the problem with all of the 5% TTO products: Helios Tea Tree Cream, E-Derma cream, Thursday Plantation Tea Tree Cream, Australian Tea Tree Cream.

When evaluating new products check for these irritating ingredients. For example Ivermectin 1% cream (Soolantra, Galderma Labs) has recently been approved for the treatment of Demodex but contains Phenoxyethanol and 10% of patients experience a burning feeling.

Best practice with evidence-based products
In July 2016, the Cliradex range of products (Biotissue, Florida USA) will be available to UK optometrists. Cliradex products are the only commercially available products that isolate T4O and are a direct result of Tighe's evidence-based research. There are three preservative-free products.

Figure 5 - Cliradex Complete

Cliradex Complete (Fig. 5) – For professional use only – contains the strongest concentration of T4O formulated as a white coloured paste for in-office application as a replacement for 50% TTO mixtures.

Cliradex Wipes - These are pre-formulated towelettes containing 4% T40, equivalent to about 25% TTO, for use by patients to support in-office treatments. Despite marketing efforts to portray this as a gentle, natural product, make no mistake the wipes are highly astringent, but have been the product of choice in our practice for one year.

Cliradex Light – A foam preparation containing 2% T4O for treated patients who commonly request a maintenance product. This is the newest product, and a welcome addition to the range.

Continued »

Professional conundrum - Would you inform and prophylactically treat an asymptomatic young person aged 20 presenting with 10 lashes with CD?

Given the increasing risk of demodicosis with age, we would recommend that you inform the patient, warn them of the possible symptoms and risks and proceed with treatment if consensual. As a profession, we should be routinely educating our young patients in the importance of prophylactic lid hygiene.

In order to demonstrate with certainty the diagnosis of ocular demodecosis, we epilate up to two eyelashes from each lid, place them on a microscope slide with a drop of sodium fluorescein[17] and examine them at 540x magnification, using a digital video microscope.

Diagnosis and treatment protocol

In our Edinburgh optometry practice we find around 15% of all patients show the signs of cylindrical dandruff (CD), which can only be observed by slit-lamp biomicroscopy. Recording the number of upper lid lashes affected per eye (in most cases this is not symmetrical):

Up to 5 lashes with CD	borderline-mild *NB: patient not advised unless young and symptomatic*
Up to 5 - 10 CD	mild – moderate (easier to treat)
More than 10 CD	moderate – severe (harder to eradicate)

Treatment is based on delivering miticidal agents over two life cycles. This is done by a combination of in-practice "clean and kill" sessions lasting 45 minutes and a supportive home treatment aimed at disrupting their reproductive cycle. Currently there is no effective way for a patient to self-treat their Demodex. Up to 6 weekly return visits are needed and eradication of Demodex is achieved for 7 out of 9 patients.

In every patient treated, a resurgence of CD production is seen at the one-week follow up (which suggests step four of the home procedure is ineffective).

Continued overleaf »

Clinical tip – pull the lash round in a full circle four times before epilation otherwise no demodex may be seen. Because the shaft of the lash has a slate-like texture, moving the hair acts like a geared pump that forces Demodex upwards and out.

Presenting the evidence of active Demodex to the patient confirms the nature of their problem.

Visit cetpoints.com to watch videos of Demodex folliculorum feeding from cuticle sebum, and Demodex brevis with two Demodex folliculorum on each side.

How to guide

In-office procedure

1. Without anesthesia, dry debride large CDs using a "Golf Spud" tool

   Clinical tip - if the CDs become wet they become difficult to see
2. Apply topical anesthetic to upper and lower lid margins
3. Insert daily disposable contact lens as protective bandage.
4. Use BlephEx procedure to "open" the follicles by spinning the sponge tip along the edge of the eyelids and lashes to remove scurf and debris. This action has a similar effect to eyelash rotation. (A lid scrub solution is fine for this purpose).
5. Using a fine "paint" brush target lash bases with 50% TTO / 50% Jojoba Oil* mixture. (see video)

   Clinical tip - *in preference to Macadamia nut oil.
6. Leave for 15 minutes and remove with dry cotton buds.
7. Demonstrate application of Cliradex wipes (first visit only).
8. Remove contact lens, discharge patient and review one week.

Home procedure

1. Replace pillowcases / towels on night of every in-office treatment session.
2. Abandon eyeliners, mascara, eye shadow and skin moisturisers during the treatment period.
3. Use Cliradex wipes nightly before sleep, do not wash off.
4. TTO shampoo eyelids in a morning shower to remove previous night's CD.

Despite the patient exiting the first treatment session with perfectly clean-to-the-base lashes, the CD's return to the extent that they appear similar to the pre-treatment visit. As the treatment weeks advance, there is progressively less returning CD to deal with. Because TTO or T4O usage promotes outward migration of Demodex, the quick reformation of CD after opening the follicles is expected, as Demodex are being purged. With a decreasing active population of Demodex, the amount of CD being formed also reduces and this is conformational the treatment is working. We have noticed a proportional relationship between the amount of resurgent CD and the initial pre-treatment CD count.

Innovative treatment

Tea tree oil contains chemically sensitive substances. Several oil constituents oxidize on contact with air at room temperature, especially when there's light, too. In this way, air greatly reduces the terpinen-4-ol content. What's worse is that the gradual loss of active constituents is accompanied by a dramatic rise in the concentration of substances, such as p cymol, ascaridol and 1,2,4-trihydroxymenthane, which irritate the skin and can cause allergic reactions.

One way out of this predicament is the molecular inclusion of T4O in a suitable cyclodextrin – a method that has proved effective for fragrances, vitamins, and other lipophilic substances. Cyclodextrins are ring-shaped sugar molecules comprising several interlinked glucose units. Each cyclodextrin molecule can house a lipophilic guest molecule in its cavity, and will release it again under suitable conditions. It is best to imagine a cyclodextrin molecule as a tiny safe in which an individual molecule is kept and protected against the influence of oxygen, light and heat. When necessary, the safe is opened and the molecule emerges completely unchanged – as fresh as when it was put inside. The key to opening these molecular safes is moisture.

For as long as the T4O remains enclosed in the cyclodextrin, it enjoys perfect protection – it can neither evaporate nor be altered chemically. The skin's natural moisture and temperature are sufficient to release the T4O. The T4O thus reaches the skin in juvenile form. There are no skin irritating and sensitising oxidation and degradation products.

Accelerated treatment

To improve patient outcomes for severe cases, we have tried a slow release version of T40 entrapped in Cyclodextrin on four patients, to deliver 10% T4O active over 12 hours. The product particles are around 5000nm in size, which is far too large for deep follicular penetration and resemble talcum powder. Applied onto the eyelids and lashes before sleep it is absent upon wakening. Patients report no irritation whatsoever. We have observed a greater production of resurgent CD, which may imply a quicker evacuation of Demodex.

Another agent, related to limonene and a by-product of the orange juice industry is also miticidal but has not yet been commercialised. There is scope for further product development.

Currently, Demodex treatment is an arduous process for both practitioner and patient. The time burden, commitment required and commercial revenue lost in the disruption of the provision of spectacles and contact lenses makes this work unattractive for most practices. However the professional reward in curing a condition where others have failed is priceless and the patients are extremely grateful.

About the author

David Crystal transferred from an undergraduate degree course in Physics with Computing at Bradford University to study Optometry at Caledonian University Glasgow in 1980. He established Scotland's first specialised dry and watery eye clinic, with routine punctal occlusion and tear duct syringing procedures. David gained his Post Graduate Diploma in Ocular Therapeutics in 2002, becoming the first of his kind in Scotland. He now occasionally facilitates workshops for Glasgow Caledonian University Ocular Therapeutics course. David is currently pursuing treatments that eradicate Demodex; the most common indirect cause of evaporative dry eye. Outside of optometry, his interests are snowboarding and website SEO. He also created EyeDispense, Just Reading Test Types and Maddox Rod iPad apps.

David Crystal can be contacted at www.crystaloptometry.co.uk

References

[1] English FP, Nutting WB (1981), 'Demodicosis of ophthalmic concern' Am J Ophthalmol, 91:362–372.

[2] Lee SH, Chun YS, Kim JH, et al. (2010), 'The relationship between demodex and ocular discomfort', Invest Ophthalmol Vis Sci. 51:2906–2911

[3] Spickett SG (1961), 'Studies on Demodex folliculorum', Parasitology, May, 51:181-192.

[4] www.bbc.co.uk/earth/story/20150508-these-mites-live-on-your-face

[5] Turk M, Ozturk I, Sener AG, et al. (2007), 'Comparison of incidence of Demodex folliculorum on the eyelash follicule in normal people and blepharitis patients', Turkiye Parazitol Derg. 31:296–297.

[6] Liu J, Sheha H, Tseng SC (2010), 'Pathogenic role of Demodex mites in blepharitis', Curr Opin Allergy Clin Immunol, 10:505-10

[7] Kheirkhah A, Casas V, Li W, et al. 'Corneal manifestations of ocular Demodex infestation'.

[8] English FP, Nutting WB (1981), 'Demodicosis of ophthalmic concern', Am J Ophthalmol, 91:362–372.

[9] Bonnar E, Eustace P, Powell FC (1993), 'The Demodex mite population in rosacea', J Am Acad Dermatol. 28:443–448.

[10] Huang Y, He H, Sheha H, Tseng SCG (2013), 'Ocular demodicosis as a risk factor of pterygium recurrence'. Ophthalmology, 120:1341–1347.

[11] Gao Y-Y, Di Pascuale MA, Li W, et al. (2005), 'High prevalence of ocular Demodex in lashes with cylindrical dandruffs'. Invest Ophthalmol Vis Sci. 46:3089–3094. [PubMed]

[12] Nichols KK, Foulks GN, Bron AJ, et al. (2011), 'The inter- national workshop on meibomian gland dysfunc- tion: executive summary' Invest Ophthalmol Vis Sci. 52(4):1922-9.

[13] Gao Y-Y, Di Pascuale MA, Li W, et al. (2005), 'High prevalence of ocular Demodex in lashes with cylindrical dandruffs'. Invest Ophthalmol Vis Sci. 46:3089–3094. [PubMed]

[14] Tighe et al. (2013), 'Terpinen-4-ol is the Most Active Ingredient of Tea Tree Oil to Kill Demodex Mites' http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860352/

[15] Gao YY, Xu DL, Huang lJ, Wang R, Tseng SC. (2012), 'Treatment of ocular itching associated with ocular demodicosis by 5% tea tree oil ointment', Cornea. Jan. 31(1):14-7. [Medline].

[16] Simpson et al. (2004) 'Prevalence of botanical extract allergy in patients with contact dermatitis', Dermatitis 15:67-72.

[17] Kheirkhah A, Blanco G, Casas V, Tseng SC (2007), 'Fluorescein dye improves microscopic evaluation and counting of demodex in blepharitis with cylindrical dandruff', Cornea. Jul. 26(6):697-700. [Medline].

Further sources:

English FP, Cohn D, Groeneveld ER. (1985), 'Demodectic mites and chalazion. Am J Ophthalmol', 100:482–483. [PubMed]

Kheirkhah A, Casas V, Li W, et al. (2007), 'Corneal manifestations of ocular Demodex infestation', Am J Ophthalmol. 143:743–749.

Kim J, Chun Y, Kim J. (2011), 'Clinical and immunological responses in ocular demodecosis', J Korean Med. 26:1231–1237.

Knop E, Knop N, Millar T, et al. (2011), 'The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysi- ology of the meibomian gland', Invest Ophthalmol Vis Sci. 52(4):1938-78.

Koksal M, Kargi S, Taysi BN, Ugurbas SH. (2003), 'A rare agent of chalazion: demodectic mites', Can J Ophthalmol. 38:605–606. [PubMed]

Liang L, Safran S, Gao Y, et al. (2010), 'Ocular demodicosis as a potential cause of pediatric blepharoconjunctivitis', Cornea. 29:1386–1391.

Obata H. (2002), 'Anatomy and histopathology of human meibomian gland',

Cornea. 21(7 Suppl):S70-4 24.

Wertz PW (2009), 'Human synthetic sebum formulation and stability under conditions of use and storage', Int J Cosmet Sci. Feb, 31(1):21-25