

The Pursuit of the Ideal Contact Lens: A 40 Year Journey

H. Dwight Cavanagh, M.D., Ph.D., F.A.C.S.,
F.A.A.(Oph), F.A.A.(Opt)(Hon), F.R.S. (Med), F.R.
Micros.Soc.

UT Southwestern Medical Center, Dallas, Texas, USA

This lecture is dedicated to my
good friend and 3-decade fellow
companion on the quest.

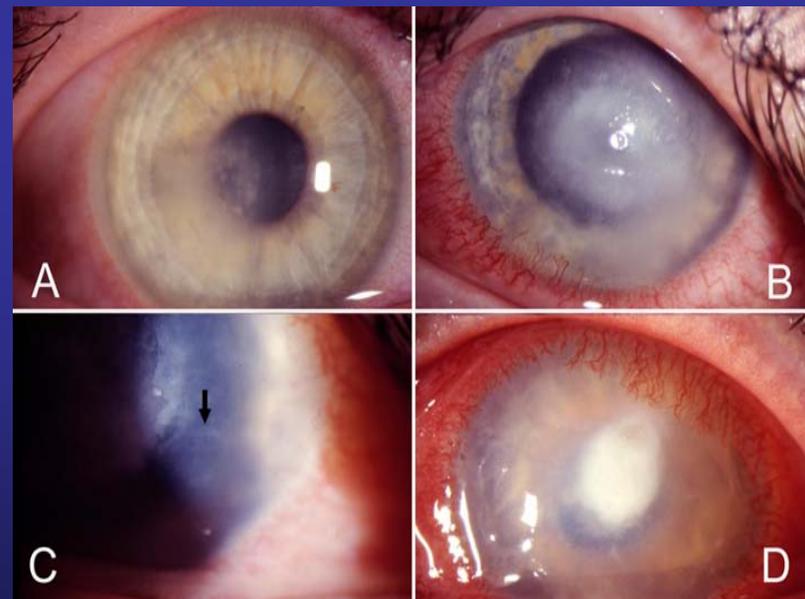


Kyoichi Tanaka
Nagoya, Japan

Infection is THE major sight-threatening complication of CTL wear.....can we prevent it is the subject of this lecture.



Pseudomonas



Acanthamoeba

Why Acanthamoeba?

- 0.2% per 10,000 contact lens wearers per year
38 million x 0.2 = 109 cases/year
- ? Increasing in frequency
- 33% of 1st 50 cases MK worldwide in orthokeratology
- Potential oral vaccine
 - Low tear IgA levels

Why Pseudomonas?

- Pre-disposable lenses, >50% cases of lens-related microbial keratitis
(Schein and Poggio, *New England J of Medicine*, 1989).
- 10 years *after* disposable lenses, >50% cases of lens-related MK still *Pseudomonas* (Cheng; *The Lancet*, 1999).
- 52% of 1st 50 cases MK/OK

Milestones and Giants

- **1960's:** Otto Wichterle: The hydrogel lens
- **1970's:** John De Carle: 1st high water lens;
Don Korb & Miquel Refojo: thin membrane lens
 - Holden-Mertz curve: the search for more O₂ begins....
- **1980's:** Extended wear produces an “epidemic” of infection
 - Pure silicone lenses fail
 - The Hilton Head Conference 1986
 - Schein and Poggio papers 1989
 - Keystone Conference 1989

Milestones and Giants

- **1990's**: Disposable lenses dominate with **LESS O₂**
- **1999**: Cheng study: *Lancet*; no progress in reducing infections
- **2000's**: Silicone hydrogels: The San Diego Conference 2003
- ***Where are we now?***

Pathogenesis and Prevention of Pseudomonas Corneal Infectious Keratitis

- PA attaches to surface or deeper epithelial layer cells (pilli, LPS)...***no damage, no binding; no binding, no infection.***
- Epithelial cells take up PA intracellularly by membrane lipid raft-mediated endocytosis...***block with anti-cholesterol inhibitors: statins***

Pathogenesis and Prevention of Pseudomonas Corneal Infectious Keratitis

- If basal lamina (BL) is intact, actual infection still may not occur in contact lens wear (*Orthokeratology, filter paper damage*)
- If BL is breached, infection **ALWAYS** occurs....“scrape/cut” injury.....
 - *Is this relevant to contact lens wear?*

HYPOTHESIS

- **Overnight CTL-wear causes hypoxia which produces graded damage to the epithelium in inverse proportion to the Dk/L of the lens.**

and

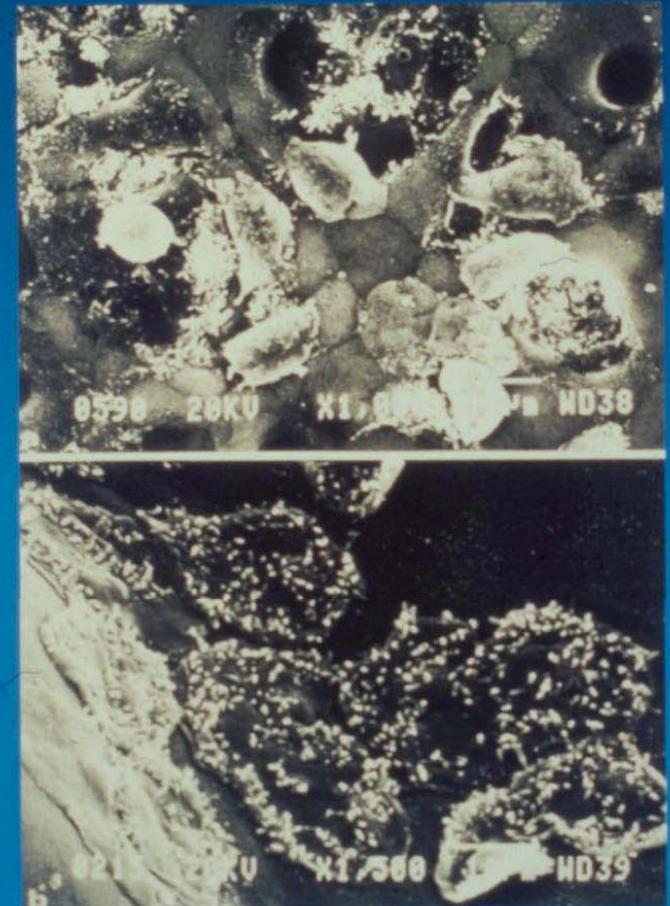
- **The amount of epithelial damage determines the amount of PA-binding, hence the risk of infection.**

Pseudomonas aeruginosa American Type Culture Collection (ATCC) #27853

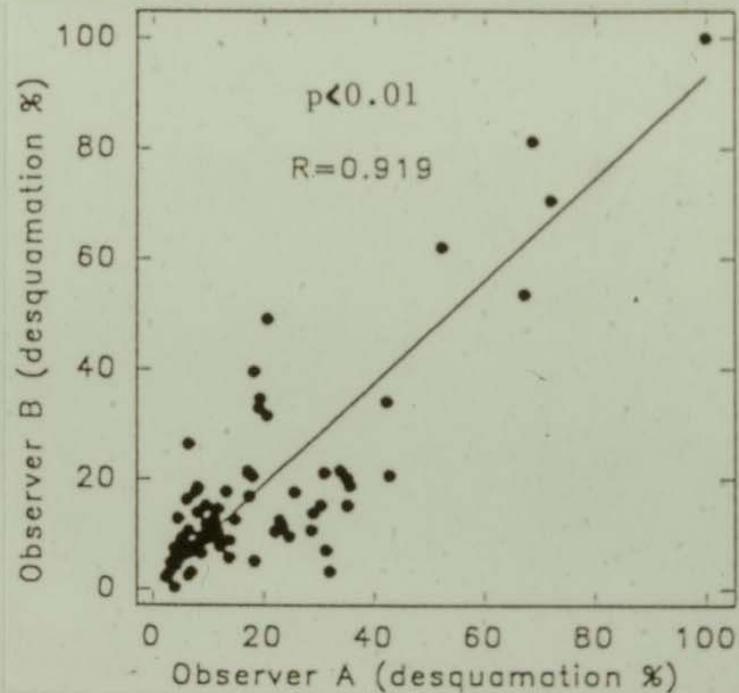
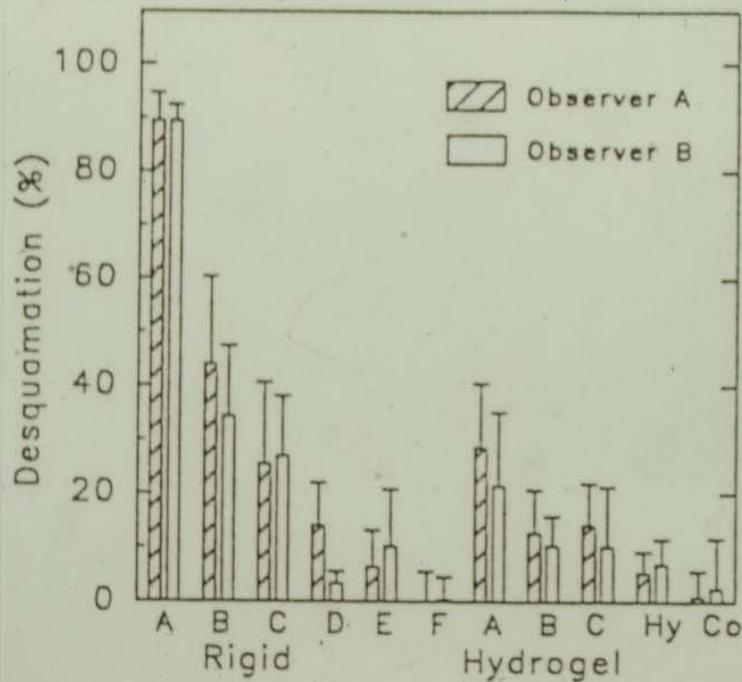
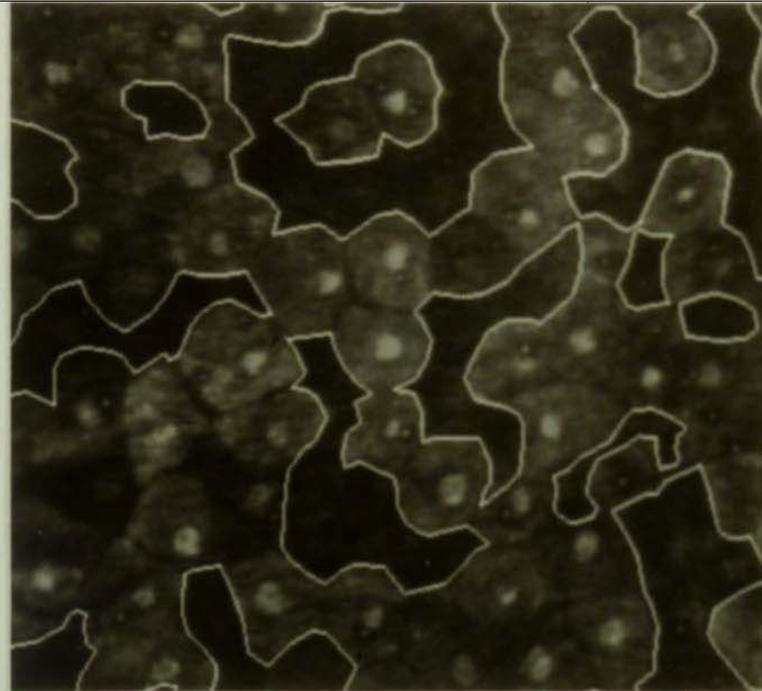
- **1974, selected as the world's standard infectious test strain for antibiotic testing.¹**
- **Piliated, infects the cornea easily in animal keratitis models.²**

1. J. Infect Dis 130: 454-463 (1974)

2. Invest Ophthalmol Vis Sci
36:1107-1114 (1995)



QUANTITATIVE
 DETERMINATION OF
 CONTACT LENS-INDUCED
 DESQUAMATION BY *IN VIVO*
 CONFOCAL MICROSCOPY

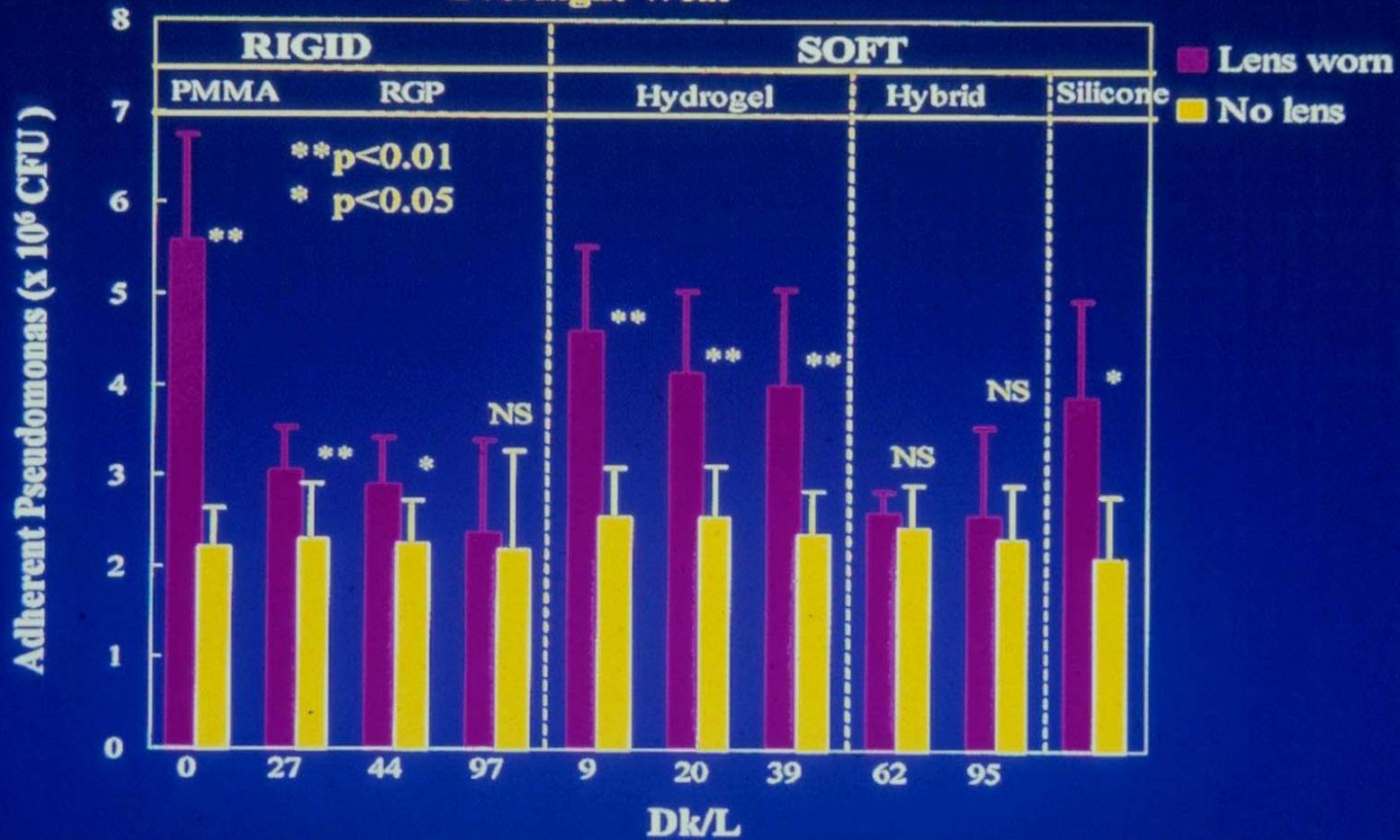


LENSES TESTED

***in vivo* Rabbit Model**

- **6 rigid lenses: Dk/L: 0, 10, 27, 44, 84, 97**
- **4 hydrogel lenses: Dk/L: 9, 20, 39, 51***
- **ALL LENSES 14.0 mm dia./0.15 mm thickness**
- *** Hybrid hydrogel with silicone acrylate.**

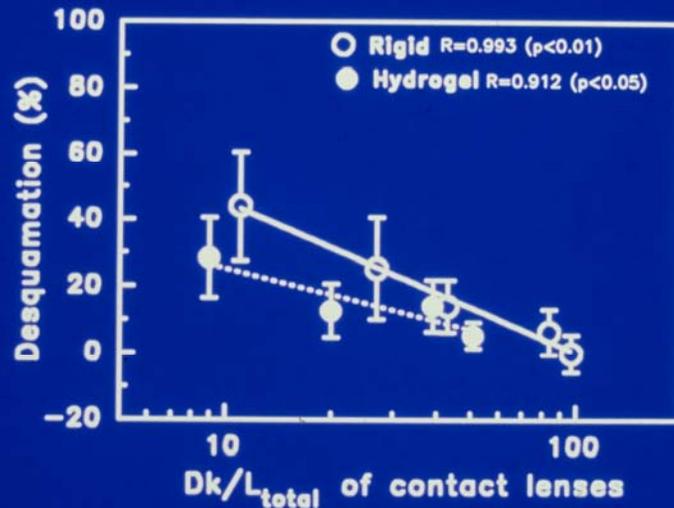
Total Corneal Surface Pseudomonas Binding: Rabbit Studies
Overnight Wear



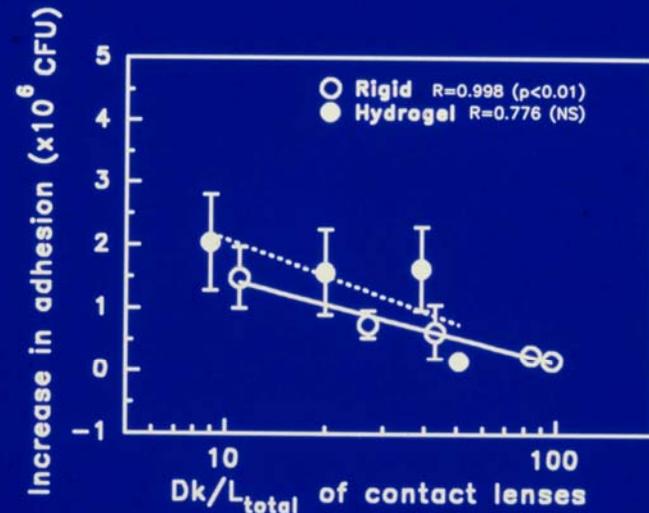
Imayasu et al., Ophthalmology 1994; 101:371-88.

In Vivo Rabbit Studies

Imayasu et al. Ophthalmol. 1994; 101: 371-88.



At a fixed Dk/L value....rigid lenses produce *more* epithelial damage than hydrogel lenses...? **Mechanical effect ?**

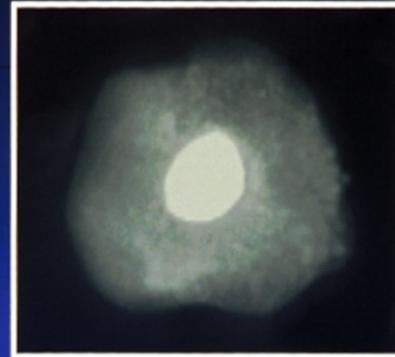


At a fixed Dk/L value....hydrogel lenses produce *more* bacterial binding than rigid lenses...? **Stagnant tear lake – trapping effect ?**

Epithelial cells collection



Eye irrigation chamber



Epithelial cell
after collection



Incubation with *P.A.*



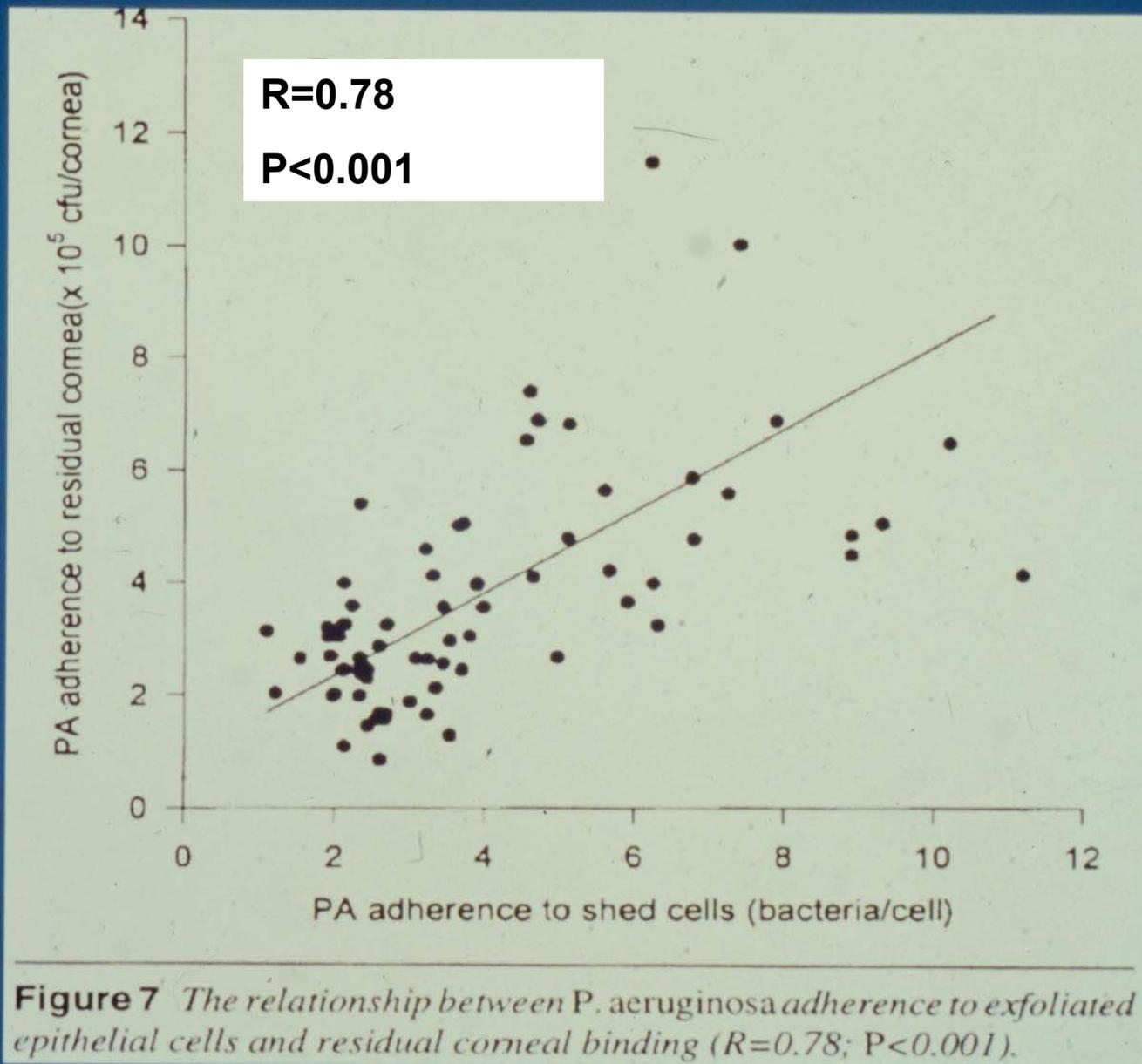
Epithelial cell
with *P.A.*

Total surface corneal PA binding correlates with PA binding to exfoliated corneal epithelial cells (rabbit model) $p < 0.01$

Ren et al. CLAO J 1997;23:63-68

**Does total surface corneal PA
binding correlate with PA
binding to exfoliated epithelial
cells in the rabbit model?**

Ren et al. CLAO J 1997;23:63-68

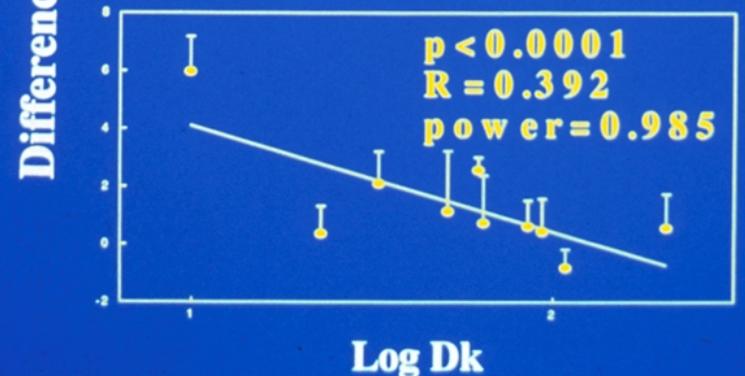
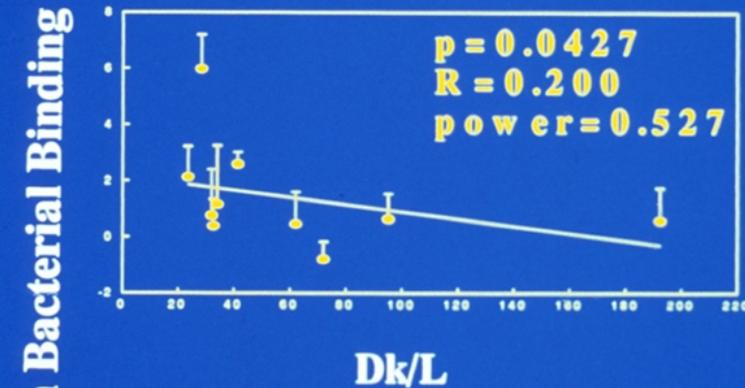
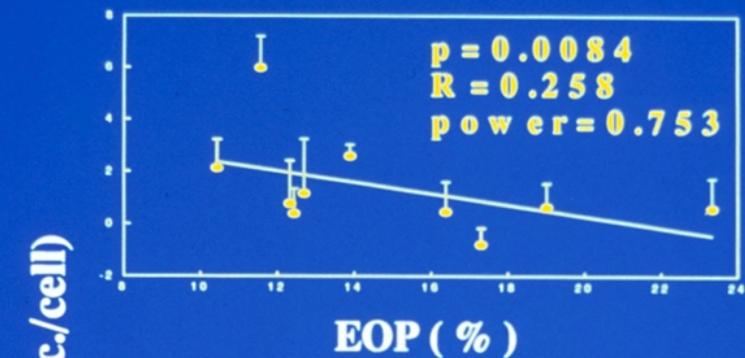


Test lenses

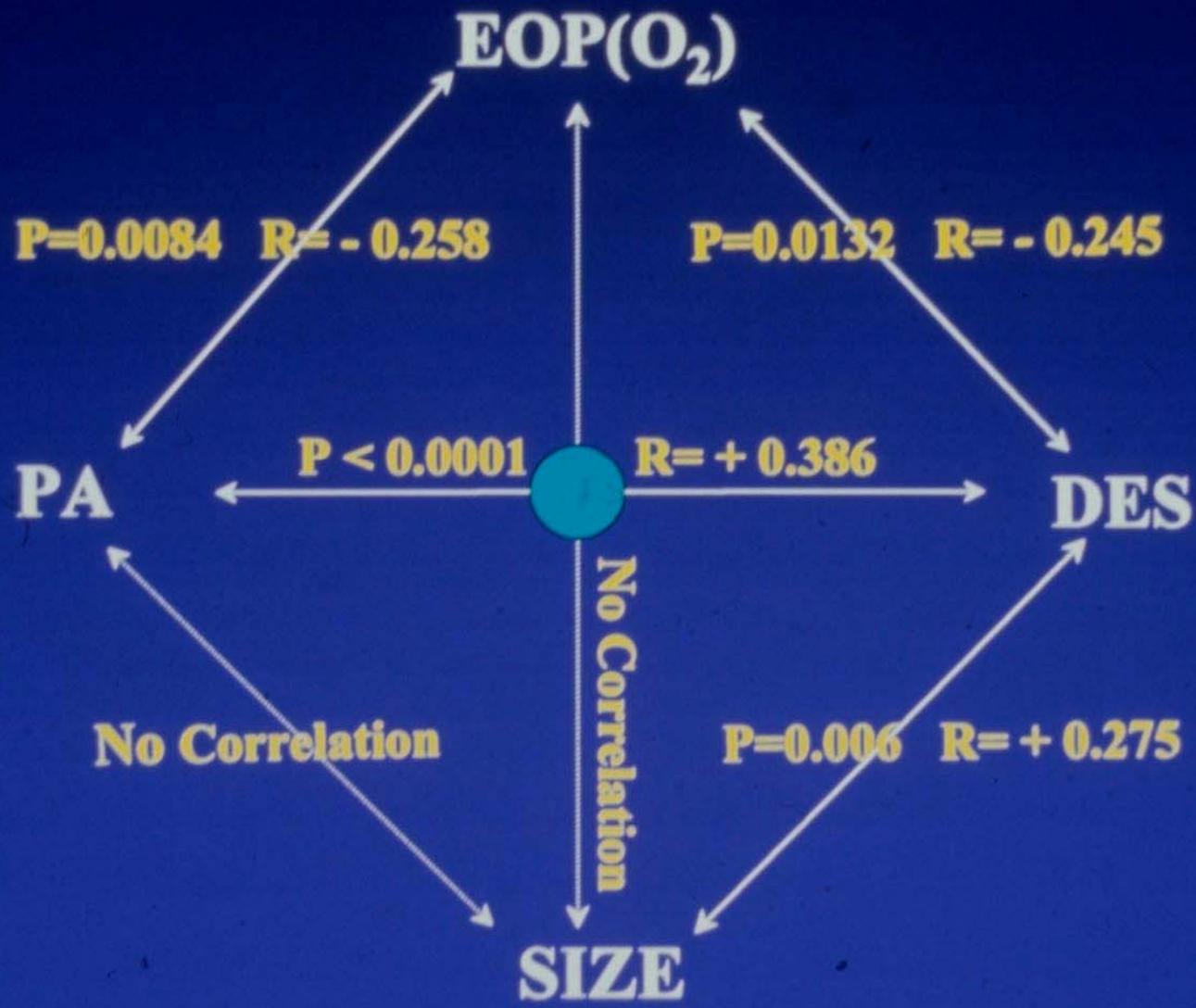
- Rigid gas permeable lenses (n=3): Dk 40,66,146
- Soft lenses (n=7): Dk 10,23,33,51,64,83*,96*
- Randomized, prospective, masked clinical trial 110 patients

* Silicone hydrogel lenses

Ren et al. CLAO J 1999;25:80-100



3 Months Continuous Wear

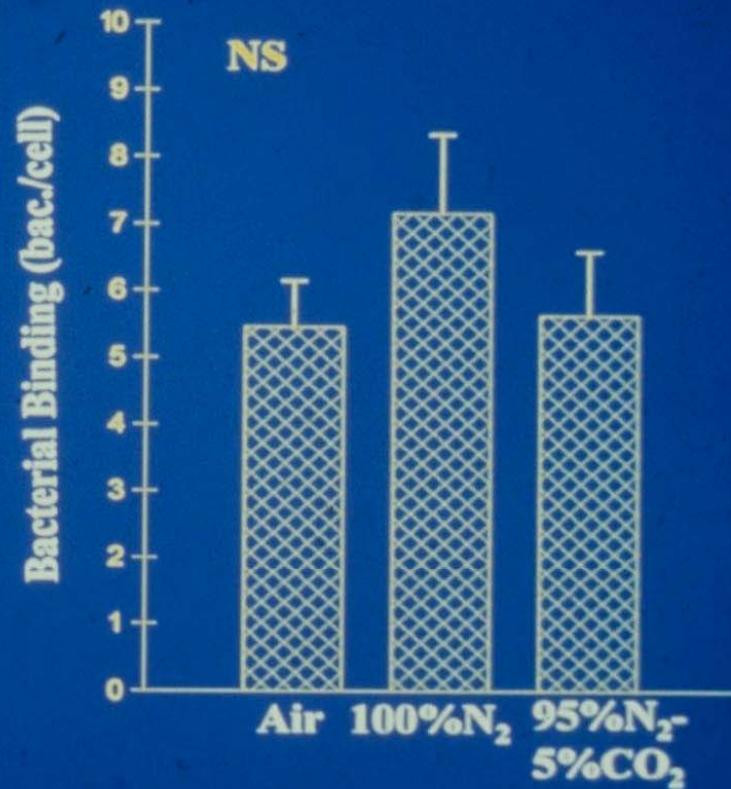
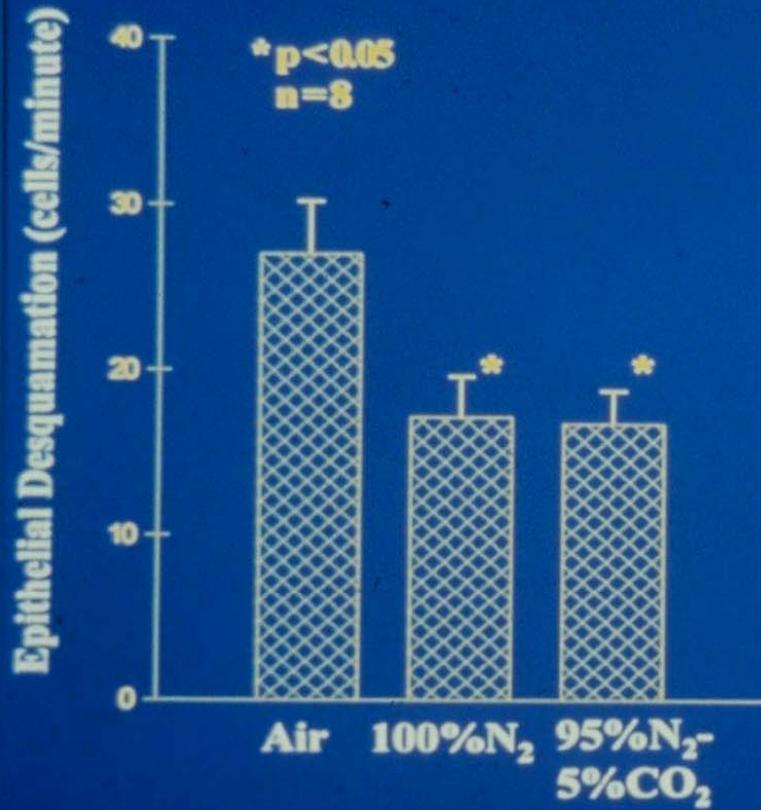


Effects of 6-hours total corneal hypoxia

- **7% corneal swelling**
- **No significant increase in Pseudomonas binding**
- **Significant decrease in surface cell exfoliation (apoptosis)**

Ren et al. CLAO J 1997;23:63-68

Gas Goggle Experiments



Ren et al. *CLAO J* 1999; 25: 80-100

Discussion & Conclusions

- Hypoxia alone produces no increased bacterial binding: presence of a lens and hypoxia are required
- Lens O₂ properties drive bacterial binding: new hyper Dk lenses produced no significant increase vs no lens wear in a pilot study.

Ren et al. CLAO J 1999;25:80-100

Discussion & Conclusions

- All lens wear shuts down normal surface cell shedding (apoptosis)
- Cell exfoliation significantly correlates with O₂ transmission
- But: aging surface cells, gradually increasing in size do not bind more bacteria unless hypoxically challenged

Ren et al. CLAO J 1999;25:80-100

Pseudomonas Binding Clinical Studies 1998-2002

- | | Dk/L |
|--|------|
| <ul style="list-style-type: none">• Prospective, Randomized, Double-masked, Single center, Parallel treatment groups• Prior to study: 1 month no contact lens wear• Prelens baseline exam (control)• 2,4 weeks daily wear• 1,3,6,9,12 months extended wear | |
| <ul style="list-style-type: none">• Acuvue <i>N</i>=70
Conventional hydrogel | 24 |
| <ul style="list-style-type: none">• PureVision <i>N</i>=135
Silicone hydrogel | 125 |
| <ul style="list-style-type: none">• Menicon Z <i>N</i>=75
RGP | 250 |
| <ul style="list-style-type: none">• Night & Day <i>N</i>=98
Silicone hydrogel | 175 |

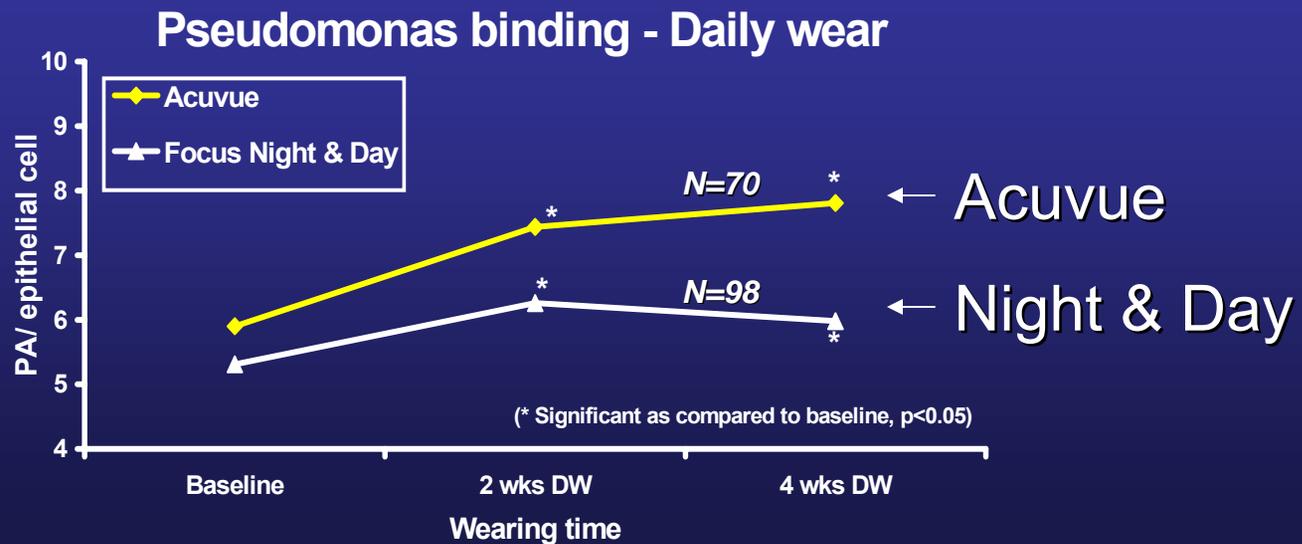
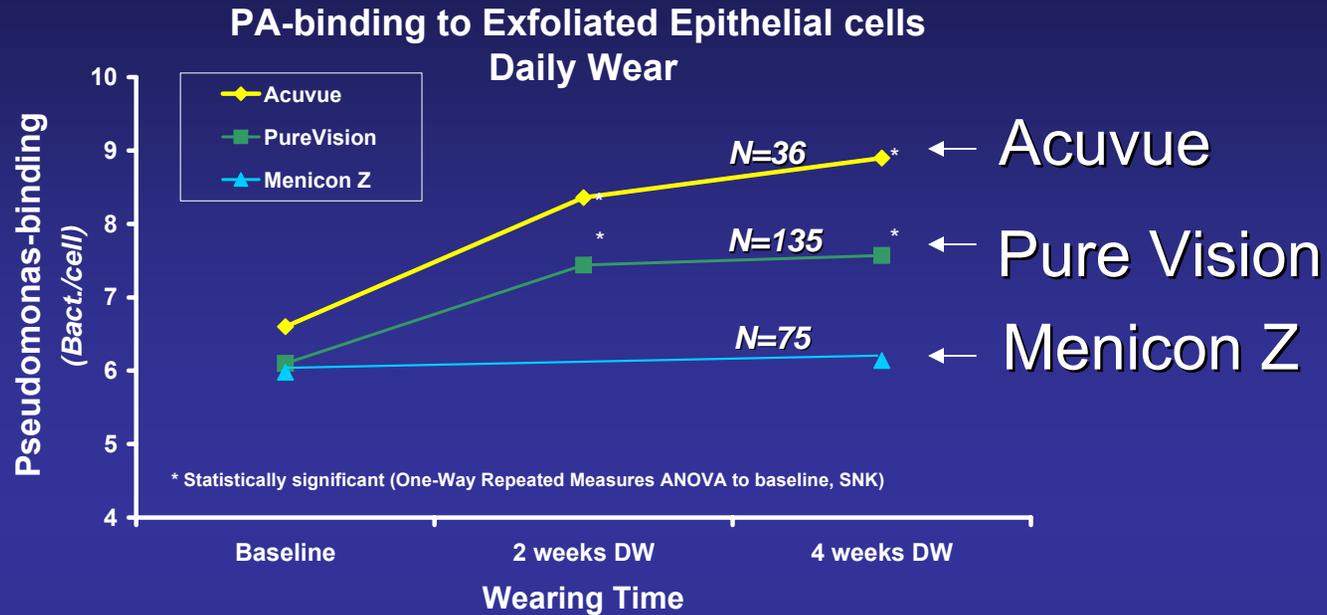
Ladage et al. Ophthalmology 2001;108:1279-88

Ren et al. Ophthalmology 2002;109:27-39

Cavanagh et al. Ophthalmology 2002; 109:1957-1969

PA Binding

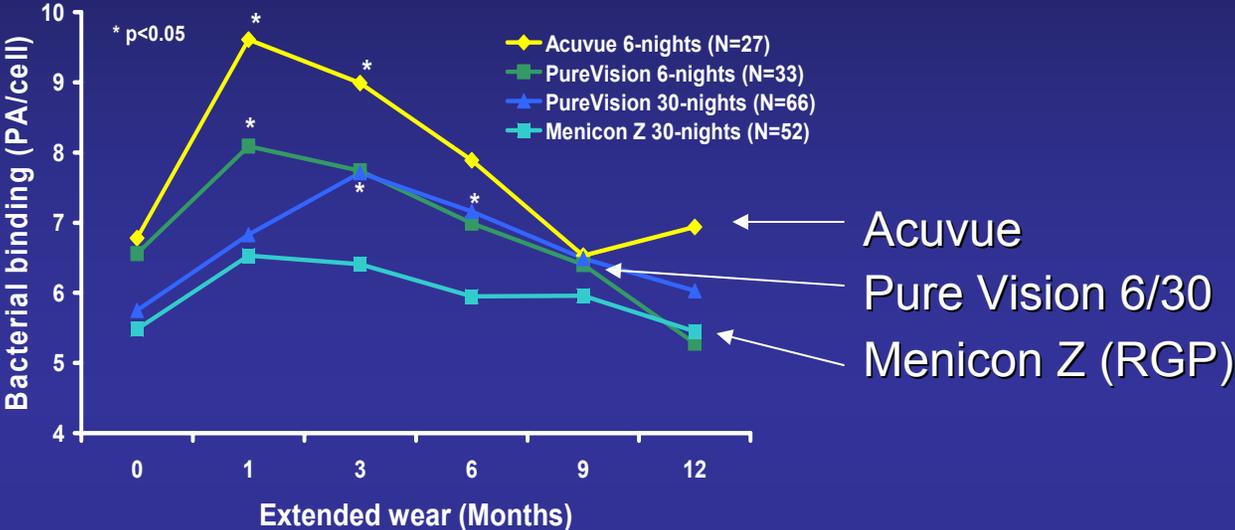
Daily Wear



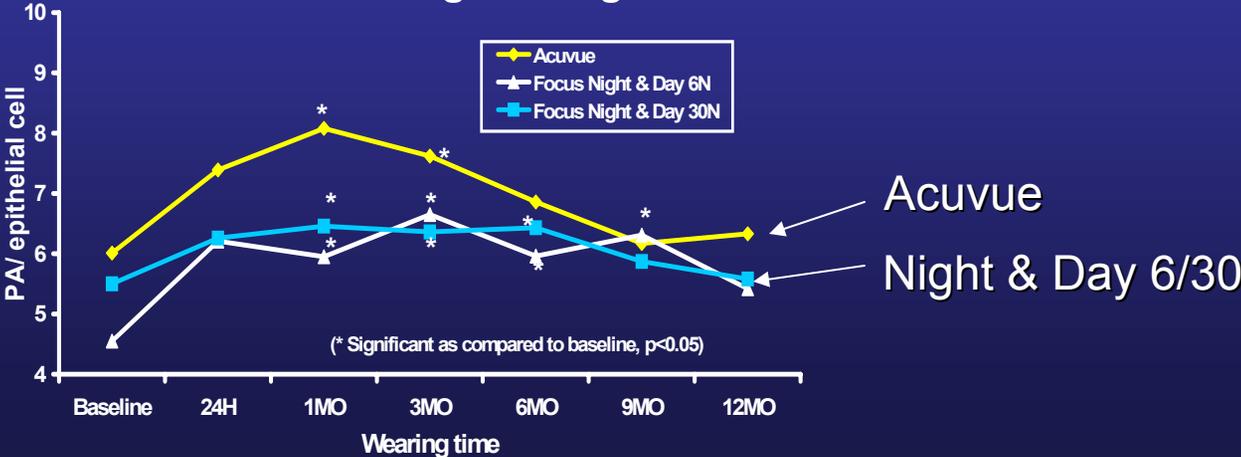
Extended Wear: Clinical Studies 12 Months

PA Binding

Bacterial binding to exfoliated corneal epithelial cells



Pseudomonas binding - Overnight wear



Conclusions

- Physiological adaptation occurs with all lens wear
Prediction: >6M adapted wearers should show lower MK rate
- Lens- O_2 and not wearing schedule (DW, EW) regulates *Pseudomonas* (PA) corneal surface binding
Prediction: MK rates should drop or not increase significantly with EW hyper O_2 lenses
- Lens-type also regulates PA-binding:
RGP < SH < conventional hydrogel lens wear
Prediction: MK rate will be the lowest for hyper RGP lens DW or EW

Orthokeratology and Microbial Keratitis

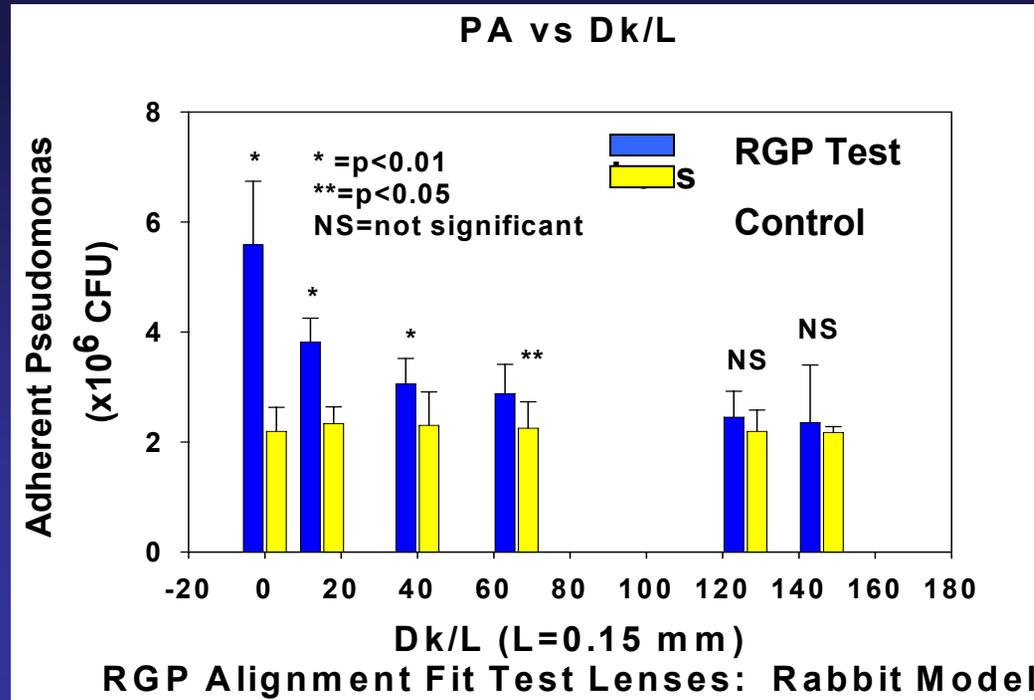
- Of 1st 50 cases reported worldwide:
 - **26/46** cases with cultured pathogens were *Pseudomonas* (57%)
 - **15/46** cases were *Acanthamoeba* (33%)

Swarbrick, *Eye & Contact Lens*, Sept, 2005

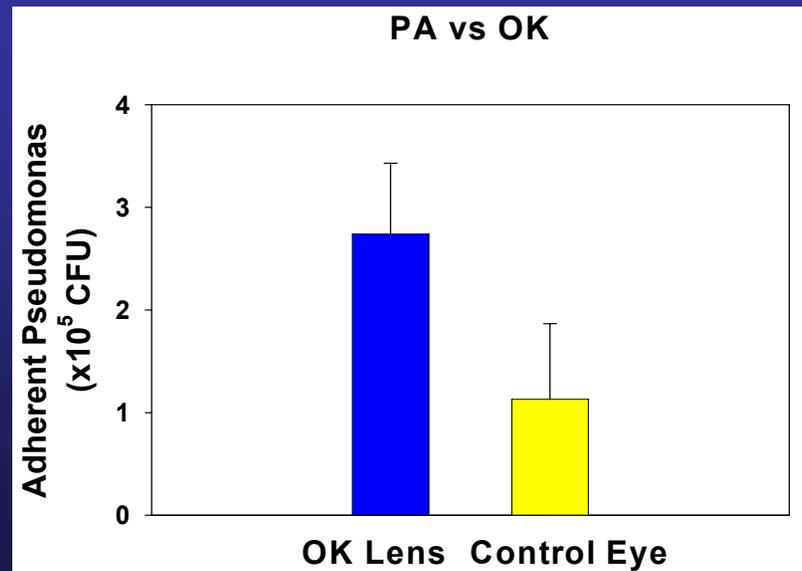
PA Binding

Rabbit Model

RGP Wear



Conventional



Ortho K

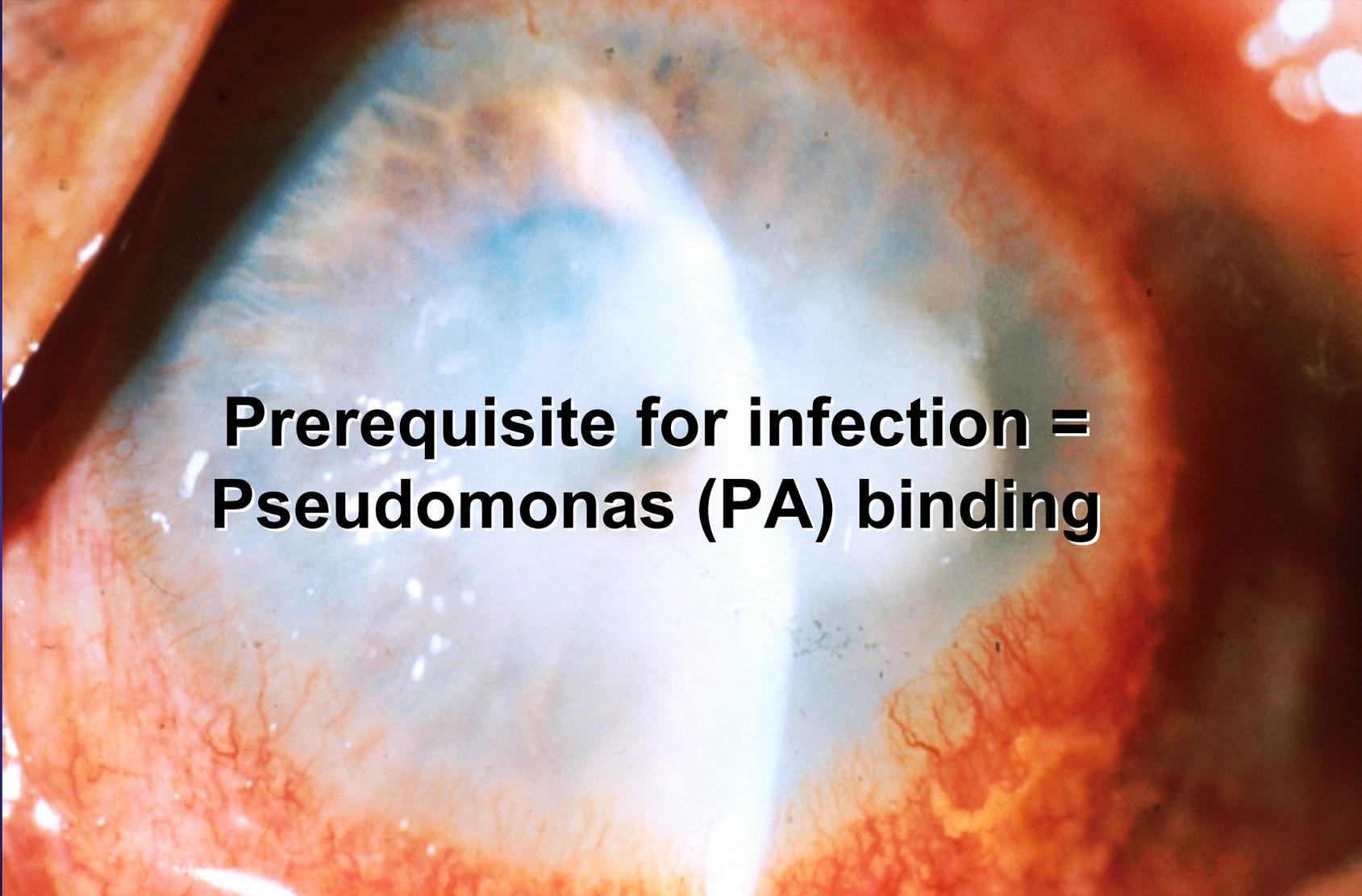
2008: The Bottom Line

- The new generation of both rigid and soft hyper-O₂ transmitting lenses should replace conventional, lower-O₂ lens use.
- Caution must be exercised when mechanical compression (Ortho K) lenses are used clinically, especially in children

**A 12-Month Clinical Trial
Comparing The Effects of Wearing
Modality of Hyper-Dk Silicone
Hydrogel Contact Lenses with
Non-preserved Solutions on
Human Corneal Epithelium**

**Danielle M. Robertson, O.D., Ph.D. and
H. Dwight Cavanagh, M.D., Ph.D.**

**The University of Texas Southwestern
Medical Center at Dallas, TX**

A close-up photograph of a contact lens on a cornea. The lens is a light blue color and is being held in place by a dark, thin instrument. The surrounding corneal tissue is a reddish-orange color. The text "Prerequisite for infection = Pseudomonas (PA) binding" is overlaid in the center of the image.

**Prerequisite for infection =
Pseudomonas (PA) binding**

Critical Questions Revisited

- What are the effects of long-term daily wear compared to de novo overnight (extended) wear of three hyper-O₂ permeable silicone hydrogel contact lenses on human corneal epithelium with non-preserved solutions?

→ *Prior studies used preserved care solutions.*

→ *Solution effects secondary to the use of chemically preserved multi-purpose solutions?*

Robertson et al., Invest Ophthalm & Vis Sci, 2008

Study Design

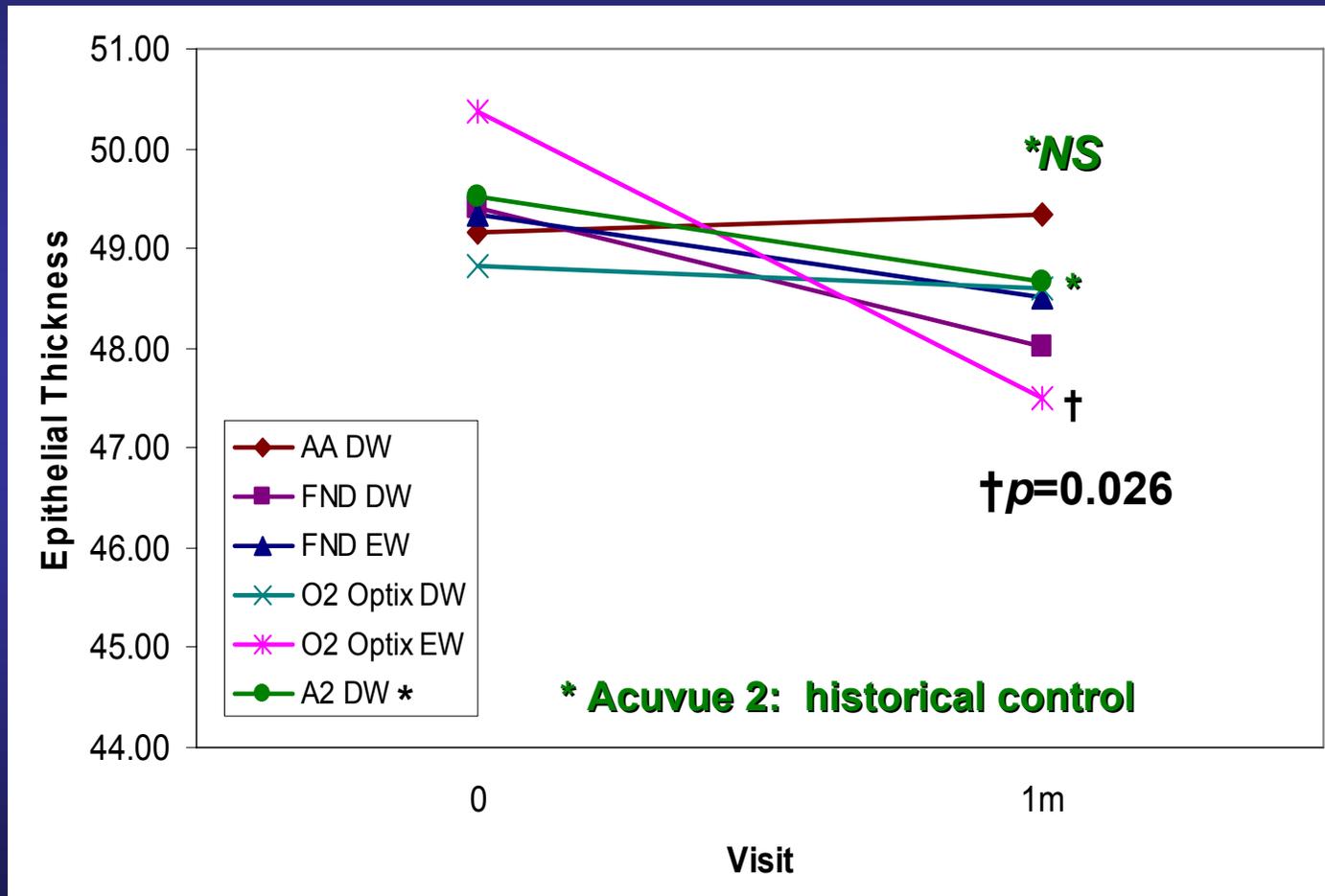
- **Prospective, Randomized, Double-masked, Single center, Parallel treatment groups**
 - National Clinical Trial (NCT00344643)
- **115 patients completed the study**
- **30 day washout period prior to lens wear**
- **Patients were assessed at baseline, 1 week, 1, 3, 6, 9 and 12 months of lens wear**

Study Design

- Lotrafilcon A
 - DW (N=31)
 - 30 N EW (N=29)
- Lotrafilcon B
 - DW (N=21)
 - 6 N EW (N=20)
- Galyfilcon A
 - DW (N=20)
- Central epithelial thickness (in vivo confocal microscopy)
- Epithelial cell exfoliation
- Pseudomonas aeruginosa binding

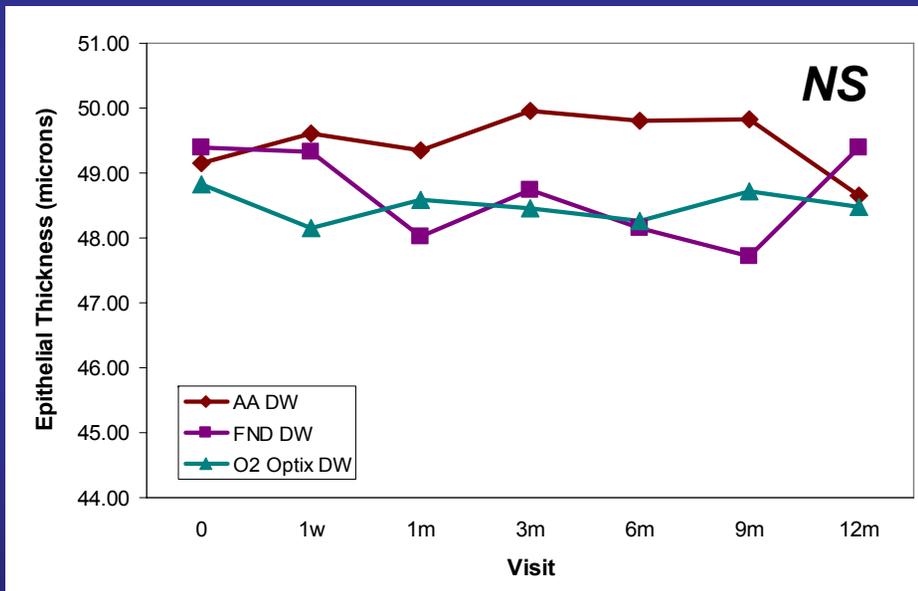
All patients dispensed Clear Care

Central Epithelial Thickness: 1 Month Lens Wear



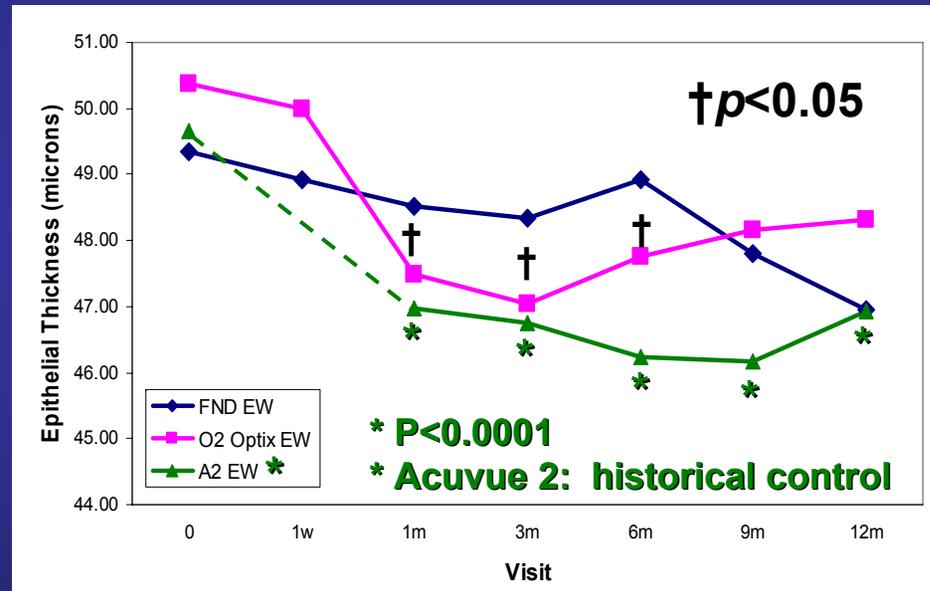
CET: 12 Months of Lens Wear

Daily Wear



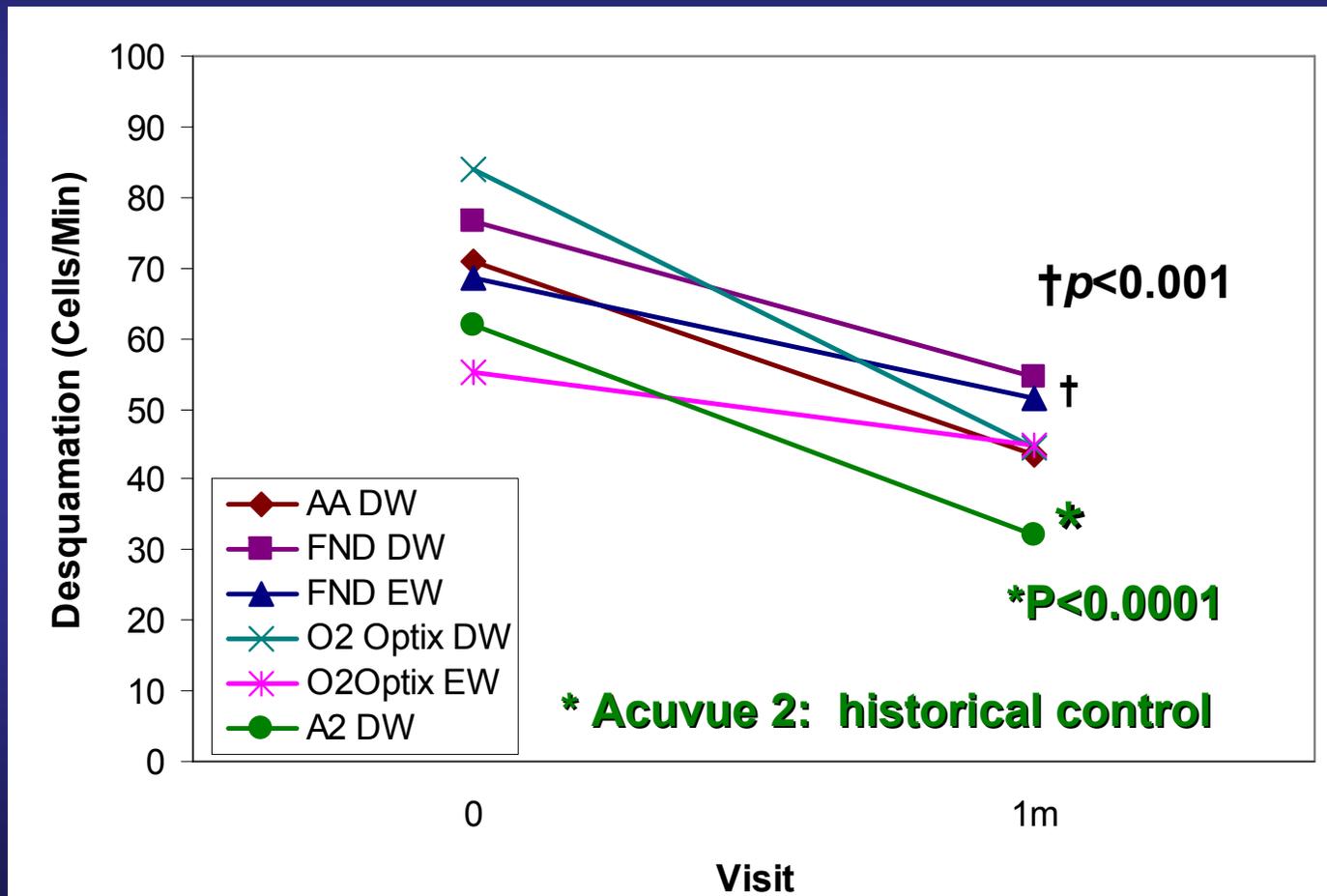
**No Effect on CET
with DW**

Extended Wear



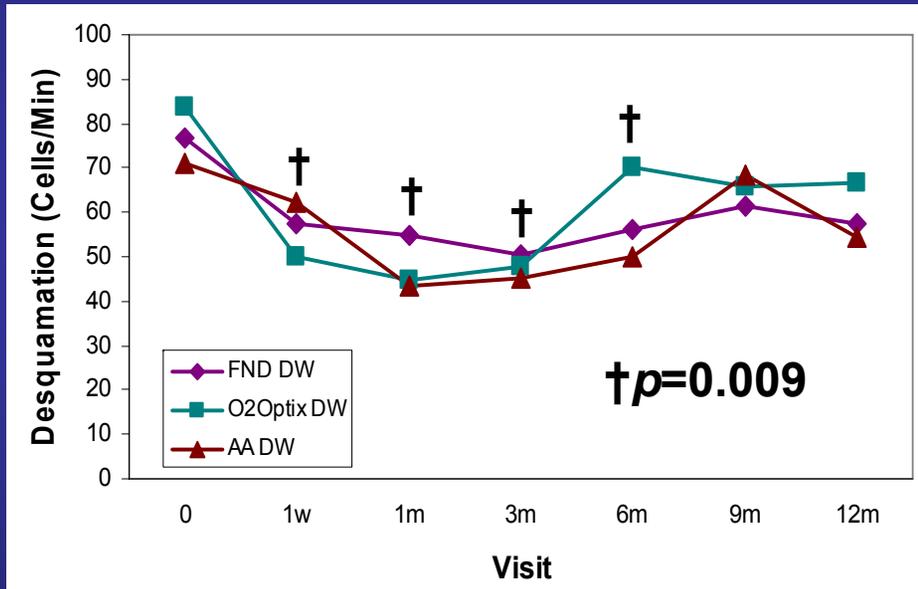
CET Thinning in EW

Epithelial Cell Exfoliation: 1 Month Lens Wear

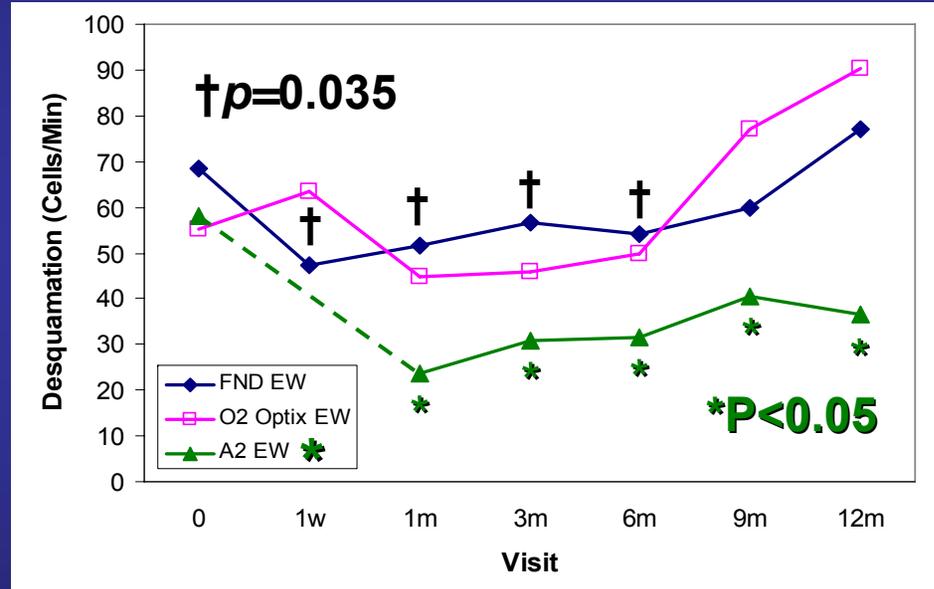


Exfoliation: 12 Months of Lens Wear

Daily Wear



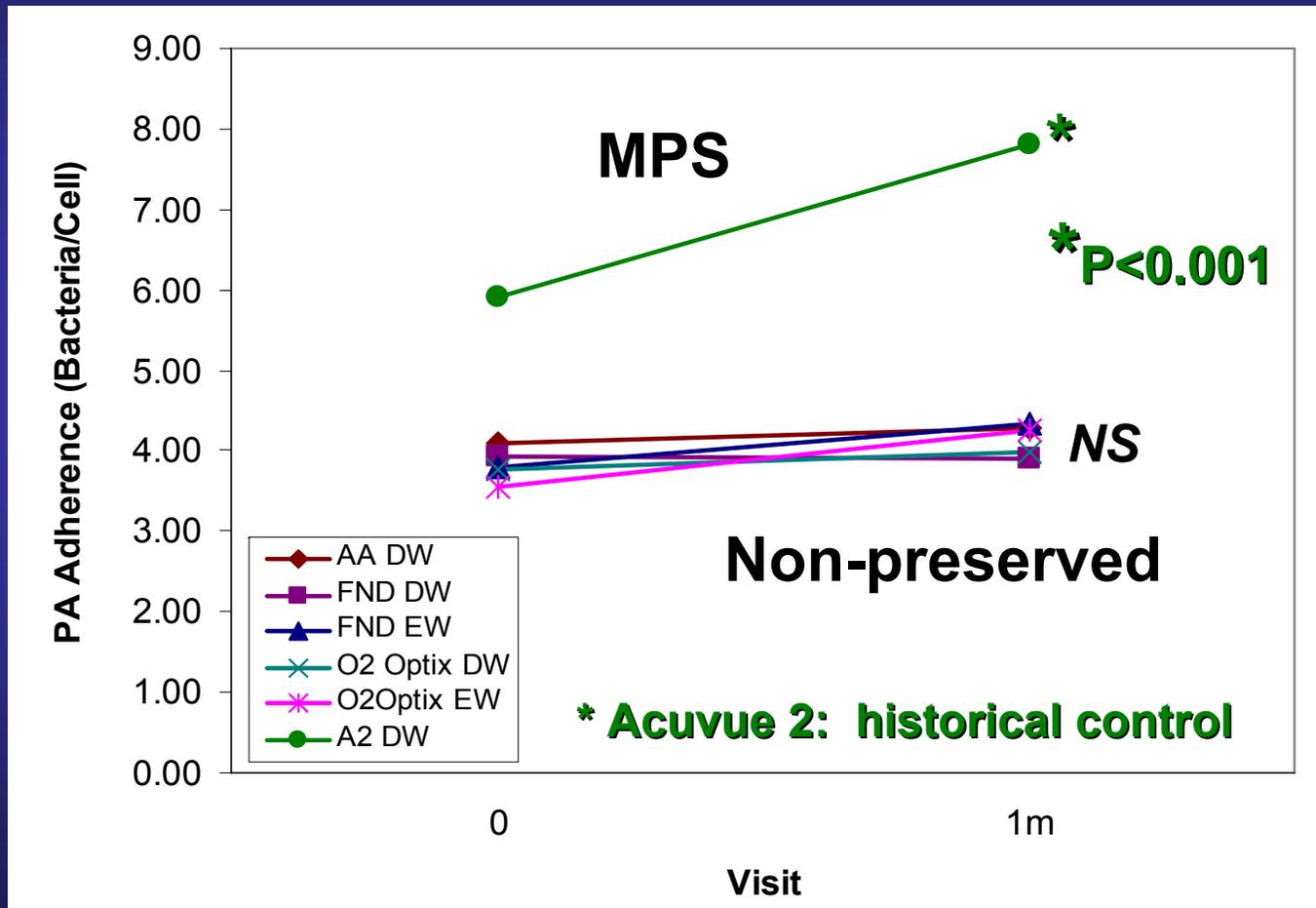
Extended Wear



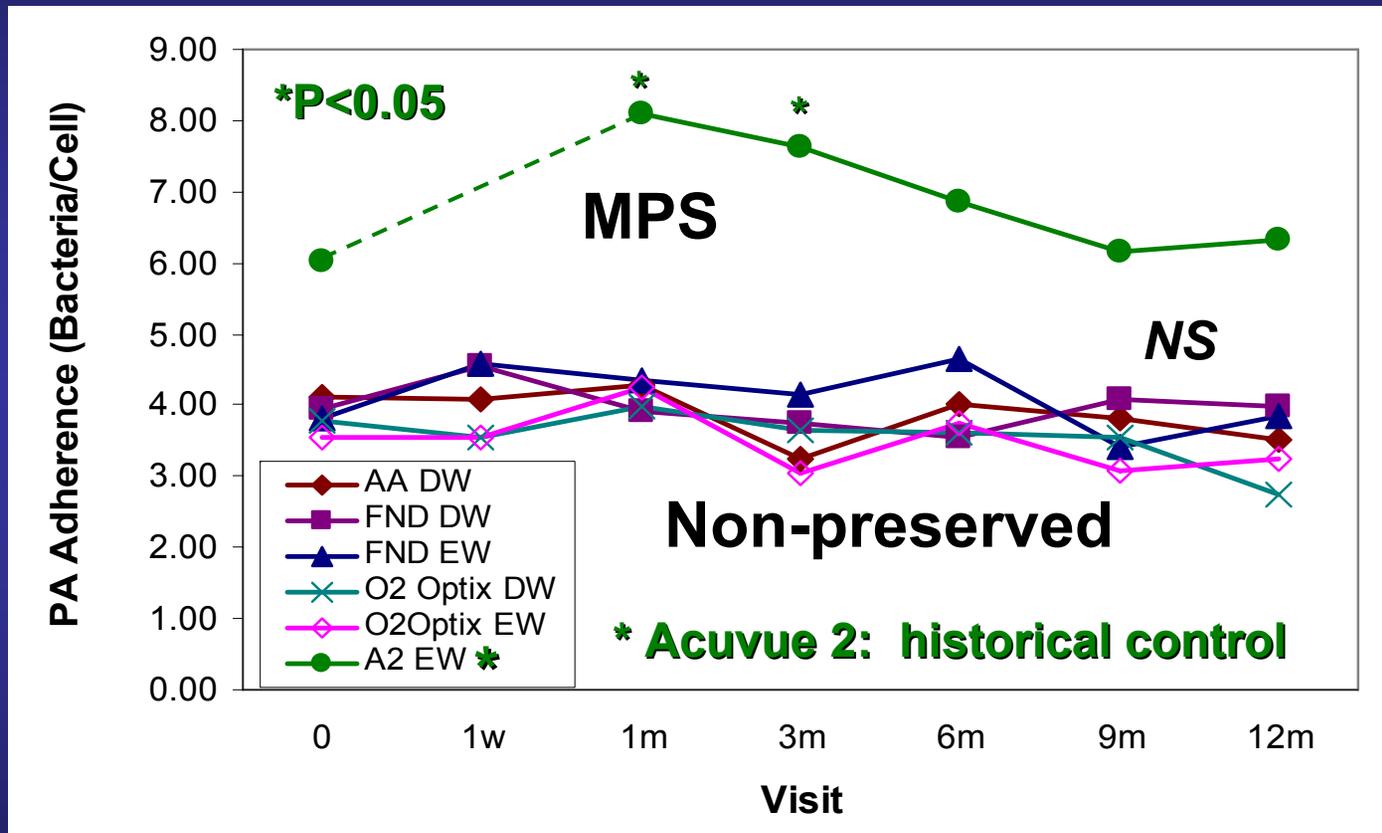
* Acuvue 2: historical control

Decrease in exfoliation in DW & EW during the initial 6 months of lens wear

PA Binding: 1 Month Lens Wear



PA Binding: 12 Months Lens Wear



No increase in PA binding was seen with any hyper-Dk lens regardless of wearing modality

Conclusions #1

- **Effects of DW on CET are Independent of Lens- O_2 .**
- **In EW mode, even with hyper Dk lenses, CET appears to decrease significantly, but recovers over one year (adapts).**
- **All lens wear (DW, EW), hyper or high oxygen transmission, decreases central epithelial surface cell desquamation with adaptive effects over 1 year.**

Conclusions #2

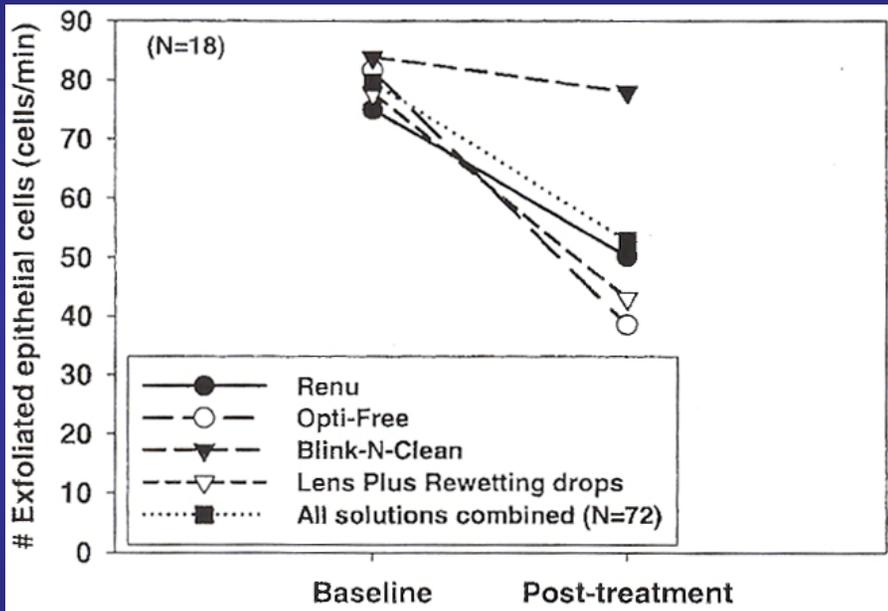
- Binding data predict the risk for PA CTL-keratitis should be *the same* for DW and *de novo* EW silicone hydrogel lens wear over 1 year.
- Assumes **NO solution-induced corneal surface damage** that could increase PA binding (Clear Care used in all studies).

Chemically Preserved Contact Lens Care Solutions

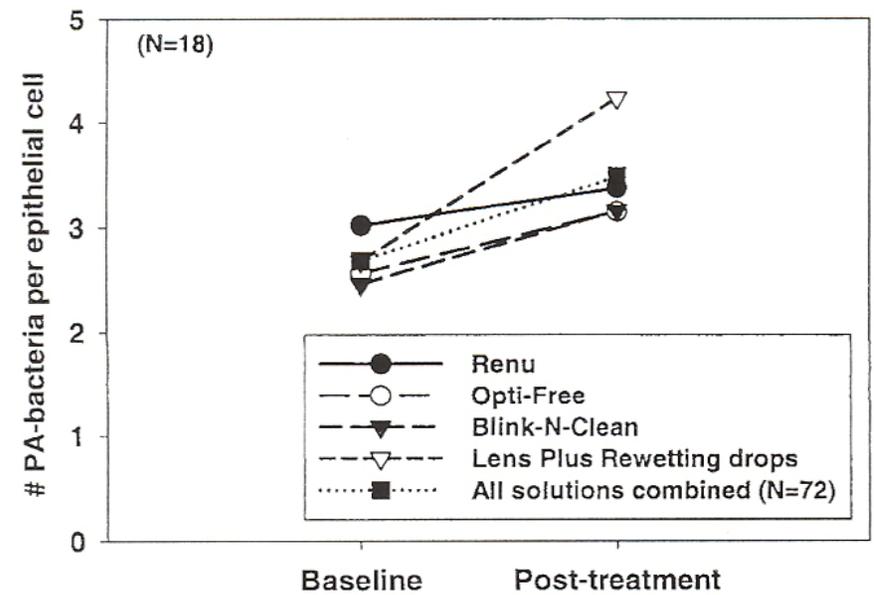
- **Li, S et al. *Eye & Contact Lens* 2003; 29: 27-30.**
- **Prospective, double-masked, randomized, cross-over clinical trial.**
- **N=20 patients (10 male; 10 female).**
- **4 lens care solutions: ReNu Multiplus; Optifree Express; Complete Blink-n-Clean, and Lens Plus Rewetting drops.**
- **Outcome measures: PA binding to exfoliated surface corneal epithelial cells; exfoliation rates.**

Results

Exfoliation



PA Binding



- All solutions decreased surface cell exfoliation ($P < 0.004$)
- All solutions raised PA binding ($P < 0.02$)

Conclusions #3

- An ↑ in PA binding suggests an ↑ in risk of infection
- No ↑ in PA binding suggests **no** ↑ in risk of infection
- An optimal **lens-solution** combination exists

