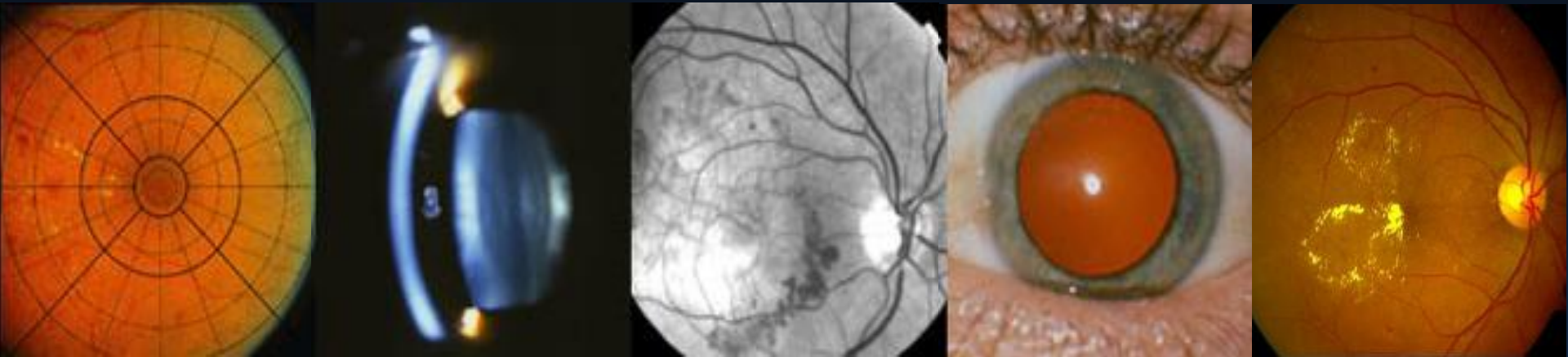


Diabetic Retinopathy Past, Present & Future

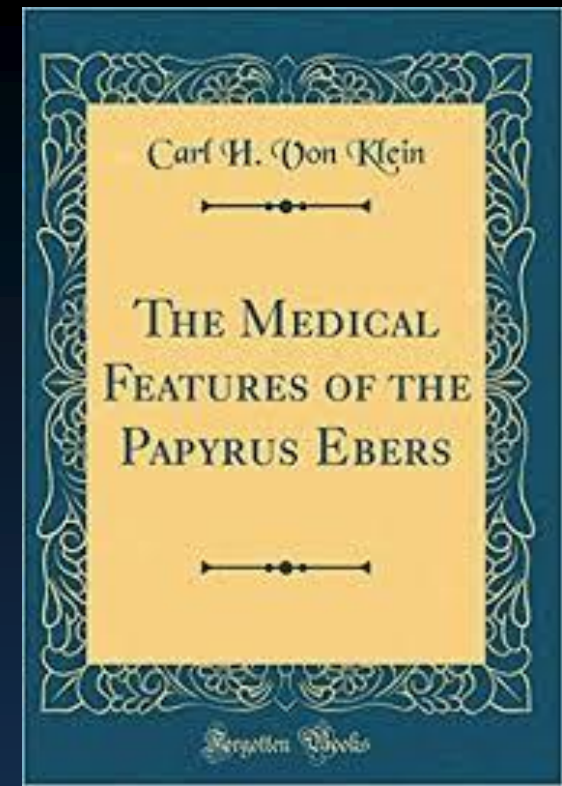


Dr. R.D.Ravindran
Chairman
Aravind Eye Hospital,
Madurai



Diabetes

- Diabetes was described in 1552 B.C. in the Papyrus Ebers by Dr. Hesa-Ra, an Egyptian physician as a disease involving urination and emaciation
- The term has a Greek origin meaning copious urination, & “honey”, characterizing the loss of sugars in urine.
- By 500 A. D.: had been differentiated into Type 1 disease - apparent in young individuals & Type 2 disease, which affects adults & is related to weight.



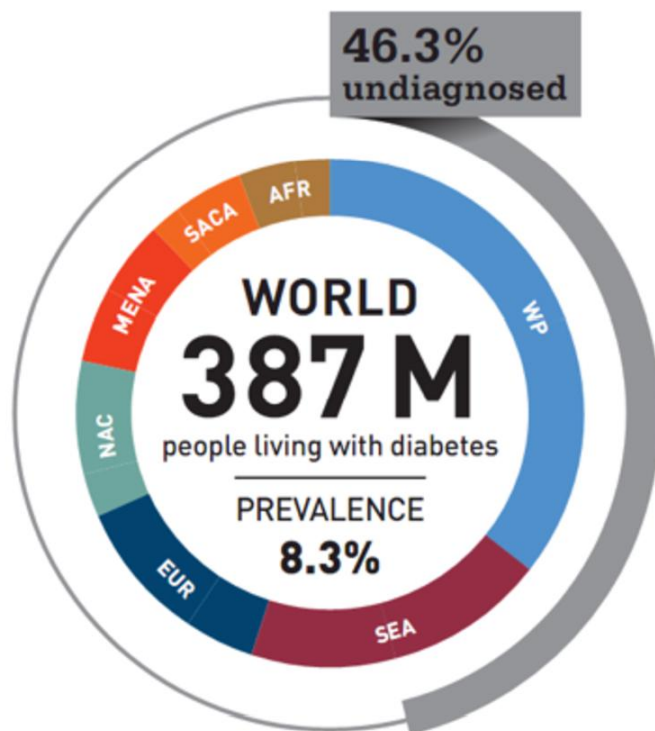
Diabetes is a huge and growing problem...

WORLD
592
million

53%
Increase

2014

2035



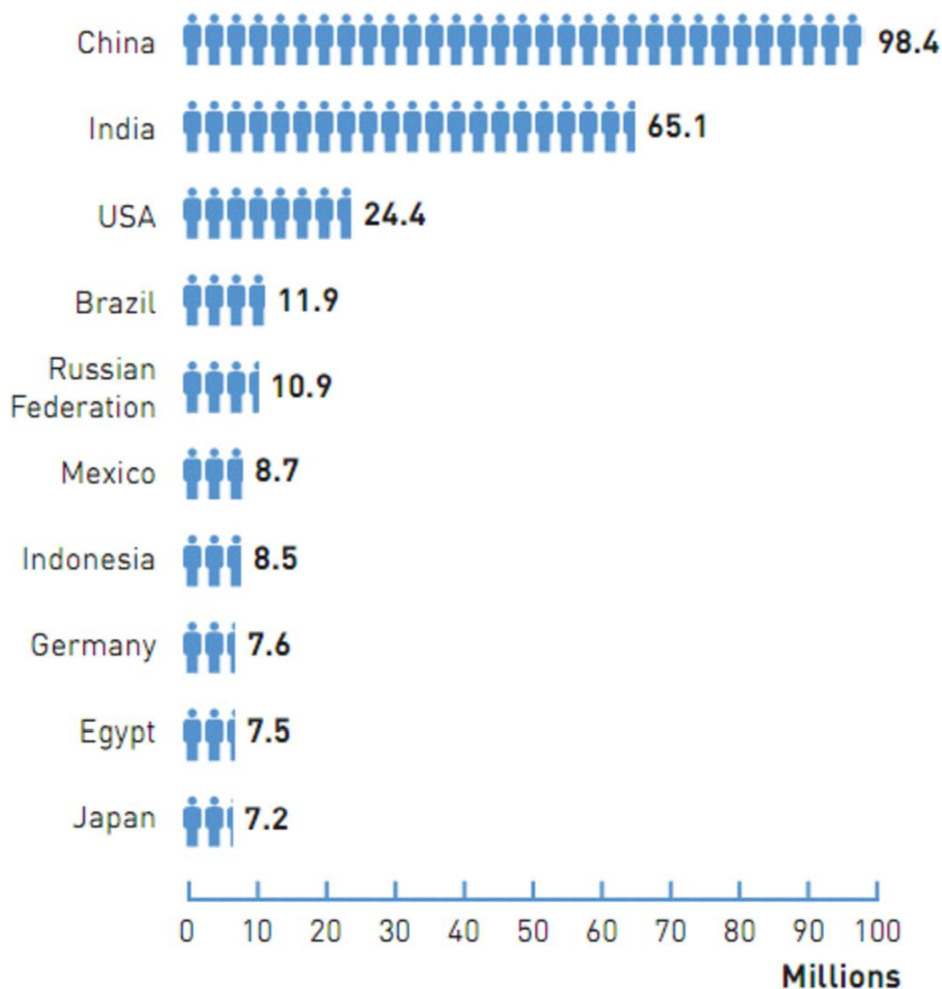
**+205
MILLION**



International
Diabetes
Federation



Top 10 countries/territories of number
of people with diabetes (20-79 years), 2013



Almost **half** of all
people with diabetes
live in just three
countries

China
India
USA

Diabetes : Epidemic in India

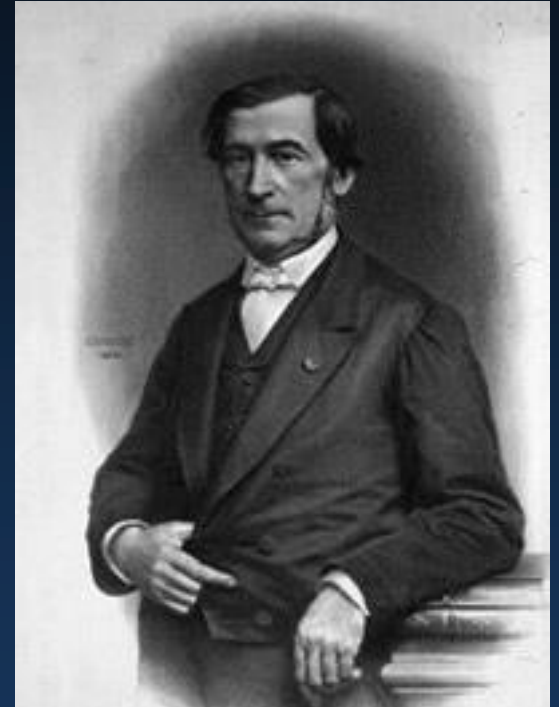
Prevalence

- 1980: 2.1% in Urban: 1.5% in Rural
- 2001: Natinal Urban Diabetes Survey NUDS
 - 12.1% for DM; 14% for IGT in 6 metro cities
- 2004: Prevalence of Diabetes in India Study, PODIS 5.9% in small towns; 2.7% in rural areas
- 2011: Rising Prevalence in India
 - Around 13% in Urban and 7% in Rural



Diabetes & Retinopathy

- Diabetes affects many organ systems of the body, including the eye.
- Effect on the retinal vasculature causes microvascular angiopathy & leads to vascular leakage of serum & blood, ultimately, proliferation of microvasculature in the late stage of diabetic retinopathy.
- Diabetic retinopathy was reported for perhaps the first time by Appolinaire Bouchardat in 1846.



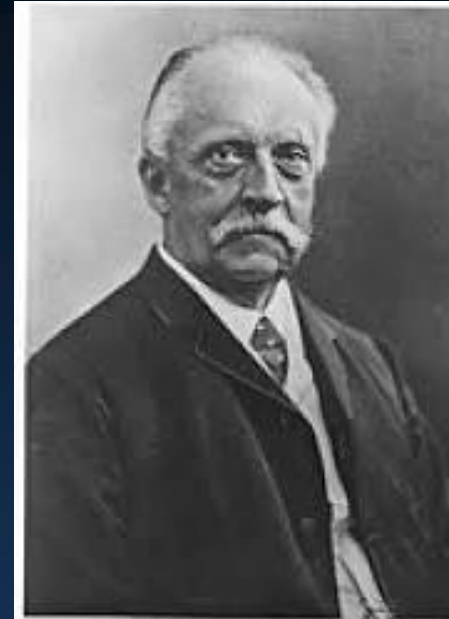
Diabetes & Retinopathy

- Lot of understanding of this disease have occurred since then.
- The first phase began with the first description in 1846 and continued into the middle of the 20th century when various clinical aspects of the conditions were described.

Past

Diabetic Retinopathy: Developing an Understanding

- The 1st seminal event in developing a medical & clinical understanding of DR came with invention of ophthalmoscope by Hermann von Helmholtz in 1851.
- Allowed physicians to directly view ocular fundus to observe the integrity of the blood vessels.

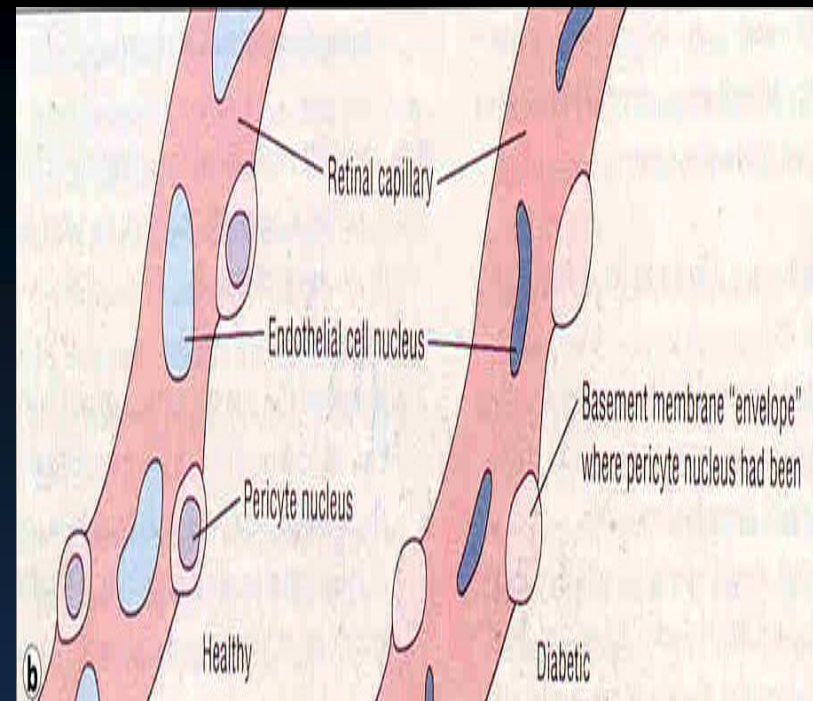


Past

Diabetic Retinopathy: Developing an Understanding

- By the turn of the 20th century, vascular problems were clearly known to be associated with longer-duration diabetes
- Post-mortem retinal tissue from affected individuals showed the retinal changes were associated with capillary micro-aneurisms

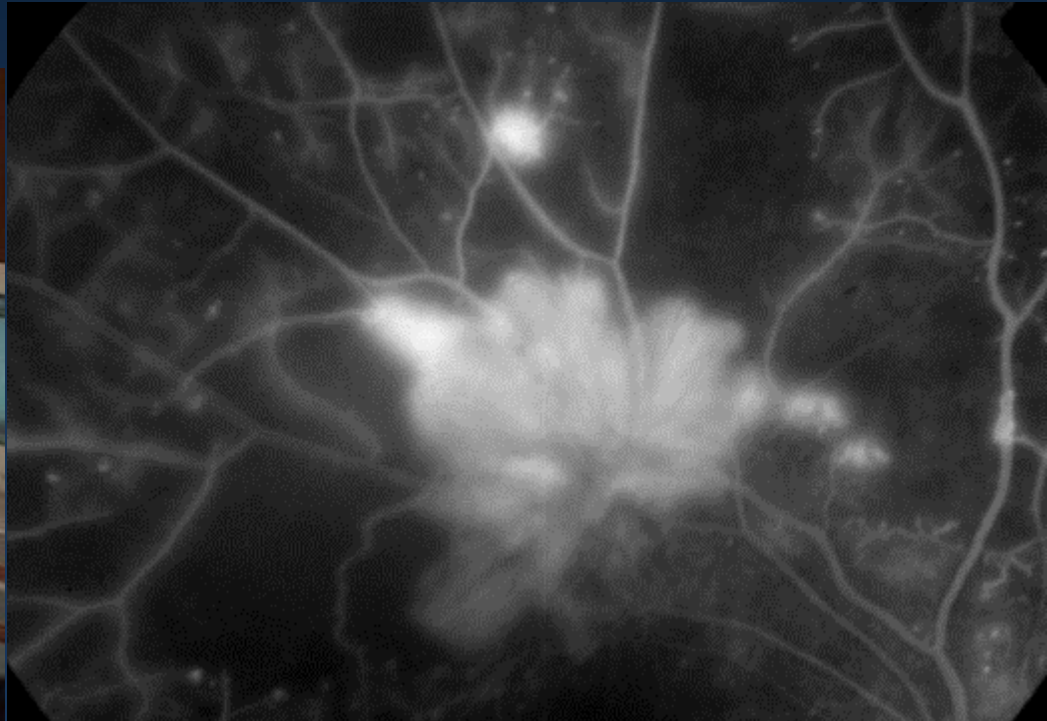
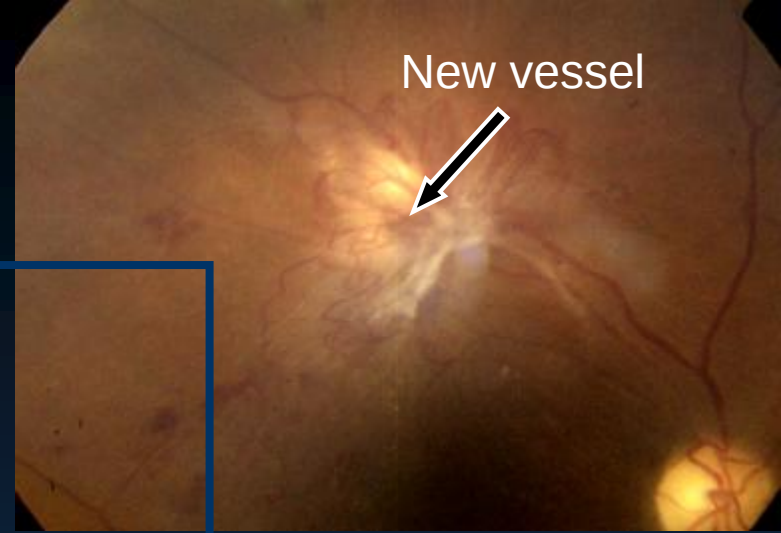
- Hyperglycemia
- Activation of sorbitol pathway
 - Permeability to small molecules
 - Capillary BM thickening
 - Pericyte loss



Basic Pathology

- Abnormal platelet function
- Abnormality of erythrocytes
- Elevated blood viscosity
- vascular occlusion
- Vasoproliferative factors

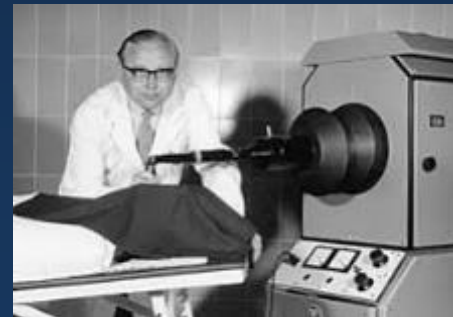
Fundus Fluorescein Angiography (1960s)



Past

Diabetic Retinopathy: Developing an Understanding

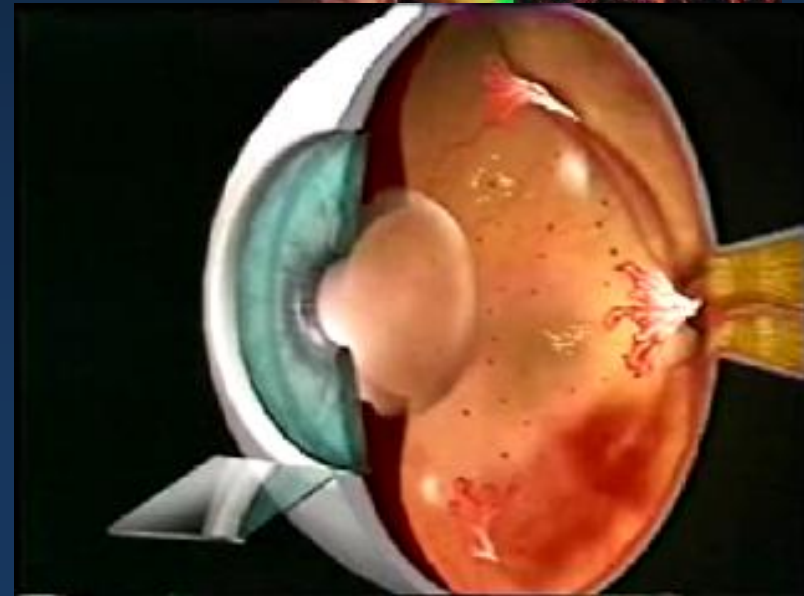
- Gerhard Meyer-Schwickerath, a German ophthalmologist, in 1950 observed spots of retinal damage in individuals who had viewed a solar eclipse
- He looked for ways to apply light deliberately to destroy lesions in the retina by photocoagulating retinal tissue in a controlled fashion with sunlight.
- Later used high-intensity focused light from a xenon-arc lamp to photo-cauterize retinal tissue.
- In 1960s, the development of concentrated light from the ruby laser was applied to the retina
- William P. Beetham & Lloyd M. Aiello recognized photocoagulation to be effective in treating PDR



Past

Diabetic Retinopathy: Developing an Understanding

- The **second stage** began in the 1970s with a series of interventional treatments that began with pan-retinal photocoagulation (PRP).
- PRP remains the mainstay of medical treatment for the ocular component of advanced diabetes.

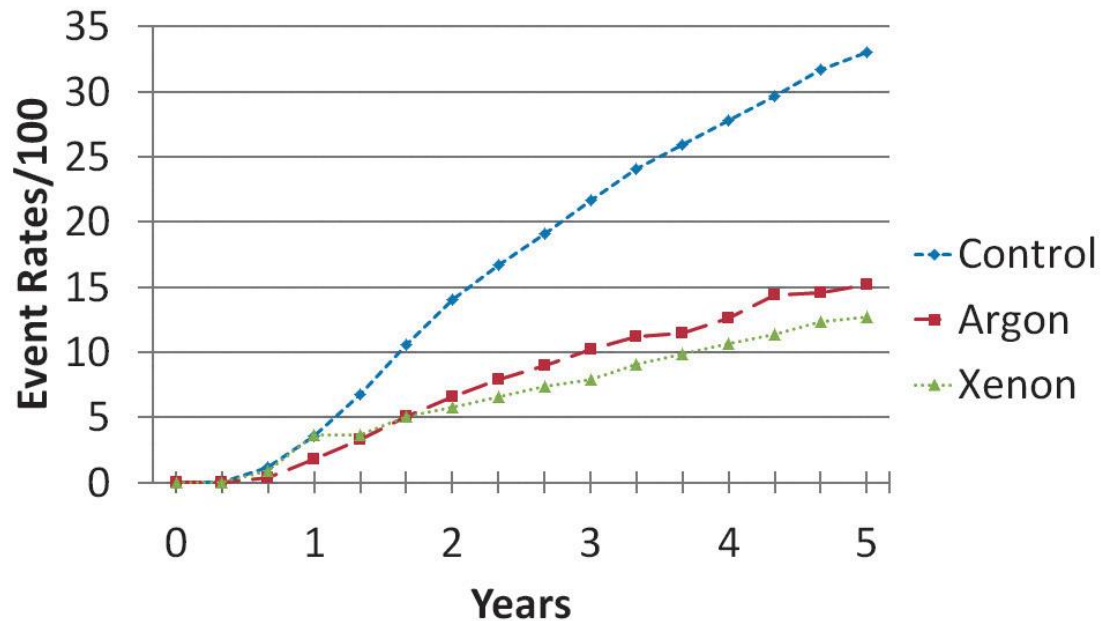


Past

Diabetic Retinopathy: Developing an Understanding

- This led to the pioneering large-scale ophthalmic clinical trial, termed the Diabetic Retinopathy Study (DRS), initiated in 1970s.
- This randomized controlled trial enrolled approximately 1700 patients with advanced proliferative retinopathy
- Eyes were randomized to receive PHC & the fellow control eyes were followed but not treated.

Effect of Photocoagulation Therapy on Diabetic Retinopathy



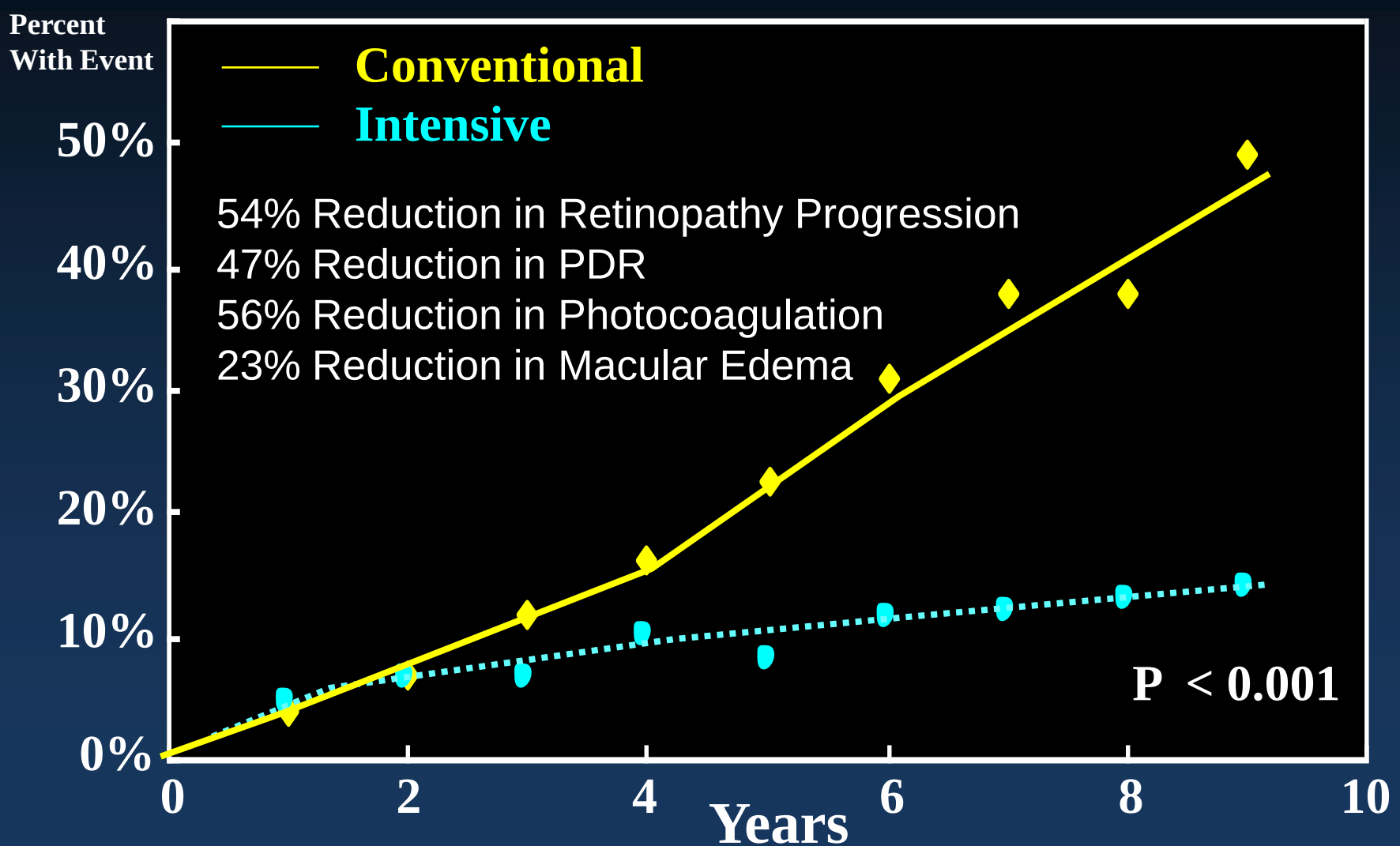
A greater than 50 % risk reduction for progression to severe vision loss was found for eyes treated with pan-retinal argon laser or xenon arc photocoagulation

Past

Diabetic Retinopathy: Developing an Understanding

- Clinical trials for DR then shifted to controlling the underlying diabetes to learn whether this lessened the risk of vision impairment from diabetic retinopathy.
- The first of these trials was launched in 1983: the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Intervention and Complications Trial, and the United Kingdom Prospective Diabetes Study.
- These demonstrated tight control of glucose reduced diabetic complications, particularly when stratified by maintaining a hemoglobin A1c value of 7 % or less.
- This was associated with substantial reduction in progression of retinopathy.

Diabetes Control and Complications Trial



Medical Management of Diabetic Retinopathy



Overall
Metabolic
control....



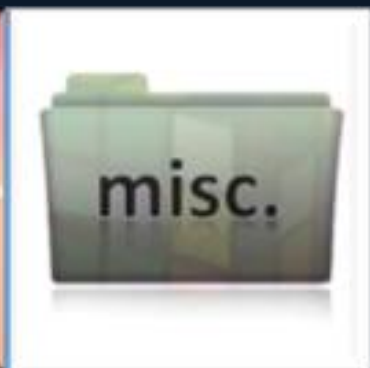
Glycemic
control



Control of BP



Dyslipidemia



Other
Coexisting
Medical
problems

Present

DR – Understanding at Cellular Level & Molecular level

- We have now entered a third phase, which heralds the future based on biologic intervention at the molecular level.
- Success of this molecular approach has gathered speed in the last decade as we began to understand the pathology at a cellular and system biology level.



Role of Vascular Endothelial Growth Factor (VEGF)

1. Stimulator of angiogenesis
2. Potent inducer of vascular permeability
3. Vessel survival factor
4. Fenestration factor
5. Proinflammatory effects
6. Neuroprotective effects



VEGF stimulates angiogenesis

- Triggers basement membrane of endothelial cells
- Endothelial cells then
 - Change shape and invade surrounding stroma
 - Proliferate and form migrating column
 - Cease proliferating, change shape, and adhere to each other
 - Form new capillary tube
- Sprouting tubes fuse into loops, creating circulation



VEGF is a potent inducer of vascular permeability

- 50,000 times more potent than histamine in inducing vascular permeability
- Induces vessel leakage via multiple mechanisms
 - Leukocyte-mediated injury of endothelial cells
 - Formation of fenestrae
 - Dissolution of tight junctions
 - Transcellular bulk flow
- Vascular permeability may be antecedent and necessary step for neovascularization

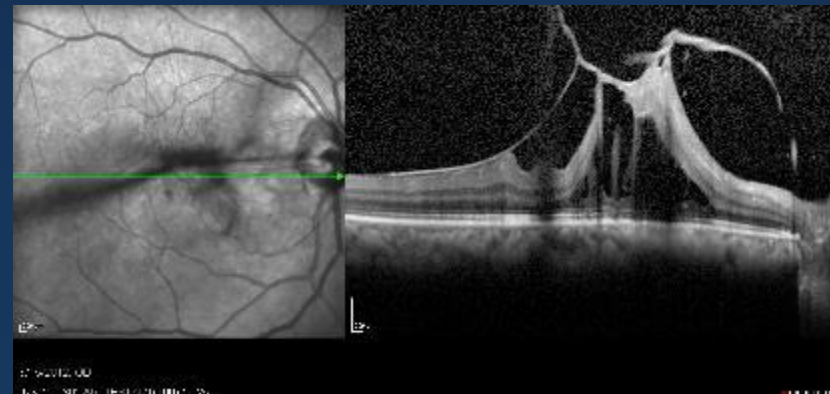
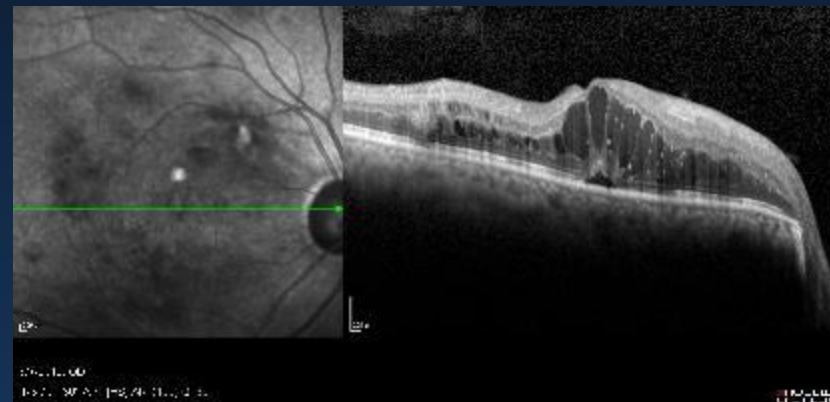
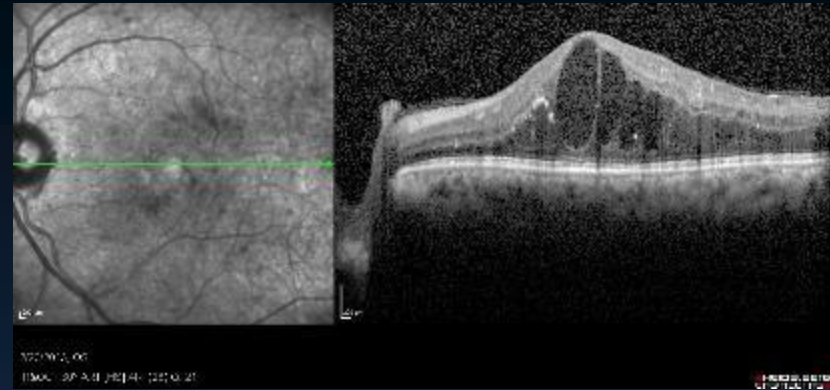
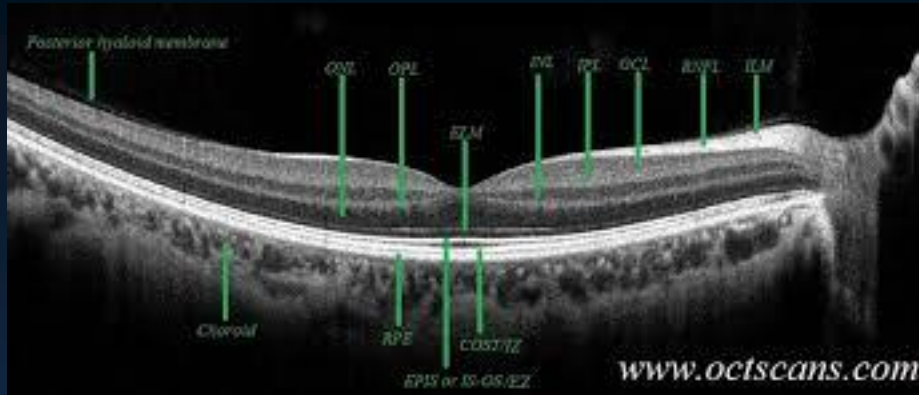


Milestones in VEGF research

- 1971** Folkman publishes “tumor angiogenesis factor” hypothesis
- 1983** Dvorak demonstrates tumor secretion of vascular permeability factor (VPF)
- 1997** First clinical trials of antiangiogenic therapy in cancer patients initiated
- 1999** First anti-VEGF therapy tested in humans with AMD
- 2003** VEGF₁₆₄₍₁₆₅₎ found to be required for pathologic, but not physiologic, retinal neovascularization
- 2003** Optimal methods of long-term controlled delivery of an anti-VEGF agent evaluated in animal studies
- 2004** First FDA-approved anti-VEGF therapy for colorectal cancer



Optical Coherence Tomography (OCT)



Intravitreal injections

- **Anti-VEGF Therapy** - many clinical trials have established the efficacy of these group of drugs



- Intravitreal Steroids

Intra vitreal Injections

- Anti VEGF –
 - Avastin
 - Lucentis
 - Eyelea
- Steroids
 - Triamcinalone
 - Ozurdex(Dexamethasone)
- Needs multiple injections
- Expensive
- Risk of infections



Present

DR – Understanding at Cellular Level & Molecular level

- Pharmacotherapy
 - Has changed the treatment of DR especially DME
 - From preserving vision to improving vision



Present

DR – Understanding at Cellular Level & Molecular level

- Through the DRCR.net, this quickly led to consideration of anti-VEGF treatment for diabetic macular edema, and a study was begun, which ran from 2007–2010.
- The study design compared ranibizumab treatment, with or without immediate laser, *versus* laser retinal photocoagulation, with or without concomitant intraocular steroid (Triamcinolone).

Present

DR – Understanding at Cellular Level & Molecular level

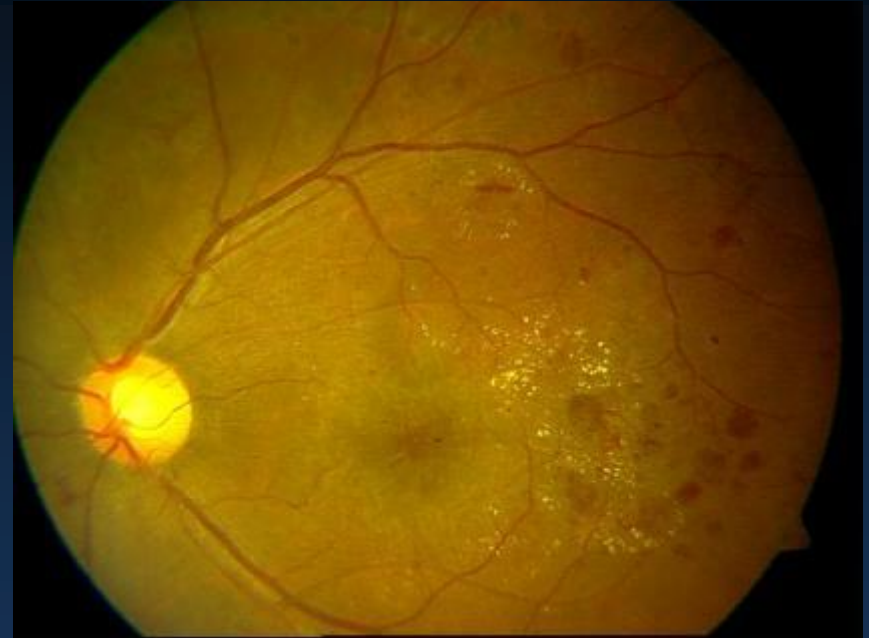
- Anti-VEGF treatment provided clear benefit compared to laser treatment, with improvement in visual acuity compared to laser treatment
- Fewer eyes suffered visual impairment compared to laser treatment.

Treatment of DME



Center involving

Anti-VEGF



Non-Center involving

Laser

India - 20% have DR

Prevalence of Diabetic Retinopathy in Urban India: The Chennai Urban Rural Epidemiology Study (CURES) Eye Study, I

Mohan Rema, Sundararaman, Raj Deepa, Rajendra Pradeepa, and Viswanathan

Prevalence of DR - 17.6%

Prevalence and risk factors for Diabetic Retinopathy: A population based assessment from Theni District, South India

Namperumalsamy Perumalsamy, Kim Ramasamy, Vignesh, Neelakantan, Royes Joseph, Gijo Thomas, Thulasiraj, and V

Prevalence of DR - 12.2%

Prevalence of Diabetic Retinopathy in India

Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study Report 2

Prevalence of DR - 18.0%





Numbers does matter.....

Estimated that 6 million diabetics in India
have sight threatening retinopathy

URBAN

- 1 in 5 diabetic has DR
- Prevalence of STDR: 3.2%
- Prevalence of DR in newly diagnosed DM: 6%

RURAL

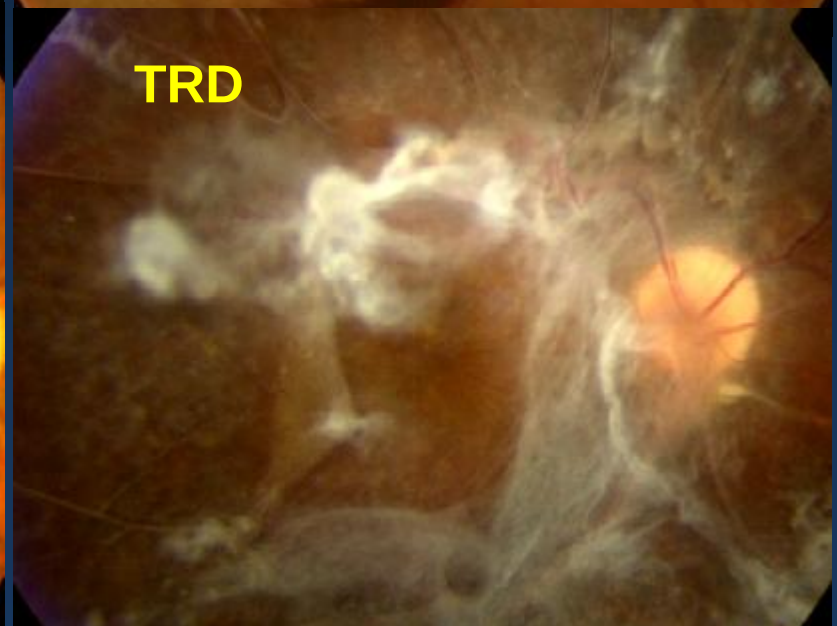
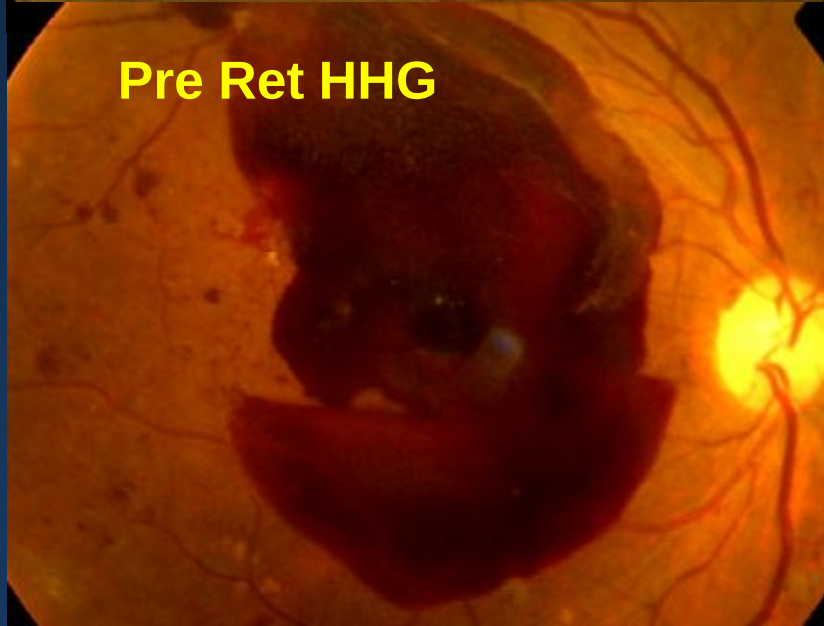
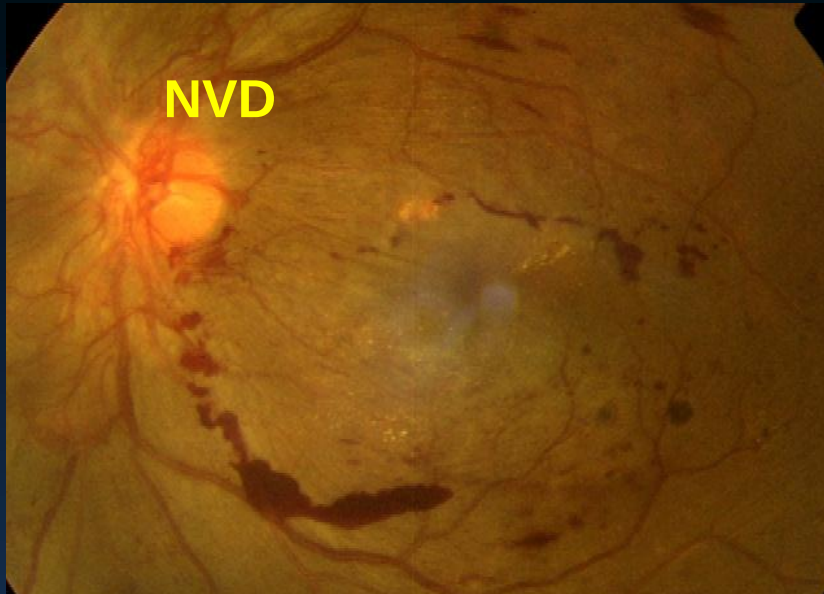
- 1 in 10 diabetic has DR
- Prevalence of STDR: 3.8%
- Prevalence of DR in newly diagnosed DM: 2.8%

Enormous public health challenge and financial burden for India

Symptoms

- No early warning signs
- Gradual in onset
- Decrease in vision mostly in late stages
- Sudden onset of red floaters noticed in front of the eye
- Loss of a field of vision

Currently much disease is detected too late for any effective treatment



Eye care in comparison to WEST

- In the Western population, currently advanced DR changes like tractional retinal detachment are rare.
 - improvement in primary care for Diabetes.

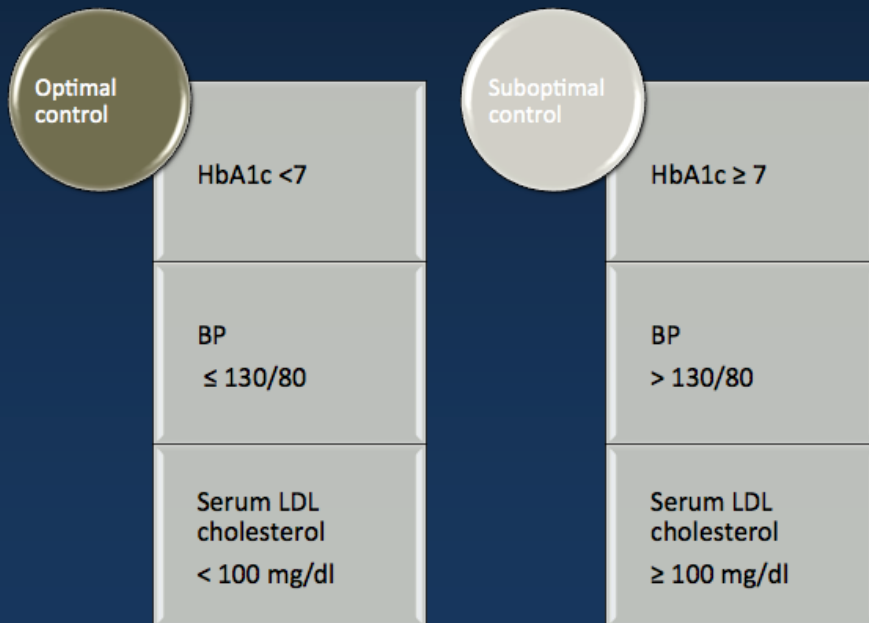
Vnitr Lek. 2010 Apr;56(4):333-9.[Angiopathy and the eye].

How well are the controls in our population.....

ORIGINAL ARTICLE

Prevalence and Risk Factors of Diabetic Retinopathy in Subjects with Suboptimal Glycemic, Blood Pressure and Lipid Control. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS, Report 33)

Rajiv Raman, MS, DNB¹, Aditi Gupta, MS¹, Vaitheeswaran Kulothungan, MSc, Mphil², and Tarun Sharma, MD, FRCSEd, MBA³



DR Care

- 45% of patients with DR, attending eye units, had already lost vision before the condition was diagnosed.
- This shows that too little is being done too late.

The Emerging Epidemic of Diabetic Retinopathy in India

Report of a Situation Analysis and Evaluation of Existing Programmes for Screening and Treatment for Diabetic Retinopathy



PUBLIC
HEALTH
FOUNDATION
OF INDIA



THE QUEEN ELIZABETH
DIAMOND JUBILEE TRUST

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



What should be done?

- Screening for DR – Should not be limited to the ophthalmologists
 - Find alternative resources
 - Screening by physician using direct ophthalmoscope
 - Screening in the community
 - Using technology - telemedicine



Screening by Physician

- Only 1.3 per cent of general practitioners actually use direct ophthalmoscopes.
- The chief current barriers are
 - lack of time,
 - lack of training
 - lack of awareness about DR
 - Community Eye Health. 2006 Mar;19(57):13-4.



Options for screening



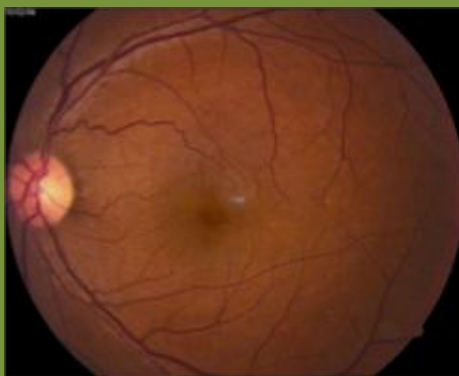
Do/IO: Dilated Ophthalmoscopy is best

Dilate with Tropicamide... Avoid Phenylephrine





No DR



Mild NPDR



Mod NPDR

DR Screening

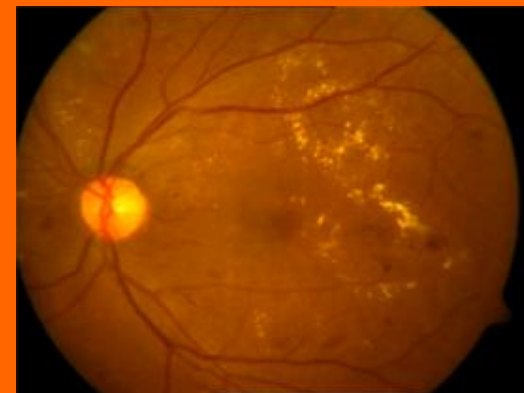
Severe NPDR



PDR



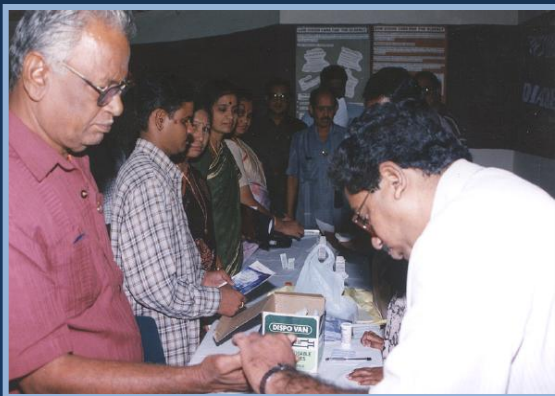
DME



Diabetic Screening Camp

- Important to partner with local Ophthalmologists
 - Potential source for the target population
 - Support for regular follow-up and ensure continuity of care
 - Win-win Situation

Diabetes Care. 2003;26:1831-1835.



Telemedicine

- Telemedicine is the answer to the problem of
 - access
 - lack of trained human resources
- Screening for DR in diabetologist / Physician's office using technology, since they are the first contact point for diabetics
- Just as they get their blood investigations, the eye screening of these diabetic patients can be done, using Technology



DR Tele screening



Mobile vans - at PHC's on diabetic medicine days



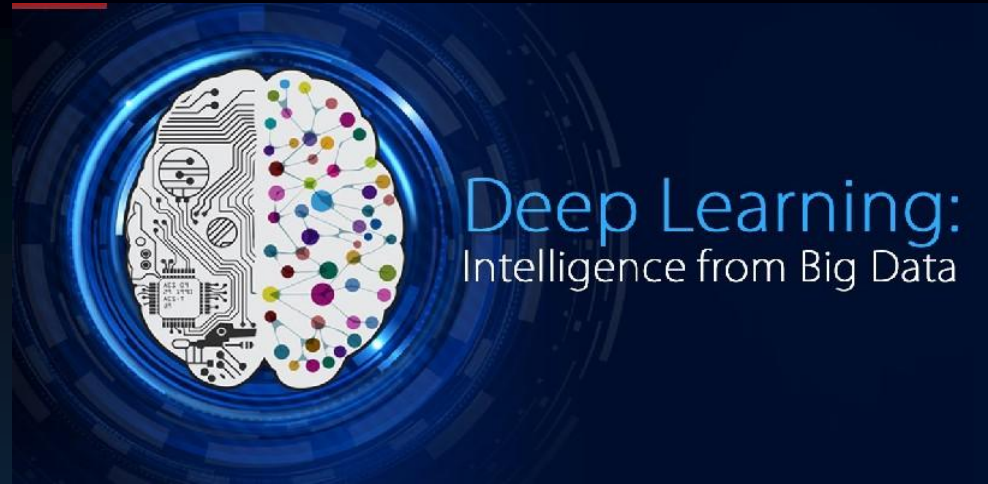
- In the Primary health Centers – DM pts. come for collecting medicines once a week
- Opportunistic Tele-screening for these DM patients using these mobile vans with fundus cameras

Recent developments

- Cheaper fundus cameras
- Good cheaper communication systems
- Automated image processing (in the horizon)



Google – AI in DR Screening



- To apply deep learning to create an algorithm for automated detection of diabetic retinopathy and diabetic macular edema in retinal fundus photographs.

Arda



Drag and drop image to analyze, or **CHOOSE IMAGE**



Drag image here
to analyze



JAMA | **Original Investigation** | INNOVATIONS IN HEALTH CARE DELIVERY

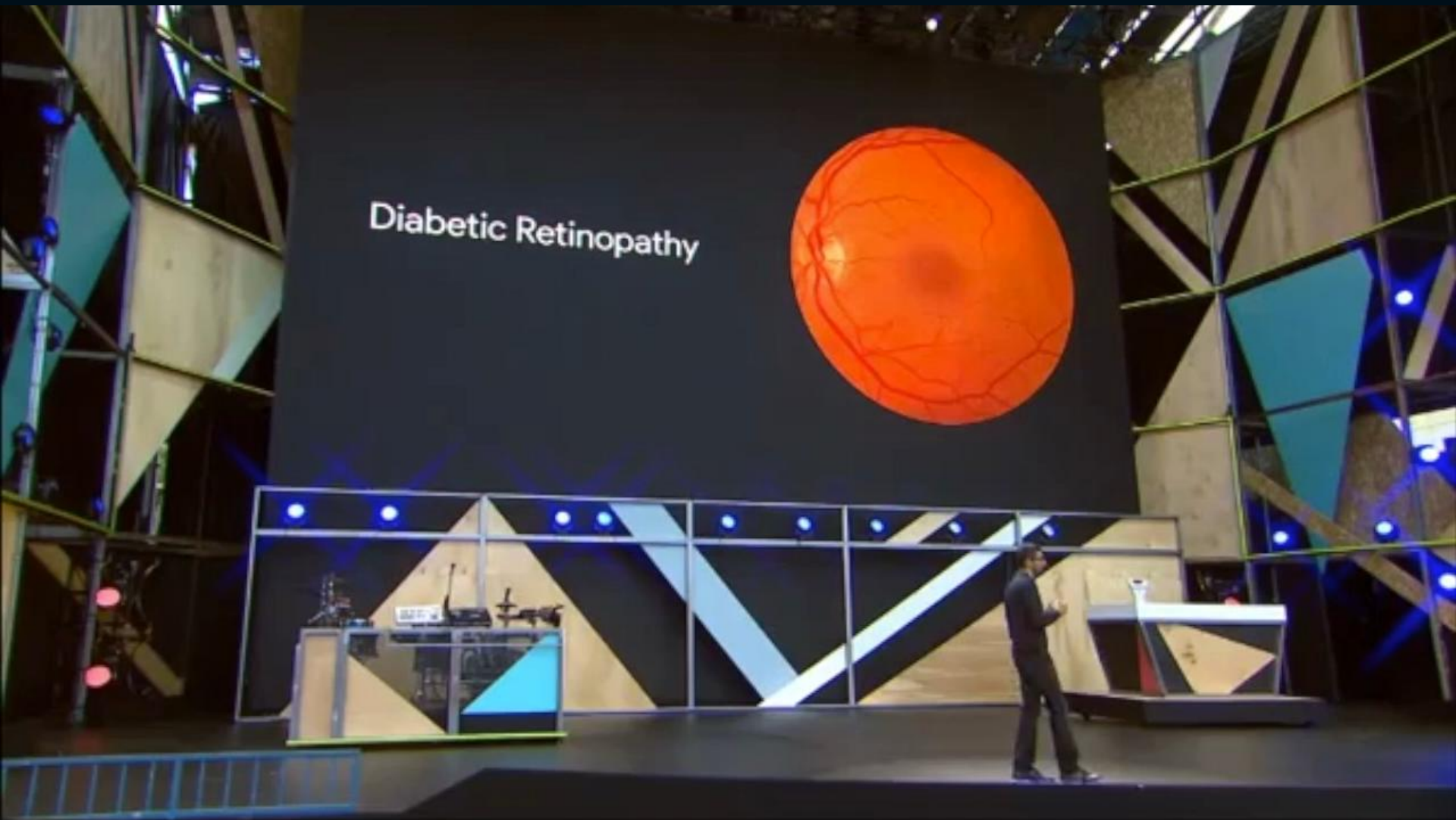
Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Varun Gulshan, PhD; Lily Peng, MD, PhD; Marc Coram, PhD; Martin C. Stumpe, PhD; Derek Wu, BS; Arunachalam Narayanaswamy, PhD; Subhashini Venugopalan, MS; Kasumi Widner, MS; Tom Madams, MEng; Jorge Cuadros, OD, PhD; Ramasamy Kim, OD, DNB; Rajiv Raman, MS, DNB; Philip C. Nelson, BS; Jessica L. Mega, MD, MPH; Dale R. Webster, PhD

- In this study, sensitivities of 97.5% and 96.1% were achieved for detecting Referable DR



DR and Google



Management of DR

- The Gold Standards:
 - Systemic control
 - ~~Laser treatment~~
- Anti-VEGF Approaches
- Intravitreal Steroids
- Laser treatment



Physician



Ophthalmologist

Diabetic Retinopathy - Present

- Urgent need to improve the awareness about diabetes and its related complications
 - while improving the primary care for diabetes.
 - It is critical that Primary care physicians take ownership of screening the DM patients for DR
- For diagnosed cases of DR, the care available today is at par with that available in the developed countries.
- Care is still not accessible to those in the rural areas.
 - With technological advances patients can have better access to proper screening and treatment and thereby preventing needless blindness.

Diabetic Retinopathy: The Future

- Not all individuals with long-standing DM progress to DR
- A recent meta-analysis of 35 population-based studies of diabetics worldwide indicates that about one third of diabetic individuals have some degree of diabetic retinopathy, and fewer than 10 % have either diabetic macular edema or proliferative diabetic retinopathy.
- A substantial number of individuals with underlying diabetes do not progress to overt diabetic retinopathy.
- One pathway is through the use of molecular genetics to identify factors that contribute risks for conversion from diabetes to diabetic retinopathy.

DR & Genetics: The Future

- Despite these promising early indications of genetic association, identifying genes strongly associated with diabetic retinopathy has proven difficult.
- This may stem from several factors. Perhaps each gene makes only a small contribution that segments the risks and thereby requires a large number of cases for genetic analysis.
- Other factors complicating the gene search would include diverse clinical features at different stages of disease progression.
- Environmental component is actually so large that it swamps the genetic determinants.

To Conclude

- Viewing diabetes and diabetic retinopathy across several millennia provides a perspective of our current unique position in biologic history.
- Medicine has clearly begun to study disease pathophysiology at the cellular level and to intervene with knowledge of how the biological system is failing at a systems level.
- Many of these techniques and biologic insights come only with years of scientific training and years of carefully developed research methodologies.

To Conclude

- At the other end of the spectrum, human disease develops in human patients and requires careful investigation by clinical research physicians.
- The future will require increased collaborative interactions between basic scientists and clinical investigators to build a strong platform that supports clinical research.
- We must continue to foster such interactions to ameliorate vision loss and to restore and preserve health in diabetic retinopathy and diabetes.

Thank You

