An ophthalmic conspiracy theory

How would nature see our corneal triumphs?

Gerrit R.J. Melles & Jack S. Parker

Table of contents

Prologue

Chapter 1
- Our Earth is flattening
- The world upside down
- The flat eye perspective

Chapter 2
- Corneal hydration and the endothelium
- Corneal transplantation
- Dynamic corneal hydration
- Static corneal hydration
- Combined static and dynamic hydration
- Relation endothelium and imbibition pressure
- Intraocular pressure and POAG
- Steroid response
- Glaucoma as a remedy response
- Relationship intraocular and imbibition pressure
- Endothelium anchored mucopolysaccharide rods
- Imbibition pressure paradox in Fuchs dystrophy
- Guttae as a remedy response
- Corneal mucopolysaccharide organisation
- Fuchs dystrophy as mucopolysaccharide disorder
- Corneal glaucoma: Fuchs puzzle key to solving glaucoma etiology
- Future research directions
- The eye's anterior segment in different perspective

Acknowledgements
Prologue
Melles

The aim of the current essay was to provide more in depth reflection for the audiences of the Jackson Memorial Lecture at the American Academy meeting in Chicago and the Champalimaud ceremony in Lisbon. Over the years, the true challenge for us may have shifted from developing new ophthalmic surgical techniques to a closer review of how our scientific world operates and its effect on society. Our scientific truths may be tainted by creative interpretation of our clinical observations to our own logic. We may not be teaching what we see, but what we should see. Human arrogance that seems rather silly, since time after time we have been proven wrong: what is scientifically correct today, is ridiculed tomorrow and vice versa.

One question that I always enjoy asking our fellows is: if a skilled ophthalmologist like professor Ernst Fuchs 'missed' the endothelium in the early 1900s, what structure or mechanism do we fail to recognize in our era, for which we will be mocked in 100 years from now? What is staring us in the face, but goes by unnoticed? Perhaps it is time to figurally take a step back and intellectually do a step forward, since it may open the door to interesting opportunities and more effective treatments.

Moreover, the purely clinical perspective that I tried to take created a problem, since writing this essay with a routine scientific approach, embedding it in published literature, would undermine the objective of questioning these very scientific values. You cannot really present a different, more down-to-earth argumentation and back it up with citations heralding the opposite. So for that reason, this essay only seeks to paint an alternative line of thinking, an attempt to trigger further discussion for solving a most interesting ophthalmic puzzle.
Chapter 1
Melles

Our Earth is flattening

From the time I started my residency in ophthalmology, I felt as if you were trained for a different universe, since quite a lot of textbook materials did not seem to hold up in real life, did not agree with clinical observation, and many of the concepts on disease origin and treatment were concoctive at best, if not misleading and bordering on absurdity. Not a popular point of view, but it engendered a line of thinking that worked out very well for me throughout my scientific career. A strategic philosophy if you will, the chassis for most of our projects at the Netherlands Institute for Innovative Ocular Surgery (NIIOS), an organisation that I founded in the year 2000. NIIOS consists of a clinic, an eye bank, an educational branch and a R&D department, and over the years, our team developed various ophthalmic surgical techniques that found their way to peers across the globe.

My perception may be completely wrong, and it probably is according to 99.9% of readers, but it would be my hope that the remaining 0.1% benefit from such a deviating opinion, especially when they come to realize the enormous opportunities unwittingly created by our educational system, which may be erroneously based on human logic. In this essay, I would want to expand on a lecture that I gave in November 2019 (Appendix A) to further support the idea that, although it appears to be of value to us, human intellect more often than not works against us. Ironically, the more something makes sense to us, the more we are willing to defend or hold on to such a belief, so that common sense quickly fades into human arrogance.

Quite recently I blamed myself for doing just that. Possibly owing to a pandemic-induced revolte, one of our employees at NIIOS - in fact, one of our best and well-liked employees - was captured by a rainbow of conspiracy theories, culminating in the stance that the Earth is flat. Flat as a leaf or a pancake, you choose. Further discussion was pointless, and since others supported her point of view or took a fierce position against her, it forced me to face the music and dig a bit deeper, since heated verbal arguments were about to end up in mutual resentment, office fights or worse.

Although initially little impressed by her opinion and in reflex mode trying to mitigate the problem by presenting compelling evidence and some nuance, I came to realize that our rebellious co-worker might actually have touched upon such an interesting point, aligning so very well with the philosophy of our NIIOS organization, also further defining the core problem in our scientific world. So much so, that I decided to write a few thoughts down for further discussion. For the reader, this may be a good moment to ask yourself where you stand, and I would be eager to learn if you reconsidered your position by the time you reach the end of this chapter.
The world upside down

It would be my guess that the far majority of people in any audience would vehemently defend the idea that the Earth is round or elliptical, let's say a sphere of some sort. As a toddler you were already able to draw our planet, as well as the sun, the moon and some stars, all floating in space, and there has probably been little reason to revisit this widely accepted and fascinating image.

The problem is, however, that your 'real' impression of the world is based on a different, more mundane perspective, a very limited surface area of some square meters up to a square mile or so, your field of perception in daily life. Even when you are in a hilly area, you 'feel' that the ground is leveled, in fact, you are convinced that it is. The combined observations of your surroundings mount into a notion of experience: you act on what appears relevant, picturing your world into a 'realistic' flat-earth framework.

In other words, the fact that the Earth is a sphere, and that its architecture largely conditiones the entire ecosystem you live in, the unseen dimension that really determines whether you live or die, is basically ignored. You can make do with a simplified version of your surroundings. You can live a perfect life without any knowledge of the Earth being a sphere, in fact, your life would be largely similar when just spent in a flat-earth bubble. Conveniently, the human brain tends to reinforce your understanding of your surroundings by reasoning back any observations that do not fit the flat-earth model. Until a few centuries ago, generations of intellectuals must have seen the sun emerging from and disappearing into the ocean, offhand assuming that the Earth has an edge at the horizon, even though it did not explain why the ocean had not long been drained by a waterfall plunging over that edge.

Today, such an interpretation might sound absurd to the well educated reader, but the problem is that identical, flat-earth observations and its associated twisted rationals may form the very corner stone of our medical field, if not our entire scientific empire. Let's have a look at Ophthalmology, a specialty in which generations of eye doctors have made sincere and valid observations, which have been translated into diagnoses and acted upon by so-called evidence-based treatments, meticulously documented in brick-like textbooks. The expertise is well established and beyond dispute and mandatory for students at all levels. In reality, however, there has not been a single colleague who actually has had the opportunity to look beyond the boundaries of the eye, just like people could not obtain a perspective of Earth other than flat, for thousands of years. Instead of a square mile, we are routinely observing a square inch, from only one, 'flat-earth', perspective, and all further interpretations have been based on this confined field of view. Just as a mind game: what if the eye, that we clearly perceive as a globe, would actually be flat? You might reject the possibility immediately, because in your experience, if not expert opinion, this is complete nonsense. But why exactly? If you disregard the Earth being flat, because it was found to be a sphere from a different perspective, why would our ophthalmic knowledge than be correct if the entire profession was built on day-to-day 'flat-earth' observations?

In other words, to what extent are we facing a similar lack of perspective in ophthalmology that materialized into irrational assumptions? I would want to give some
clinical arguments in later chapters, but first, just for the fun of it, let's explore the idea that the eye may indeed be 'flat', at least in some conceptual form, like a harmonica that can be sized depending on the functionality in question.

**The flat eye perspective**

In Ophthalmology, we use a widely accepted array of categories for various subspecialties, like Cornea, Lens, Glaucoma, Retina, Neuroophthalmology, etc, based on the anatomical structures that can be distinguished within the spatial configuration of a sphere that we refer to as 'the eye'. I am not aware of a single valid argument for such categories other than overzealous administrative purposes. Nevertheless, from our one-inch, 'flat-earth' perspective, it seems to make perfect sense, so much so that eye doctors worldwide 'think' in these categories and act accordingly. Where few people know where to find the Earth's edges, all eye doctors seem to have no problem defining the boundaries of the eye and its internal structures. We even identify with these structures by presenting ourselves as a subspecialist. My business card reads 'corneal surgeon', even though the idea of a cornea as a separate entity with distinct boundaries is arbitrary and misleading.

Just as an example, corneal transplants do better in phakic (ie. in the presence of the eye's own crystalline lens) than in pseudophakic eyes, suggesting that the crystalline lens may have a role to play in maintaining corneal physiology. Similar interactions between tissues are seen throughout the eye, making it plausible that the eye's anatomical structures are closely intertwined, if not meaningless in isolation. Therefore, from a perspective of viability - the main reason for having a field of ophthalmic science to begin with - the eye may conceptually be 'flat', with all of its components 'merged' on all but an anatomical level, requiring subtle co-dependence to be 'alive'. Just like the recognition of individual countries is irrelevant to the spherical dimensions of the Earth, the categorization and selective attention to anatomical eye structures may distract and
divert from its actual configuration producing health and disease.

The visceral response to the above may be that categorization benefits disease understanding or arguments akin. However, to what extent does man-made simplification contribute to just the opposite? As an example, Glaucoma is a well recognized subspecialty, with 'primary open-angle glaucoma' (POAG, i.e. an elevated intraocular pressure not explained by other factors) as its most frequent and nebulous clinical manifestation. The vast majority of pathomechanisms presented in the published literature focus on mechanical-anatomical explanations, projecting everyday household problems - like 'a clogged sink' - onto the cause of an elevated intraocular pressure. Such hypotheses, presumably embraced for its educational simplicity, may hinder perceiving the body as a far more complex, living entity. More like a 'biochemical soup' with endless feedback loops, a fluid environment not so easily imaginable for us as humans, but that better reflects the overall functionality of an organism. If the anatomy is considered subervient to the eye's ecosystem required for life and the human body is primarily perceived as an amorphic complex with an almost infinite number of parameters continuously balanced within narrow margins (levels of glucose, hormones, neurotransmitters, etc.), an elevated intraocular pressure in POAG is more likely to result from a remedying response, a corrective action fencing off a larger threat to the eye's viability, than an isolated auto-destructive pathology. Our desire for ophthalmic categories should be questioned even further if the ocular pathology would originate from outside the truism referred to as the eye.

For those who wonder why a corneal specialist would feel the urge to enter Glaucoma territory: clinical observation apparently not fitting any narrative on glaucoma etiology might indicate that the cornea participates in regulating the intraocular pressure, as is further discussed in a later chapter. To mention it here may not only be an effective cliff-hanger, but also an attempt to mold the reader in a more receptive state of mind, away from the delineated 'spherical eye' concept, to potentially bring the number of skeptics down from 99.9% to, say, 99%.

The point is that our ophthalmic world is so thoroughly saturated with doctored hypotheses, debatable assumptions and mispresentations, that if representative for the whole system, 'science' may have transformed into its own antonym. If that is too strong of a verdict, it may be better defined as 'a collection of realities digestable for men'. Most philosophers took human intellect as a starting point, but what if, contrary to popular belief, our unique capacity to 'understand' the nature is just a big hoax? Just like politics often stand in the way of effective policies, our self-proclaimed rational way of thinking, especially when ratified after peer review, may not be the solution, but the very problem.

Research investigations performed may be accurate and the outcomes correct, but if the concept of disease, the framework of understanding, or the overall mindset is off, any interpretation or conclusion drawn is bound to miss its mark. For that reason, I tried to use clinical observation as the only starting point, not our current teachings or household human logic.
Chapter 2
Melles & Parker

Corneal hydration and the endothelium

In the past decades, NIIOS developed several techniques to replace the corneal endothelium, the most inner layer of the cornea, believed to regulate corneal hydration and therefore corneal transparency. The most refined technique may be Descemet membrane endothelial keratoplasty (DMEK), in which the endothelium and its basal membrane, Descemet membrane, are selectively replaced by donor tissue (Figure 1).

The described function of the endothelial cells may be summarized by maintaining corneal dehydration through their active cell pump, to counter corneal hydration through passive leakage of aqueous humor (the liquid in the anterior chamber of the eye) carrying nutrients into the cornea. Furthermore, the presence of zonulae occludentes ('tight junctions') in between the cells would make the endothelial cell layer impermeable to fluid.

Maintaining corneal physiology and nutrition through the mechanism described above would therefore consist of a localized fluid circulation over the endothelial cell layer (Figure 2). Although widely adopted, the concept might be a bit shaky on closer inspection. First, passive leakage from the anterior chamber towards the cornea in the presence of tight junctions sounds like a theory torn between two ideas: there is either passive leakage over the endothelium or the endothelium has an impermeable fluid barrier, but you cannot have it both ways. Second and of more importance would be the apparent inefficiency of such a circulatory pumping mechanism. Any combination of active and

Figure 1. Slit-lamp images of an eye after (top) deep lamellar endothelial keratoplasty (DLEK), and of an eye after Descemet membrane endothelial keratoplasty (bottom). Image NIIOS.
passive in- and outflux by the same cell (area) might not explain distribution of nutrients over the full corneal thickness. For that to happen, some sort of flow towards the anterior cornea would be required. So a circular flow mechanism over a single cell layer might be a questionable concept, both from a functional and anatomical point of view.¹

Hence, putting the ophthalmic literature aside, clinical observation may suggest that the endothelium plays a more secondary role in corneal physiology, particularly where it comes to hydration and nutrition. Such a consideration may not only allow for a different approach toward corneal disorders, but also touch upon the potential role of the cornea in other diseases, for example glaucoma. Let’s go over some routine clinical observations and the secrets they may reveal to us.

**Corneal transplantation**

In the past century, full-thickness corneal transplants have proven effective in the treatment of corneal endothelial disease. From DLEK, DSEK/DSAEK and DMEK we learned that it is indeed the donor endothelium that can reverse overhydration of a host cornea. For example, in bullous keratopathy (ie. an absolute fall of the number of endothelial cells below a threshold for maintaining corneal transparency), DMEK may

---

¹ For purpose of clarity in the text below, the widely adopted consensus on a passive corneal inflow combined with an outflow through an active endothelial cell pump is referred to as a 'circular endothelial flow mechanism', to distinguish it from a 'uni-directional endothelial cell pump' that would only establish outflow from the cornea into the aqueous.
bring a swollen cornea back from 800-1000 µm to a physiological pachymetry of 550 µm. This would seem to support the widely accepted idea that the endothelium has the primary, if not solitary role in the status of corneal hydration. The problem is that an array of clinical observations seems to tell us otherwise.

If bullous keratopathy is compared to Fuchs endothelial dystrophy (characterized by the formation of collagen warts onto Descemet membrane, the so-called 'Hassall Henle bodies' or 'guttae' and a disappearance of the endothelial cell layer), the hydralional and overall morphologic appearance of the overlying corneal stroma is remarkably different. Although both entities are categorized as 'corneal endothelial disorders', severe bullous keratoplasty is usually accompanied by extensive stromal swelling and diffuse opacification, whereas only a limited increase in pachymetry to 600-650 µm may be found in advanced Fuchs endothelial dystrophy (Figures 3 and 4). Descemet folds, presumably induced by overhydration of the posterior corneal stroma, reducing the posterior corneal chord length, are almost invariably present in bullous keratopathy.

2 For purpose of brevity, 'Fuchs endothelial dystrophy' is referred to below as 'Fuchs dystrophy' or 'a Fuchs cornea'.

3 The increase in pachymetry may in part even be attributed to a multilayered Descemet membrane, often found in Fuchs dystrophy pathology specimens.

Figure 3. Slit-lamp, pachymetry, Scheimpflug and specular microscopy images of an eye with bullous keratopathy. Note that although the cornea is edematous, endothelial cells are still present. The vague image of the endothelial cell layer with specular microscopy may be attributed to the corneal edema. Images NIIOS.
whereas eyes with Fuchs endothelial dystrophy may show a near normal posterior stromal architecture, even in the absence of any indentifiable endothelium on specular microscopy. Similarly, epithelial edema is almost invariably present in bullous keratopathy, but relatively rare or confined in Fuchs endothelial dystrophy, even in cases eligible for DMEK surgery.

In numerous cases operated on for Fuchs dystrophy, we had the impression that DMEK provided visual recovery through removal of the visually disturbing guttae, rather than through restored corneal transparency.4

However, since both disease entities suffer from a severely compromised endothelial cell layer; the difference in response between bullous keratopathy and Fuchs dystrophy is not so easily explained with the endothelium as the primary motor in regulating corneal hydration. Hence, it would seem a fair statement that if the absence of functional endothelium does not correlate with the degree of corneal overhydration, a

---

4 Published slit-lamp photographs, admittedly in NIIOS’ own publications as well, may be a bit misleading, since they often do not reflect the ‘average Fuchs cornea’, because images clearly showing a diseased recipient cornea are selected, to get sufficient contrast between pre- and postoperative disease presentation.

Figure 4. Slit-lamp, pachymetry, Scheimpflug and specular microscopy images of an eye with Fuchs endothelial dystrophy. Note that the cornea shows only mild edema, in the presence of large guttae and a virtually absent endothelial cell layer. The image of the endothelium is quite clear. Images NIIOS.
'circular endothelium flow mechanism' - or possibly even a 'uni-directional endothelial cell pump' - may be an unlikely candidate in solely regulating corneal hydration.

**Dynamic corneal hydration**

But if not the endothelium, what other factors or anatomical structures could play a role then in regulating corneal hydration? Its importance is again of two minds. For its functionality, the cornea should be transparent, which is achieved through 'constructive interference': light rays within the spectrum of visible light 'bouncing' over the cornea from anterior to posterior, enabled by precisely distanced collagen fibers within the corneal stroma. The interfibrillar distance would be maintained by mucopolysaccharides, hydrophilic strings of sugar-like molecules, that aim to provide 'static' hydration to space the collagen fibers within the corneal stroma. At the same time, however, 'dynamic' hydration allowing a nutrient flow, would be required to maintain corneal health.

Such a distinction between the need for both static and dynamic hydration may at first glance seem trivial, since the 'circular endothelial flow mechanism' is believed to cover both requirements by creating a negative imbibition pressure (Figure 2). This suction force would result from active cellular transport, pumping liquid out, turning the cornea stroma into sponge-like tissue, passively drawing in nutrients from the anterior chamber of the eye. This theory would entail that the endothelium is crucial in maintaining corneal physiology. As a rule of thumb, all tissues in the human body require continuous perfusion for survival (with debatable exception of hair, nails and tooth enamel, etc.), so without nutrients, the cornea should deteriorate quickly, since it can not sustain itself. From clinical observation, however, we know that bullous keratopathy, even with the endothelium replaced by a fibrotic retrocorneal membrane, can continue to exist for decades if not an entire lifetime, without any sign of necrosis, breakdown or 'melt'. Hence, if the cornea survives in the absence of endothelium, this should indicate that the imbibition pressure does not play a key role in the flow of nutrients (or at least that there is a back-up mechanism for dynamic corneal hydration in case of endothelial failure).

**Static corneal hydration**

The role of the endothelium in static hydration would also seem more challenging than described. Pachymetry is relatively stable in a healthy cornea at about 550 µm, but if endothelial cell density falls below a threshold of 300-500 cells/mm², stromal swelling through overhydration is seen, known as 'corneal decompensation'. This would mean that, if the endothelium irrespective of its cell density is responsible for static corneal hydration, there must be some form of feedback system, monitoring and titrating the 'uni-directional endothelial cell pump' activity for maintaining an exact interfibrillar distance allowing the passage of visible light.

In other words, for corneal transparency to be present at a sensory level, there

---

5 For purpose of clarity in the text below, we are introducing the terms 'static' and 'dynamic' hydration, to distinguish between stromal hydration for the purpose of 1) corneal clarity by establishing the exact right volume of mucopolysaccharides that are spacing the collagen fibers at half the distance of light in the visible spectrum, and 2) corneal health, through securing a permanent nutrient flow across the diameter as well as over the thickness of the cornea.
must be feedback to control the interfibrillar distance between collagen fibers at a nano-level. It may be important to note that the margin of error is rather unforgiving, since the cornea quickly turns opaque to wavelengths outside the visible light spectrum, illustrated for example by milky white corneas on infrared images. If so, a feed-back loop would make a 'uni-directional endothelial cell pump' as a stand-alone entity rather unlikely: not only should the entire endothelial cell layer function as one unit, but the engine throttle would have to respond relatively quickly to continuously changing circumstances potentially affecting corneal hydration. Swimming, Valsalva manoeuvres, eye rubbing, etc., none of these actions result in detectable loss of vision through a temporary change or imbalance in corneal hydration and therefore opacification. How can that be explained?

As mentioned, the corneal stroma consists mainly of collagen fibers spaced at half the wavelength of visible light through interposition of mucopolysaccharides. The collagen fibers run in one direction from limbus to limbus within a lamella, and about 200-250 lamellae, stacked at 'random' in parallel fashion, would provide tensile strength in all directions, over $360^\circ$. There is a vast body of literature on the biochemical details and interaction of these molecules, but to the best of our knowledge, some clinical 'telling sign' features of this biochemical complex have rarely, if ever, been described.

First, although collagen and mucopolysaccharide molecules should not differ chemically between individuals, the corneal stroma of each person nevertheless has fingerprint-like characteristics. After conventional penetrating keratoplasty, such individual textures used to stand out beautifully, with donor and host stroma positioned adjacent to each other, allowing for direct comparison. Even decades after surgery, any type of transplant can be clearly distinguished from recipient tissue, indicating that the stromal construct has a highly individual component to it, that perseveres over time. This in itself is most interesting, because the corneal stroma is believed to be continuously renewed, and near complete regeneration may be seen after tissue disruption by corneal decompensation or scarring, but the framework carrying individual properties apparently is not subjected to remodeling or change.

Second, the corneal stroma seems to display the overall condition of the eye, as a rough indicator of its state of health, a bit similar to how the skin reflects somebody's

Figure 5. Anterior segment OCT image of a corneal hydrops (yellow arrow) nine years after Bowman layer transplantation for advanced keratoconus. Note that the hydrops is confined to the area posterior to the Bowman layer graft (white arrows), with substantial stromal edema and large horizontal 'stroma lakes'. Descemet membrane is intact and does not show the typical retracted edges in the presence of a break in the membrane; the apparent defect is an artifact resulting from limited image resolution. Image NIIOS.
viability. Such subtle abnormalities may be numerous but challenging, if not impossible to describe, and certainly form no straight path to a diagnosis, but mandate more scrutiny during examination. Every ophthalmologist is familiar with the gut-feeling of an elevated intraocular pressure in an eye on biomicroscopy examination, which might result from recognition of just a slightly abnormal texture of the corneal stroma, if not the entire anterior segment of the eye. Third, towards the other end of the texture spectrum, the stroma may act as an indicator of specific disease or point in a certain direction. For example, subclinical inflammation preceding allograft rejection, various types of scarring and depositions, a yellow-greenish hue in eyes with glaucoma, etc. Moreover, during surgery, the stromal rigidity or cohesion has a specific ‘feel’ in eyes with specific disorders, like bullous keratopathy, Fuchs endothelial dystrophy, keratoconus, corneal dystrophies, etc., allowing the surgeon to anticipate on specific manoeuvres by preoperative recognition of subtle changes in stromal texture typical for each of these conditions.

Fourth, the corneal stroma may give some indication of an alternative 'flow' pattern across the cornea. As discussed above, it may seem inexplicable that the cornea would solely depend on the endothelium for its nutritional status, since tissue survival is never compromised in the absence of endothelium. Sheen-like reflections in between the lamellae may point towards the presence of a thin tissue layer or film hydrated differently than the adjacent stromal tissue. Such potential 'irrigation films' seem to become more distinct in borderline decompensated corneas and would explain the formation of massive 'stromal lakes' in between the lamellae in corneal hydrops, a pathognomonic feature of keratoconus (Figure 5).

**Combined static and dynamic hydration**

A horizontal nutrition pathway across the cornea, that is, through a flow running parallel with the lamellae and collagen fibers, should also - compared to a 'circular endothelial flow mechanism' - form a more efficient and better fitting perfusion system for several reasons (Figure 2). First, it would allow for all anterior to posterior corneal layers to be perfused homogeneously. Second, instead of an indirect route through the anterior chamber, nutrients and other relevant factors would orginate directly from the limbal vasculature, the main regenerative area of the cornea. Third, dynamic hydration through a horizontal flow in between the corneal lamellae might be expected to show less interference with the static hydration required for collagen spacing within those lamellae. Fourth, a horizontal flow might also explain how a break in Descemet membrane could be secondary to stromal fluid accumulation in corneal hydrops, instead of its assumed primary cause.

To briefly address the latter issue: years after intrastromal Bowman layer transplantation for advanced keratoconus, a posterior hydrops was seen in some cases, in the presence of an intact Descemet membrane. Based on this finding, the current hypothesis on the pathogenesis of corneal hydrops may be questioned for two reasons. First, if it truly is the causal factor, a hydrops simply can not occur without a break in Descemet membrane. Second, the hydrops developed in the presence of a donor Bowman layer stromal inlay, fixing the anterior corneal curvature, ie. in the presence of a
stable corneal topography. In other words, the hydrops could not have resulted from progressive corneal protrusion associated with overextension of Descemet membrane. This challenges the current idea that progressive ectasia leads to hydrops development, i.e. a different source of fluid influx causing overhydration should be considered to explain the clinical picture (Figure 5).

So let’s expand on the potential existence of interlamellar irrigation films, which may present as reflective sheens at the slit-lamp. Over the years, we were never able to find evidence of such structures in pathology specimens. However, it would stand to reason that, if present, such hydrophilic sheets would not survive the ‘hydrophobic’ tissue embedding process. Clinically, however, there may be further indication to support the possibility of a system enabling a horizontal nutritional flow within the cornea. Just as an example: during my residency, a patient presented with bilateral, thin and sharply demarcated, ring-like opacities, about 7 mm in diameter, in the absence of any ocular or systemic disease, while foregoing corneal surgery was denied (Figure 6). Such opacifications, presumably depositions of some sort, might have resulted from an ‘electrophoresis-like process’ from the limbus to the corneal center; any explanation involving a vertical flow would be most challenging. As another example, various depositions may tend to accumulate in between the stromal lamellae, and therefore be

positioned perfectly parallel to the lamellae, for example in macular corneal dystrophy.

Although some deposition patterns of material 'foreign' to the cornea might seem to support a horizontal flow concept, it should be noted that there are multiple disorders showing diffuse deposition, apparently ignoring the lamellar corneal architecture. Molecular weight, tissue affinity and whether the deposition originates from outside the cornea or not, may play a role in their clinical manifestation. But as a general rule, most depositions show a relatively equal distribution throughout the cornea. This in itself may lead away from an endothelial pump (and/or passive leakage) as the main engine in corneal hydration, not only because the posterior stromal layers would be expected to be primarily affected in various dystrophies and pathological depositions, but also because there is no proof of any future deposition first being released into the anterior chamber, before entering the cornea. Hence, a more direct route from and close relationship to the limbal vascular arcade as the origin of nutrients and depositions would seem far more plausible.

The bottom line is that clinical observation would suggest different hydration pathways for static hydration and dynamic perfusion: a dynamic horizontal interlamellar flow - possibly just through capillary pressure - providing corneal nutrition originating from the limbal vascular arcade, and a static form of mucopolysaccharide hydration meticulously regulating the interfibrillar distance within the lamellae, providing corneal transparency (Figure 2). As mentioned above, corneal transparency for the entire visible light spectrum is preserved even under the most extreme of circumstances, suggesting an extremely reliable and efficient method for maintaining exact interfibrillar distance.

Relation endothelium and imbibition pressure

The ophthalmic literature describes that the endothelium dehydrates the cornea, squeezing the mucopolysaccharides to the volume required for fibrillar spacing, which results into a negative imbibition pressure, a passive suction force which in turn draws in aqueous humor from the anterior chamber. It may be argued that the exact interfibrillar distance is reached by just squeezing the mucopolysaccharides to their minimal hydrophilic volume, like a one-size fits all sponge-like cushion in between the collagen fibers. In the end, however, this argument may only shift the attention from the imbibition pressure to the exact amount of mucopolysaccharides to be deposited, to obtain corneal transparency. Even badly scarred corneas show restoration of corneal clarity over time, presumably through continuous remodeling of the corneal tissue. In healthy eyes it would already be puzzling how any unchecked system can keep the mucopolysaccharide density and associated imbibition pressure at a level that secures corneal transparency. It may prove inexplicable for eyes with corneal disorders, for example in advanced Fuchs dystrophy, only showing a slightly increased pachymetry, while no functional endothelium can be detected. According to the textbooks, such corneas should be subjected to uncontrolled passive leakage, which is clearly incompatible with the clinical image.

The above may raise two main questions:

1. What role does the endothelium have in corneal hydration and/or in the reversal of corneal decompensation after keratoplasty, and
II. How is the imbibition pressure controlled; if some sort of feedback mechanism is mandatory to retain corneal clarity, how would such a system work?

Expanding on the latter point: in the human body, there are numerous endocrinic, neurologic and other processes disciplined by sensory feedback. If so, the optical quality of the cornea could direct the level of imbibition pressure required, as a long term calibration of the system. However, visual feedback would not explain the fact that corneal transparency is maintained during sleep, that is, in a healthy eye, the cornea is clear upon awakening. Alternatively, the cornea may (also) contain a pressure gauge for the imbibition pressure or another measure that would somehow monitor the interfibrillar distance. Since various body fluids (eg. blood, liquor, synovia, the cochlear and vestibular fluids, and of course aqueous humor) are pressurized within specific margins, the question could therefore also be reversed: why would there not be an imbibition pressure gauge if uninterrupted corneal transparency is obviously so important? Even more so when you come to realize the cornea is one of six ‘adjacent’ pressure systems: 1) the ‘outside’ atmospheric pressure, 2) the corneal imbibition pressure, 3) the intraocular pressure, 4) the subretinal suction pressure created by the retinal pigment epithelium, 5) the intraocular arterial and venous pressures, and 6) the orbital pressure.

Furthermore, if we disregard the concept of a ‘circular endothelial flow mechanism’, it leaves us with a uni-directional endothelial cell pump at the interface of the cornea and the aqueous humor. If so, this would imply that the cornea is not a consumer of aqueous, but a potentially significant source for its production. This consideration may be supported by clinical observation of a flow from the cornea towards the anterior chamber of the eye, but not vice versa. For example, fluorescein applied on the ocular surface quickly finds its way into the anterior chamber (once it passed the epithelial barrier), but trypan blue injected into the anterior chamber during surgery never enters the cornea. Differences in molecular size may explain this, but then again, a healthy cornea also stays crystal clear when exposed to even the smallest molecules, for example during pressurization of the anterior chamber with balanced salt solution in phacoemulsification surgery, or in vitreoretinal surgeries with a longer surgical time.

If the cornea would 1) maintain its transparency through some sort of a pressure gauge and/or optical feedback loop, and 2) potentially be a fountainhead contributing to the volume and composition of the aqueous, it may be of interest to consider the potential relationship with glaucoma, i.e. POAG, in essence overpressurized aqueous. In fact, at this point, it seems almost mandatory to better consider the interaction between the cornea and the intraocular pressure in more detail.

**Intraocular pressure and POAG**

Instead of using the ophthalmic literature on glaucoma as a starting point, let us ask ourselves the following question: if you were the first ophthalmologist to walk the Earth, making the first observations in the field, which clinical surprises would stand out managing the intraocular pressure and POAG development?

The first and foremost revelation is probably that in the far majority of eyes, the intraocular pressure is carefully maintained between 8 and 21 mmHg. The eye is seemingly
well aware of the fact that higher intraocular pressures may cause neurologic or vascular damage, but that it needs to balance this risk with allowing sufficient pressure to steady the ocular anatomy, to support the eye’s visual functions. Then, unexpectedly the intraocular pressure - every ophthalmic resident is drilled to know this - may suddenly go up around the time presbyopia sets in, around 40-45 years of age. These may be the two most striking clinical observations in relation to POAG, the 'hard' evidence, if you will.

The question then is how the ophthalmic literature came to agree on a pathomechanism for POAG that may be summarized as 'an increased resistance to aqueous outflow', the 'clogged sink' metaphor in layman's terms. Although ingrained in our ophthalmic practice, little evidence exists to support this idea. In fact, the theory intuitively feels flawed: if the intraocular pressure is kept within specific margins, there should exist some sort of regulatory feedback mechanism to surveil the pressure. If an outflow obstruction would develop, the system would just dial back aqueous production, to lower the intraocular pressure back into the safe zone. In other words, the current consensus would suggest random, autonomous aqueous production effectively without feedback or control, which does not align with a tightly controlled intraocular pressure, under ever changing circumstances, for decades, usually during life in its entirety.

Perhaps the consensus resulted from the fallacy that secondary glaucoma is often associated with anterior chamber angle abnormalities and that treatments facilitating aqueous outflow (topical medication, trabeculoplasty, trabeculectomy, drainage devices) should be indicative for the cause of the disease. Similarly, anatomical changes in the trabecular meshwork and Schlemm's canal that would 'prove' obstructed outflow, may very well be secondary, mimicking hypertrophic tissue or subclinical inflammatory reactions to focal 'overpressure' found elsewhere in the human body. Only when there is a factor or combination of factors, for example a lowering pH by accumulation of metabolic waste products in the anterior chamber, that mandate an increased wash out, a relative outflow obstruction may exist. In that case, aqueous overproduction to restore a biochemical balance should be perceived as a remedy response, not as primary pathology. Such an argument would further support the presence of a (biochemical) feedback system. However, the lack of intraocular damage associated with long term use of topical glaucoma medication that decreases aqueous production would seem to plead against this idea.

Steroid response

Another intriguing observation might be that quite a few eyes show a 'steroid-response', an intraocular pressure increase following the use of topical steroids. Although the pathway toward increased intraocular pressure could be different than in POAG, it may still reveal two important points. First, it would lead away from anatomical changes in

---

6 Although possibly of interest in relation to the cornea, low tension glaucoma may be outside the scope of this essay.
7 Potential causes of POAG may be distinguished from alleged risk factors (like age, race, diabetes, hypertension, myopia, thin cornea, etc.), which are not discussed here for the purpose of readability.
8 It may be argued that some sort of intoxication (or starvation) of the eye's entire inner environment (and not the intraocular pressure per se) is the cause of optic nerve damage in POAG. This entails a discussion that seems to be outside the scope of this essay.
the anterior chamber angle causing outflow resistance, because the condition is completely reversible after steroid application is discontinued. Second and of even greater interest: in the absence of anatomical outflow obstruction, it indicates that the intraocular pressure control mechanism can temporarily be changed, overruled or possibly re-calibrated by a steroid molecule.

Here, the obvious counter argument is that there are numerous topical agents available to lower the intraocular pressure. These agents are effective through decreased aqueous production or increased aqueous outflow and classified in seven groups: beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors; and miotic or cholinergic agents, prostaglandins, rho-kinase inhibitors, and nitric oxides, respectively). As such, these agents align with the current consensus on the clogged sink analogy, ie. symptomatic treatment for lowering the intraocular pressure through widening the sink (more outflow) or closing the tap a bit (less inflow). Clinically, these medications prove effective in managing glaucoma on a daily basis, but when discontinued, the intraocular pressure usually goes back up, which would confirm their symptomatic treatment effect. The agents do not procure a re-set of the intraocular pressure to a normal, physiological level. If steroids can produce a recalibration of the intraocular pressure level and if the ‘increased resistance to aqueous outflow’ hypothesis is flawed by the fact that the intraocular pressure is calibrated to stay within specific margins, its regulatory mechanism may deserve more recognition, since it opens the door to a discussion why the intraocular pressure may be elevated to begin with.

Glaucoma as a remedy response

As mentioned, the human body manages an almost infinite number of mechanical and biochemical parameters that are carefully balanced within specific margins, essentially for self-preservation and survival. A celebrated example: your muscles could potentially break your bones but for neurologic inhibition, which may be downregulated in acute danger, allowing you to suddenly run faster than lightning. When you are facing a lion, the risk of musculoskeletal damage is overruled, since taking your chances running is always better than to serve as dinner. Although destabilization may stem from pathology, a feedback loop is usually purposely overruled for the greater good. If so, it may be worth considering the possibility that the apparent re-set of the intraocular pressure in POAG might reflect a defense of the eye to a significant ‘threat’, some type of distress that just has to be corrected. A corrective or healing response to a condition that outweighs the potential damage to ocular structures, demanding a system that is perfectly tuned, that knows how to balance enough pressure to keep the eye anatomically formed, with not too much pressure to cause damage to its delicate tissues, to be re-calibrated. The question would then be: what can be so important to the eye that it justifies upregulation of the intraocular pressure? Or could the eye just be collateral damage: what if glaucoma results from a signal outside the eye indirectly overruling the ocular feedback mechanism?

The latter may sound unlikely, but the fact that POAG sets in around the menopause, which is evidently accompanied by significant hormonal changes, while the hormones involved (estrogen, testosterone, prostaglandins) belong to the biochemical

---

9 For purpose of readability, the term 'menopause' is used for mid-life, systemic hormone changes, independent of gender.
group of steroids, and as mentioned, steroids are in turn notorious for increasing the intraocular pressure. With such a level of synchronism, it is almost hard to argue against the possibility that glaucoma could primarily be a systemic disease?

Hormone therapy in menopause has been reported not to affect the intraocular pressure, which would lead away from a response of the intraocular pressure to systemic change in hormone levels. But what effect might the menopause have on the eye and its internal structures, for the intraocular pressure to show a secondary response? The elephant in the room might be the crystalline lens, because of its functional loss of accommodation, supposedly caused by an overall stiffening of the lenticular mass. Is there any clinical evidence that such a change in the crystalline lens is related to hormonal changes? Tissue elasticity decreases with age, but there may also be an intriguing observation closer to home. During pregnancy, the cornea may show a reversible keratoconic contour change, an ectasia attributed to a systemic increase in connective tissue elasticity required for the passage of the child through the birth canal. Apparently, the so-called 'sex-hormones' have a strong potential to affect the corneal stroma, and since the crystalline lens and the cornea share an intimate embryonic development and therefore potential wound healing response, some hormonal effect on the crystalline lens may not be too outlandish, both during pregnancy and in the menopause.

And there may be yet another hormone link: also belonging to the group of steroids is 'growth hormone', known to be involved in the process of emmetropization after birth. It would stand to reason that growth hormone also uses the intraocular pressure to target the exact axial length of the eye, a process that derails into buphthalmos when congenital glaucoma is present. If involved in emmetropisation, the intraocular pressure should be directly or indirectly subjected to a sensory feedback system. The visual input should then evidently be based on the refractive error of the eye with the crystalline lens in its relaxed state, i.e. only with rest-accommodation. If so, it could explain why the intraocular pressure later in life responds to presbyopia, that is, when accommodation starts to fail and visual input again triggers 'the intraocular pressure feedback system' for emmetropisation. This might also explain why eyes with a refractive error are more prone to developing POAG. Similarly, it may explain POAG development in eyes that become 'hypermetropic' late after radial keratotomy, or a pressure spike after phacoemulsification due to a change of the eye's refractive error. All in all, given its various potential associations, the importance of steroid hormone pathways in the development of glaucoma may be underestimated.

**Relationship intraocular and imbibition pressure**

Apart from potential biochemical or sensory feedback to maintain the intraocular pressure within range, there should also be a pressure gauge generating a mechanical signal similar to that of other pressure systems in the human body. When you come to think about it, the cornea itself might be exceptionally well situated for the task, especially when the 'circular endothelial flow mechanism' is dismissed. With its endothelial tight junctions blocking aqueous inflow as well as a virtually defined chord length at its anterior surface, the cornea should act as a compressible cushion, 'breathing' with the intraocular
pressure. As mentioned, the corneal stroma can clinically be seen to shift towards a greenish hue when the intraocular pressure is too high, a signal that would seem perfectly designed as sensory input for a feedback mechanism.

The same may hold true for the crystalline lens: it might be perfectly suited to function as a mechanical pressure gauge, since the brain could potentially 'read' the intraocular pressure by the compression induced change in refractive power of the lenticular tissue or the induced amount of accommodative correction. The intraocular pressure may be re-calibrated to a higher level when the lens develops age-related stiffening, since a higher pressure would be required for the same amount of deformation, ie. the same effect on the pressure gauge. Such a clinical relationship may not exist for the cornea though. The intraocular pressure does not seem to respond to corneal tissue changes or to vary with corneal transparency, like diffuse scarring or even a leukoma.

Furthermore, could the assumption that corneal thinning in glaucoma - a cornea that is 'too clear' - is caused by mechanical compression of the stroma be too nonchalant? It may fail to explain the opposite situation, ie. the development of corneal edema when the intraocular pressure is too low. The latter might in itself be yet another clinical observation that defies the current consensus on a 'circular endothelial flow mechanism', because passive leakage would likely be diminished when there is no intraocular pressure, resulting in better cornea clarity. Low intraocular pressure edema would, however, fit a hypothesis on 'horizontal' corneal hydration via the limbus. For example after glaucoma filter surgery: with unbalanced iatrogenic outflow, the eye will be gunning for aqueous production in overdrive, and if the cornea is a nett contributor of aqueous, an uptick in corneal hydration, perceived as edema, may result from an increased flow through the cornea.

In other words, the corneal imbibition pressure and the intraocular pressure appear to act in concert. As if they can both be upregulated or downregulated to

Figure 7. Anterior segment OCT image of a cornea one week after DMEK. Note that the 'vertical cylindrical' area in the corneal center has cleared (arbitrarily outlined by the dashed lines), while the paracentral to peripheral areas are still edematous, presumably due to a partial graft detachment (arrows) or the relative short postoperative time interval. This case may illustrate that a clear cornea with normal pachymetry values (normal imbibition pressure) can be present directly adjacent to areas with various degrees of edema (imbition pressure low or zero). Image NIIOS.
complement each other, to tune aqueous production by the ciliary body and the cornea. Such an alignment would probably be difficult to accomplish without a shared regulatory pathway for both pressure systems.\textsuperscript{10} Interestingly, the corpus ciliare, Schlemm’s canal and the limbus are anatomically all in close vicinity. If corneal hydration would primarily occur through a flow originating from the limbus, some sort of a pressure sensitive feedback system or structure, that we may tentatively call a ‘limbal-ciliary nodus’, would likely be localized in the ocular tissue ring stretching from the limbus to the ciliary body. It would stand to reason that such a shared feedback mechanism for the intraocular and imbibition pressures would be effective through a sensory, biochemical or mechanical signal, or a combination thereof.

**Endothelium anchored mucopolysaccharide rods**

How is this relevant to the endothelium and can we deduct the answer to the question above: *what role does the endothelium have in corneal hydration and/or in the reversal of corneal decompensation after keratoplasty?* If the cornea is a nett contributor of aqueous presumably through the ‘active endothelial cellular pump’ and given its anatomical location, the endothelium is at the very frontier, effectively at the interface between two pressure systems: that for imbibition pressure and that for intraocular pressure. Both these systems would seem to benefit from the endothelium: nett production of aqueous in a posterior direction, while transplantation of an isolated donor Descemet membrane carrying donor endothelium in DMEK confirmed that the endothelium also has a role in regulating the corneal imbibition pressure in an anterior direction. From eyes with Fuchs dystrophy, however, we learned that the imbibition pressure may still be maintained at a near normal level in the absence of a discernible endothelial cell layer. These findings would seem impossible to wed, so how then does the imbibition pressure relate to the presence of endothelial cells?

A potential clue may be found in eyes with an unquestioned, partial endothelial absence. Say that 1/3 of the endothelial surface area is ‘missing’ due to inadvertent Descemet membrane detachment after phacoemulsification or a partial DMEK graft detachment, two similar, unambiguous clinical images. Through such an opening of Titanic proportions, the entire cornea should quickly go opaque due to, in complete absence of the endothelial tight junctions, massive influx of aqueous into the stroma. Surprisingly, however, the edema is always confined to the area overlying the defective Descemet membrane. The inverse situation may even be more puzzling: within the first week after DMEK, it is not uncommon for patients to reach a near normal visual acuity with just a tiny area cleared up in the very corneal center. These mirroring conditions would seem birds of a feather: the cornea can exhibit near normal transparency while a large portion of that same cornea is opaque due to decompensation. Apparently, the cornea is equipped

\textsuperscript{10} A systematic flaw in intraocular pressure measurement might stem from its dependency on the condition of the cornea, since objective methods are routinely based on corneal deformation assessment, like applanation tonometry and air-puff tonometry. It is commonly assumed that a high intraocular pressure measured on a decompensated cornea can be attributed to increased corneal rigidity, and a low intraocular pressure measured on a keratoconic cornea to a floppy cornea. Such teachings may not really be supported by physics, since overhydration should not contribute to strctural tissue rigidity and it could also be argued that more applanation is actually required in ectasia with steeper keratometric readings. If so, readings on edematous or floppy corneas could reflect true values or misreadings outside the margin of calibration.
with a sagittal organisation, a fence mechanism from anterior to posterior, a form of compartmentalization that serves as a functional or structural barrier to liquid from traveling horizontally across the cornea. To the best of our knowledge, no anatomical structure capable of isolating the stroma overlying a random area of dysfunctional endothelium, has been identified in pathology specimens or otherwise. Hence, the opposite may be true: the cornea can only reach static hydration in a specific manner and as argued above, and the endothelium plays a key role in this process. So what pattern is seen in reaching corneal transparency, ie. how does the imbibition pressure build up?

The clinical image in early post DMEK eyes may consistently show corneal thinning and transparency to extend homogeneously over the corneal thickness, usually with a ‘vertical cylindrical shape’ (Figure 7). In other words, the imbibition pressure is first restored over the full cornea, that is, not parallel to the corneal surfaces as is to be expected with any form of passive leakage, but in a direction perpendicular to the corneal surfaces. Since the (donor) endothelium is clearly involved in restoring corneal transparency, this should imply the presence of a mechanism for static hydration running from the posterior to anterior cornea. Such hydration channels would need to have such a delicate distribution that it allows for a precise representation of the condition of the underlying endothelial cells, both in area size and central to peripheral location. Since mucopolysaccharides were found to be responsible for the imbibition pressure, it would stand to reason that the clinical image is indicative for the distribution of

![Diagrammatic representation of the ‘vertical’, anterior to posterior mucopolysaccharide rod organization, that might explain the clinical observation of clear and edematous areas within the same cornea, for example in the presence of a partial DMEK graft detachment. Because the edema is always confined to the area overlying an endothelial defect, the corneal stroma should contain a barrier to a horizontal flow of fluid. In the absence of an anatomical structure, the mucopolysaccharide rods could be organized in such a way that horizonal fluid dispersion cannot occur, for example through biochemically sheated mucopolysaccharide bundles connecting to individual endothelial cells. Image NIIOS.](image-url)
mucopolysaccharide molecules, which should then run all the way up from the endothelium towards the anterior cornea (Figure 8). Given the remarkable ability of fencing off an edematous area within the cornea, each molecule or bundle of molecules may function as a separate unit, anchored in an endothelial cell with a (close to) 1:1 correspondence. Such a mucopolysaccharide-endothelial complex could also explain the need of tubular structures running vertically in Descemet membrane, as seen in transmission electron microscopy (Figure 9), for accommodating mucopolysaccharide pillars to connect to the endothelium.

An organisation with endothelium-controlled-mucopolysaccharide-pillars may also explain sequestration of decompensated areas with an even sharper demarcation line. A nice example may be an old penetrating keratoplasty performed for keratoconus (Figure 10). After the graft has failed, the opaque, edematous donor tissue sits directly adjacent to a clear recipient rim. Unless the circular transplant wound would somehow have developed into an impermeable barrier to liquid, such a clinical image should indicate that extreme differences in imbibition pressure can exist and unceasingly be maintained over the width of a corneal wound. If each endothelial cell would indeed service a single (or small number of) mucopolysaccharide-rod(s) running anteriorly, it would stand to reason that the cells carry an active cell pump not necessarily for hydration of cornea, but rather for titrating the imbibition pressure overlying their location, potentially even through secondary molecules determining mucopolysaccharide composition and its hydration status. If so, the endothelium may not be improvising on its own, but should be steered by an overarching regulatory system balancing the intraocular and imbibition pressure.

All of the clinical observations above may form a work hypothesis consisting of two main assumptions (Figure 2):

1) The cornea may be perfused from limbus to limbus, through horizontal ‘interlamellar irrigation sheets’, parallel to the corneal surfaces. This would secure corneal nutrition, that would therefore be independent of its endothelial condition.

2) The endothelium may then have a role in regulating the imbibition pressure,

Figure 10. Failed penetrating keratoplasty performed for keratoconus. Note the abrupt difference in corneal transparency between the failed, edematous graft and the clear host peripheral rim. The clinical picture suggests the presence of a large step in imbibition pressure across the circular transplant wound (arrows), i.e. near normal peripherally and extremely low centrally from the wound. The abrupt delta may indicate a ‘vertical’ control of the imbibition pressure. Internet source: Journal of Clinical Ophthalmology and Research; no further reference available.
through stabilizing the hydration of the mucopolysaccharide rods running from the posterior to anterior cornea, perpendicular to the corneal surface. This would secure corneal transparency, potentially depending on a single control mechanism shared by the imbibition and intraocular pressures.

**Imbibition pressure paradox in Fuchs dystrophy**

Now, if we use this perspective to have another look at the main corneal endothelial disorders, ie. bullous keratopathy and Fuchs dystrophy, what do we see? In bullous keratopathy, endothelial cells can usually be visualized on specular microscopy, albeit that the cells are lower in density, larger in size and more polymorphous in shape than those in a healthy cornea. If the endothelial cells would be dedicated to a circumscribed mucopolysaccharide bundle, 'corneal decompensation' would imply that a cell can only service so many mucopolysaccharide pillars. Replacement of the recipient endothelial layer by donor endothelium would therefore be successful by increasing cell density and restoring the cell-to-pillar ratio.

The fact that endothelial cells are difficult to visualize with specular microscopy in bullous keratopathy, can commonly be attributed to poor optical quality of the cornea due to the presence of stromal edema. Cells are not completely absent, but most often the images are just too vague to perform a cell count. In Fuchs dystrophy the situation is quite different. Most often the posterior corneal surface can be viewed in detail and edema is rarely interfering with image quality. Depending on disease stage, cell pallisades are visible surrounding guttae, and in more advanced cases, a near complete lack of cells is noted without significant degradation of image quality. So where cells are present in bullous keratopathy (albeit in lower numbers), there is a virtual absence of cells in Fuchs dystrophy, and specular microscopy imaging quality is reversely correlated. In other words, the clinical slit-lamp image, pachymetry readings as well as image quality with specular microscopy may all point in the same direction: stromal edema is not a main factor in Fuchs dystrophy. If so, how is the corneal imbibition pressure then maintained in the absence of endothelial cells?

There may only be two options to really explain this: the static hydration of the stromal mucopolysaccharides is taken over by another type of cell or mechanism, or Fuchs endothelial dystrophy is not an endothelial disease, at least not primarily. Apart from the apparent loss of endothelial cells, the true hallmark of Fuchs endothelial dystrophy is the formation of guttae, small hypertrophic depositions of Descemet-like collagenous material protruding from Descemet membrane into the anterior chamber, presumably laid down by the endothelial cells. The endothelium continuously produces new Descemet membrane material, which results in the membrane steadily thickening with age. Also, if the endothelium repopulates denuded corneal stroma, for example a surgical wound, it will form a new Descemet membrane over the defect. The development of guttae is also not pathological per se, since these crescences are also observed in small numbers in the periphery of healthy eyes, then referred to as 'Hassall Henle bodies'. The latter process has been speculated to be a 'fill-in' for local endothelial cell death, although

---

11 Although difficult to quantify, there is also a difference in 'surgical feel' upon dissection of a 'looser' cornea in bullous keratopathy (more edema) than in Fuchs dystrophy (less edema).
it is not entirely clear why a cell would produce such a wart before dying off, especially because adjacent cells tend to fill in the gap.

**Guttae as a remedy response**

Since endothelial wounds or defects are usually closed through migration of neighbouring endothelial cells, it may be more likely that Hassall Henle bodies or guttae result from some type of repair signal, possibly accompanied by a controlled form of apoptosis. This may be further substantiated by the finding that advanced cases of Fuchs dystrophy often show a multilayered Descemet membrane in pathology specimens. The mere development of such a double or triple Descemet membrane as well as that of the guttae themselves, may point towards a massive ‘wound healing response’, apparently without any detectable inflammation. Also, there is no detectable scarring in the overlying stroma, it just appears as if the snail-pace process of continued Descemet membrane deposition associated with normal ageing is disrupted, and replaced by seemingly uncontrolled repair at posterior surface of Descemet membrane. As if the cells are trying...
to seal off Descemet membrane, while making their own presence redundant.

Although Fuchs endothelial dystrophy is generally considered an attested disease of the endothelial cells themselves, an argument against this idea might be that the cells located in the corneal periphery are usually still healthy and showing normal cell morphology. In contrast to an apparent depletion or exhaustion of the entire endothelial cell layer as seen in bullous keratopathy, a Fuchs cornea carries potent cells outside the affected area, that are ready, willing and able to cover an endothelial defect without any clinical sign of impairment. Even in subtotal DMEK graft detachments, the bare recipient posterior stroma frequently will be repopulated in its entirety within a few months, often with near complete recovery of the visual acuity (Figure 11). If the endothelium would indeed be seriously compromised in Fuchs dystrophy, such a clinical outcome would seem virtually impossible to achieve.

Moreover the morphologic patterns observed with specular microscopy may be noteworthy. In early stages, a Fuchs cornea may show dispersed guttae surrounded by flower-like corona of endothelial cells. With disease progression, these guttae appear to get distributed more evenly, with a relatively constant number of cells in between them, mimicking a wired fence. Even if the cornea is severely affected, the cells do not appear 'stressed', but rather functional. Again, if the endothelium would be in some sort of an end-stage disease, both the continued organization and near normal cell morphology would seem unlikely.13

If we therefore expand on the possibility that in Fuchs dystrophy the endothelial cells are a priori healthy and subjected to a wound healing response, it unleashes the possibility that the actual cause of the disorder lies elsewhere. It would appear that the endothelial response is initially aimed at containing a very localized issue through the formation of tiny guttae, while over time a more radical sequestration of the area develops with the formation of a multilayered Descemet membrane. If endothelial cells would primarily play a role in regulating the imbibition pressure within their vertical mucopolysaccharide pillars, Fuchs dystrophy could potentially be a disorder originating from the stromal mucopolysaccharide molecules or an abnormal content thereof.

Such a consideration, that is, the idea that the endothelial cells would be able to 'seal off' the overlying mucopolysaccharides to secure the imbibition at a level at which corneal transparency is maintained, may appear unlikely. However, several clinical situations may hint towards the presence of a normal imbibition pressure in the absence of endothelial involvement. For example, remnant visco elastic material trapped inside the posterior stroma or at the stroma-to-Descemet membrane interface, does not result in the formation of corneal edema in that area. Instead, the cornea is always crystal clear with no apparent change in stromal thickness, over extended time periods.14 Theoretically, deep stromal injection of visco elastic material could prove to be a preventive step in the development of Fuchs dystrophy, since an 'early seal' might discharge the endothelial

12 During descemetorhexis, such a multilayered Descemet membrane may have to be removed in multiple layers.
13 Any interpretation of the morphology of the endothelial cell layer in Fuchs dystrophy may be somewhat complicated by the frequent occurrence of 'dark spots' at a level slightly anterior to the endothelium. Such 'dark spots' can usually be distinguished from guttae by the lack of interference with the endothelial cell borders.
cells from sequestering mucopolysaccharide molecules by the formation of guttae.

Now if we zoom out, how might Fuchs dystrophy further be characterized? First, the disorder is never accompanied by inflammation, pain or discomfort, rendering infectious or autoimmune disease unlikely as its primary cause. Second, it is usually seen in otherwise healthy eyes with no relevant medical history, other than (prior) smoking and sometimes genetic predisposition with affected family members. Although associated with Fuchs dystrophy, cataract formation may align with age distribution, since younger Fuchs patients rarely need to undergo phacoemulsification. Moreover, the presence of guttae may change the optical quality of the cornea in such a way that the crystalline lens develops a deceitful cataractous appearance, as these changes disappear after DMEK surgery. Third, Fuchs dystrophy may present with a diffuse distribution of guttae across the cornea, but these guttae are frequently limited to the corneal center and paracentral areas. The mirror image, an abundance of guttae restricted to the corneal periphery does not exist, it is the corneal center that is always involved. Fourth, the formation of guttae and Descemet duplication should be mediated by some form of repair signal, for example growth hormone release.

In other words, Fuchs dystrophy would seem a non-inflammatory repair process focused on the corneal center, with variable association to family predisposition, lifestyle and cognitive development, possibly genetic susceptibility to some form of exposure or intoxication. Could these factors relate to a stromal mucopolysaccharide disorder triggering a hypertrophic tissue reaction at the level of Descemet membrane? Could the endothelial response be an attempt to contain some form of intoxication or non-inflammatory disruption?

Corneal mucopolysaccharide organisation

What clinical conditions may be attributed to mucopolysaccharide abnormalities in the corneal stroma? In macular corneal dystrophy, a condition characterized by a diffuse, nebulous clouding of the entire corneal stroma, mucopolysaccharide deposition is scattered in between the stromal lamellae. As mentioned, their interlamellar position might hold several important clues about the functional organisation of mucopolysaccharides in the normal, healthy cornea. First, tiny volumes of apparently disorganised mucopolysaccharide depositions prove to result in substantial opacification. This should indicate that in order to reach just the opposite, that is, corneal transparency through constructive interference, there must be an extremely elaborate mucopolysaccharide structure. A refined fabric that not only allows for mucopolysaccharide molecules to be present in abundance throughout the cornea, but that also enables exact spacing of collagen fibers, plus a localized control of the imbibition pressure throughout the cornea. Hence, individual mucopolysaccharide molecules or small bundles thereof, must be furnished with some sort of mechanism to separate them from each other, to control their volume and dimension. Since no anatomical structures

14 It is referred to the stromal thickness anterior to the stromal pocket filled with visco elastic, since overall pachymetry values will be increased due to the volume of the visco elastic material itself. The clinical image was sometimes observed in the early days of 'deep anterior lamellar keratoplasty' performed by manual spatula dissection or pre-Descemet dissection with a visco elastic, as a result of incomplete visco elastic removal from the dissected interface.
have been identified to explain this, there should likely be some form of sheathing, for example of a biochemical nature. Such enveloped molecules may very well support the idea of mucopolysaccharide rods running vertically over the cornea from posterior to anterior and connecting to individual endothelial cells.

Vertical, biochemically isolated mucopolysaccharide rods may also better explain 'corneal hydrops' in advanced keratoconus. The current consensus teaches that progressive ectasia eventually leads to a rupture of Descemet membrane, which in turn results in a massive influx of aqueous into the stroma and the development of eruptive central corneal edema. This theory may be flawed for a couple reasons. First, Descemet membrane has a relatively high tensile strength that can easily withstand the intraocular pressure, as can be seen in corneal ulcers with a local melt of the overlying corneal stroma. Second, in eyes with an intrastromal Bowman layer transplant, a hydrops was found to develop posterior to the graft, without a preceding change in topography, indicating that ectasia is not a prerequisite for corneal hydrops development. Third, some of the latter eyes showed a hydrops in the absence of a defect in Descemet membrane, which may suggests that a rupture of Descemet membrane sequels intrastromal fluid accumulation and not vice versa.

If there would be a system of vertical mucopolysaccharide rods and a horizontal nutritional flow originating from the limbus, it may not be implausible that eye rubbing, recognized as a main factor in keratoconus development, could damage the biochemical envelopes and expose the mucopolysaccharide-cores to the nutritional flow. This would disrupt the entire structure responsible for collagen spacing, explaining massive stromal 'lakes' and corneal opacification. It would appear that keratoconus itself is not a priori a mucopolysaccharide disorder, since these corneas are most often, apart from contact lens induced surface scarring, relatively clear, suggesting that mucopolysaccharide organisation is intact and rather robust, as it arguably takes substantial manual force to cause a hydrops.

**Fuchs dystrophy as mucopolysaccharide disorder**

Now to return to Fuchs dystrophy with its puzzling deterioration and complete loss of the central endothelium, while the imbibition pressure in the overlying stroma is often marginally affected. Based on the arguments given above, the stromal mucopolysaccharides must be involved, because their hydration determines the imbibition pressure. If the imbibition pressure remains 'controlled' in the absence of endothelium, and near normal corneal transparency is maintained from an optical perspective, it would seem most likely that the vertical mucopolysaccharide rods are purposely disconnected and sealed off from their corresponding endothelial cells. Since the process is never accompanied by detectable inflammation, the formation of guttae and doubling of Descemet membrane may not be a true wound healing response. Instead, it could be speculated that a growth hormone-like factor ordinarily involved in continued Descemet membrane production by the endothelial cells, is released in too high a concentration. If

---

15 In the group metabolic keratopathies are different types of mucopolysaccharidoses. These disorders are invariably characterized by severe malformations, an array of nonocular symptoms, or lower life expectancy. Since Fuchs endothelial dystrophy has not been associated with congenital or systemic disease, metabolic keratopathies would not seem relevant in the present context.
the endothelial cells play a secondary role, it would stand to reason that any such growth hormone factor originates from or because of the mucopolysaccharide network. If unbalanced, whether through genetic predisposition, exposure or intoxication or a combination thereof, the central endothelium would appear to receive an apoptosis-like signal to contain the 'mucopolysaccharide problem' by sequestration of the corneal optical center.

The efficacy of DMEK or other types of endothelial cell replacement in the treatment of corneal endothelial disorders may fuel the idea that 'the cornea needs the endothelium'. But what if, contrary to popular believe, it is the other way around? What if the endothelium receives marching orders from the overlying stroma? Such a consideration may particularly be of interest, given the capacity of endothelial cells to transform into other cell types. A partial DMEK graft detachment should preferably be repositioned within 4-8 weeks, because the endothelial cells change into fibroblast-type cells producing scar tissue over the unattached donor tissue flap. A similar fibroblastic transformation may precede the formation of a retrocorneal membrane and duplication of Descemet membrane in advanced Fuchs dystrophy should also result from some form of a fibroblastic endothelial cell response. In ICE syndrome, endothelial cells are supposed to be able to transform in epithelial-like cells, which may be poorly understood both on cytological and causative level. If so, the presence of an overlying cornea could be a prerequisite for maintaining the endothelial phenotype. Also, given the intimate interaction between the corneal epithelium and the stroma, and a potential connection between stromal mucopolysaccharide rods and the endothelium, it may not be too far fetched that these mucopolysaccharide rods act as a communication tool between the corneal epithelium, stroma and endothelium.

As argued, it may be most challenging to further defend the idea that Fuchs endothelial dystrophy is primarily an endothelial disorder. In fact, a stabilization of the imbibition pressure at near normal levels in the absence of endothelial cells would suggest the exact opposite. If so, professor Ernst Fuchs may have been right after all, to ignore the endothelium. He might just have said: "DMEK is effective in the treatment of my dystrophy only because a descemetorhexis is performed as part of the procedure, therewith removing the guttus as the main cause for visual impairment." In his honor, we may even again consider the possibility that the corneal epithelium is involved, as his disorder was originally described as an epithelial dystrophy.

That all being said, it may be worth it to recognize the discrepancies between clinical observation and current teaching materials, since the slit-lamp characteristics of Fuchs dystrophy may unlock a different understanding of the corneal endothelium and in its wake a completely different approach in terms of treatment options in corneal disease.

**Corneal glaucoma: Fuchs puzzle key to solving glaucoma etiology**

Clinical observation may suggest that corneal nutrition, hydration and transparency must stem from a far more sophisticated system than currently described in

---

16 Penetrating keratoplasty for Fuchs dystrophy is notorious for a lack of wound healing along the circular transplant wound, which may show would dehiscence after minor trauma years after surgery. If so, Fuchs dystrophy may rather be characterized by impaired wound healing, suggesting that the formation of guttus and a doubled Descemet membrane results from a different pathway.
the literature. There simply must be a framework built from extremely delicate biochemical components as well as a refined regulatory feedback system for maintaining optical quality to such a high degree under virtually all circumstances.

When such elaborate control is at the basis of the physiology of the cornea, it would seem rather unlikely that the intraocular pressure is not regulated by a similar type of sophisticated control, especially given the overlap in responses, their anatomical vicinity and similarity in clinical image. Particularly POAG and Fuchs dystrophy may seem to represent as two different clinical reactions to the same trigger. Both would appear to be a remedy response rather than an auto-destructive disorder; both may be involved in a re-calibrated (imbibition or intraocular) pressure; both tend to start surreptitiously around middle age, with a potential association with the steroid hormone group; and both may present with or without corneal edema, which would seem difficult to explain other than by an increased dynamic, horizontal corneal flow from the limbus. Two birds of a feather in a response to some factor that produces 'overactivity', but that does not evoke inflammation.

This line of thinking may be further illustrated by regarding Fuchs dystrophy from a somewhat different perspective, with 'glaucoma semantics' if you will. If the imbibition pressure is relatively normal in the virtual absence of endothelial cells, you could also argue that the imbibition pressure is 'too high' (ie. too negative, since it is a suction force). This would imply that - since loss of endothelium should result in a lower imbibition pressure level according to the current consensus - Fuchs dystrophy is characterized by the presence of an increased imbibition pressure, therefore qualifying as 'corneal glaucoma'. Such terminology may be confusing, but it also shows how nomenclature determines our perception of a disorder as well as our considerations for treatment. Using this perspective, it may feel more obvious that if the imbibition and intraocular pressure can be elevated e.c.i. and are possibly linked and functionally orchestrated in some shape or form, unraveling the secret of 'corneal glaucoma' in Fuchs dystrophy may very well solve the mystery of POAG.

**Future research directions**

The bottom line is that clinical observation may suggest that:

• The existence of a 'circulatory endothelial flow mechanism' (passive leakage) over the corneal endothelium is unlikely;

• Corneal hydration has a dynamic component, a flow from limbus to limbus, potentially through perfusion of interlamellar films running parallel to the corneal surfaces;

• Corneal hydration has a static component through detailed distribution of mucopolysaccharide rods connected to an endothelial cell, running over the entire corneal thickness from the endothelium anteriorly;

• The corneal endothelium is involved, but not required for maintaining stromal imbibition pressure;
• The ‘active cellular endothelial pump’ of the corneal endothelium contributes mucopolysaccharide composition but may have a limited role in regulation of the corneal hydration status;

• The cornea is, through its endothelium, a nett contributor to the aqueous volume and composition;

• The corneal imbibition pressure and intraocular pressure act in concert and should have a shared feedback system, possibly with a long term calibration through sensory input (for example via compressive crystalline lens refractive changes) and a rapid response through some sort of pressure gauge (for example via a ‘limbal-ciliary nodus’);

• The corneal endothelium pump is subjected to the feedback system for the imbibition and intraocular pressure;

• POAG and Fuchs dystrophy should be perceived as remedy responses to a factor that triggers an overreaction without inflammation, possibly a factor that disrupts a steroid hormone balance.

• If Fuchs dystrophy is characterized by an imbibition pressure level that is too high (too negative), the disorder should not be perceived as an endothelial disorder but as ‘corneal glaucoma’.

The eye's anterior segment in different perspective

To get back to the one question at the beginning of this essay: If a skilled ophthalmologist like professor Ernst Fuchs 'missed' the endothelium in the early 1900s, what structure or mechanism do we fail to recognize today, for which we will be mocked in 100 years from now? Mark our words, there is a conspiracy going on within the anterior segment of the eye, with the cornea as a main culprit or at least as a person of interest in glaucoma: understanding the cornea should solve the mystery around POAG.

Such a conspiracy theory fits in so well with the current trend in our societies, especially since this essay contains a lot of "if's", "maybe's" etc, and for the purpose of readability a lot of information has been, possibly erroneously, left out. References were omitted, because the literature would tend to draw us back into mainstream teachings, that, in our opinion, so clearly disagree with clinical observation. We may have to look differently at the anterior segment of the eye, with a flat-eye perspective as if all ocular structures form different functional combinations, depending on the tissues involved or affected. Disorders now perceived as separate disease entities may be co-dependent, overlapping, originating from the same root cause in or outside the eye.

If this essay would let you perceive the eye's anterior segment in a slightly different way, we feel we have achieved our goal. And for the future century colleagues puzzled by the fact that our generation overlooked some obvious causes in anterior segment disease, we can cover our ass by pointing out: "We told them so!"
Acknowledgements

Melles

Many thanks to all of our colleagues who engaged in discussions on the subject over the years, from fellows and students to NIIOS course participants and the many colleagues at ophthalmic meetings. Our entire NIIOS team delivered, as always, vital and indispensable suggestions and contributions. And last but not least, we are grateful to our patients, who are showing us what is really going on!