CORNEAL OXYGEN: 2014
Barry A Weissman, OD, PhD, FAAO

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Disclosures:
Professor of Optometry, Southern California College of Optometry, Marshall B Ketchum University

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- COA Board of Trustees
- Advisor NKCI, Inc
- All comments & errors, however, are completely my own…..

Or:
Does Dk mean “don’t know”?

Professor Brien Holden
DMM BAppSc PhD DSc, Chief Executive Officer (CEO) of the Institute for Eye Research, Vision CRC, International Centre for Eyecare Education(ICEE); CEO and President of Adventus Technology Inc; Executive Chair of Optometry Giving Sight

The 1950 question asked in corneal biophysics:
“WHAT MAKES THE CORNEA TRANSPARENT TO VISIBLE LIGHT WHILE THE SCLERA IS OPAQUE?”

EARLY THEORY SUGGESTED CORNEAL TRANSPARENCY WAS DUE TO SIMILARITY IN REFRACTIVE INDEX OF STROMAL COLLAGEN & “GROUND SUBSTANCE” (THEN MPS, NOW GAG)

CORNEAL LIGHT TRANSMISSION VARIES BY λ

10% <310 nm
>90% at 400 nm

Experiential values for the fraction of light transmitted through normal and edematous rabbit corneas as a function of wavelength. The ratio of the thickness of the edematous corneas to normal thickness values and the number of corneas used for each curve are given in the key. Farrell RA et al J Physiol 1973

VA UNAFFECTED UNTIL STROMAL HYDRATION INCREASED 100% (7 g H₂O/g DW)

EPITHELIAL EDEMA IS MUCH MORE DESTRUCTIVE TO VISION THAN STROMAL EDEMA B/C OF SURFACE DISTORTION

IF YOU PLACE AN EXCISED CORNEA IN WATER...

=> IT WILL THICKEN (SWELL) & BECOME CLOUDY

=> THE CORNEA SWELLS ABOUT 100% W/ EPITHELIAL REMOVAL, MORE WITH ENDOTHELIAL DESTRUCTION

MAURICE & GIARDINI BJO 1951

ALSO, NOTE THE TEMPERATURE REVERSAL EFFECT

DAVISON, BIOCHEM J, 1955; HARRIS & NORDQUIST, AJO, 1955

MAURICE J PHYSIOL 1957

MAURICE PROPOSED THAT THE STROMA IS TRANSPARENT B/C THE AXES OF ITS COLLAGEN FIBRILS ARE ARRANGED IN A LATTICE W/SPACING LESS THAN THE WAVELENGTH OF VISIBLE LIGHT => DIRECTIONAL CONSTRUCTIVE INTERFERENCE

SUPPORTED BY LATER WORK, GOLDMAN ET AL 1968, HART & FARRELL 1969, FARRELL ET AL 1973

COLLAGEN LAMELLAE WITH KERATOCYTES

SCHEMATIC OF NL & SWOLLEN COLLAGEN FIBRIL AXES
Effects of corneal environment on oxygen tension in the anterior chambers of rabbits

Ronald E. Barr and Jan A. Silver

Oxygen tension in the aqueous of the anterior chamber of rabbit eye was measured for a number of conditions at the corneal surface. The conditions were: (A) normal exposure to air with eyelids open, (B) a hard contact lens placed on the cornea, (C) a 15 μm thick piece of cellulose placed on the cornea, (D) eyelids held closed, and (E) gas-free oxygen, air, and nitrogen gas on the cornea. The technique employed in vivo measurements using needle-shaped oxygen electrodes which were inserted into the eye from behind the lids. The normal (Condition A) oxygen tension in the anterior chamber aqueous was 32 ± 9 mm. Hg. Oxygen tension in the aqueous for conditions B, C, and D, and when nitrogen was placed on the cornea were similar and equalized about 9 mm. Hg. Eventually no change was observed when air was placed on the cornea and anterior chamber oxygen tension rose to 106 mm. Hg when oxygen was placed on the cornea. The results indicate that oxygen tension levels through the cornea are dependent on environmental conditions at its anterior surface.

In vivo measurements of oxygen tension in the cornea, aqueous humor, and anterior lens of the open eye

Marcus Evans,* John Nishikado,** and Thomas E. Silver

Measurements of oxygen profile across the cornea, aqueous humor, and anterior lens were obtained from experimentally isolated rabbit eyes. The anterior chamber oxygen tension was measured with the use of a needle-shaped electrode. The tip of the electrode was inserted into the eye from behind the lids. The normal (Condition A) oxygen tension in the anterior chamber aqueous was 32 ± 9 mm. Hg. Oxygen tension in the aqueous for conditions B, C, and D, and when nitrogen was placed on the cornea were similar and equalized about 9 mm. Hg. Eventually no change was observed when air was placed on the cornea and anterior chamber oxygen tension rose to 106 mm. Hg when oxygen was placed on the cornea. The results indicate that oxygen tension levels through the cornea are dependent on environmental conditions at its anterior surface.

In vivo aqueous humor oxygen tension — as estimated from measurements on bare stroma

R. N. Kastenholz, M. Hanna, I. Fatt, and R. A. Weissman

Aqueous humor oxygen tension in the intact rabbit eye was estimated by a relatively simple technique. The anterior chamber surface of the eye was first exposed free of its outer corneal layer. A needle-shaped oxygen electrode was then used to measure the oxygen tension at the bare surface. Aqueous humor oxygen tensions were then estimated from the measured oxygen tension at the bare anterior chamber surface. The technique employed in vivo measurements using needle-shaped oxygen electrodes which were inserted into the eye from behind the lids. The normal (Condition A) oxygen tension in the anterior chamber aqueous was 32 ± 9 mm. Hg. Oxygen tension in the aqueous for conditions B, C, and D, and when nitrogen was placed on the cornea were similar and equalized about 9 mm. Hg. Eventually no change was observed when air was placed on the cornea and anterior chamber oxygen tension rose to 106 mm. Hg when oxygen was placed on the cornea. The results indicate that oxygen tension levels through the cornea are dependent on environmental conditions at its anterior surface.
Slit lamp images of FL stained anterior chamber at various times after opening lids in goggles at body temperature. The dark area in front of the pupil corresponds to a volume of freshly secreted aqueous humor that entered from posterior chamber while the eye was closed. This area gradually fades out as fluorescein diffuses into it, but does not drift from its original site.

The eye makes six rapid side to side rotations shortly after opening the eye. The freshly secreted aqueous appears to be dispersed through the anterior chamber almost immediately.

**KLYCE J PHYSIOL 1981**

EPITHELIAL HYPOXIA ENHANCES LACTATE PRODUCTION (ANAEROBIC GLYCOLYSIS) => RELEASE TO THE STROMA

=> INCREASES STROMAL LACTATE => INC OSMOTIC LOAD => DECREASING ENDOThelial PUMP EFFECTIVITY => STROMAL EDEMA

Other factors that affect endothelial function

1) Mechanical 2) Disease states
2) Chemical damage 3) Ca**++** free solutions
3) Chemical damage 4) Oxidation of intracellular glutathione
4) Oxidation of intracellular glutathione 5) pH
5) pH 6) Preservatives

**Boundary Conditions:**

UNDER NL CONDITIONS, BOTH ENDOThELIUM & POSTERIOR STROMA RECEIVE O**2** FROM THE AQUEOUS HUMOR

KLEINSTEIN, KWAN, FATT, WEISSMAN IOVS 1981

**Boundary Conditions:**

EPITHELIUM & ANT STROMA RECEIVE O**2** FROM THE ATMOSPHERE WHEN THE EYE IS OPEN (@ SEA LEVEL: 20% x 760 mmHg = 155 mmHg)

AND THE TARSAL CONJ (~50 mmHg) WHEN THE EYE IS CLOSED

THRU THE TEARS
ABSTRACT: The purpose of this study is to compute total corneal oxygen consumption during contact lens wear and evaluate the concept as an index for describing corneal oxygenation during contact lens wear as opposed to flux, partial pressure, or Dk/t.

Method. Estimates of total corneal oxygen consumption were generated using a previously described eight-layer model based on oxygen diffusion equations and eye geometry, and the contact lens product. Oxygen consumption was calculated for the open and closed eye scenarios, thereby providing an index of the chronic hypoxic effect of contact lens wear.

Results. Corneal oxygen consumption is calculated to converge to the same value of 44.8 nL/cm³/sec above a Dk/t of approximately 20 and 300 10⁻⁹ (cm/sec)(mL02/mL/mm Hg) for the open and closed eye scenarios, respectively. Lenses with Dk/t values of 15 and 50 10⁻⁹ (cm/sec)(mL02/mL/mm Hg) allow about 96% of normal long-term total oxygen consumption without a contact lens in place for daily wear and continuous wear, respectively.

Conclusion. Total corneal oxygen consumption is based on physical parameters, represents a direct index of corneal oxygen metabolism and thus cellular energy (ATP) production, allows direct comparison between two lenses or a lens and nonlens-wearing state, and eliminates the ambiguity of other measures, thereby providing an attractive means of describing corneal oxygenation.
Oxygen transmissibility or $Dk/t$

$D$ is a material’s oxygen diffusion coefficient & $k$ its oxygen solubility.

$Dk$ is oxygen permeability, a material property. $Dk$ is directly dependant on CL material’s oxygen permeable moieties, usually silicone and/or water.

$L$ is sample (eg lens) thickness, later replaced by $t$.

Lens $Dk/t$ measures *in-vitro* oxygen diffusion and is not a direct measure of “on-eye” (in-vivo) performance.

**Fick’s Law of diffusion:**

$$j = (Dk/t)_{CL} (\Delta P)$$

Where $j$ is oxygen flux
And $\Delta P = P_1 - P_2$, the difference in $O_2$ tension between the front and back of the CL.

$O_2$ tension at the lens anterior surface ($P_1$)

- At sea-level, $P_1 = ~21\%$ of 760 mmHg (or Torr) or ~155 mmHg (w/a few mmHg of water vapor)
- Under the closed eyelid, $P_1 = ~55-60$ mmHg

**Critical $O_2$ tension values**

- Mandell & Polse, Arch Ophth 1970: 11-19 mmHg
- Uniacke et al, AJ Optom 1972: 40 mmHg
- Mandell & Farrell, IVOS 1980: 23-35 mmHg
- Millidot & O’Leary, Acta Ophth 1980: 60 mmHg
- Hamano et al, Jpn J Ophthal 1983: 100 mmHg
- Holden et al, IVOS 1984: 70 mmHg
- Holden & Mertz, IVOS 1984: Dk/t of 24 DW & 87 ExW Fatt/cm
- Harvitt & Bonanno, OVS 1999: Dk/t of 125 Fatt/cm

**Critical $Dk/t$ values**

Holden-Mertz ’84 Dk/t criteria: ~25 for DW & ~87 for ExW

**Corneal Swelling vs Oxygen Transmissibility ($Dk/t$)**

The Holden-Mertz Criterion 1984

Holden BA: At 2012 AAO: lens induced overnight corneal swelling % & Dk/t
**SAMPLE HYDROGEL Dks**

- POLYHEMA (38% H2O) 10
- 55% H2O SCL 20
- 75% H2O SCL 30
- SI HYDROGEL (AVA) 60
- SI HYDROGEL (PV) 99
- SI HYDROGEL (FND) 140

**SAMPLE RGP Dks**

- PMMA ~9
- POLYCON II & CAB 10
- BOSTON ES 30
- SGP II 40
- BOSTON EO 70
- BOSTON XO 100
- FLP 151 100
- MENICON Z 170

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**Oxygen Tension Under a Soft or Hard, Gas-Permeable Contact Lens in the Presence of Tear Pumping**

Irving Fatt and Doris Hennes
School of Optometry, University of California, Berkeley, California

AM J OPTOM & PHYSIOLOGICAL OPTICS Vol. 53, No. 6

Dk/t complicated by variability in t between lenses & from point to point on optically powered lenses.

As CLs are usually quite thin compared to their areas, calculations often simply assume that the lenses are made of uniform t.

Optical CLs, however, only really have uniform thickness at about 0.75 D.

Morris & Fatt suggested that the central value of thickness was close enough between +1.50 D.

Several proposed several mathematical techniques to provide an average thickness, especially for CLs of F > +1.50 D.

Morris & Fatt, Optician 1977
Fatt, Am J Optom Physiol Opt 1979
Brennan, Am J Optom Physiol Opt 1984
Weissman, Am J Optom Physiol Opt 1986

Holden & Mertz and Tomlinson & Bibby suggested that t should only be averaged over a central zone about 6 mm in diameter.

Fatt & Neumann alternatively argued that average t is not appropriate for predicting lens physiological performance; the thickest portion of the lens is most important as it is the Dk/t at that site which will produce the greatest hypoxic stress to the underlying corneal tissues.

Morris & Fatt, Optician 1977
Fatt, Am J Optom Physiol Opt 1979
Brennan, Am J Optom Physiol Opt 1984
Weissman, Am J Optom Physiol Opt 1986

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*Fig. 1*: Oxygen tension under contact lenses with tear pumping (top) as compared to non-tear pumping (bottom). Dots show oxygen permeable lens with tear pump-line, and oxygen impermeable lens with non-pumping line.
Proof of principle:

On at least 2 occasions, after babies were allowed to inadvertently sleep in low Dk aphakic SCLs, I have noted corneal apical abrasions at UCLA.

2 Errors in measurement of Dk/t

Due to increasing lens’ Dk values to approach that of water (~80 Fatt units) boundary layers of fluid lens surfaces (lead to under-estimations of Dk and Dk/t)

Fatt & Chaston, ICLC 1982
Fatt et al, ICLC 1987

Resistance in Series

As long as Dk close to 10 Fatt Dk units (Dk of water/tears is ~ 80 Fatt Dk units), boundary layers could be ignored

As CL Dk increases (now >100 Fatt Dk units), boundary resistance becomes more important

\[(Dk/t)_{total} = \frac{1}{(t/Dk)_1} + (t/Dk)_2 + (t/Dk)_3\]
The “edge” effect caused by the polarographic sensor collecting oxygen which has diffused across the lens through an area greater than its own diameter: leads to over-estimations of Dk and Dk/t.

Correction: flux ratio = 1 + 4.72L for cathode of 4 mm diameter.

Equivalent Oxygen Percentage or EOP technique/ later called “OSU” (R.M. Hill)

First: calibrate: Expose corneas (e.g., rabbit or human) to various known oxygen environments in humidified goggles (e.g., 0% to 20%) for at least 300 seconds.

Remove the goggle and rapidly.

Evaluate with a oxygen electrode connected to a chart recorder; pO2 in the electrode asymptotes towards zero over a few minutes.

THEN expose the cornea to a specific test condition (e.g., contact lens or series of lenses).

Challenge with the oxygen electrode.

Find that known environment whose curve matches the new reduction in pO2 from the now calibrated electrode.

The “edge” effect caused by the polarographic sensor collecting oxygen which has diffused across the lens through an area greater than its own diameter: leads to over-estimations of Dk and Dk/t.

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Local oxygen transmissibility of disposable contact lenses

Equivalent Oxygen Percentage Technique: from Hill ICLC 1975

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The “edge” effect caused by the polarographic sensor collecting oxygen which has diffused across the lens through an area greater than its own diameter: leads to over-estimations of Dk and Dk/t.

Correction: flux ratio = 1 + 4.72L for cathode of 4 mm diameter.
Equivalent Oxygen Percentage or EOP

developed to model in-vivo contact lens oxygen performance

Advantage: in vivo derived from measurements on living eyes (rabbits & human)

Suffers: technical difficulties, low precision, & known wide variability in corneal oxygen uptake

Fatt: EOP may not be a good measure because it is so strongly empirical

Hill & Fatt, Am J Optom Arch Am Acad Optom 1964
Hill & Fatt, Am J Optom Arch Am Acad Optom 1964
Fatt, ICLC 1993
OXYGENATION OF THE ANTERIOR CORNEA IS RESTRICTED BY CLs, HOWEVER, TO VARIOUS DEGREES => CORNEA SWELLING & VARIOUS TISSUE CHANGES

Oxygen flux vs CL Dk/t
from Brennan OVS 2005 model

CLOSED EYE
OPEN EYE

3 MODELS:
ORIGINAL
FATT/HUANG
BRENNAN
NEW

Holden et al
Mandell/Farrell
Polse/Mandell
Calculated in situ tear oxygen tension under hybrid contact lenses
Karen Lee, OD, Diana Nguyen, OD, Timothy Edrington, OD, MS, Barry A. Weissman, OD, PhD
Unpublished data - submitted

Table 5: Predicted tear oxygen tension under hybrid contact lenses.

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<tr>
<th>Subject</th>
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Table 5: Predicted tear oxygen tension at the central corneal surface under hybrid contact lenses.

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CORNEAL GLUCOSE SUPPLY

- AC-AQUEOUS ~80%
- LIMBAL VESSELS ~20%
- TEARS SUPPLY LITTLE
- AN IMPERMEABLE BARRIER IMPLANTED IN THE STROMA WILL RESULT IN ANTERIOR CORNEAL NECROSIS (BOCK & MAUMENEE, ARCH OPHTHALM, 1953)

Two clinical examples:

Corneal endothelial damage can be expected w/uveitis in the following situations:

- Herpetic endotheliitis
- Large granulomatous KP
- Uveitis complicated by prolonged high IOP
- Infectious endophthalmitis
- Extensive PAS onto clear cornea

Flap melt anterior to epithelial ingrowth (from R Hamilton, MD)

Dohlman Kpro
Extruding INTAC

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- Infectious endophthalmitis
- Extensive PAS onto clear cornea
Stromal edema 2° endothelial damage (from B&L online library)

Modern SiHy CLs are in the “hyper” permeable range and hypoxia therefore less of a concern under open eye conditions...

- Low (Dk/T < 15): normal oxygenation levels that are available in the normal closed eye
- Moderate (Dk/T = 15-25): normal oxygenation similar to that in the normal closed eye.
- High (Dk/T > 25-35): normal oxygenation significantly above that available in the normal closed eye, although can be significantly affected by lens design.
- Super (Dk/T > 35-45): normal oxygenation significantly above that available in the normal closed eye, with lens design having a reduced effect, but substantially below that required for the corneal oxygenation of the open eye.
- Hyper (Dk/T > 45): normal oxygenation just below that required by the normal cornea of the open eye, with minimal effect of lens design.