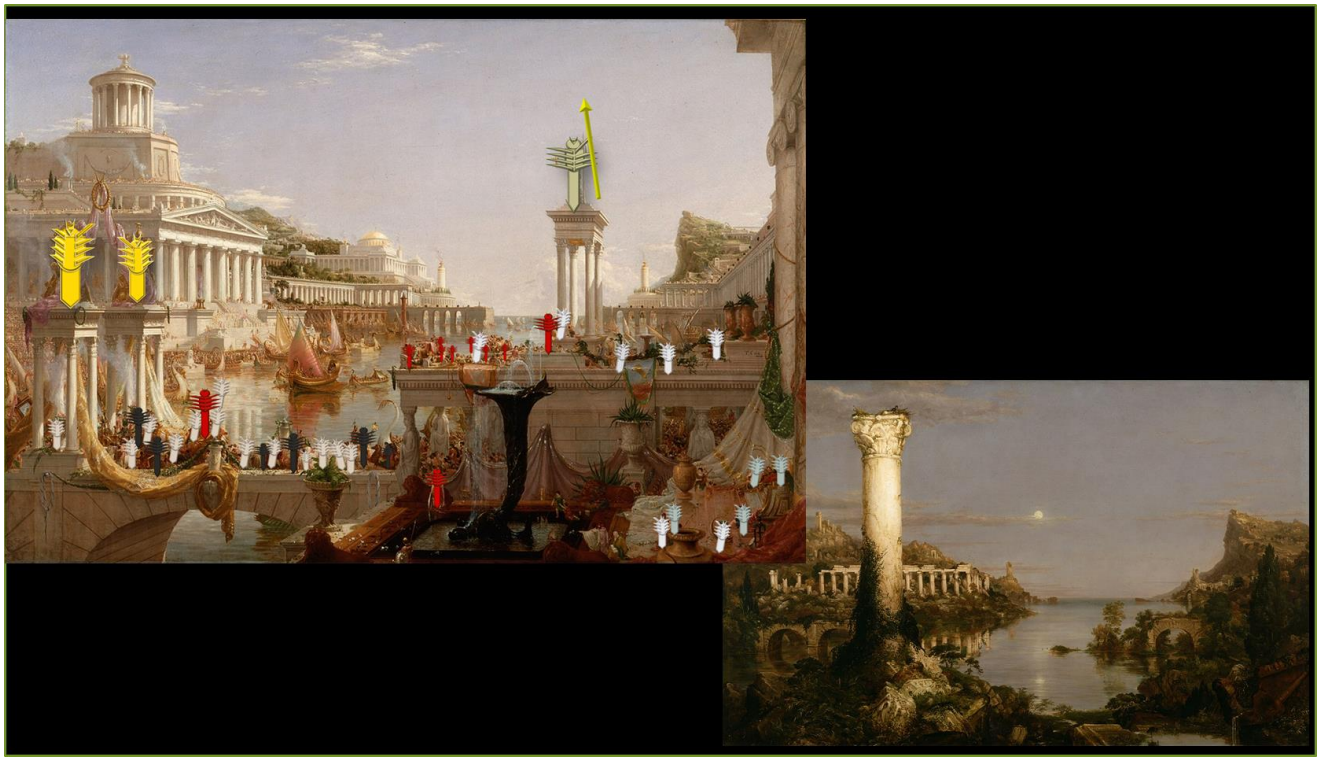
I & Vision Research Centre

Dry Eye: Pulsed Lights and Pore Mites



How the Mites Fall: Picture *Consummation* and *Desolation* by Thomas Cole. After plentiful times sipping sebum from human lids, new tech and gene loss eliminate the *demodex*. A lone, crumbling collarette remains

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It is estimated that around 700 million people are experiencing or have had symptoms of dry eye disease (DED), with population estimates in developed countries like Australia as high as 85% (Insight News). Other reports have figures ranging from 5-50% of populations, highlighting a great deal of ambiguity in terms of diagnostic criteria (Boboridis, 2023). The symptoms include dryness, redness, pain, itch, ocular fatigue and swelling, and lid crustiness, but are highly variable. The condition is now recognised as debilitating and disruptive to quality of life, mental health and work productivity, and symptoms have become a major reason for clinic visits outside of routine examination. The time spent indoors and on screens may be responsible for a large portion of new cases, with significant mechanistic roles played by inflammation (e.g. allergies, gut dysbiosis) and the immune system.

As initiatives and specialties have evolved over the years, we now know that there are a variety of actors, pathologies, and sub-types that require different treatment and diagnostics. A data science approach to underlie the technology developed for clinical use may be facilitated through international registries like those of the *Save Sight Institute*. Hopefully, molecular as well as data-driven methodologies will force untangling and refinement of the complex condition and players. A closer look at the microscopic biological world involved may then warrant a glance at topics like evolutionary parasitology, symbiosis, and acarology.

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If 2023 is truly a year for dry eye medications (Hornick, 2023) and the microbiome in disease, as holobionts, we may as well explore all avenues and creatures (justly maligned or otherwise) in the microbial milieu (See Pitlik & Koren, 2017).

Research & Therapeutics

Although curiosity is tilting towards genetics, demographic and environmental factors are still considered extremely influential. As such, in a recent report by the *Tear Film and Ocular Surface Society* (TFOS) 8 topic areas related to the impact of lifestyle on ocular surface disease were delineated and explored by sub-committees (*Introduction* by Craig *et al.* 2023). The aim of the material is to guide research as well as communication capabilities of clinicians, eventually reaching patients to encourage personal risk mitigation and preventive behaviours.

More in the clinician's toolkit: Latest treatments include a nasal spray (covered here), various eye drops, Intense Pulsed Light (IPL, IPL + radiofrequency), and Quantum Molecular Resonance (QMR). Subjective evaluation & self-reported post-procedure comfort of patients is noted carefully in addition to technological diagnostics. Going through materials on various machines, the word 'quantum' is also peculiarly popular, portending at least some contentious perspectives on species annihilation (See Harris, 2022, but it is a bit of a rabbithole) if not concerns for precipitating in-clinic multiverse events.

Reactive Aldehyde Species (RASP) Inhibitors

Systemic and local inflammation seems to be a main contributor to signs & self-reported symptoms. Topical reproxalap, a reactive aldehyde species (RASP) inhibitor, is therefore *en route* to becoming a DED drug and alternative to corticosteroids for treating anterior ocular inflammation (Mandell *et al.* 2020). Other RASP-inhibitor applications are under investigation for conditions like asthma and alcoholic liver disease, while a whole other angle for DED focuses on anti-inflammatory and to a lesser extent antioxidant diets.

RASP are involved in the pathways of numerous pathological conditions because they are a result of 'prooxidant forces overcoming natural antioxidant capacities' in a microenvironment, yielding cytotoxicity (Fritz & Petersen, 2013). Think of it as hostile elements overwhelming capacity of state security forces, leading to sweeping criminality and institutional instability. Compounds like reproxalap basically seize the troublemakers and isolate them from ordered cellular society, while additional dietary antioxidants are a pro-regime capacity-injection.

Quantum Molecular Resonance (QMR)

QMR is a high-frequency electrotherapy. QMR mechanically affects membranes and chemically (calcium, other signal pathways) stimulates regeneration in target cells, with earlier applications in wound healing. Over a treatment timeline of approximately two months, the lacrimal system as well as meibomian glands seem to regenerate (Kavroulaki *et al.* 2023). For the Rexon-Eye device, improvements were also seen in patients with autoimmune diseases, meaning QMR may apply across aetiologies. Despite the 'fraught' nature of disease severity assessment on the clinical side, patient-reported symptoms are 'significantly alleviated', thought to be largely thanks to reductions in inflammation measured by MMP-9 as proxy, improved by 75% (Trivli *et al.* 2023).

Intense Pulsed Light (IPL)

IPL is another recent innovation, showing collaborative promise related to the field of dermatology (Abelman, 2023). In short, different wavelengths of light are applied to the skin to yield tissue or cell destruction via thermal energy, which makes this method unsuitable for several skin types and conditions. IPL is used in a variety of cosmetic procedures, some of which eventually became available as home devices for procedures like permanent hair reduction.

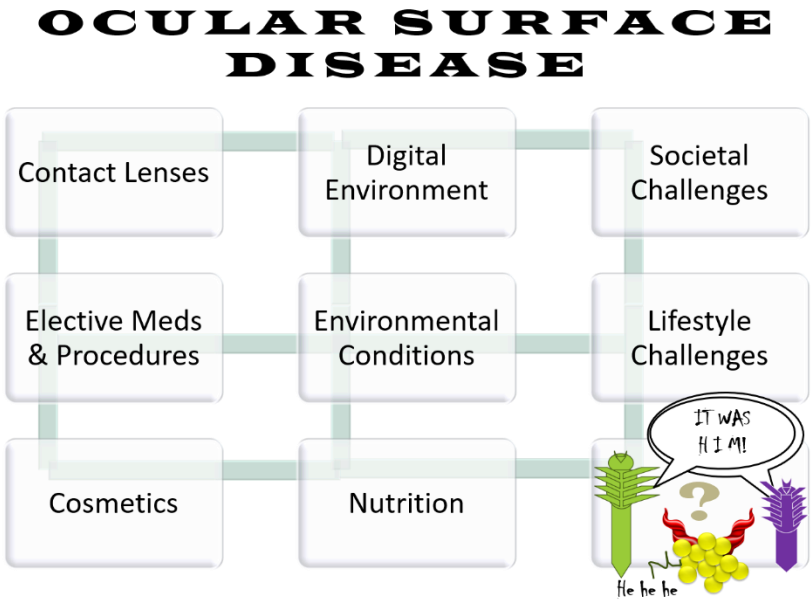
Specific to ophthalmic use, Lumenis OptiLight was FDA-approved for dry eye management – particularly the kind linked to meibomian gland dysfunction – two years ago after extensive work by R. Toyos and colleagues. Applications around eyelids and cheek are able to alter conditions of small, inflamed blood vessels involved in acne and ocular rosacea, improving not just meibum quality (oil content for tears that prevents evaporation from the eye's surface) but visage appearance and vision quality for patients (Whang *et al.* 2023; Martínez-Hergueta *et al.* 2022). Despite gathered results and numerous theories, the mechanism of action for syndrome improvement after IPL is not yet entirely clear.

For drops, compliance is reportedly an issue, in which case on-site appointments with IPL or QMR can lead to better patient outcomes. There's another issue where IPL has a multifactorial advantage: Drops like lifitegrast and cyclosporine for dry eye seem to have no effect on mites involved in a subtype of blepharitis, a major DED comorbidity characterised by redness and inflammation at eyelid margins (Trattler *et al.,* 2022).

Anti-parasitics: Exterminate. Annihilate. Destroy.

This is where Tarsus Pharmaceuticals come in, after running "Look at the Lids", a demodex awareness campaign which includes wriggling video footage of the mites responsible for a blepharitis subtype. The campaign is a lead up to prospective approval and launch of TP-03, a topical ophthalmic formulation of lotilaner for demodex blepharitis and meibomian gland dysfunction (MBG). The anti-parasitic lotilaner is also a base for TP-04 and TP-05, being tested as therapeutics for rosacea and Lyme disease.

While not dividing between types of demodex mite, the campaign points to cylindrical dandruff on eyelashes (collarettes) as pathognomonic signs and the mites as culpable via three main mechanisms: Their bacterial stowaways, chemical by-products, and mechanical damage due to scratches from their itsy-bitsy claws (plus palpal claws, because they're arachnids, subclass *Acari*).



Summary Diagram of eight topic areas in TFOS Lifestyle Report Introduction: A Lifestyle Epidemic - Ocular Surface Disease (2023). Are the life cycles and bacterial stowaways of *d. folliculorum* or *d. brevis* interacting factors?

Our Ectoparasite *Rex*: Demodex

Human occupation by demodex mites is prevalent and usually harmless, with suspicions of accord with cutaneous immunity and other surface processes (Patra *et al.* 2016). There are four phenotypes for two distinct species, although this may change as research continues. In general: *Demodex folliculorum* live in the hair follicles and Zeiss glands (Kosik-Bogacka *et al.* 2020), and are the ones most often linked to collarettes which are the suggested diagnostic and outcome observation for anterior blepharitis. *Demodex brevis* are smaller, chonky ones, around 0.15mm long, which is definitely not quantum. These are the oil hogs that cluster around sebaceous and meibomian glands, and along with *d. folliculorum* could eventually be linked to MBG-related dry eye and blepharitis (but posterior).

Veering away from the biomedical angle for a bit, the mites can be either commensal – part of the 'normal ocular flora' (Savla *et al.* 2020) – or pathogenic. Although there is an association of high mite numbers with certain disease states, the direction of causality is not certain (Litwin *et al.* 2017). Similar to configuring a beneficial vs. harmful protocol for IPL, the right amount of mite might be beneficial for skin, through their ingestion of epithelial cells and oil that IPL liquifies and unclogs from meibomian glands.

Mite Conquers Man

It is during the population explosion following a time of plenty, buttery skin and products to feed on, disease conditions and the like, where mites assume their varied roles in a pathobiome. Generally, pathogenesis depends on how the mites strike a balance with our immune system (Type 2) and other bacteria. For example, when their corpses pile up in great numbers and exacerbate host immunological response in the area (Chudzicka-Strugała *et al.*,

2023), bodies perhaps even serving as material for collarettes (Cheng *et al.* 2023). A distracted or strained immune system is also less capable of keeping mite numbers in check, permitting a breeding fest and flood to the area. Inflammatory chemicals, bacteria, and blockage of pores with rotting exoskeletons are risks following surgical procedures, are some of the ways that mite-y excess can affect management of ocular surface disease and recovery.

In this sense the feats of engineering, collarettes, are the outcome-measure for a search & destroy campaign as they are the easiest way to track magnitude of mite colonisation and stage of civilisation, rather than crudely counting numbers per sampled eyelash. Aside from the group of anti-parasitics targetting demodex, knowledge of 'immune checkpoints' like group 2 innate lymphoid cells (ILC2s), interleukin-13 (IL-13) could yield future therapeutic targets for maintainence of skin homeostasis despite disease conditions (Ricardo-Gonzalez *et al.* 2022).

In their commensal state, almost every adult human has *d. folliculorum* as pore-cleaners (In Pomeroy, 2022), *d. brevis* occupation of the face can be rare, and the mites seem to prefer men whereas DED affects more women. The gender differences in occupation are debatable, and may simply be due to favouring warm and oily habitats. Skin with rosacea, for example, is warmer, leading to an altered microenvironment that differentially influences demodex and associated bacteria (Chudzicka-Strugała *et al.*, 2023). There is a notable pattern of high *d. folliculorum* presence with wearers of glasses instead of contact lenses, perhaps this is due to a bit of a greenhouse effect? Causal directionality is – surprise, surprise – uncertain, and likely complicated.

The mites also tend to proliferate in conditions of immunocompromise, and were thought to be involved in protecting the skin from other types of pathogenic bacteria (Rather & Hassan, 2014). Essentially, we are host to several warring tribes in fragile allegiance with our homeostatic wellbeing. Perturbations affecting the biochemical borders of one species/system destabilise their power relations with another, and the result can be pathological (examples of *Staphylococcus* battles in Pitlik & Koren, 2017). In eye disease, the root of inflammation is a smuggling operation, as other micro-organisms and material borne by the mites reach vulnerable points. Overall: 'Demodex seem to promote colonization(sic) of the conjunctival sac with microbiota', including antibiotic-resistant ones (Kosik-Bogacka *et al.* 2020).

The Pageant has Passed. The Empire is Extinct (or Absorbed)

Luxurious lives on our skin and faces mean that *d. folliculorum* have lost previous survival-related genes, like those responsible for DNA repair after exposure to UV light – so they only come out at night (through use of our melatonin system) and are effectively slain by Intense Pulsed Light. Their genetic indolence could reach such an extreme in future that they become either extinct or 'endosymbionts', entirely dependent organisms that live *within* us for mutual benefit (Smith *et al.* 2022), which is what some believe happened for mitochondria.

Mitochondrial respiration, by the way, is what convert most of our 660g intake of daily oxygen into harmless water (Fritz & Peterson, 2013), and we have many more crucial bacteria in our digestive system that modulate state of mind, body, and inflammation. These are part of the expanding human microbiome approach in health research, meaning demodex are under greater scrutiny and pressure to prove either their worth or the falsity of mounting mechanism-of-action accusations. If they become unwilling and genetically incapable of movement beyond the pore, it would at least reduce the mechanical damage caused by surface foraging.

Demodex are so dedicated to their civilisational niche that their digestive systems have evolved to not include an anus. Expelling substances in this manner would trigger a large host immune response, and the price of this adaptation and others is their 'ease of dying', with a lifespan of just over two weeks (Litwin *et al.* 2017). Further, as

obligate symbionts, they cannot breed or live without us, so treaties with human skin immunity and rampaging dermotological interventions are existential.

Over our lifetime, humans are a territory inhabited by 1,262 generations (Smith *et al.* 2022) of a personal mite nation. According to parasitologists and acarologists, extra-familial horizontal transmission is rare even though there have been correlations of things like toiletry-sharing- and make-up with mite numbers. Genetic studies show that it is marital and vertical transmission that shape family-specific mite colonies, inherited maternally through mother-infant bonding, and they remain surpisingly loyal and resilient despite international migrations of their hosts (Smith *et al.*, 2022). Your demodex are therefore carriers of not just pathogens, but ancestral migratory data (Schulz, 2015).

Well, now you know. In the the spirit of loving your future symbiont self, be sure to blow a mirror-kiss at your microscopic lash scorpions before leaving for work tomorrow, especially if you're intending to blast them to bits later on. So much for millions of years as faithful face-companions.

But seriously: Keep your lids and skin clean, and the demodex and *staphyloccus* hordes in check.

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