



# Diabetes and the ocular surface

Insight into the systemic disease

Never Stand Still

Science

School of Optometry and Vision Science

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**No Commercial Relationships**

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**UNSW Australia**



**Rupert Myers Building, UNSW**



# Vision hub at UNSW Australia



Centre for Eye Health



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**Optometry and  
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# The South Island



# Diabetes and the Ocular Surface

- 1. Diabetes: the systemic disease**
- 2. Neuropathy**
- 3. Corneal neuropathy**
- 4. Ocular surface integrity**

# Diabetes

*Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.*

*- World Health Organisation*

# Diabetes

## Diagnosis

- Fasting venous plasma glucose:  $\geq 7.0\text{mmol/l}$
- 2 hours after ingestion of 75g oral glucose load:  $\geq 11.1\text{mmol/l}$

## Prevalence

- NZ prevalence: 257,776<sup>1</sup>
- Worldwide: 173 million people<sup>2</sup> and continues to be on the rise<sup>3</sup>



[www.clipartsheep.com](http://www.clipartsheep.com)

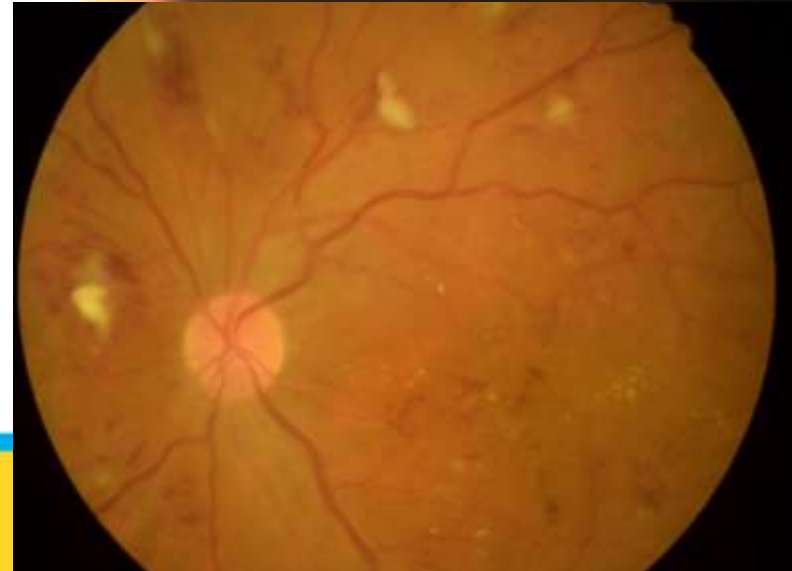
# Diabetes classification

- **Type I:**
  - 5-10% of diabetic population
  - Age onset < 30 years
  - Autoimmune destruction and loss of the secretory function of insulin-producing pancreatic  $\beta$ -cells
  - Require insulin
- **Type II:**
  - ~95% of diabetic population
  - Inadequate insulin production / utilisation
  - Risk factors: family hx, overweight, age, ethnicity
- **Impaired glucose tolerance**



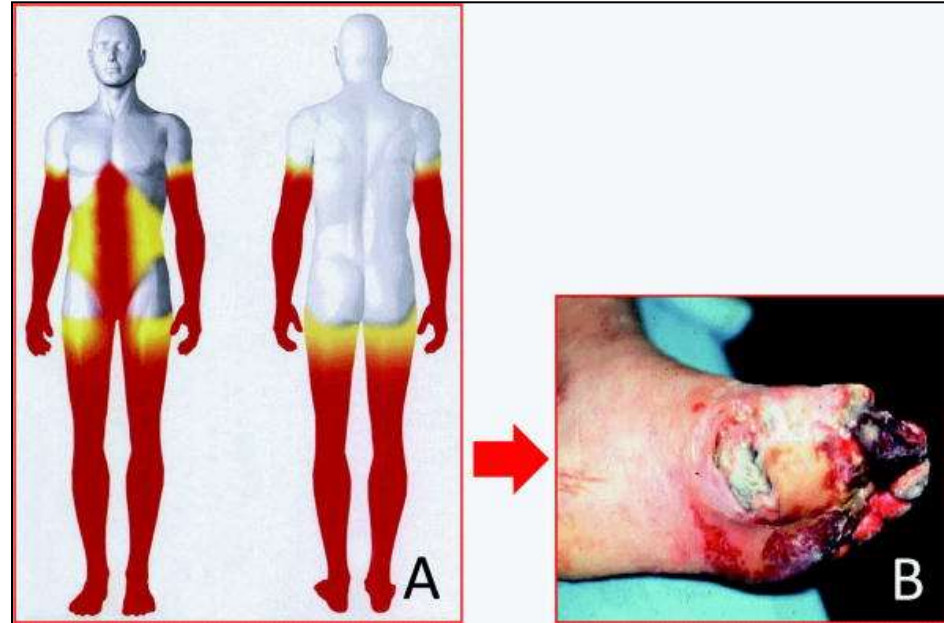
# Systemic impact of diabetes

- **Multi-system disease**
  - **Premature mortality**
  - **Macrovascular complications**
  - **Microvascular complications**
    - **Retinopathy**
      - **Retinal capillary damage**
      - **Progressive capillary occlusion → retinal ischaemia → new vessels**
    - **Nephropathy**
    - **Neuropathy**



# Diabetic Peripheral Neuropathy

- 60-70% of people with diabetes
- “chronic, symmetrical, length-dependent diabetic sensorimotor polyneuropathy”<sup>1</sup>
- Foot ulceration -> 7% of patients<sup>2</sup>
  - lower limb amputation, severe pain
  - Significant quality of life costs and financial burden (28K USD at 2 years!)<sup>3</sup>
- Early and accurate detection



The Glenn A. Fry Award Lecture 2010: Ophthalmic Markers of Diabetic Neuropathy. Efron, Nathan Optometry & Vision Science. 88(6):661-683, June 2011.

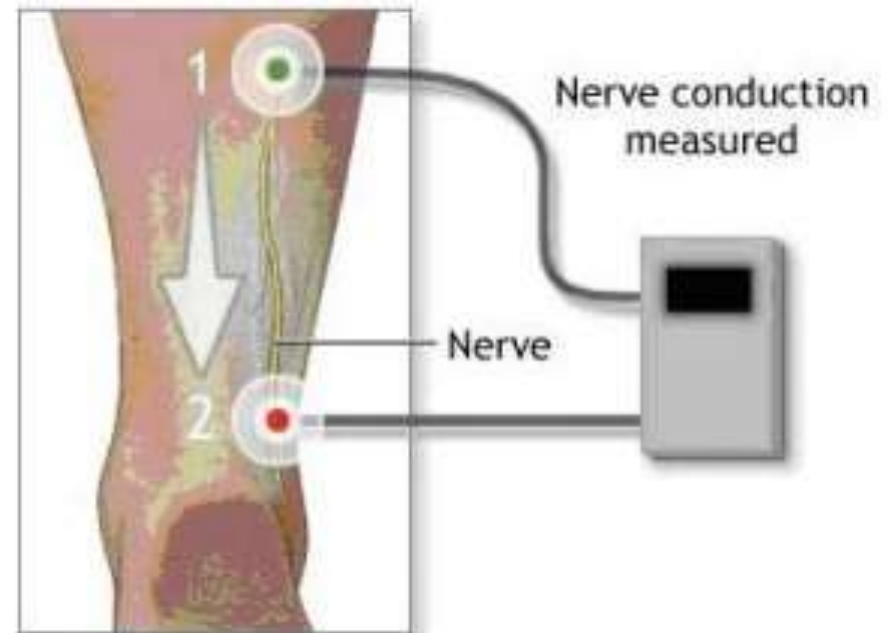
1. Toronto Diabetic Neuropathy Expert Group
2. Tavakoli M, Mitu-Pretorian M, Petropoulos IN *et al. Diabetes* 2013.
3. Ramsey SD, Newton K, Blough D *et al. Diabetes care* 1999.

# Conventional measures of diabetic peripheral neuropathy

## Quantitative Sensory Testing (QST)



## Nerve conduction testing



<http://www.americanimagingpr.com/diabetic-polyneuropathy-and-nerve-conduction-testing/>

S. Javed , I.N. Petropoulos , M. Tavakoli , R.A. Malik Chapter 20 - Clinical and diagnostic features of small fiber damage in diabetic polyneuropathy Handbook of Clinical Neurology, Volume 126, 2014, 275 - 290

# Conventional measures of diabetic peripheral neuropathy

## Intra-epithelial fiber density measurement in a skin biopsy

- Measures small nerve fiber changes objectively
- BUT... it is invasive and non-repeatable
  - Not appropriate for clinical trials or longitudinal studies



S. Javed , I.N. Petropoulos , M. Tavakoli , R.A. Malik Chapter 20 - Clinical and diagnostic features of small fiber damage in diabetic polyneuropathy Handbook of Clinical Neurology, Volume 126, 2014, 275 - 290



# Corneal confocal microscopy

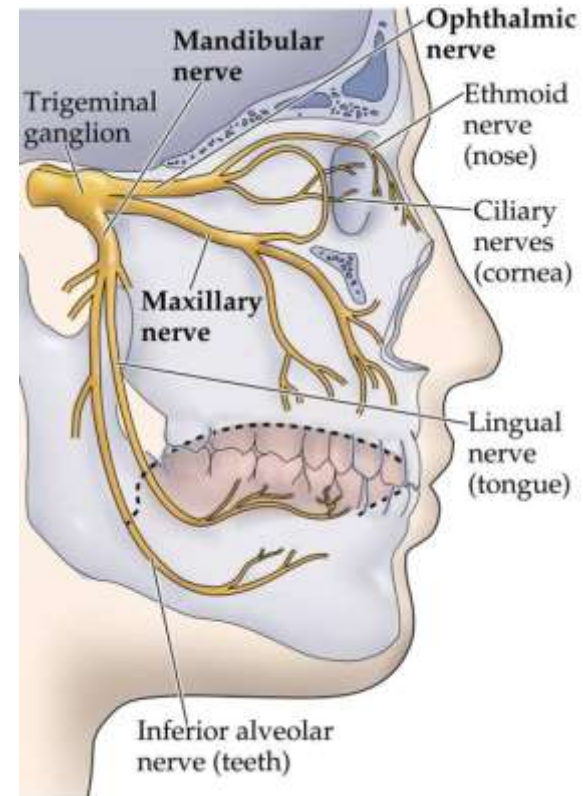
- Only organ where we can directly visualise nerves *in vivo*
- Single points of tissue simultaneously illuminated & imaged in the same plane
- Resulting image very high in resolution<sup>1</sup>
- 500× magnification
- 400 x 400  $\mu\text{m}$  dimension



Photo courtesy: Dr Vinod Maseedupally

# Corneal nerve structure and function

- Most densely innervated organ in the body<sup>1</sup>
- 100x more sensitive than the conjunctiva<sup>1</sup>
- Derived from the ophthalmic division of the trigeminal nerve

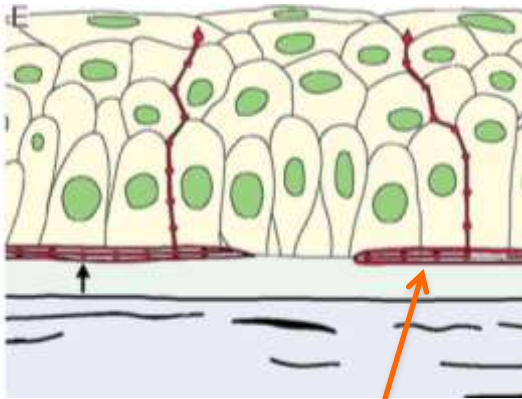


<http://www.edoctoronline.com/medical-atlas.asp?c=4&id=21956>

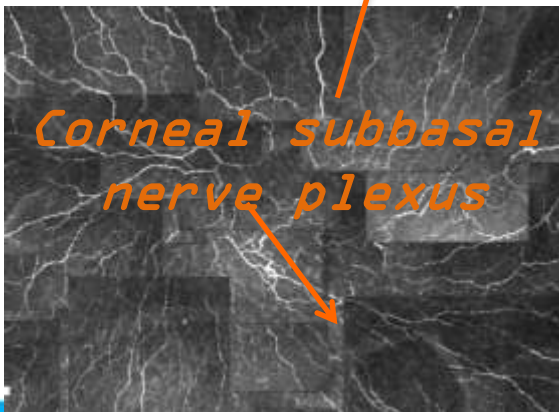
1. Cruzat A, Pavan-Langston D, Hamrah P. In vivo confocal microscopy of corneal nerves: analysis and clinical correlation. *Seminars in ophthalmology* 2010; 25: 171-177.



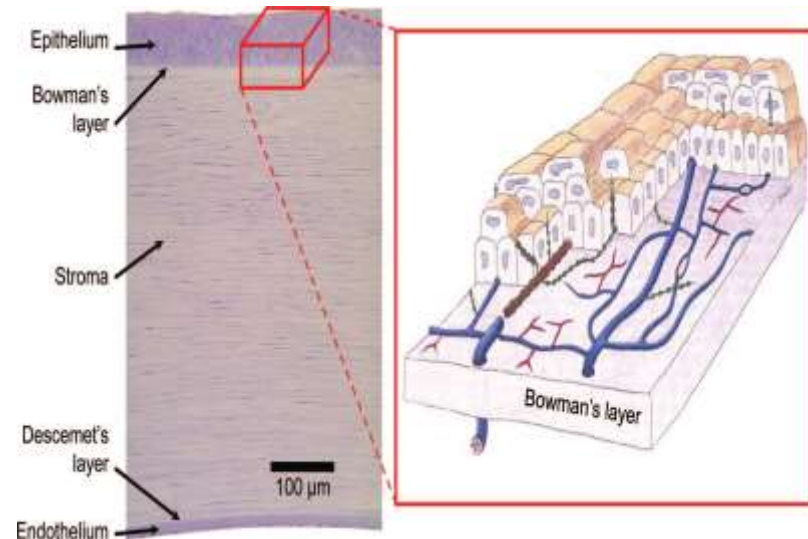
# Corneal nerve structure and function



The Glenn A. Fry Award Lecture 2010:  
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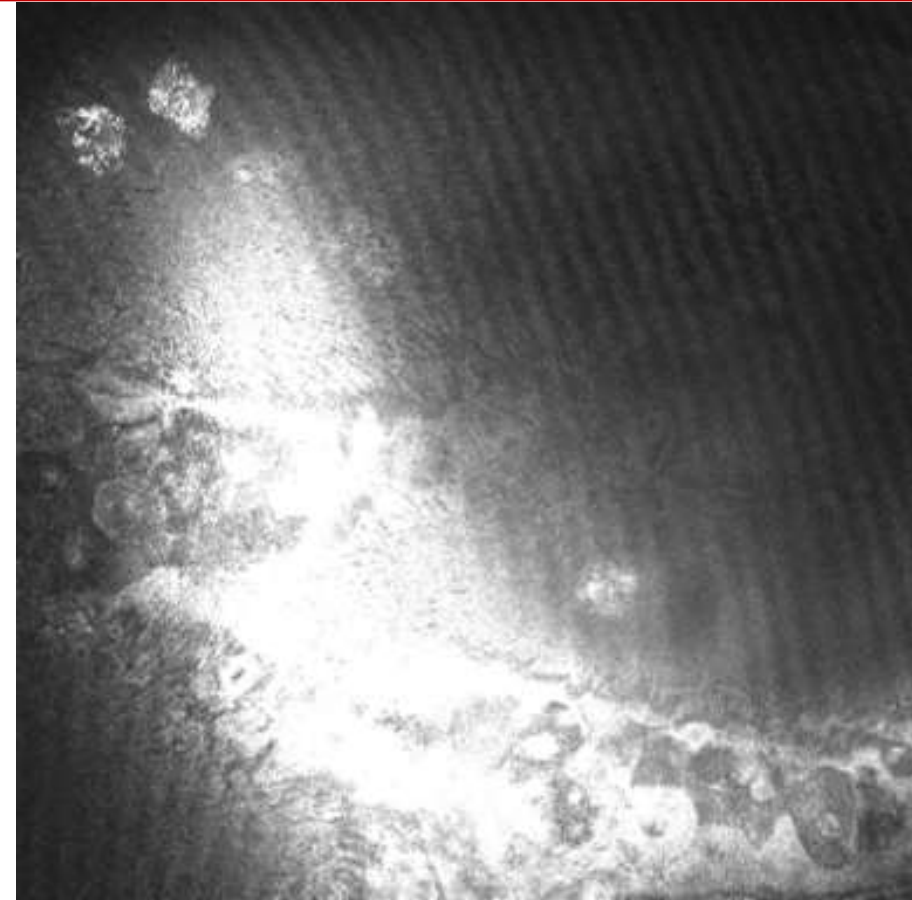


- Nerve bundles enter the cornea at the limbus parallel to the corneal surface
- Penetrate Bowman's layer to form the corneal subbasal nerve plexus



The Glenn A. Fry Award Lecture 2010: Ophthalmic Markers of Diabetic Neuropathy.  
Efron, Nathan Optometry & Vision Science. 88(6):661-683, June 2011.

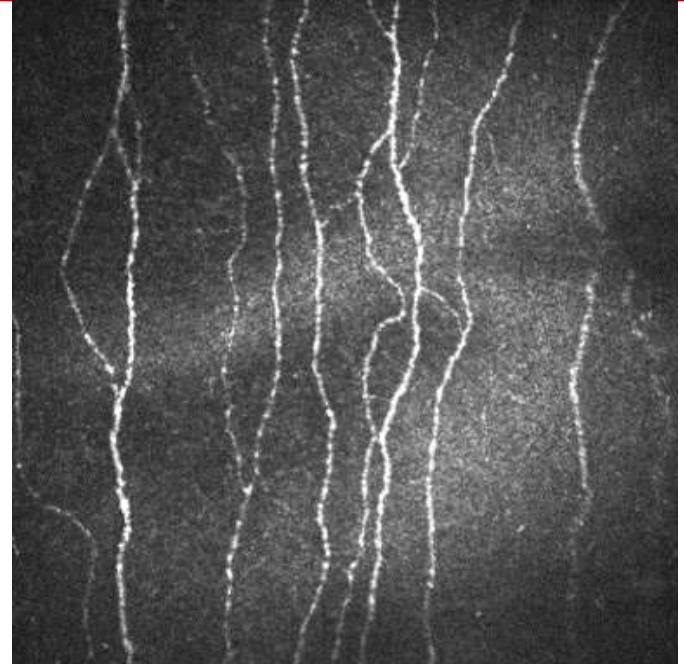
# Corneal confocal microscopy



Cornea Volume [2], 18/12/2009, OD

# 1 / 40: 97  $\mu$ m

HEIDELBERG  
ENGINEERING

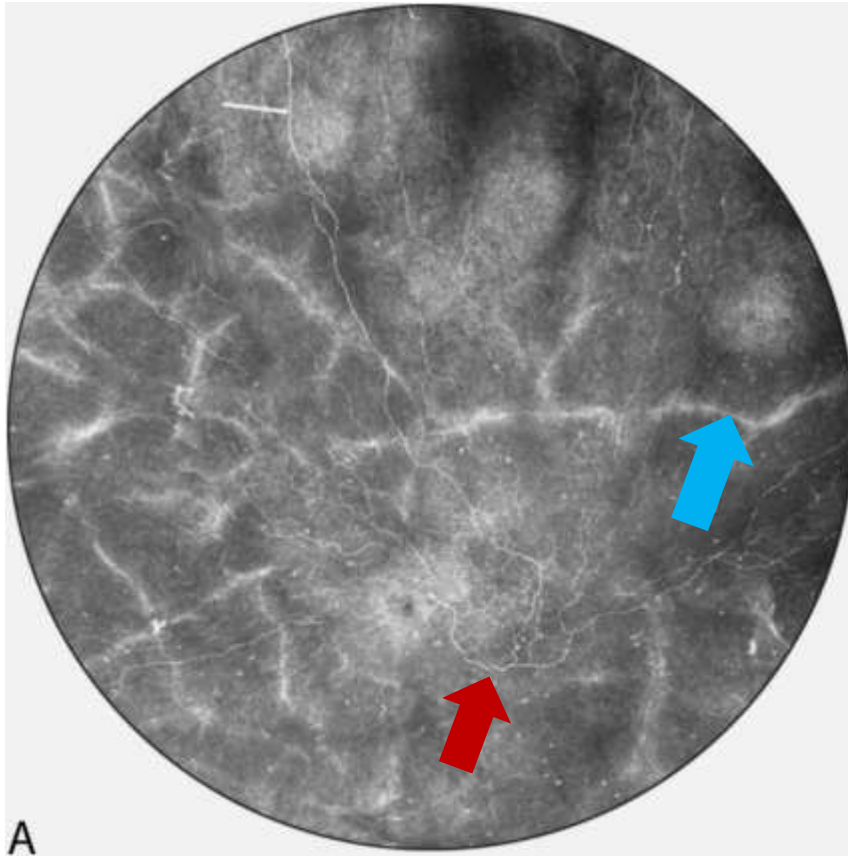


- Nerve fibre bundle density
- Nerve branch density
- Nerve fibre length
- Nerve fibre width
- Nerve fibre tortuosity

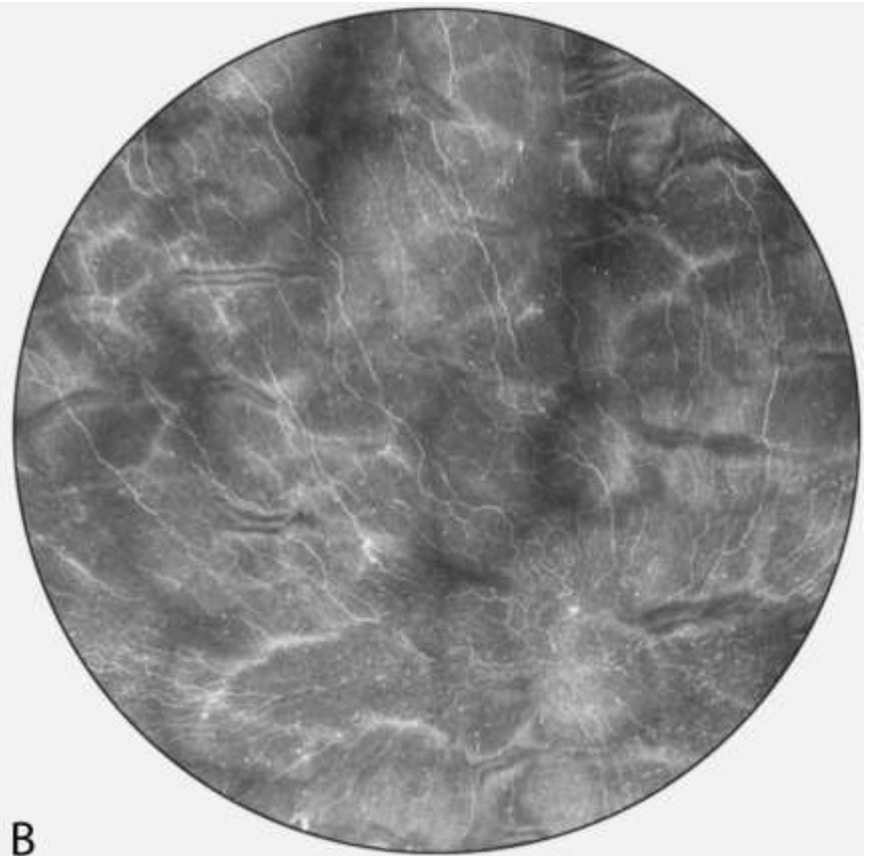


# Corneal montage

Diabetes WITH neuropathy



Diabetes WITHOUT neuropathy

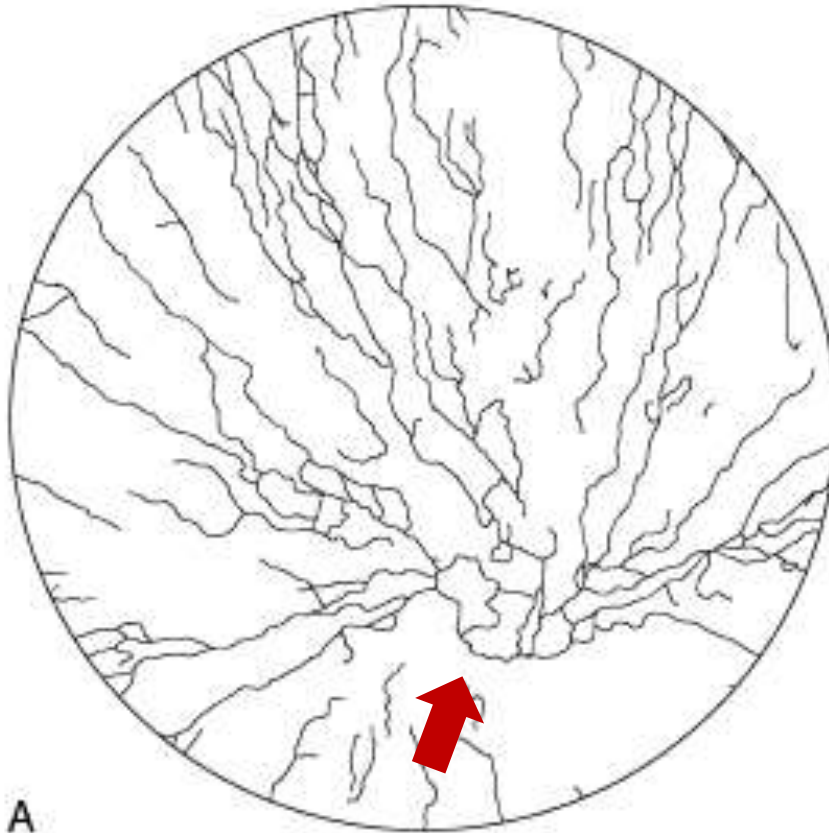


Nerve mapping technique originally developed by Patel and McGhee

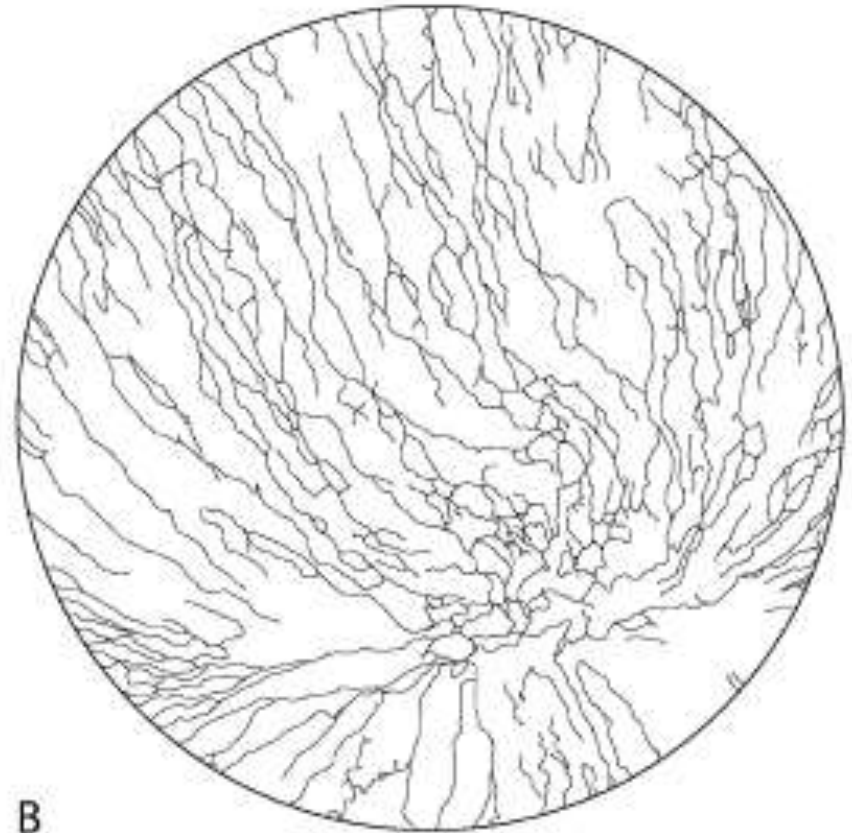


# Corneal montage

Diabetes **WITH** neuropathy

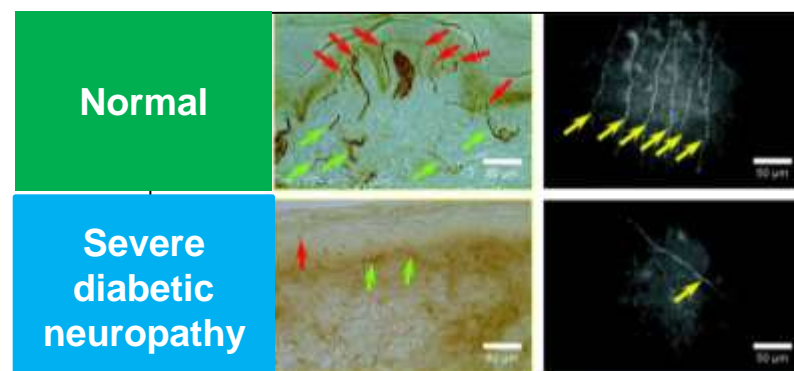
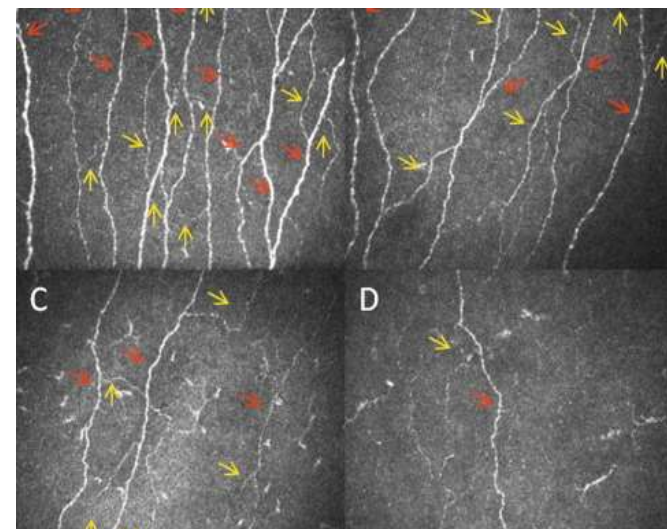


Diabetes **WITHOUT** neuropathy



# Corneal confocal microscopy

- **Diabetes with neuropathy:**
  - ↓ Corneal nerve density
  - ↓ corneal nerve length
  - ↓ corneal nerve branch density<sup>1,2</sup>
- **Corneal nerve parameters correlate well with nerve fibre loss in skin biopsy<sup>1</sup>**
- **Can be used to detect and stratify the severity of diabetic peripheral neuropathy**



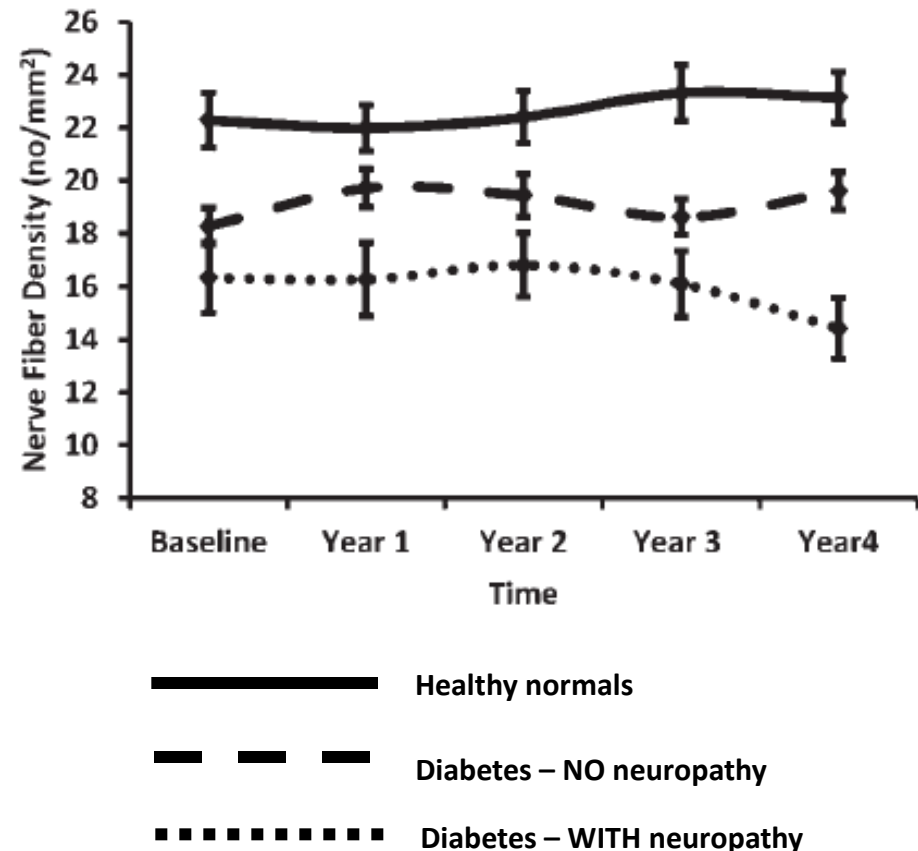
The Glenn A. Fry Award Lecture 2010: Ophthalmic Markers of Diabetic Neuropathy. Efron, Nathan Optometry & Vision Science. 88(6):661-683, June 2011.

1. Edwards K, Pritchard N, Vagenas D et al. *Clinical & Experimental Optometry*, 2012; 95: 348-354.
2. Dehgani C, Pritchard N, Edwards K et al. *Cornea*, 2014; 55: 7982-7990



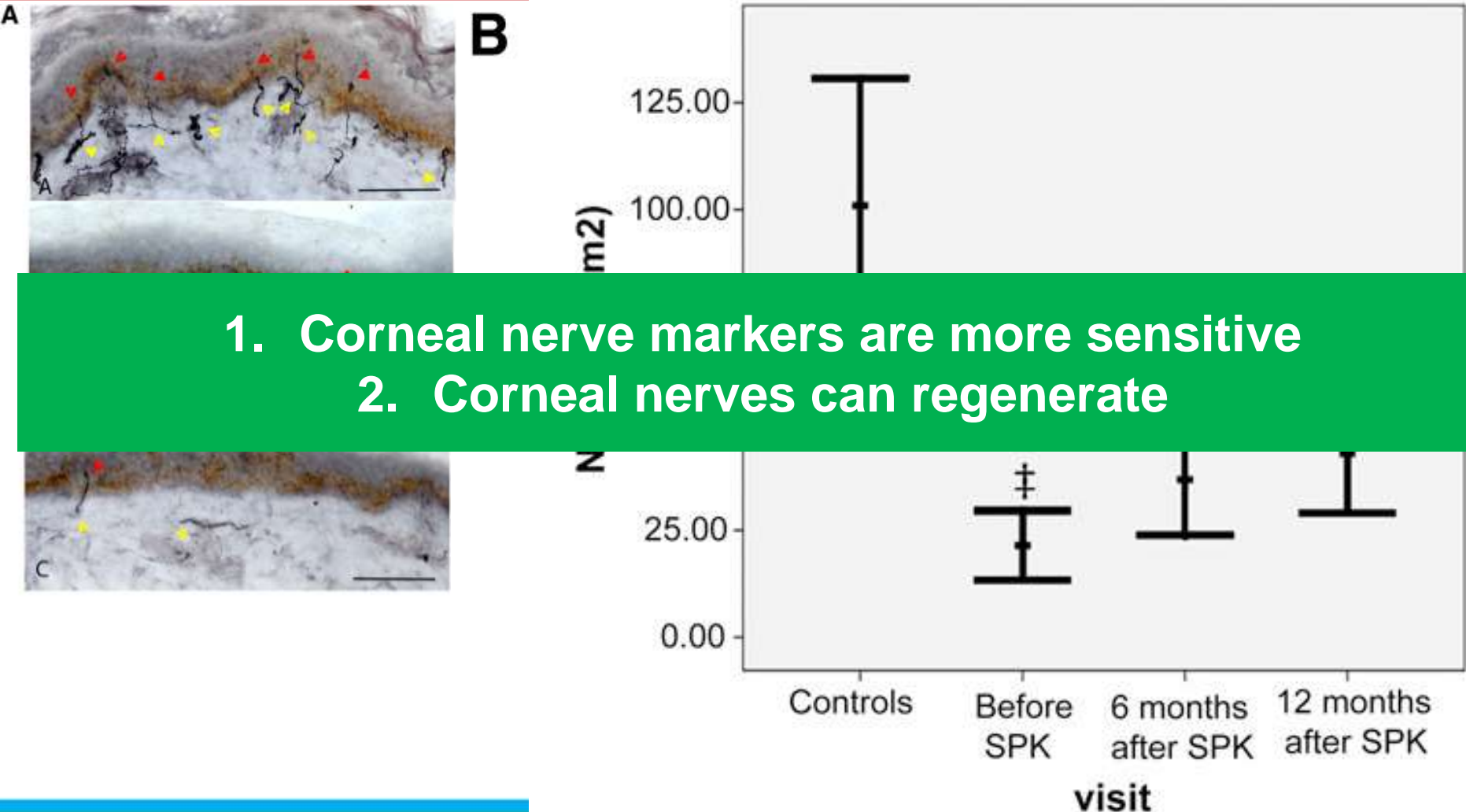
# Predicting diabetic peripheral neuropathy

- Corneal nerve length can predict peripheral neuropathy<sup>1</sup>
  - 90 px with type 1 diabetes and no DPN
  - Corneal nerve length could predict DPN incidence with 63% sensitivity and 74% specificity



# Corneal nerve regeneration

## - After pancreas and kidney transplantation-



1. Corneal nerve markers are more sensitive
2. Corneal nerves can regenerate

# Corneal nerve function

## Corneal nerves

- Trophic support to epithelial cells, lacrimal gland, and goblet cells
- Stimulate cell growth, mitosis, differentiation and migration

## Epithelial cells

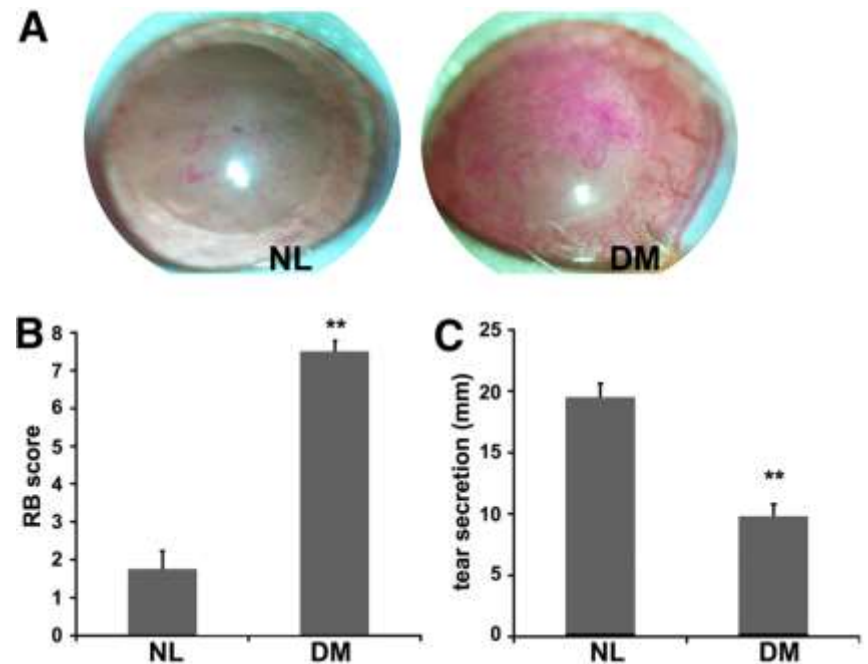
- Trophic support to neurons
- Secrete growth factors
- Promote neurite extension

## In diabetes

- Reduction in these mediators
- Disruption in epithelial integrity - ↑ risk of corneal erosions
- Neurotrophic keratopathy

# Dry eye in diabetes

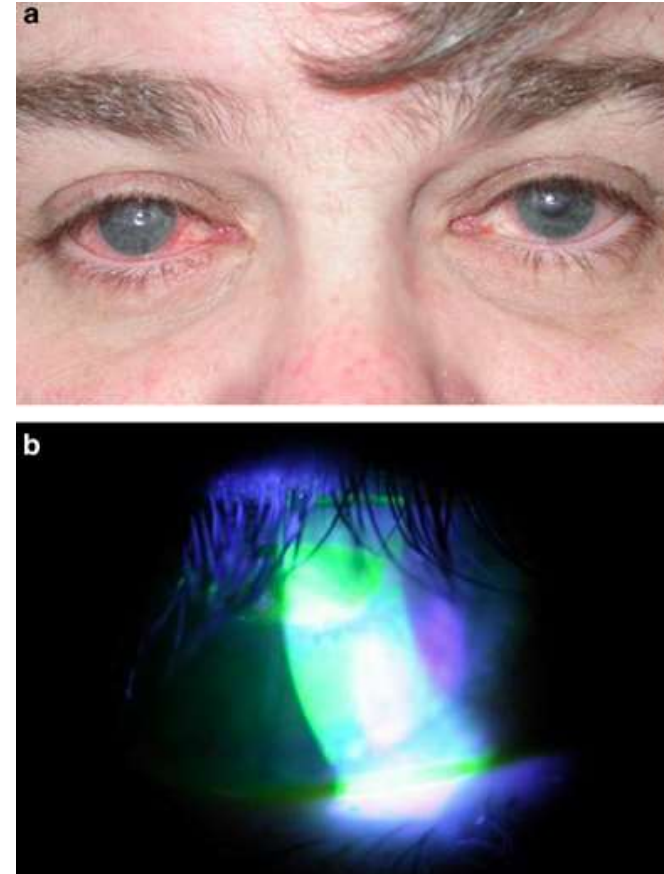
- **↑ dry eye signs & symptoms**
- **↑ severity with diabetes severity**
- **↓ Tear production**
- **↓ Tear film stability**
- **↓ goblet cell density**



Yin et al., Invest Ophthalmol Vis Sci. 2011;52:6589–6596

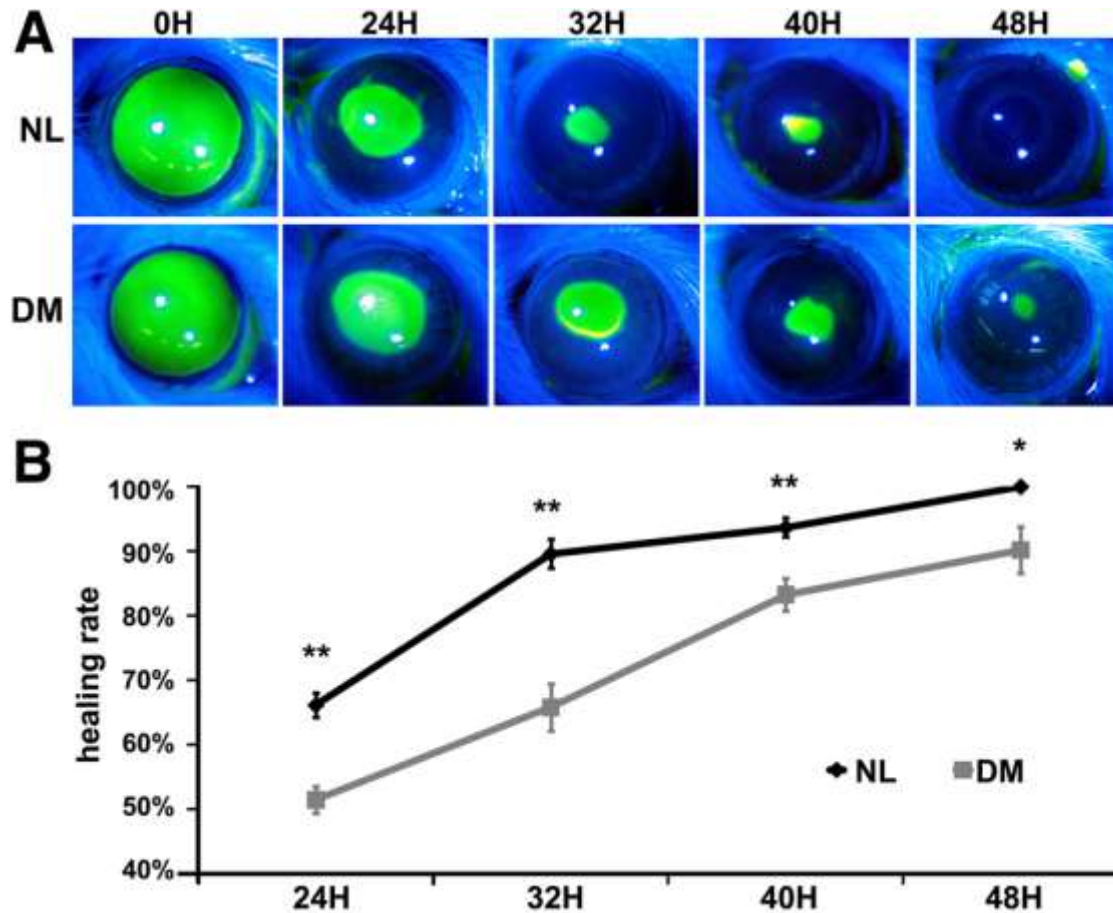
# Neurotrophic keratopathy

- Impaired corneal sensitivity
- Epithelial breakdown
- Delayed wound healing
- Corneal ulceration
- Vision loss<sup>1</sup>
- These signs increase with neuropathic severity, and severity of diabetes<sup>2</sup>



1. Alves Mde C, Carnevalheira JB, Modulo CM *et al.* Tear film and ocular surface changes in diabetes mellitus. *Arquivos brasileiros de oftalmologia* 2008; 71: 96-103.
2. O'Donnell C, Efron N. Diabetes and contact lens wear. *Clinical & experimental optometry : journal of the Australian Optometrical Association* 2012; 95: 328-337.

# Neurotrophic keratopathy





# Standard treatment

- **Preservative free lubricants**
- **Minimising evaporation – punctal plugs**
- **Topical antibiotics**
- **Bandage CL**
- **Patching**
- **Tarsorrhaphy / induced ptosis**

# Growth Factors

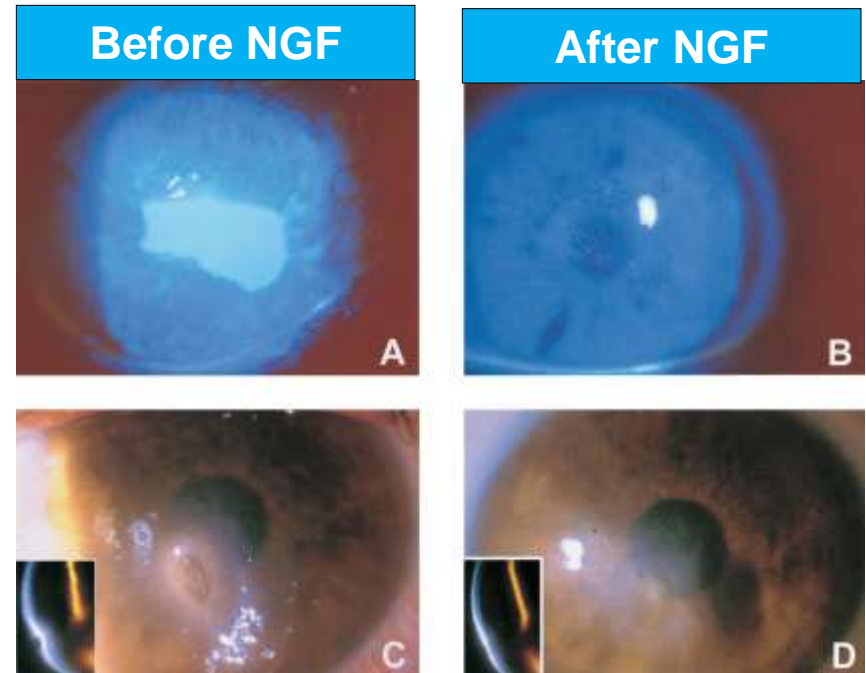
- **Insulin-like growth factor-1 (IGF-1)**
  - Mediates proliferation and differentiation
- **Substance P**
  - Neurotransmitter
  - Reduced in eyes with hypoesthesia
- **IGF-1 and Substance P**
  - *In vitro*: stimulate epithelial migration
  - *In vivo*: effective in treating neurotrophic ulcers<sup>1</sup> and superficial punctate keratitis<sup>2</sup>



# Growth Factors

- **Nerve Growth Factor**

- Modulates ocular inflammation
- Corneal epithelial proliferation and differentiation
- Wound healing promoted<sup>1</sup>
- No relapse<sup>1</sup>



Bonini et al, *Ophthalmology* 2000;107:1347–1352

# Summary

- **Expect greater application of the confocal microscopy in both research and clinical settings**
- **Beware of diabetic ocular surface disease**
- **Future treatments:**
  - NGF
  - IGF & Substance P
- **Expect expanded role of optometry in the management of diabetic peripheral neuropathy**

# Acknowledgements

**Jenny Wu**  
Canberra



New Zealand Association  
of Optometrists



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