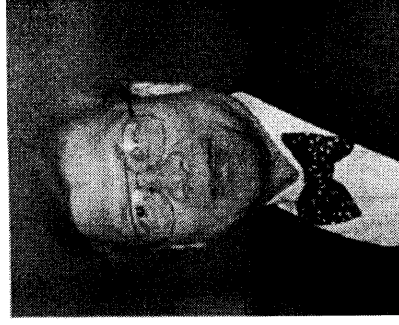


主講人簡介 (Key Note Speaker)



Professor Ching J. Chen (陳清志)

Professor Ching J. Chen is the Chairman of the Department of Ophthalmology at the University of Mississippi Medical Center (USA) and the Director of the Vitreo-Retinal Division at the same Department. He is a renowned and well respected retinal specialist. He is the past president of the Southern Retinal Study Group, past president of the American Diabetic Association-Mississippi Chapter, president elect of Diabetes Foundation of Mississippi, president of Quality Eye-care Network in Mississippi, and current president of Mississippi EENT Society.

Professor Chen is a board certified Ophthalmologist. He is a fellow of American Academy of Ophthalmology, a member of the American Society of Retinal Specialists Society, Association of University Professors of Ophthalmology, ARVO, and many other prestigious societies. He has received honors and awards from many societies including the special achievement awards from AAO and ASRS.

Professor Chen has delivered more than 200 presentations during his career in and outside the United States. He has published many papers in the Ophthalmology Journal and has served as reviewer and scientific referee for "Ophthalmology Surgery and Lasers", and "Retina" Journal. He has conducted many clinical trials and was the PI in many studies. He has also served as clinical consultant in many industrial groups.

Subjects of presentation in this symposium

1. New Treatment Paradigms for Diabetic Retinopathy.
2. Management of Posterior Dislocated Lens with New Generation Phakofragmentation, Ultra High Speed Vitrectomy and Foldable Suture in Posterior Chamber Lens Implant.

臺北醫學大學 50 週年慶

眼科學最近之發展 國際學術研討會

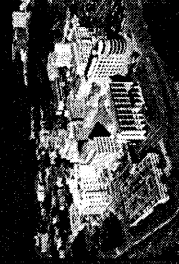
International Symposium on Current Ophthalmology

May 1st 2010 Shuang Ho Hospital

New Treatment Paradigms for Diabetic Retinopathy

Prof. Ching J. Chen (USA)

New Treatment Paradigms for Diabetic Retinopathy



Ching J. Chen, M.D.
Prof. and Chairman
Dept. of Ophthalmology
University of Mississippi
Medical Center

Prepared for: Taipei Medical University 50th Anniversary Ophthalmology Symposium

Diabetic Retinopathy

- 1922--Banting and Best introduced insulin for treatment of DM. Patients live longer to develop complications
- By 1968, DR had become leading cause of new blindness for adults under age of 65

Epidemiology of Diabetic Retinopathy

- 10.2 millions US adults 40 years and older are known to have DM
- 40.3% of the diabetic population have some degree of diabetic retinopathy
- 8.3% are affected by vision-threatening DR
- Prevalence:
 - Type I: 5-40 yrs - 27%, 10-20 yrs - 71-90%
 - Type II: 11-13 yrs - 23%, >16yrs - 60-90%
 - 20-30 yrs - 95%

Risk Factors

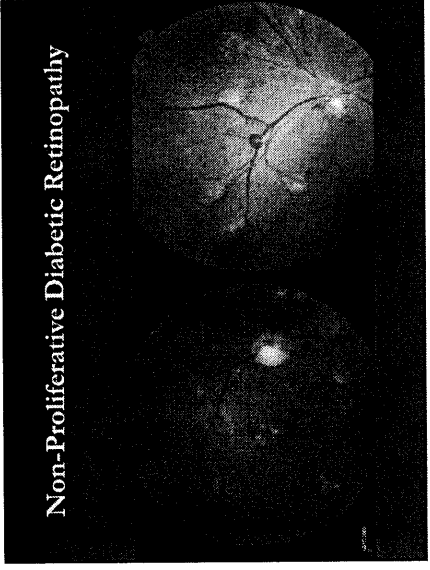
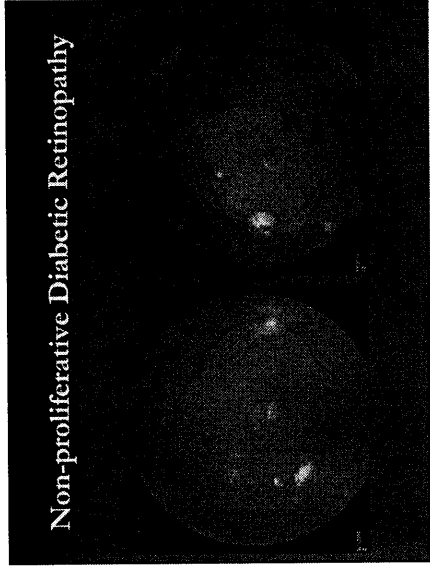
- Duration of disease
- Severity of hyperglycemia
- Other Factors:
 - 1) Type of DM
 - 2) Blood pressure
 - 3) Renal diseases
 - 4) Pregnancy
 - 5) Clotting factor

Classification of Diabetic Retinopathy

- Non-Proliferative Diabetic Retinopathy (NPDR)
- Intra-retinal retinopathy
- Proliferative Diabetic Retinopathy (PDR)
- Extra-retinal retinopathy

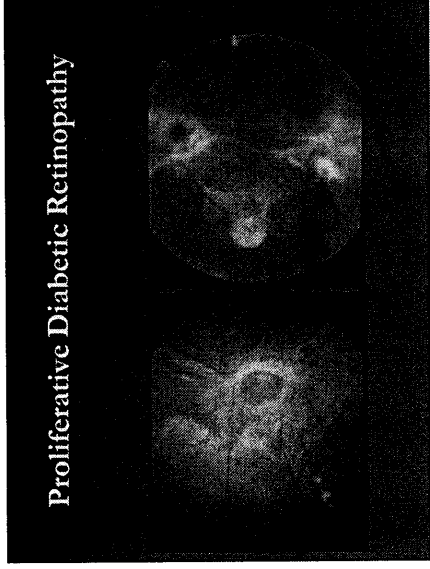
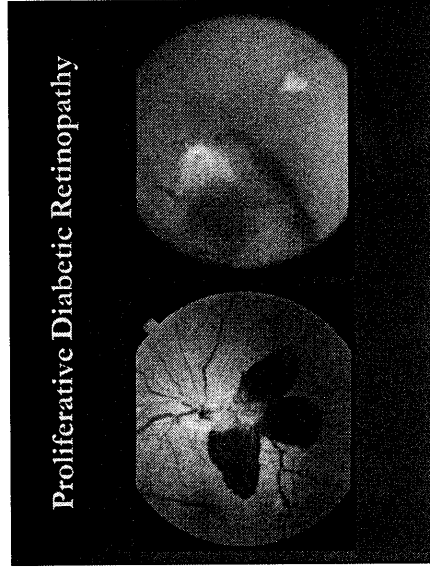
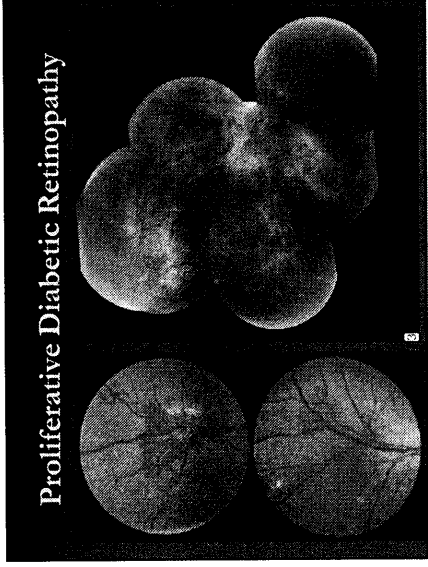
Clinical Features of NPDR

- Microaneurysm
- Retinal Hemorrhage
- Hard Exudate
- Macular Edema
- Cotton-Wool Spot
- Intra-Retinal Microvascular Abnormalities (IRMA)
- Venous Dilation, Loop



Clinical Feature of PDR

- Neovascularization from Optic Disc (NVD)
- Neovascularization from Elsewhere of Retina (NVE)
- Vitreous Hemorrhage
- Tractional Retinal Detachment



Proliferative Diabetic Retinopathy



Diagnosis of Diabetic Retinopathy

- Fundus examination with
 - Indirect Ophthalmoscopy
 - Slit lamp biomicroscopy with contact or non-contact lens
- Fundus Photography
- Fluorescein Angiography
- Optical Coherence Tomography (OCT)
- Fluorophotometry

Diagnosis of DR

Fluorescein Angiography



Diagnosis of DR

Fluorescein Angiography



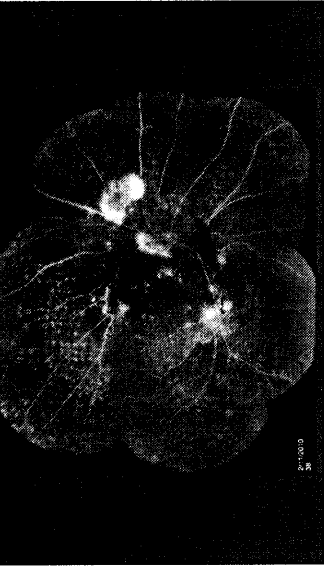
Diagnosis of DR

Fluorescein Angiography



Diagnosis of DR

Fluorescein Angiography



F-D OCT OptoVue Retina Images

Up to 1.2mm scanning. Shown with 1:1 aspect ratio display option



Mechanisms of Visual Loss in Diabetic Retinopathy

- Impairment of tissue blood perfusion due to vascular occlusion
- Increased vascular permeability with macular edema
- Mechanical traction with secondary tissue irritation: taut PHM with CME
- Mechanical blockage of light to reach retina: Pre-retinal hemorrhage and vitreous hemorrhage
- Mechanical traction with structure alteration: TRD or combined rhegmatogenous and TRD, Macular pucker or opaque membrane

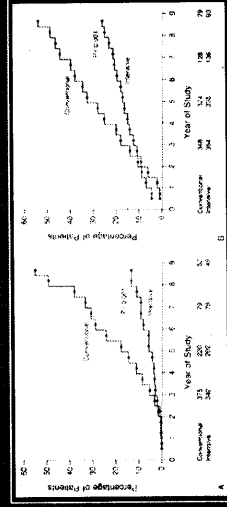
Traditional Management of Diabetic Retinopathy

- Tight control of blood sugar, blood pressure, and serum lipids
- Laser photocoagulation
 - Focal and grid treatment
 - Pan-retinal photocoagulation
- Trans-pars plana vitrectomy

Clinical Trials for Treatment of Diabetic Retinopathy

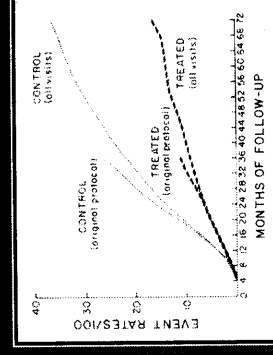
- 1971-1975: Diabetic Retinopathy Study (DRS)
- 1979-1990: Early Treatment Diabetic Retinopathy Study (ETDRS)
- 1979-1990: Diabetic Retinopathy Vitrectomy Study, First report published in 1985 (DRVS)
- 1983-1993: Diabetes Control and Complications Trial (DCCT)
- 1977-1999: United Kingdom Prospective Diabetes Study (UKPDS)

Result of DCCT



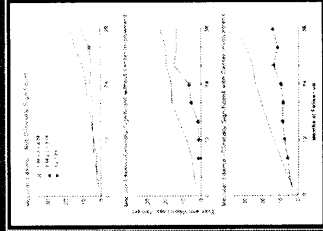
1. Intensive control reduced the risk of developing retinopathy by 76% and slowed progression of retinopathy by 54%
2. Intensive control reduced the risk of clinical neuropathy by 60% and albuminuria by 54%

Result of DRS



DRS demonstrated a 50% or greater reduction in the rate of severe visual loss in eyes treated with PRP

Result of ETDRS



1. Aspirin use did not alter the progression of diabetic retinopathy
2. Early scattered laser resulted in a small reduction in the risk of severe visual loss
3. Early scatter laser is not indicated for eyes with mild to moderate DR
4. Eyes with CSME benefit from focal laser photocoagulation
5. Treatment of CSME with focal laser
 - Reduced the risk of moderate visual loss
 - Increased the chance of moderate visual gain
 - reduced retinal thickness
 - Associated with only minor loss of visual field

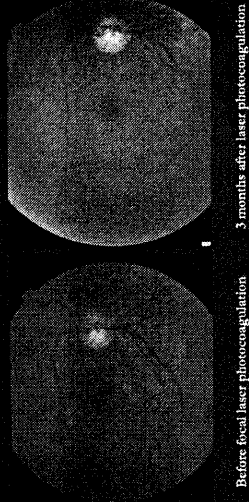
Diabetic Retinopathy Vitrectomy Study

- DRVS showed benefit of early vitrectomy for eyes with severe vitreous hemorrhage and visual loss
- Patients with type I DM with severe vitreous hemorrhage and visual loss benefit most
- DRV also showed an advantage for early vitrectomy versus conventional management in eyes with very severe PDR

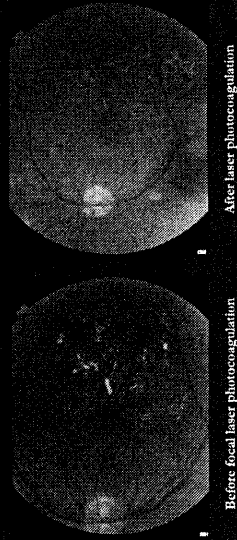
Traditional Indications for Pars Plana Vitrectomy

- Dense, non-resolving vitreous hemorrhage
- Tractional retinal detachment involving or threatening the macula
- Combined TRD and RRD
- Diffuse DME due to taut PHM traction

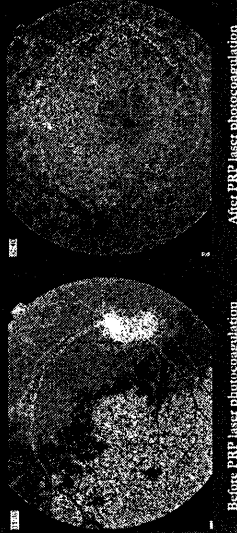
Result of focal laser for NPDR



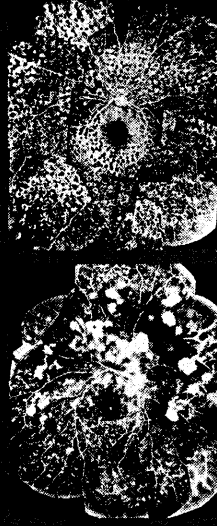
Result of focal laser for NPDR



Result of Laser PRP for PDR



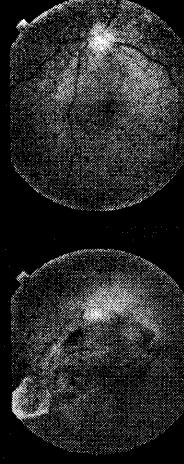
Result of Laser PRP for PDR



Composite FA showed NVD and NVE before PRP laser photocoagulation
FA showed regression of NVD and NVE after PRP

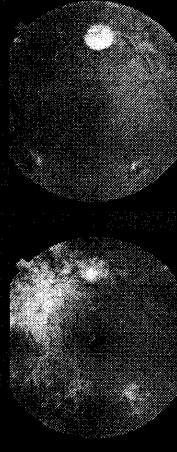
Results of Diabetic Vitrectomy

Recurrent vitreous hemorrhage with moderate proliferative tissue



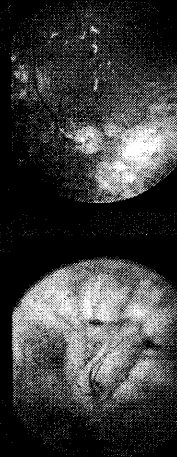
Results of Diabetic Vitrectomy

Florid fibrovascular proliferation with macular puckering



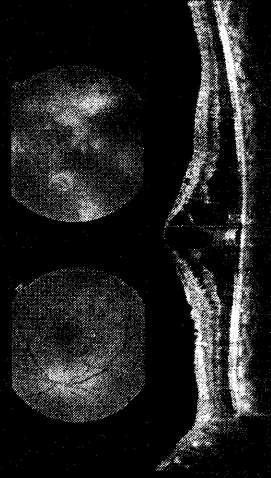
Results of Diabetic Vitrectomy

PDR with combined TRD and RRD with proliferative vitreoretinopathy



Results of Diabetic Vitrectomy

Taut PHM with severe macular edema (pre-operative)



Results of Diabetic Vitrectomy

Taut posterior hyaloid membrane with severe macular edema (post-operative)



Potential Side Effects of Focal Laser

- Paracentral scotoma
- Transient increased edema
- Choroidal neovascularization
- Subretinal fibrosis
- Photocoagulation scar expansion
- Inadvertent foveal burns

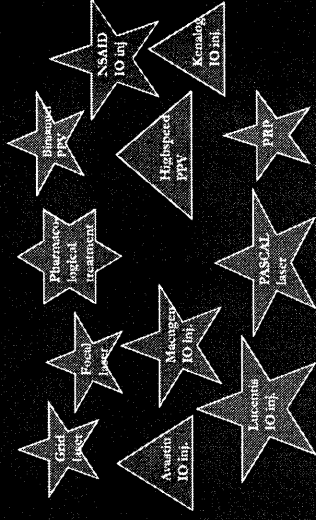
Potential Side Effects of Laser PRP

- Decreased visual acuity
- Increased macular edema
- Decreased night vision
- Constricted peripheral vision
- Decreased hue discrimination
- Loss of accommodation and pupil changes
- Exudative retinal detachment
- Choroidal effusion
- Inadvertent foveal burn
- Exacerbation of tractional retinal detachment

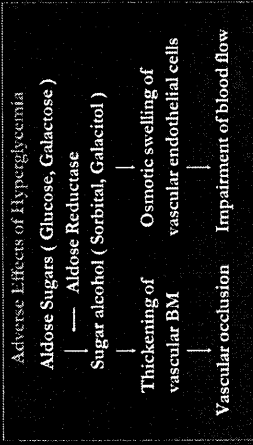
Severe proliferative DR

- Significant recurrent VH despite maximal PRP
- Severe progressive fibrovascular proliferation
- Anterior hyaloid fibrovascular proliferation
- Anterior segment neovascularization with media opacity preventing laser photocoagulation
- Dense pre-macular hemorrhage
- Severe CME without mechanical traction, fail to respond to laser, or anti-VEGF treatment

Treatment Options for DR



Pathogenesis of Diabetic Retinopathy



Pathogenesis of Diabetic Retinopathy

- Thickening of the basement membranes around the capillaries
- Loss of Pericytes
- Microaneurysm formation
- Capillary acellularity
- Break down of blood-retinal barrier
- Capillary non-perfusion
- Neovascularization

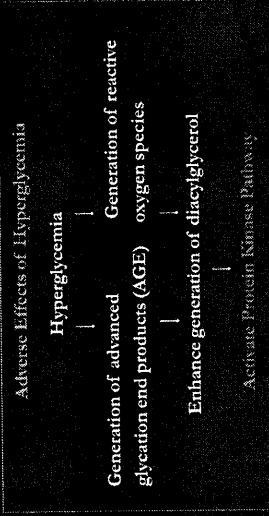
Pathogenesis of Diabetic retinopathy



Pathogenesis of Diabetic Retinopathy



Pathogenesis of Diabetic Retinopathy



Functions of Protein Kinase C

- Signaling components for
 1. Growth Factors :
 - Insulin-like GF I & II,
 - Basic fibroblast GF
 - Vascular Endothelial GF
 2. Hormones, Neurotransmitter, and Cytokines

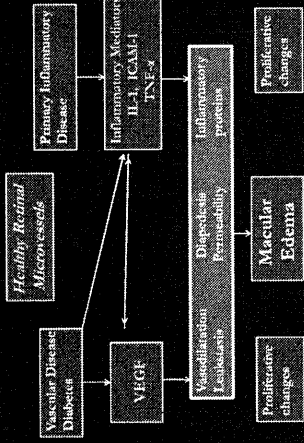
Functions of Protein Kinase C

- Stimulation of VEGF expression
- Mediate VEGF expression
- Mitogenic and Permeability-inducing effect
 - (PKC-beta) help regulate endothelial cell permeability and blood flow

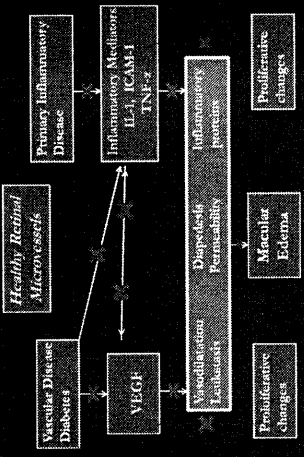
Vascular Endothelial Growth Factor

- VEGF is produced by pigment epithelial cells, pericytes and endothelial cells of the retina in response to hypoxia
- VEGF, primarily isoform VEGF 164/165, is key mediator for angiogenesis and blood-retina barrier breakdown in ischemic retina
- VEGF may also cause inflammation by inducing intercellular adhesion molecule-1 (ICAM-1) expression and leukocyte adhesion

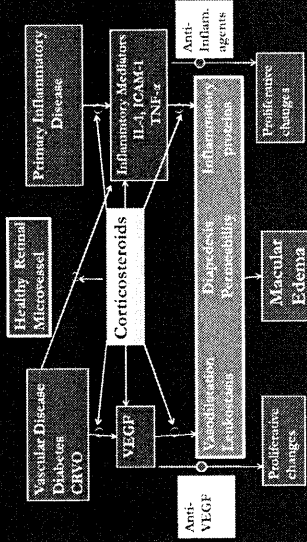
Pathophysiology of DM retinopathy and Basis of Therapies



Pathophysiology of DM Retinopathy and Basis of Therapies



Pathophysiology of DM Retinopathy and Basis of Therapies



Anti-inflammatory Agents

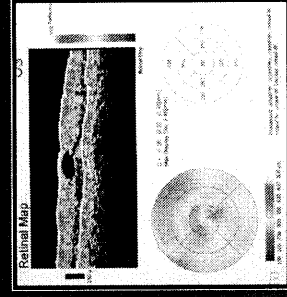
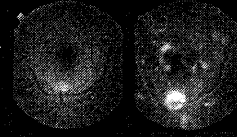
- Steroids inhibit prostaglandin production and also prevent increased vascular permeability at vascular tight junctions.
- Triamcinolone suppressed vitreous levels of stromal-derived factor 1 (SDF-1) and VEGF!

- SDF-1 is a potent stimulator of VEGF.

Bhambhaniya et al. Vitreous levels of stromal-derived factor-1 before and after intravitreal injection of triamcinolone in patients with diabetic maculopathy and vitreous hemorrhage. Retina 2004;24(12):1501-1507.

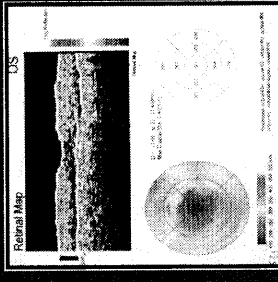
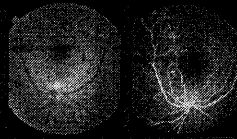
Triamcinolone Intra-ocular Injection for ME in DR

- NPDR with ME, OCT before TC injection



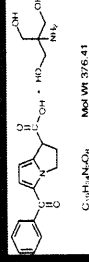
Triamcinolone Intra-ocular Injection for ME in DR

- NPDR with ME, OCT after TC injection



UMC Trial on Non-Steroid Anti-Inflammatory Agents

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Ketorolac tromethamine
 - Pyrrolo-pyrrole NSAID
 - FDA approved
 - Available for IV/IM use
 - Current ophthalmic uses include:
 - Reduction of pain associated with cataract surgery
 - Treatment of cystoid macular edema
 - Allergic conjunctivitis
 - Maintenance of mydriasis during cataract surgery



Two Phase Study

- Toxicity study to determine nontoxic dose of intravitreal Ketorolac. (Rabbit study)
- Pilot study of intravitreal Ketorolac for the treatment of diabetic macular edema. (Phase 1 human trial)

Ketorolac Toxicity Studies

- Concentration of up to 100 µg/0.1 ml was nontoxic to rabbit retinas¹.
- Concentration of up to 500 µg/0.1 ml (preservative free) was nontoxic to pigmented rabbit retinas².
- Concentration of up to 1 mg/0.1 ml of Ketorolac and Flurbiprofen was nontoxic to pigmented rabbit retinas³.

¹W. J. Chen, H. Chen, Q. Li, *Investigative Ophthalmology and Visual Science*, 48(13), 3064.
²W. J. Chen, H. Chen, Q. Li, *Investigative Ophthalmology and Visual Science*, 48(13), 3064.
³W. J. Chen, H. Chen, Q. Li, *Investigative Ophthalmology and Visual Science*, 48(13), 3064.

Intravitreal Ketorolac in Diabetic Macular Edema : Clinical Study

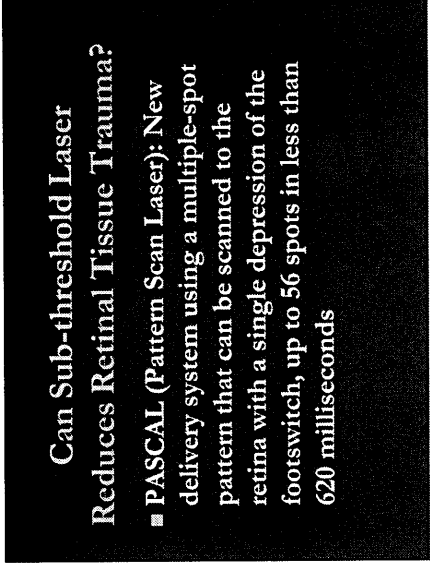
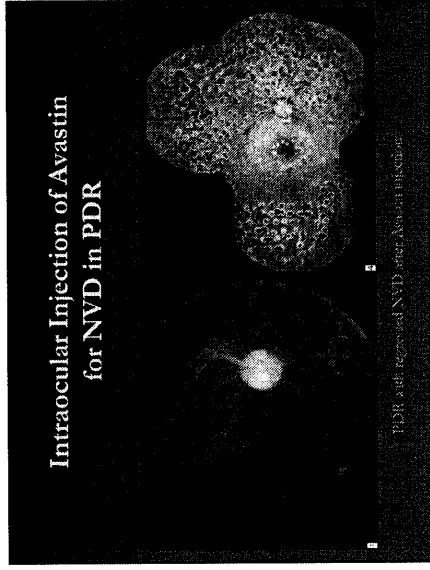
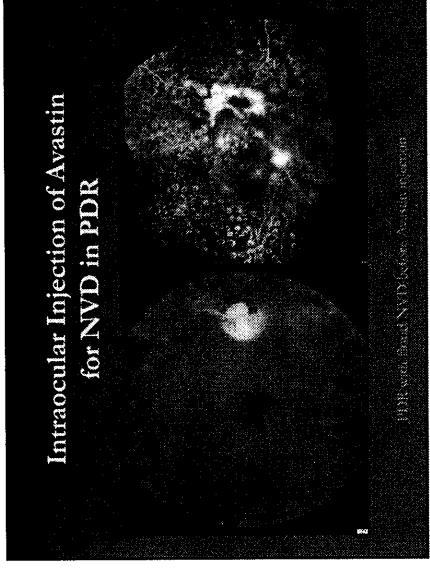
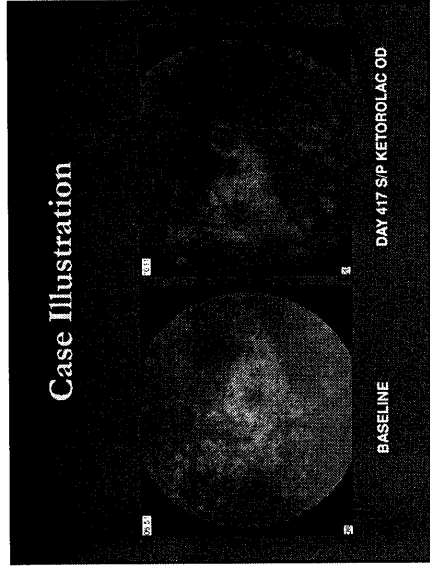
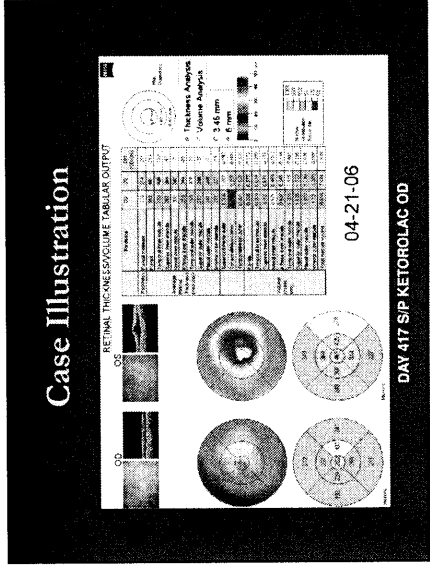
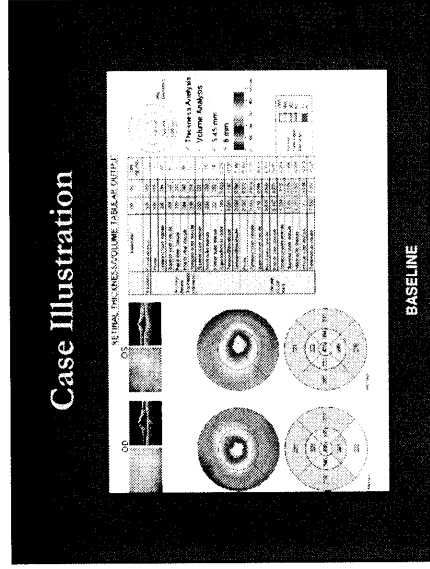
- Objective:
 - To test the hypothesis that intravitreal Ketorolac will reduce diabetic macular edema as assessed by visual acuity, biomicroscopy, OCT, and FA.
- Study Design:
 - Prospective uncontrolled study
 - IRB approved study in 10 patients
 - Inclusion criteria (patients had to meet all criteria to be enrolled):
 - Diabetic macular edema
 - Failed laser or not laser candidate
 - Glaucoma or steroid responder
 - Visual acuity of CF or better
 - OCT central macular thickness > 250 microns

Intravitreal Ketorolac in Diabetic Macular Edema : Clinical Study

- Ophthalmic Examination:
 - Visual acuity (Snellen and ETDRS VA), IOP, biomicroscopy, OCT, and FA
- Treatment:
 - Intravitreal injection of Ketorolac (50 µg-500 µg)
- Clinical Benefit:
 - Improvement in visual acuity
 - Stabilization of visual acuity
 - Reduction of retinal thickness by at least 20% as measured by OCT
 - Reduction of leakage on FA

Case Illustration

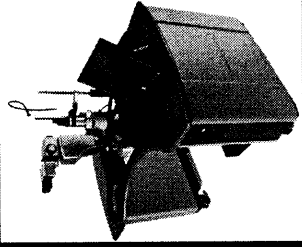
OD STUDY	Snellen Piquet acut	OCT	OS	Snellen Equivalent	OCT
Baseline	20/62.5-1	486	Baseline	20/25-4	475
Day 7	20/50-3	454	Day 7	20/20-4	454
Day 36	20/25-4	460	Day 36	20/20-1	448
Day 74	20/20-2	456	Day 74	20/20-2	464
Day 116	20/20-4	414	Day 116	20/20-2	473
Day 375	20/20	263	Day 375	20/25-3	507
Day 417	20/20-2	262	Day 417	20/25-1	481



Single Spot Laser – Standard Of Care For 30 Years

- Time consuming
- Painful on most cases
- Take 2 to 3 sessions to complete PRP
- Loss of office practice time
- Complications related to the threshold laser with retinal tissue trauma and later pigment dispersion

Future Trends of Laser: PASCAL Photocoagulator ?




How PASCAL works

Controls Laser Delivery to 3 fundamental ways

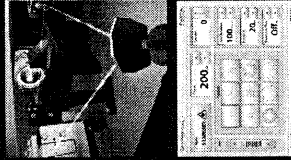
- Short Pulse Duration
- Uniform Predictable Pulses
- Precise pattern spacing

Advanced Control System is fundamentally different

- High Speed gelatinous to controls laser pulse
- Conventional laser results in uniform spots
- Reproducible, controlled through auto positioning and power safety checks
- Multiple times per second

Significant Benefits

- Controlled spacing
- Precise spot delivery
- Precise pattern spacing





PASCAL Precision

PASCAL Precision	Benefits
Short pulse duration	■ Reduced heat diffusion to retina and choroid
Uniform, predictable pulses	■ Prevents further collateral damage
Precise pattern spacing	■ Decreased anterior spread of heat to retina and reduced damage to nerve fiber layer

PASCAL Precision

Uniform, Predictable	Conventional Burns
	

10 ms pulse duration

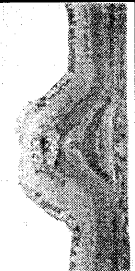
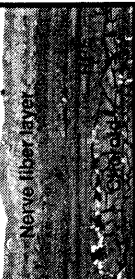
1 Hour post treatment

2 months post treatment

Retinal Healing Demonstrated by FD OCT Post Treatment




Improved Patient Tolerance and Potentially Improved Outcomes

Conventional photocoagulation	Pascal Photocoagulation
	

Laser absorbed in RPE. Goal is to heat inner retina

Conventional photocoagulation

- Treats large volume of tissue
- Causes collateral damage and inflammation
- Pain receptors are in the choroid
- Retinal nerve fiber also damaged

Localized heating and damage to outer retina

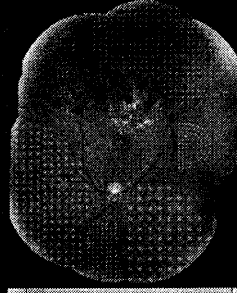
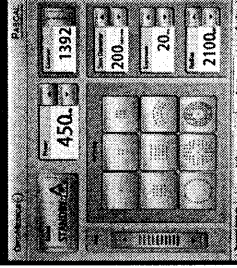
Pascal Photocoagulation

- Less heat transfer to choroid
- Improved patient tolerance
- Potential clinical benefits due to:
 - Less inflammatory response
 - Preservation of retinal nerve fiber

PDR, 2 yrs after PASCAL PRP treatment

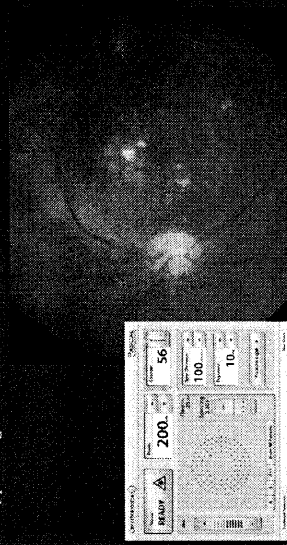


PASCAL Photocoagulator



Clinical Experience – Macular Grid

- Upper half - Long pulse duration, single shot
- Lower half - short pulse duration, pattern array photocoagulation



Treatment Options for DR NPDR with Macular Edema:

- * Focal laser
- * Grid macular laser
- Standard laser V/S
- PASCAL laser
- * Steroid injection
- Subtenon
- Intravitreal
- * Anti-VEGF injection
- Intravitreal
- * NSAID injection
- * PPV and membrane peeling



- * Slow release drug implant insertion

Treatment Options for DR

PDR with CSME:

- * Laser
 - Focal then PRP
 - Grid than PRP
- * Injection
 - Steroid
 - anti-VEGF
 - other drug
- * Injection then laser
 - Steroid
 - anti-VEGF



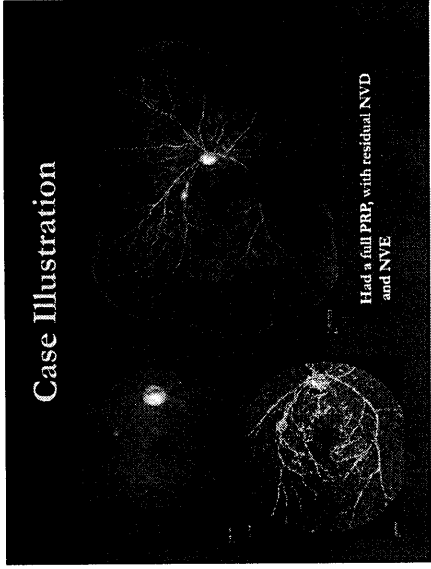
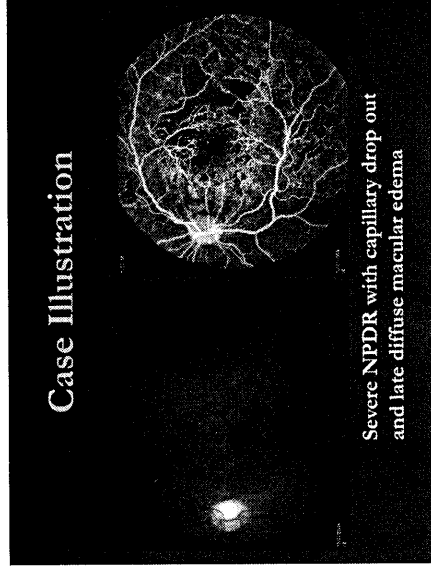
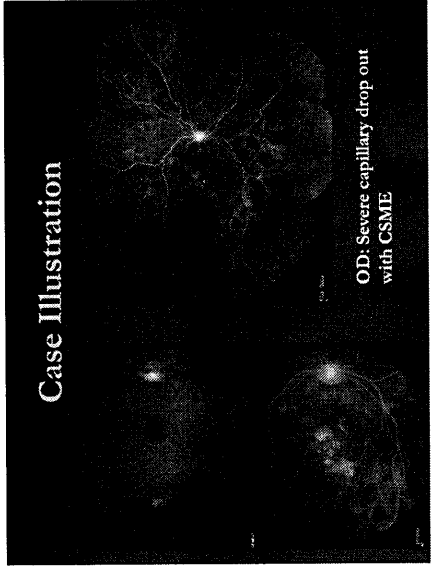
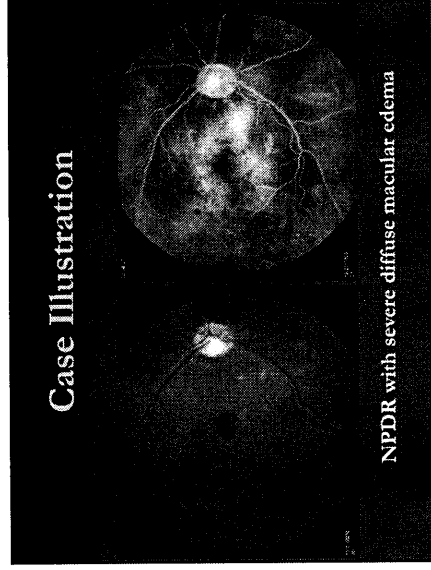
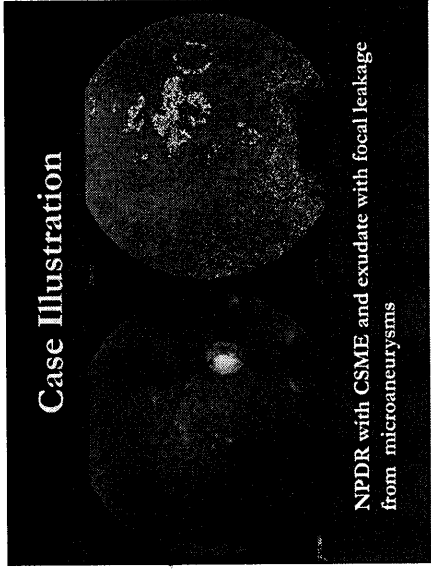
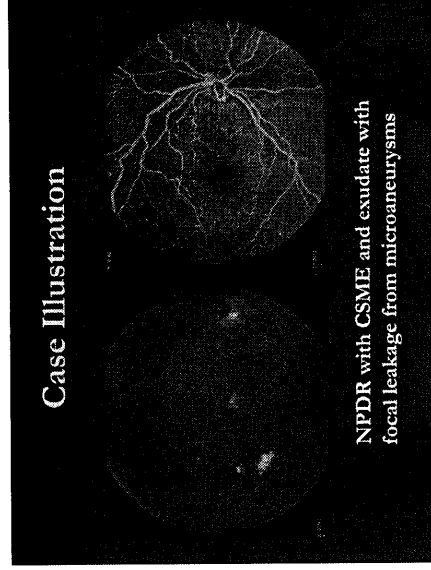
Treatment Options for DR

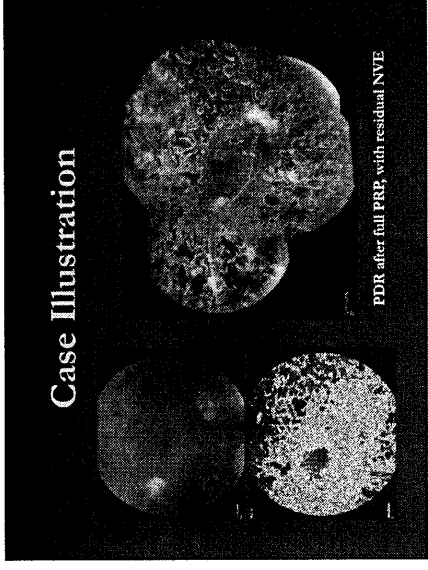
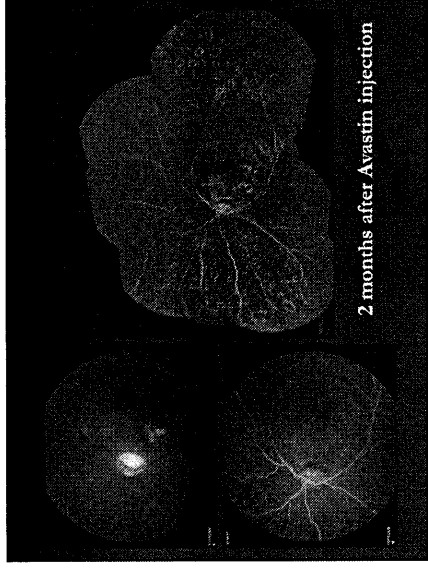
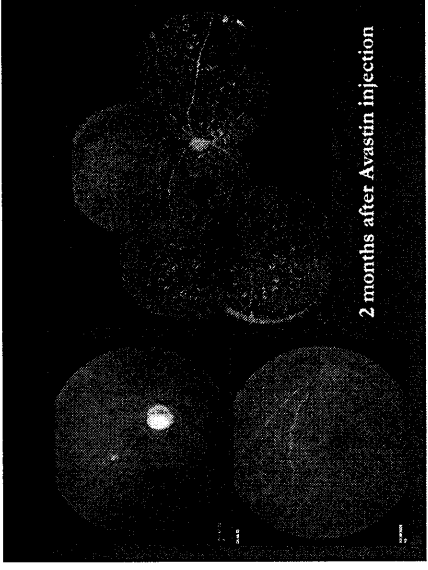
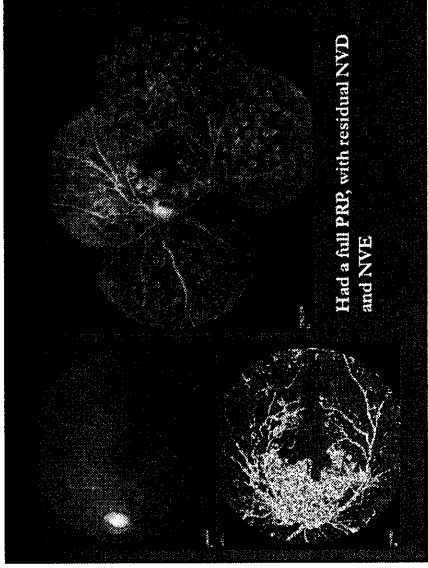
PDR with

> 10 disc areas of neovascularization

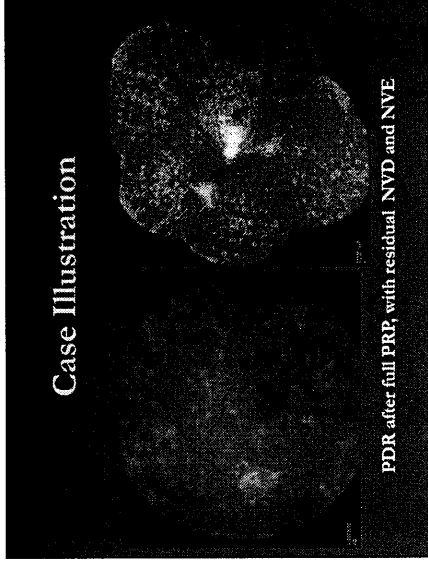
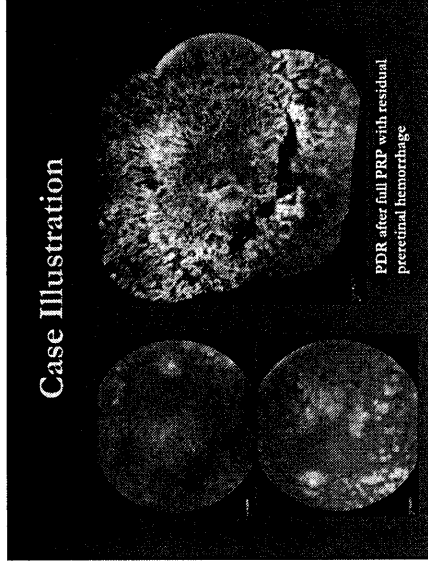
- * PRP
- * Intraocular injection
 - Steroid
 - anti-VEGF
- * Combination



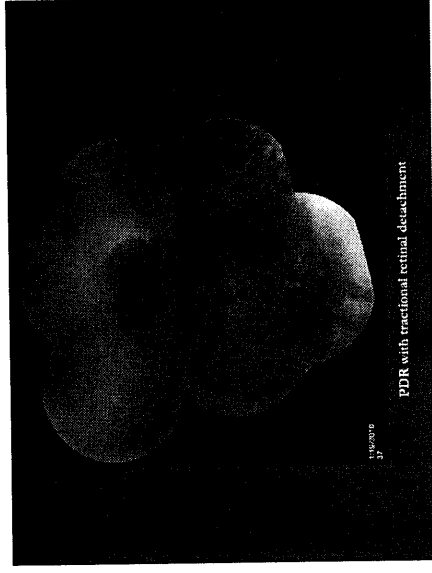
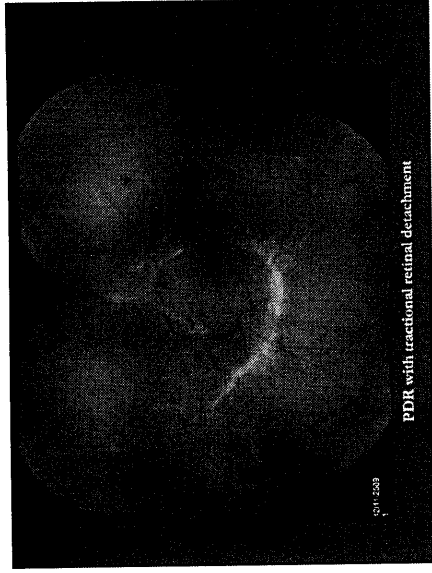




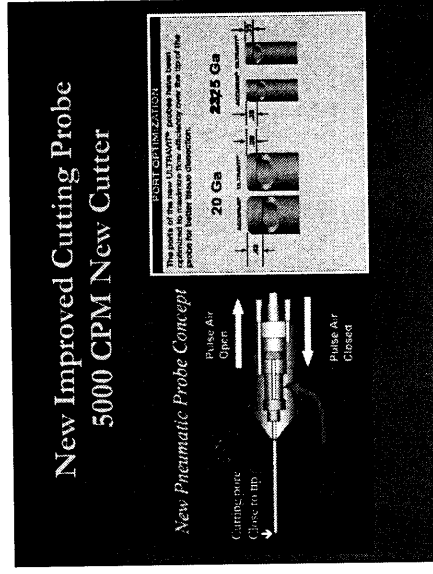
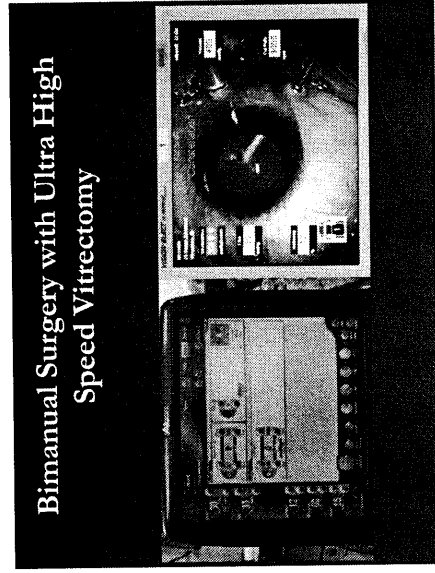
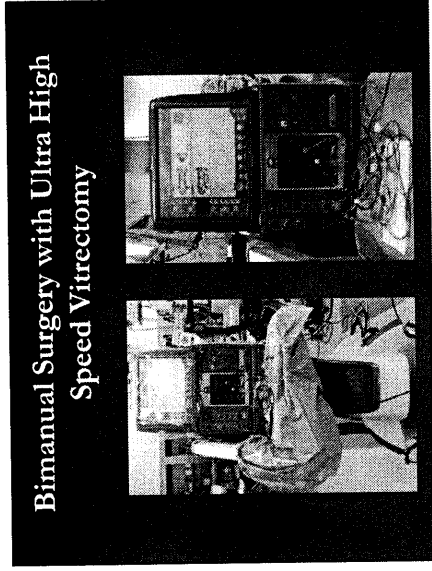
Case Illustration



Case Illustration

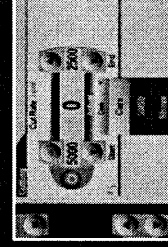


Diabetic Vitrectomy with Ultra
High Speed Vitrector and
Bimanual Membrane Dissection



Surgeon Controlled Duty Cycle

- Introducing a new variable to more precisely control flow
- Select three duty cycle options at any given cut rate

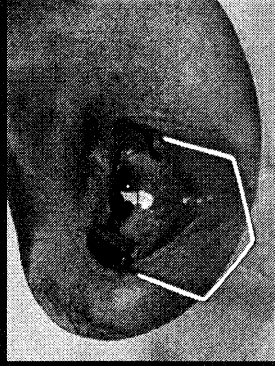


- Core (Port biased open)
- 50/50
- Shave (Port biased closed)

Major issues of vitrectomy in complicated diabetic tractional retinal detachment

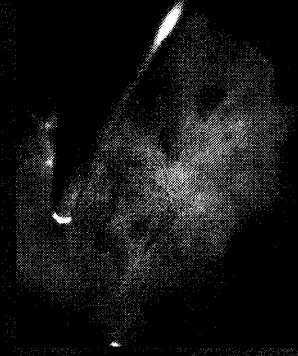
- Florid proliferative membrane with potential severe intraoperative bleeding
- Lack of posterior hyaloid membrane separation in young diabetic patients
- Extensive posterior hyaloid adhesion to the peripheral membrane and retina
- Dense adhesion of the membrane to the detached retina
- Easily breakable fragile atrophic retina in chronic TRD

Avastin IO Injection to Reduce Intraocular Bleeding During Diabetic Vitrectomy



Injection is given within 5 days before vitrectomy to avoid of TRD

Management of PDR with TRD by Perfluoron Assisted Vitrectomy



Bimanual Vitrectomy

Essential Elements

- Infusion
- Optimal intraocular illumination
 - chandelier diffusion free-standing light
 - illuminated instruments
- Vitrectomy system with efficient cutter
- Multifunction ancillary instruments
- Wide angle contact or non-contact viewing system

Xenon Illuminators

Constellation Xenon Illuminator

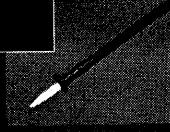
- 5-6 times brighter than the Accurus halogen
- 58 lumens measured at distal tip of standard 20 ga fiber (both channels), 40 lumens (23G), 20 lumens (25G)
- Provides 4 illumination ports powered by 2 separate illumination sources
- Employed a dual mirror system in stead of beam splitter to prevent degradation of light transmission
- Choice of straight, bullet and side-angle fibers

Self Retention Chandelier Light



Tannuabe torpedillo light

- Provides bright, wide-angle illumination
- Allows true bi-manual techniques
- Suitable for use in 20 Gauge, 23 gauge and 25 Gauge cases



23G Scelerotomy Entry with new EdgePlus Trocar Cannular System

Insertion of Self Retention Chandelier Light

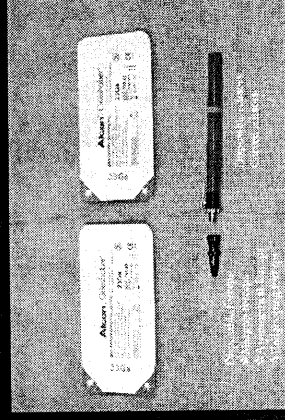
High Speed Vitrectomy with Surgeon Controlled Duty Cycle

Core Vitrectomy Made

High Speed Vitrectomy with Surgeon Controlled Duty Cycle

Slows Made for the vitrectomy near the retina or vitreous base

Disposable Forceps and Scissors



23g Bimanual Vitrectomy

Bimanual Membrane Delamination

Ultra High Speed Vitrectomy and Bimanual Surgery

- Ultra high speed vitrectomy system with surgeon controllable duty cycle allows the ophthalmologist to conduct an efficient core vitrectomy and a safe vitreous shaving near the vitreous base or retinal surface
- New profile of the vitrectomy probe allows a much easier preretinal membrane resection
- Near reference white xenon light provides an extremely bright endoillumination and facilitates a small gauge bimanual surgery

New Therapeutic Paradigm for DR

- Direct Growth factor modulators
 - VEGF inhibitors
 - PKC inhibitors
 - PDGF inhibitors
- Indirect growth factor modulators
 - Somatostatin
 - Interferon alpha
 - ACE inhibitors
 - Antioxidants
 - Corticosteroids
 - Nonsteroidal antiinflammatory agents

Future Trend on Management of Diabetic Retinopathy

- The availability of pharmaceutical therapy will result in a shift of emphasis toward treating earlier stages of DR
- Application of slow release form intraocular drug will make the pharmacological treatment more practical
- As novel therapies to treat DR develop, laser photocoagulation and pars plana vitrectomy will become less common but the technology will improve and will be more effective in the future
- DR screening with digital fundus photography to facilitate early detection and treatment of DR will become a standard of diabetic retinopathy care

Thank You for Your Attention !