DIABETIC MACULAR EDEMA:

Definitions, Epidemiology, Mechanisms, Clinical Course, Treatment

Robert N. Frank, M.D.
Kresge Eye Institute
Wayne State University School of Medicine
Detroit, MI

QUESTIONS:

- What is diabetic retinopathy?
- What is diabetic macular edema?

DIABETIC RETINOPATHY (DR)

A disease of:

- **The retinal neurons and glia**
- **The retinal blood vessels (in which the disease is initially recognized clinically)**
- **DR usually develops after several years of diabetes mellitus, either type 1 or type 2, but occasionally is seen at the time of initial diagnosis of type 2 diabetes.**

DIABETIC MACULAR EDEMA (DME)

The macula is the central area of the retinal with a high concentration of cone cells. It provides sharp central visual acuity and color vision. The fovea is the central area of the macula. It contains only tightly packed, narrowed cone cells and no retinal blood vessels.

Macular edema:

- **A disease of fluid and protein accumulation in the macula**
- **Diagnosis requires demonstration of thickening in or near the center of the macula.**
- **DME is a form of macular edema that may develop after several years of diabetes mellitus in the setting of DR. It may be severe and threaten vision.**

QUESTIONS:

- What is the incidence and prevalence of DR?
- What is the incidence and prevalence of DME?

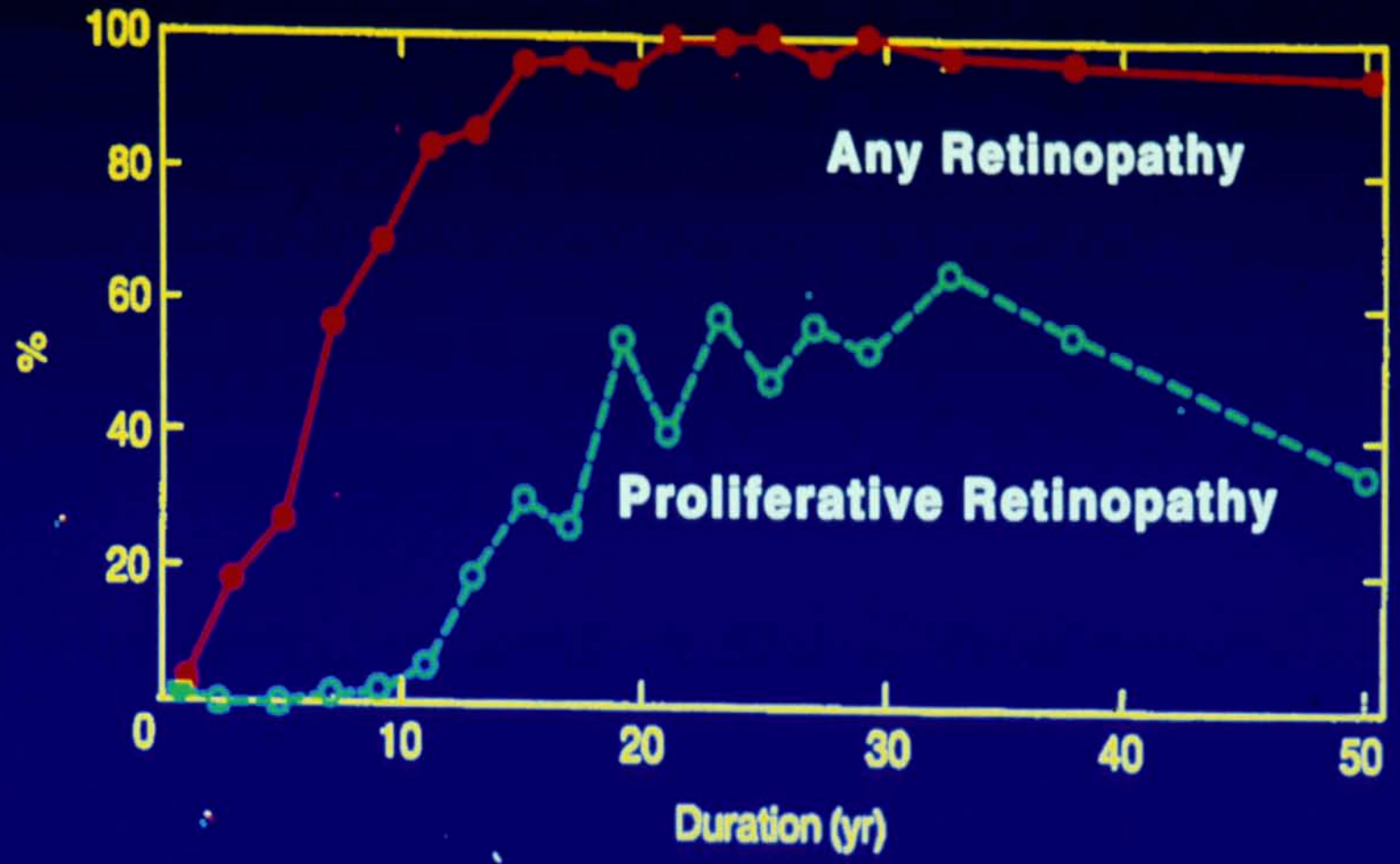
PROLIFERATIVE DIABETIC RETINOPATHY/DIABETIC MACULAR EDEMA: Incidence and Prevalence - 1

- Overall diabetes prevalence: 7% of U.S. population
- Overall retinopathy prevalence: 28.5% of these individuals.
- 4.4% have “vision-threatening” retinopathy, i.e. PDR, DME or severe NPDR.
- Prevalence is much higher in minority groups: Native Americans, Mexican-Americans, African Americans.

Reference: NHANES Study, Zhang X, et al. JAMA 2010;321:649-56.

PREVALENCE OF DIABETIC RETINOPATHY

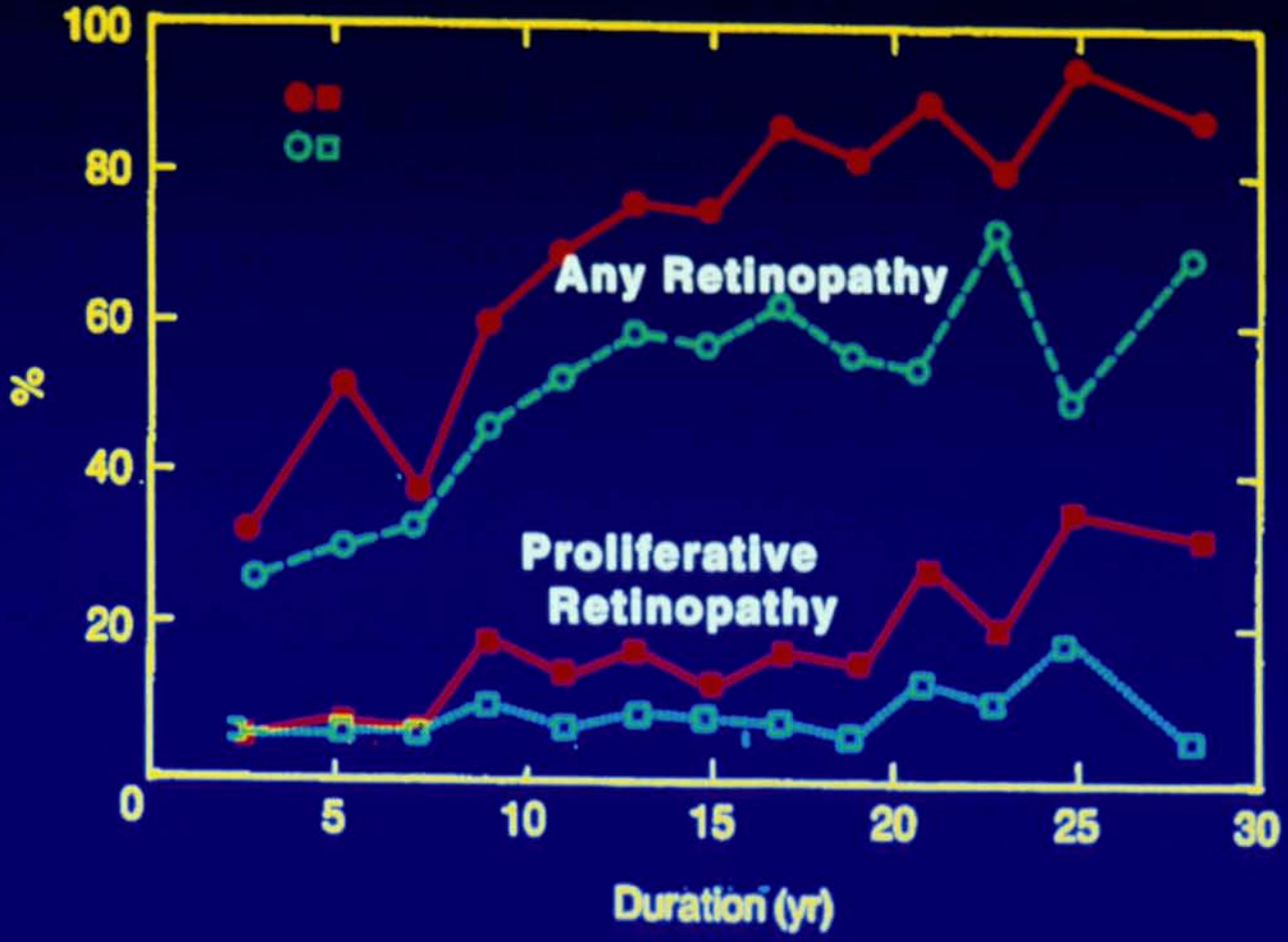
Subjects with Type I Diabetes



From R Klein, et al., Arch. Ophthalmol. 102:520-526, 1984

PREVALENCE OF DIABETIC RETINOPATHY

Subjects with Type II Diabetes



From R Klein, et al., Arch. Ophthalmol. 102:527-532, 1984

PROLIFERATIVE DR and DME:
Incidence and Prevalence

- 20-year PDR prevalence *
  - 50% in type 1
  - 25% in type 2 using insulin
  - 5% in type 2 not using insulin
- 4-year DME incidence*
  - 8.2% in type 1 diabetes
  - 8.4% in type 2 diabetes using insulin
  - 2.8% in type 2 diabetes not using insulin
- 15-year DME prevalence*
  - 18% in type 1
  - 20% type 2 on insulin
  - 12% type 2 not on insulin

**Changes in glucose, blood pressure , & lipid control over the last 20 yrs have likely decreased incidence & prevalence*

Refs.: Klein R, et al. *Ophthalmology* 1989;96:1501 & Adv Exp Biol Med 1985;189:321.

DIABETIC RETINOPATHY

- Incidence, prevalence, and severity increases as a function of diabetes duration (many studies) and
- Inadequate blood glucose control [DCCT, UKPDS randomized, controlled clinical trials (RCTs)]
- Severity and progression may be slowed by blood pressure control (in hypertensive individuals) and lipid control (UKPDS, ACCORD RCTs, forthcoming Cochrane review)
- Severity may be governed by genetic factors, as yet undetermined.

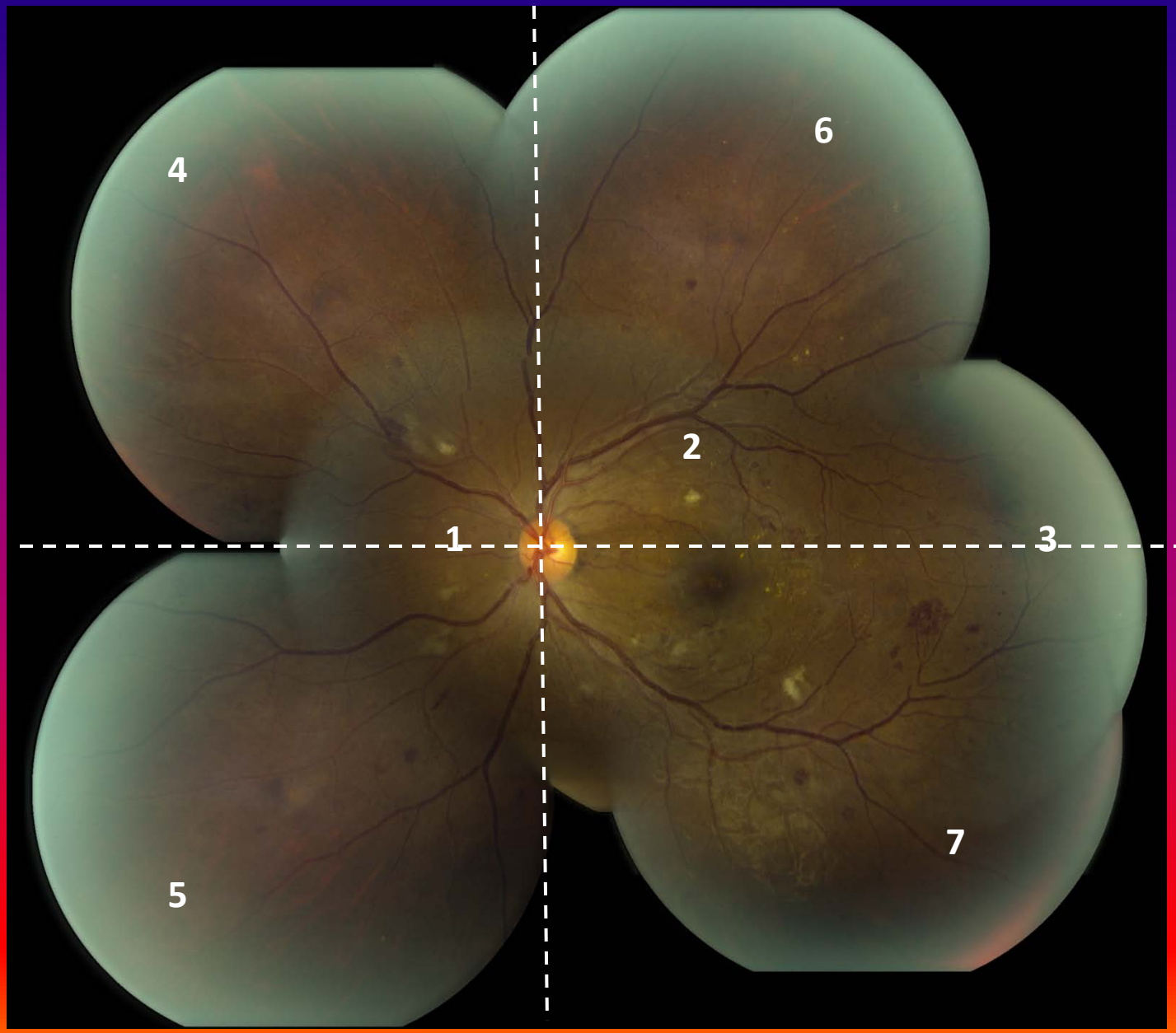
DIABETIC RETINOPATHY SEVERITY SCALE

From American Academy of Ophthalmology Preferred Practice Patterns

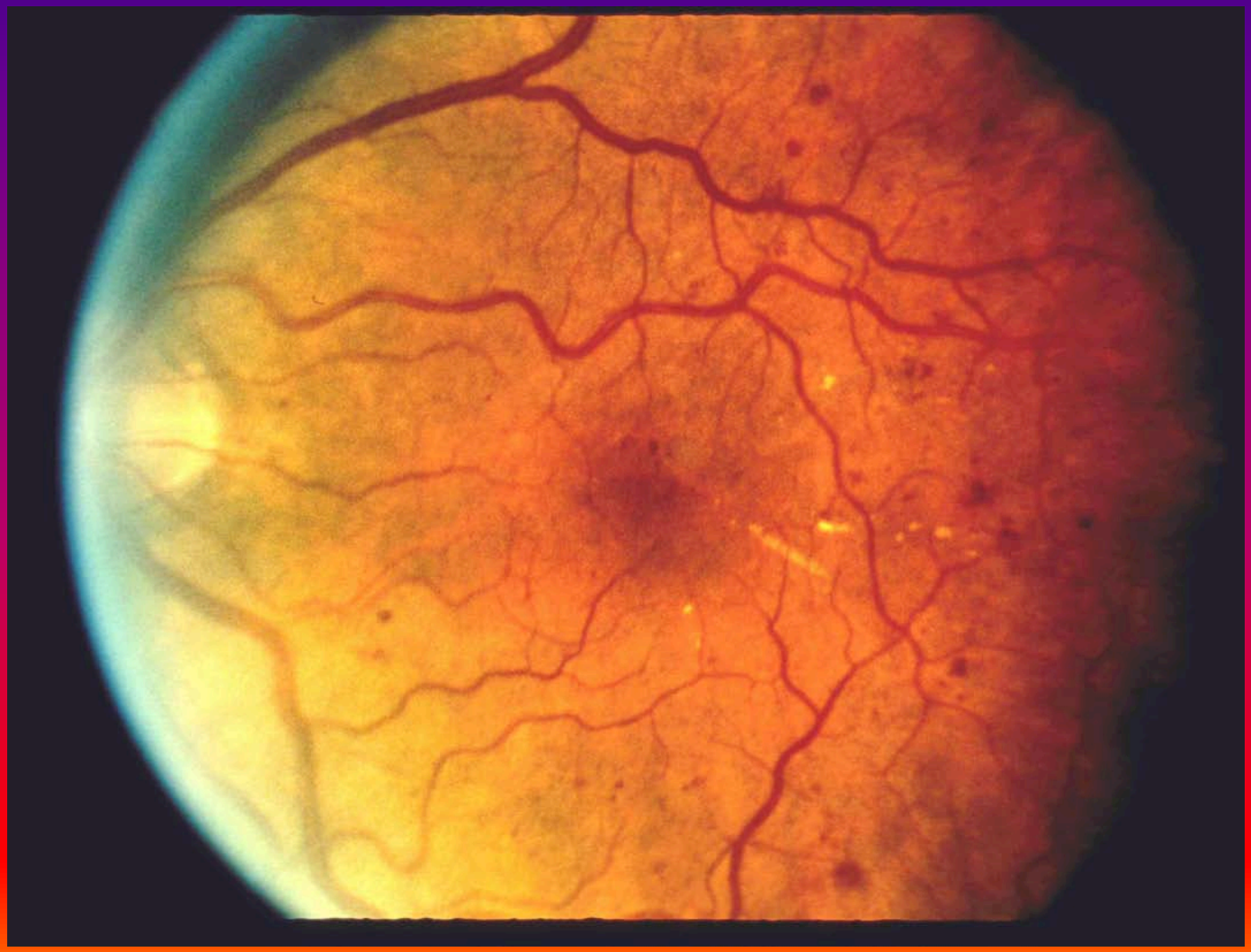
Proposed Disease Severity Level	Dilated Ophthalmoscopy Findings
No apparent retinopathy	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	More than just microaneurysms, but less than severe NPDR
Severe nonproliferative DR The "4-2-1 rule"	No signs of PDR, with any of the following: >20 intraretinal hemorrhages in each of 4 quadrants Definite venous beading in ≥2 quadrants Prominent intraretinal microvascular anomalies in ≥1 quadrants
PDR	One or more of the following: Neovascularization Hemorrhage (pre-retinal or vitreous)

http://one.aao.org/CE/PracticeGuidelines/PPP.aspx?sid=ab789157-5312-4bbe-86ed-8d164ffa9567

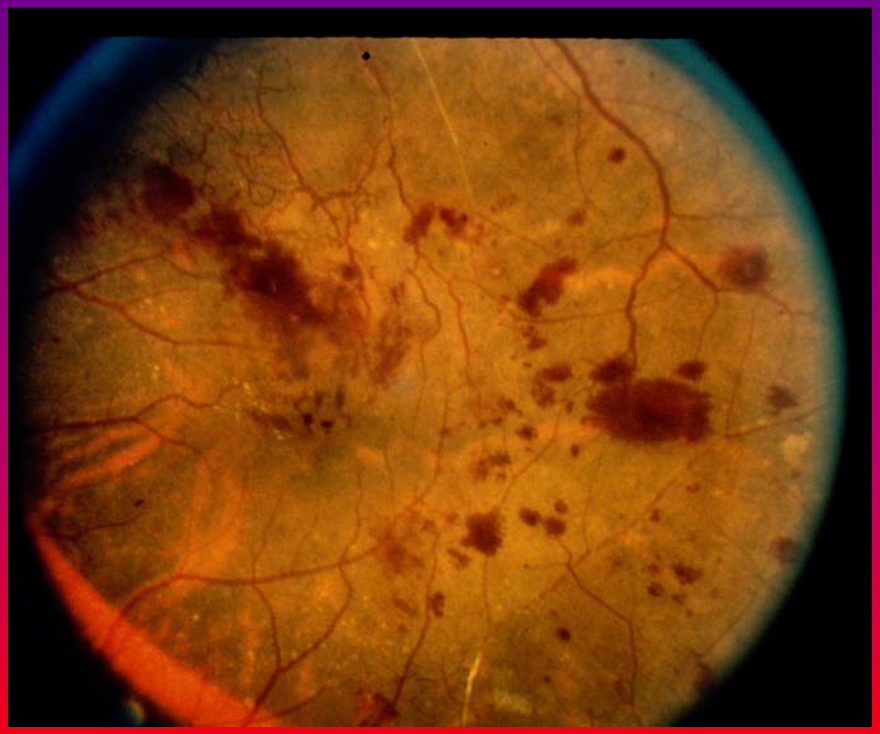
ETDRS SEVEN STANDARD FIELDS

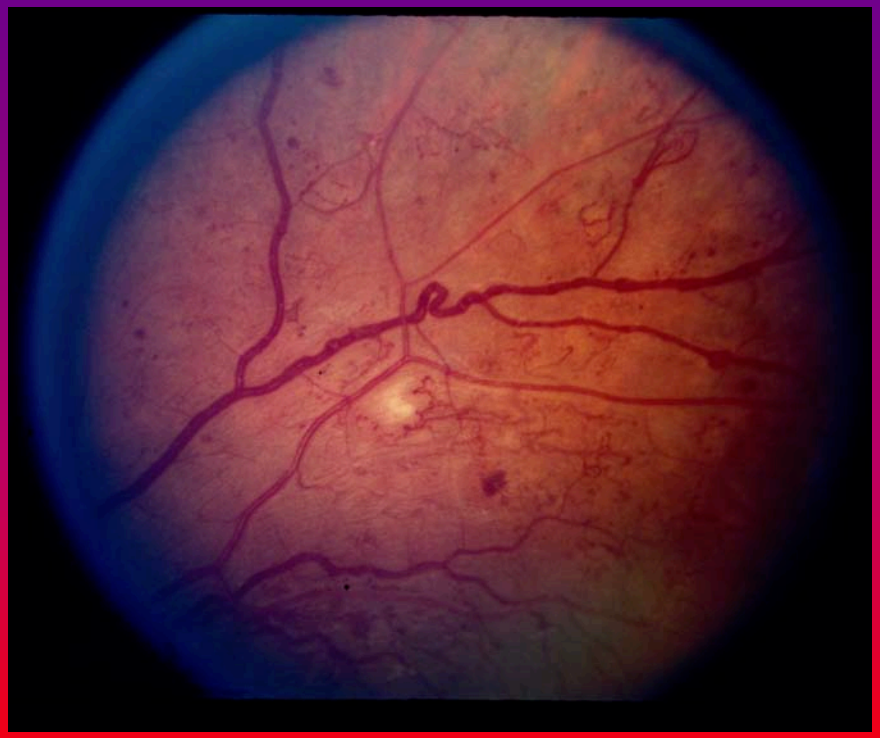


BACKGROUND or NONPROLIFERATIVE DIABETIC RETINOPATHY (BDR or NPDR): Early Lesions



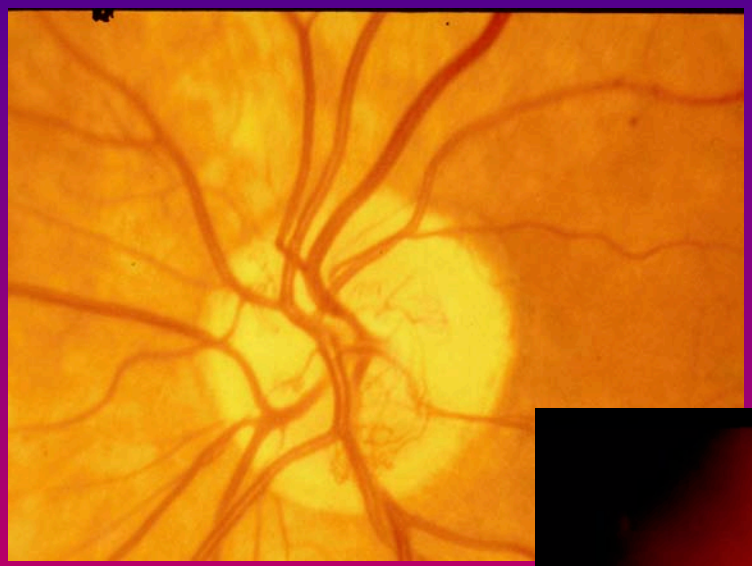
BACKGROUND or NONPROLIFERATIVE DIABETIC RETINOPATHY (BDR or NPDR): More Severe Lesions

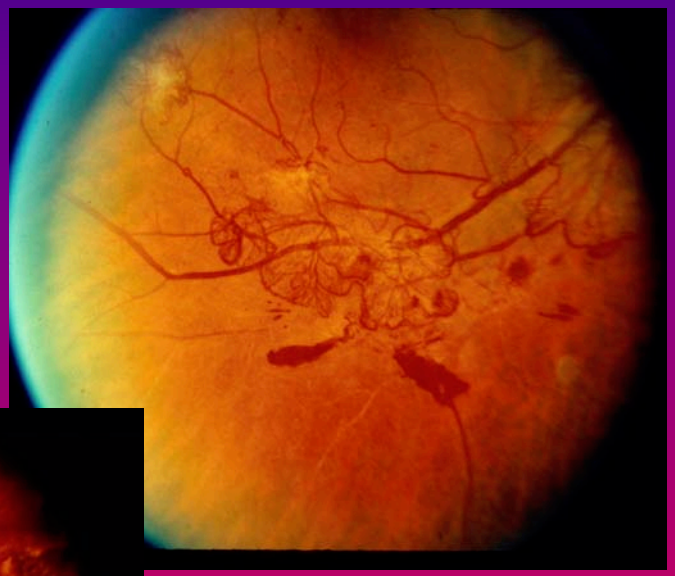


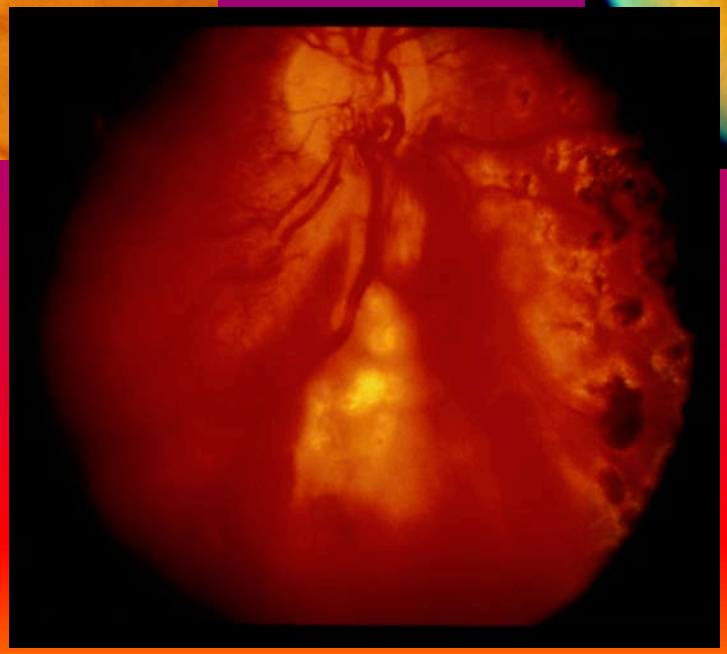


PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

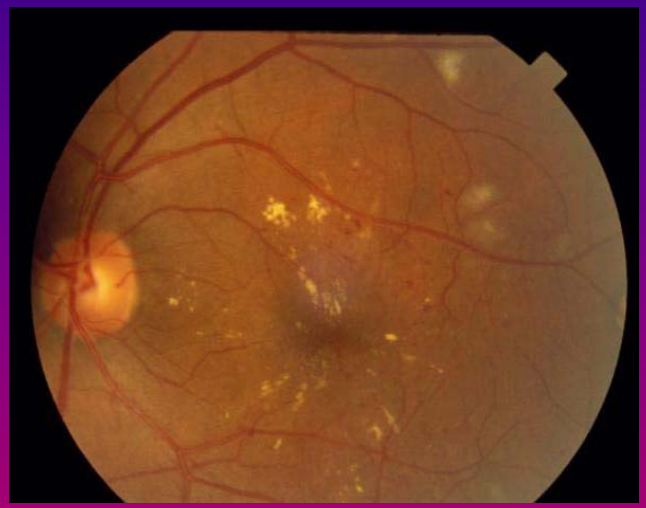
A severe, vision-threatening form of the disease

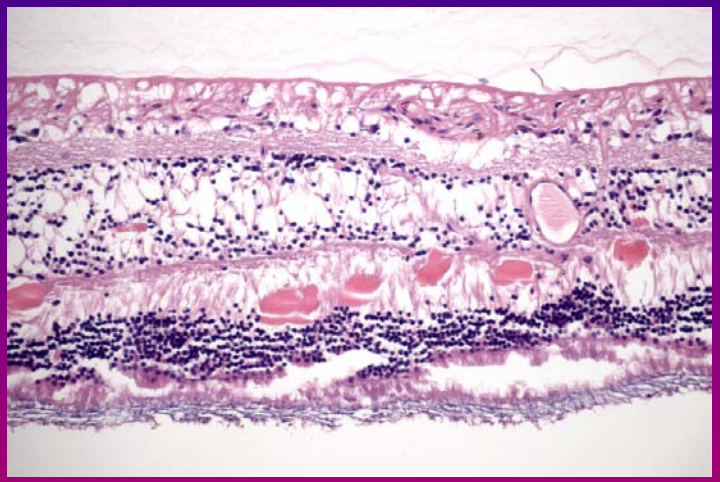


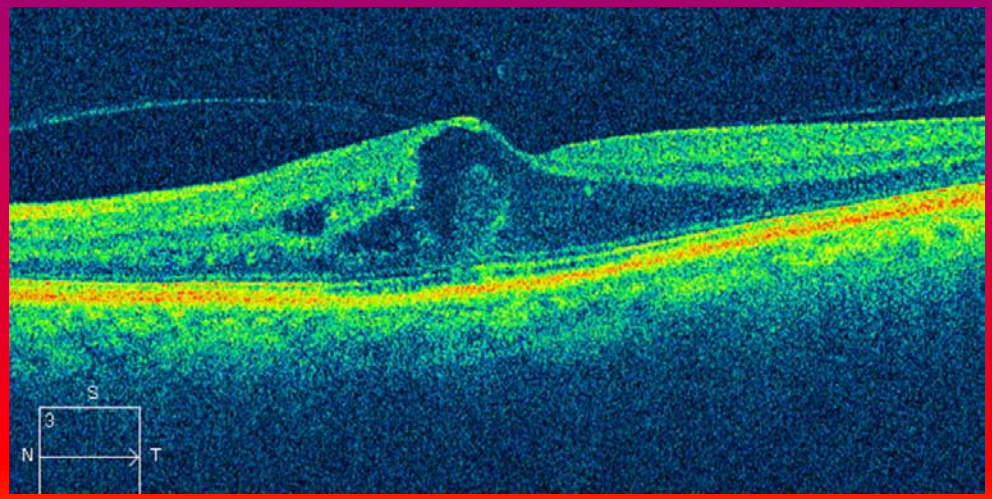




DIABETIC MACULAR EDEMA (DME):







Macular edema is common in several diseases:

- Diabetic retinopathy
- Branch and central retinal vein occlusions
- Uveitis
- Following cataract surgery (Irvine-Gass syndrome, more common following earlier, intracapsular procedures)
- In vitreomacular traction
- Some cases of retinitis pigmentosa
- Familial

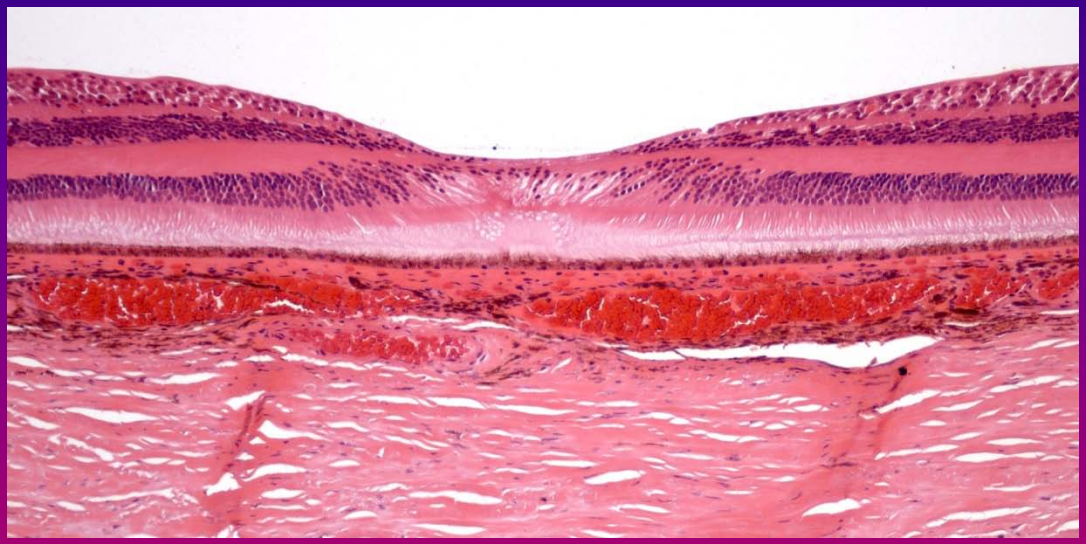
DIABETIC MACULAR EDEMA (DME)
DIAGNOSIS:

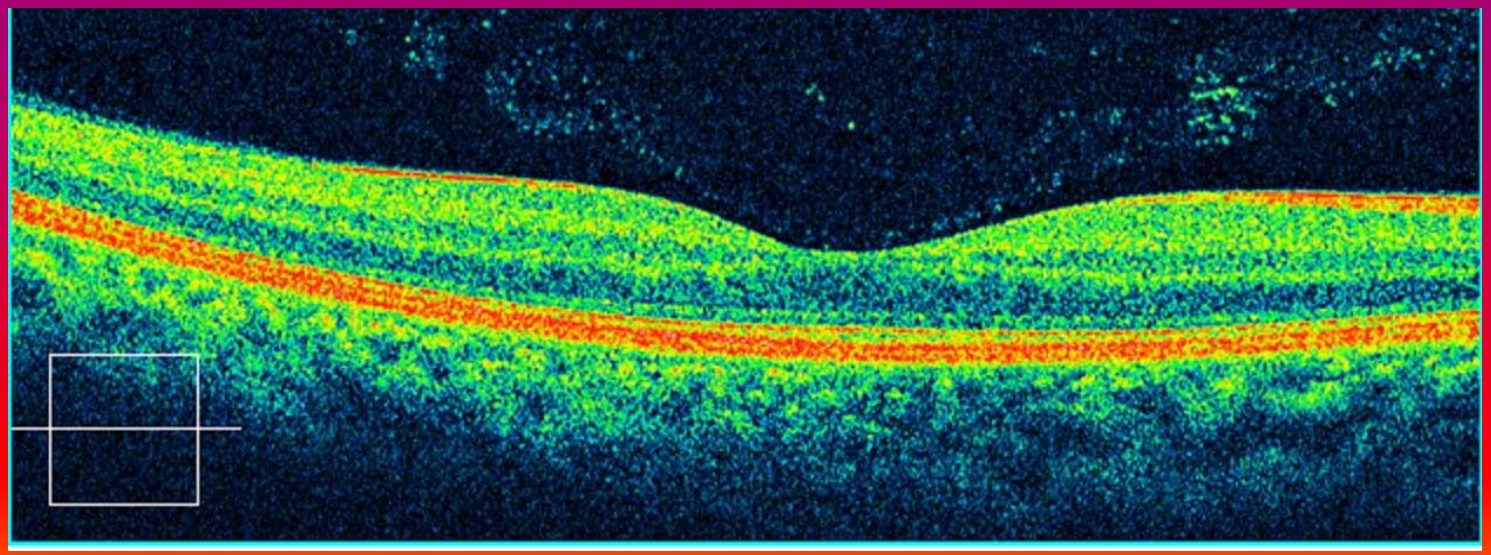
Macular thickening may be determined by several methods

- **Optical Coherence Tomography (OCT) – Most accurate, quantitative**
- **Slit lamp ophthalmoscopy – Subjective, non-quantitative**
- **Stereo Photography -- can be misleading since photos are non-simultaneous pairs, can exaggerate or suppress retinal thicknening.**
- **Fluorescein angiographic dye leakage from vessels (unless it shows a clear cystoid pattern) is not diagnostic.**

OPTICAL COHERENCE TOMOGRAPHY (OCT)

An essential technology for assessing macular edema.





DIABETIC MACULAR EDEMA (DME):

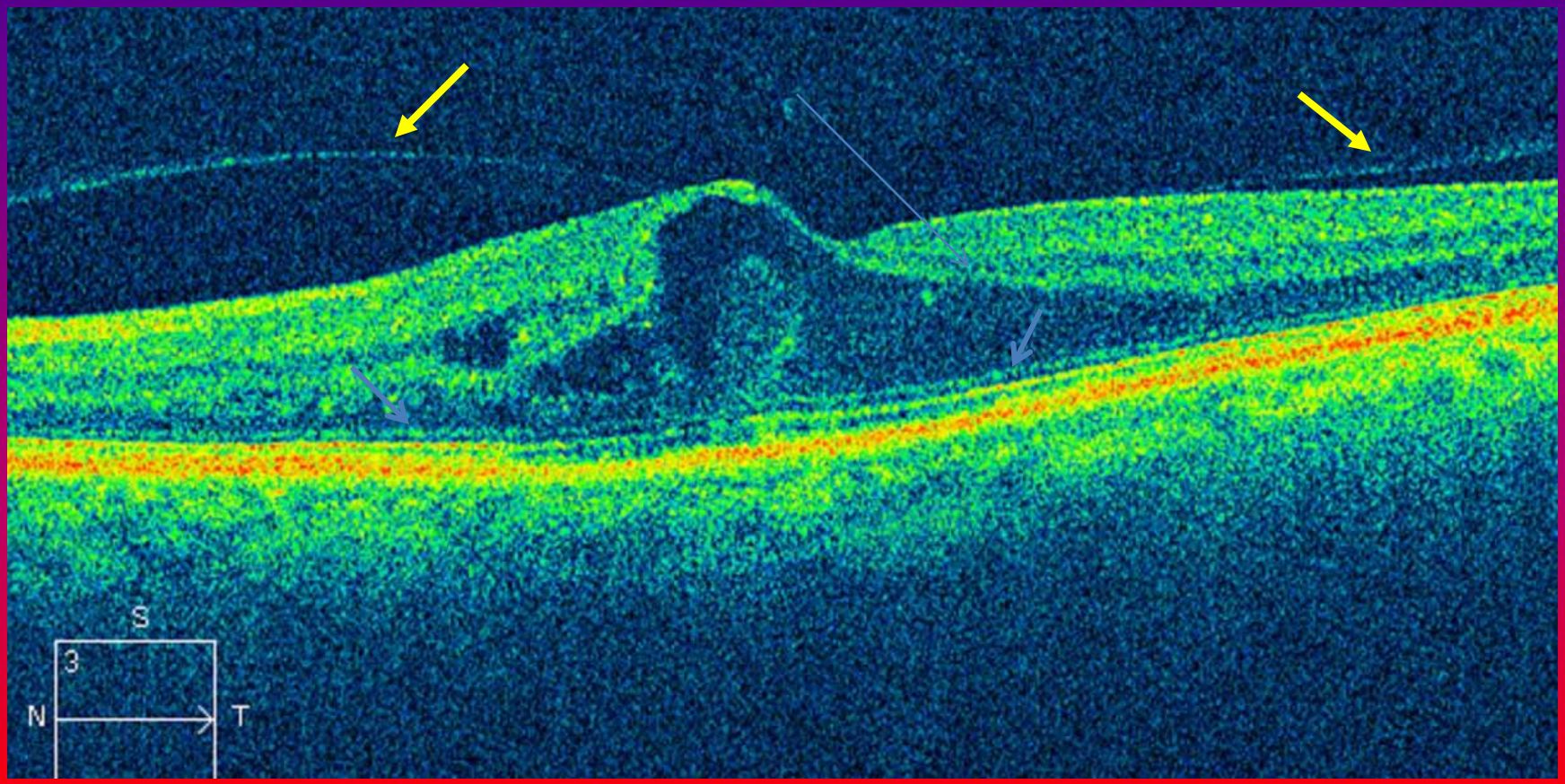
- Non-clinically significant
- Clinically significant (CSDME): Indicates presence of features that increase risk for central vision loss.

QUESTIONS:

- Is vision always impaired in CSDME?
- What factors contribute to reduced vision?

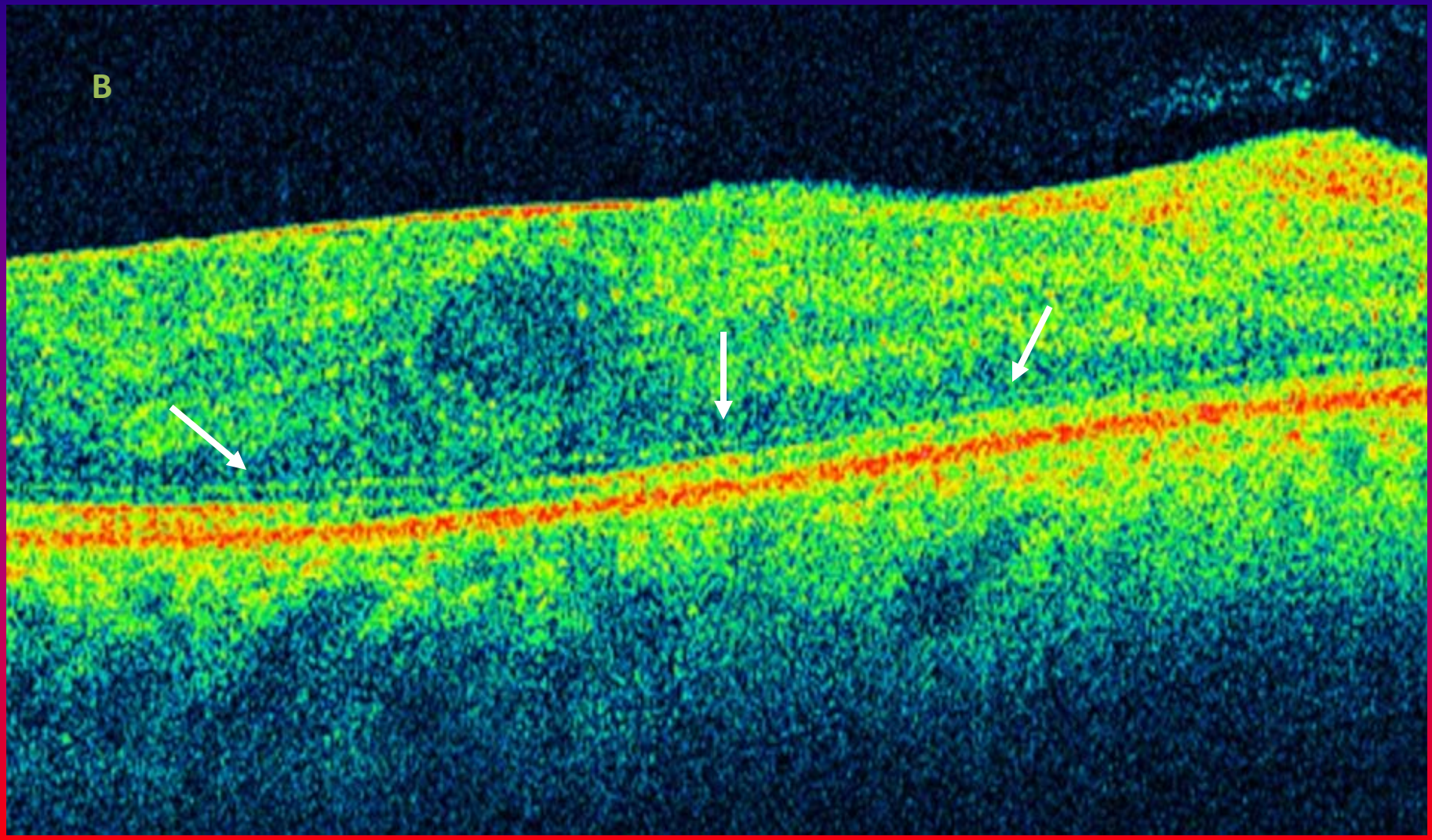
- Visual acuity is not always impaired in CSDME.
- Factors that may contribute to decreased visual acuity:
  - Duration of macular edema
  - Loss of photoreceptor layer
  - Subretinal fluid
  - Macular thickness
  - Presence of cystoid spaces
  - Alteration of other retinal layers
  - Synaptic, other biochemical changes

80 yo pseudophakic, diabetic man (no retinopathy).
Bevacizumab injections OS x3, VA still 20/60.



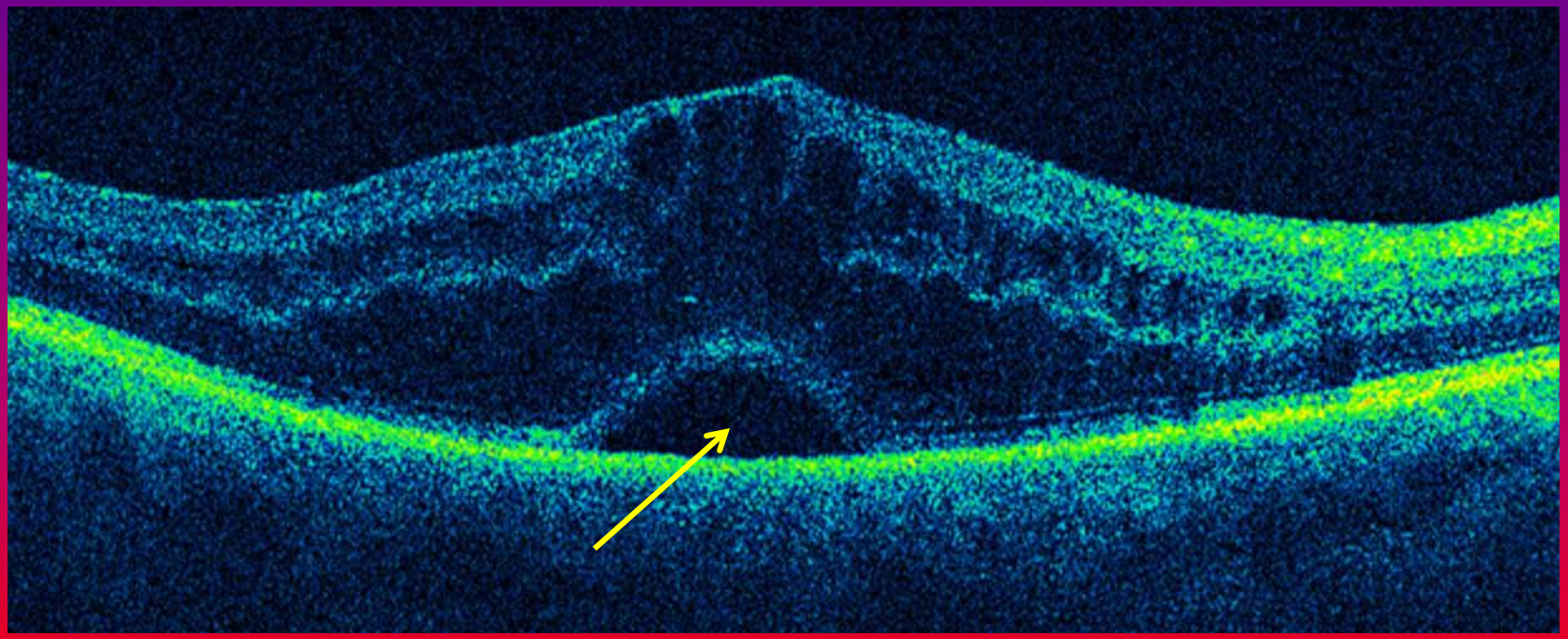
Vitreomacular traction prevents resolution of edema.

Same patient, VA OD 20/40



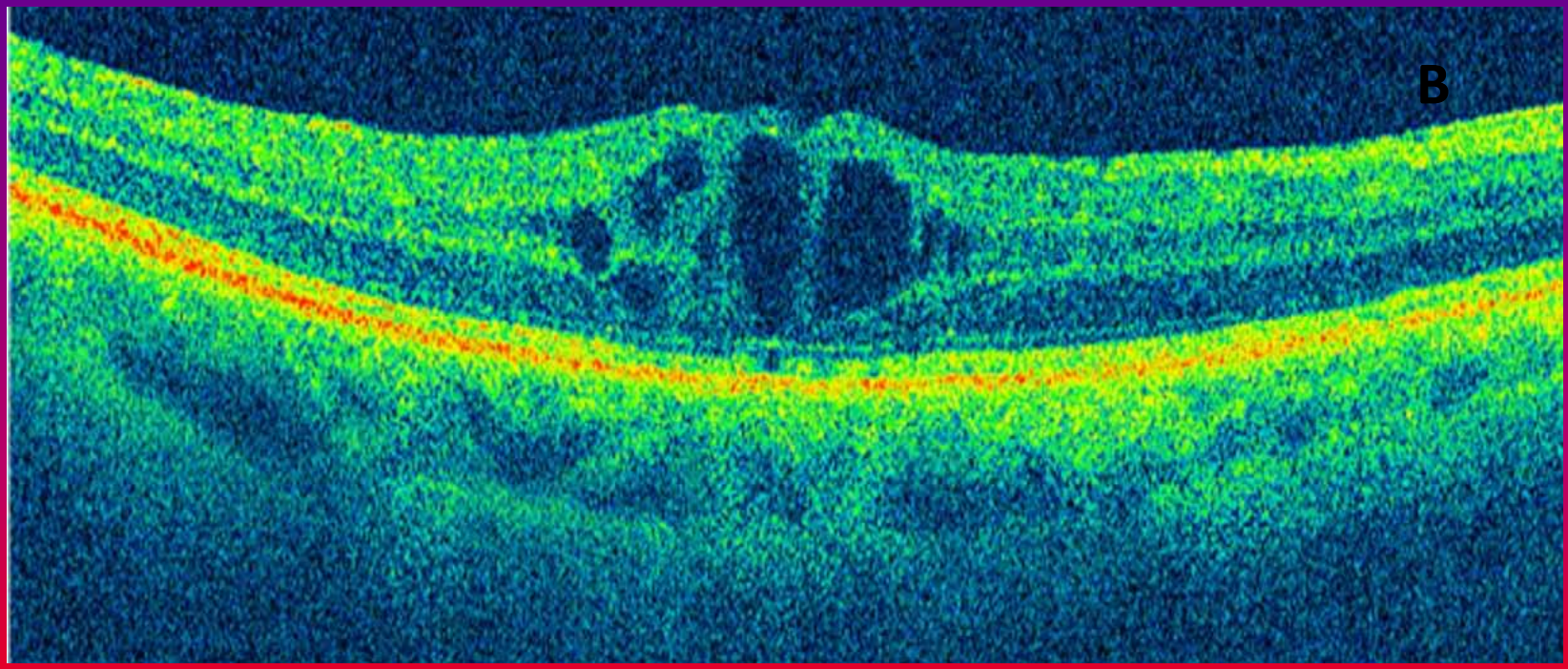
Photoreceptor layer intact; vision good despite edema.

72 yo woman, complicated cataract surgery, ruptured lens capsule, anterior chamber-intraocular lens, Subretinal fluid (arrow)

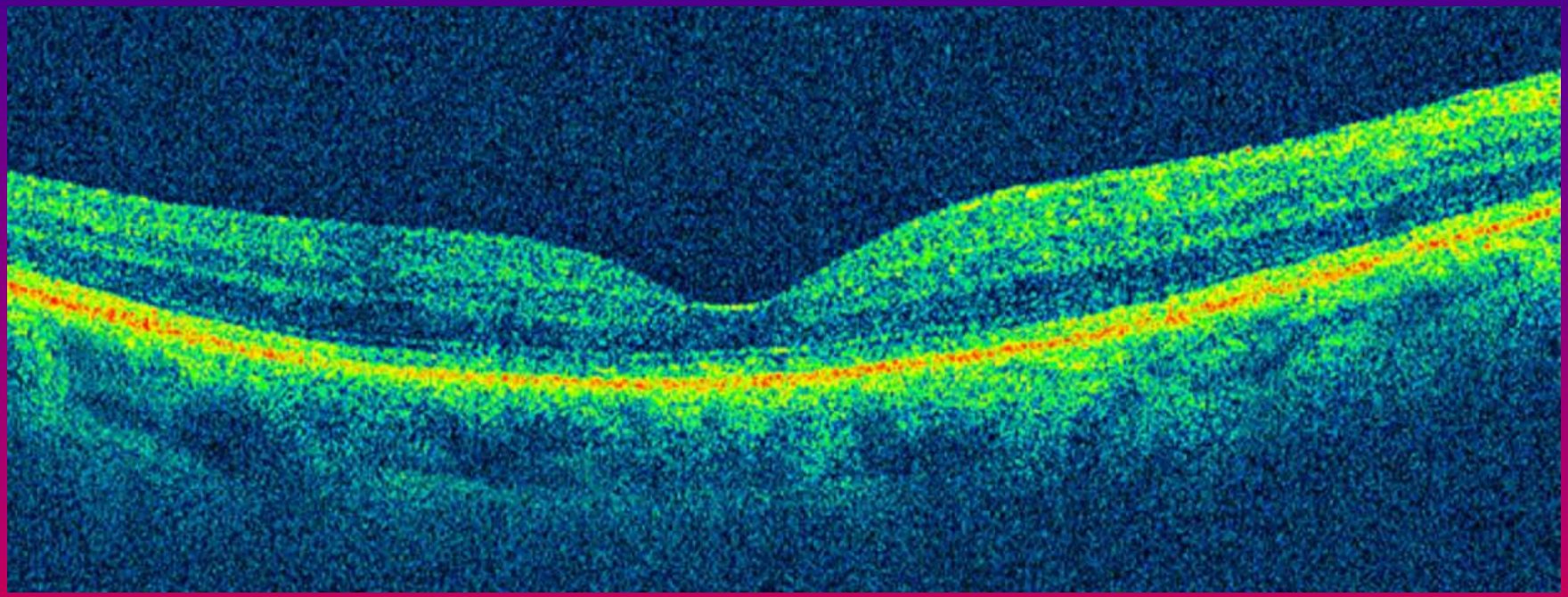


10 Aug. 2009: VA OD 20/400

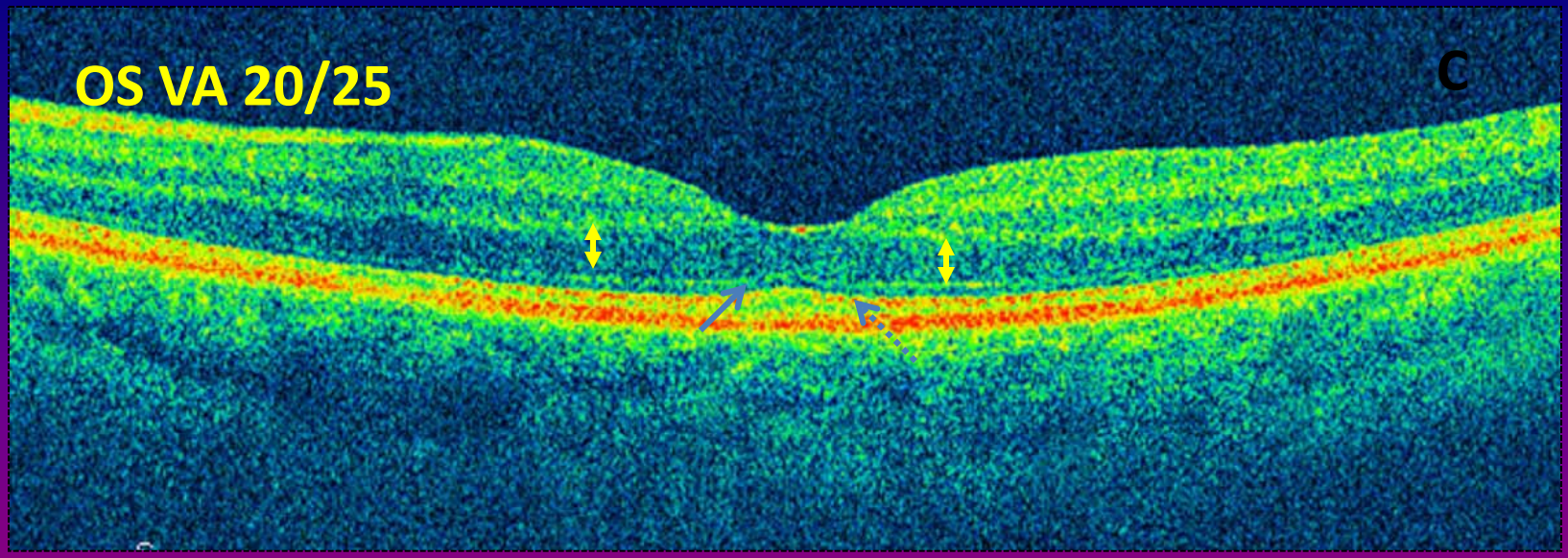
22 March 2010: vitrectomy (Oct. 2009), bevacizumab x 3, VA 20/80

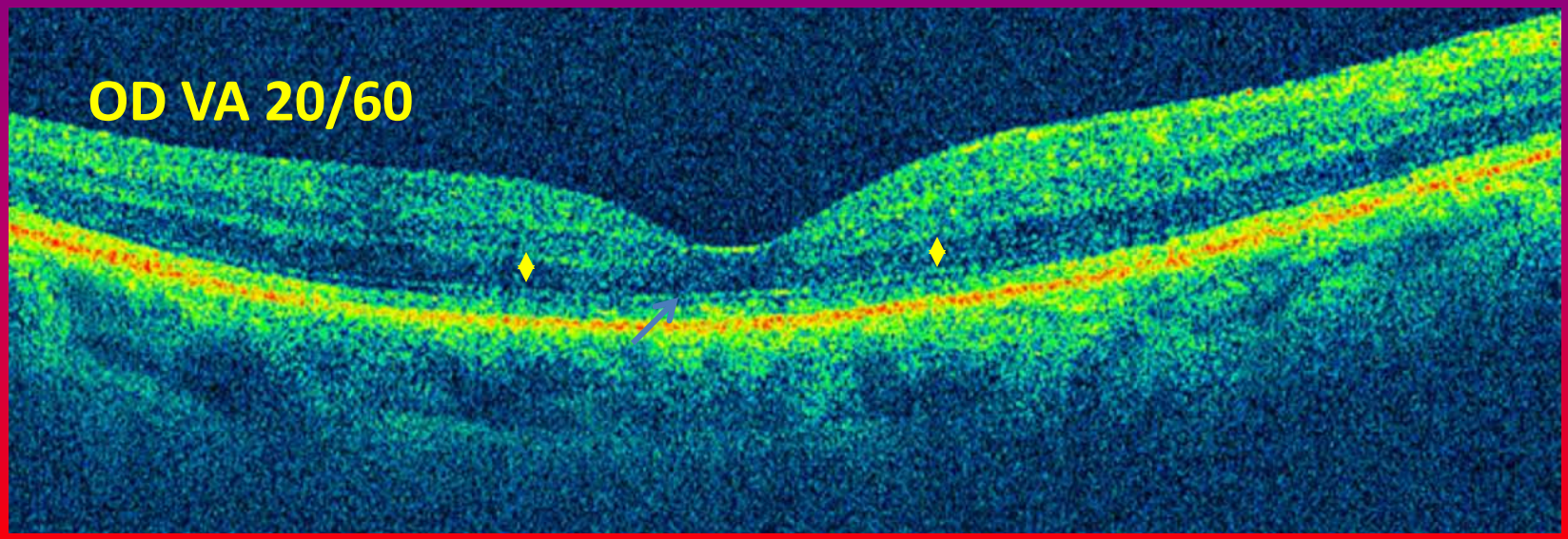


4/30/10: 2 weeks after 2 mg intravitreal triamcinolone, VA 20/80



Why is vision not better? Loss of photoreceptors? Photoreceptor disorientation?





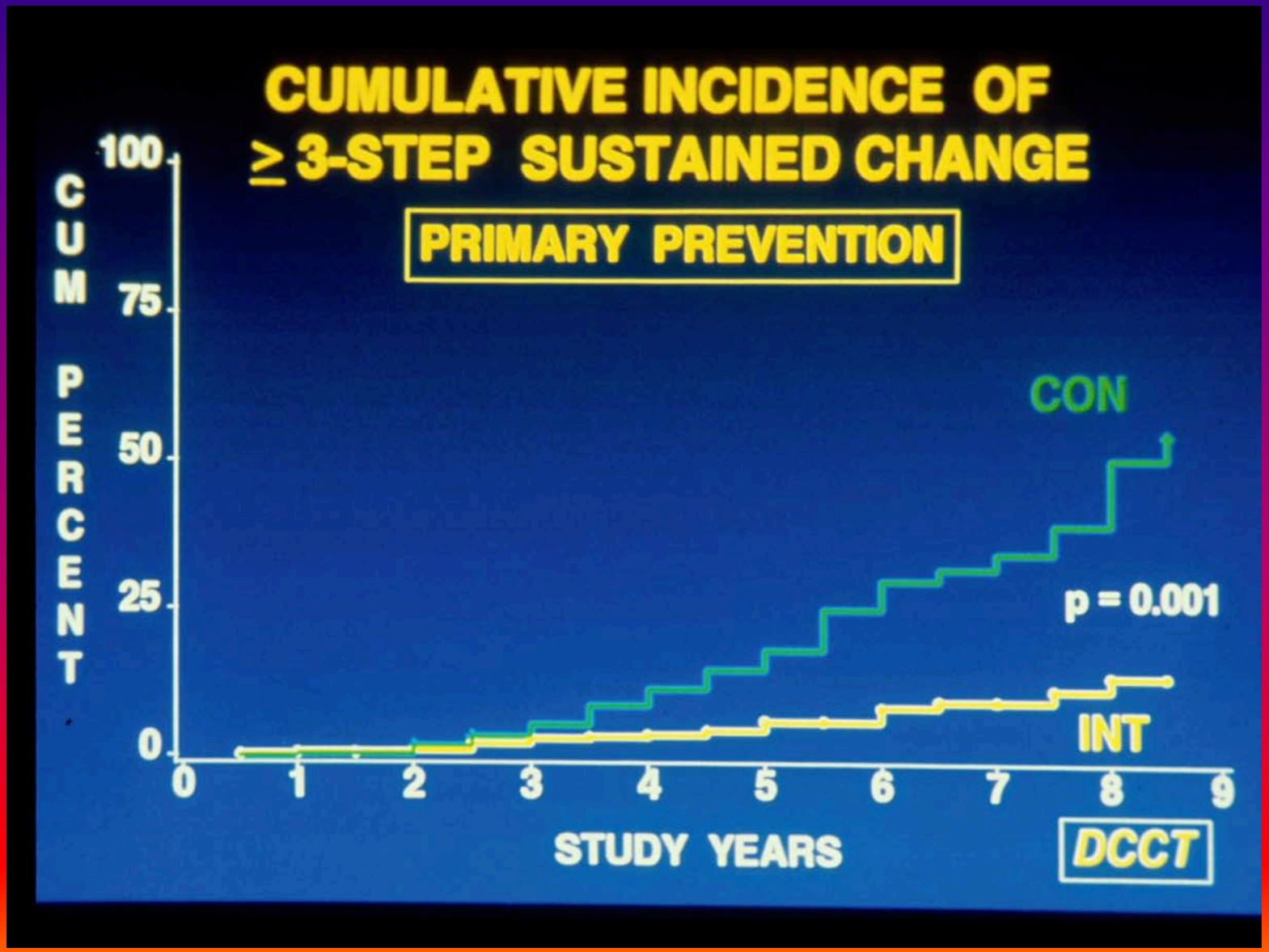
30 Apr. 2010: 2 wks after 2 mg triamcinolone OD

QUESTIONS:

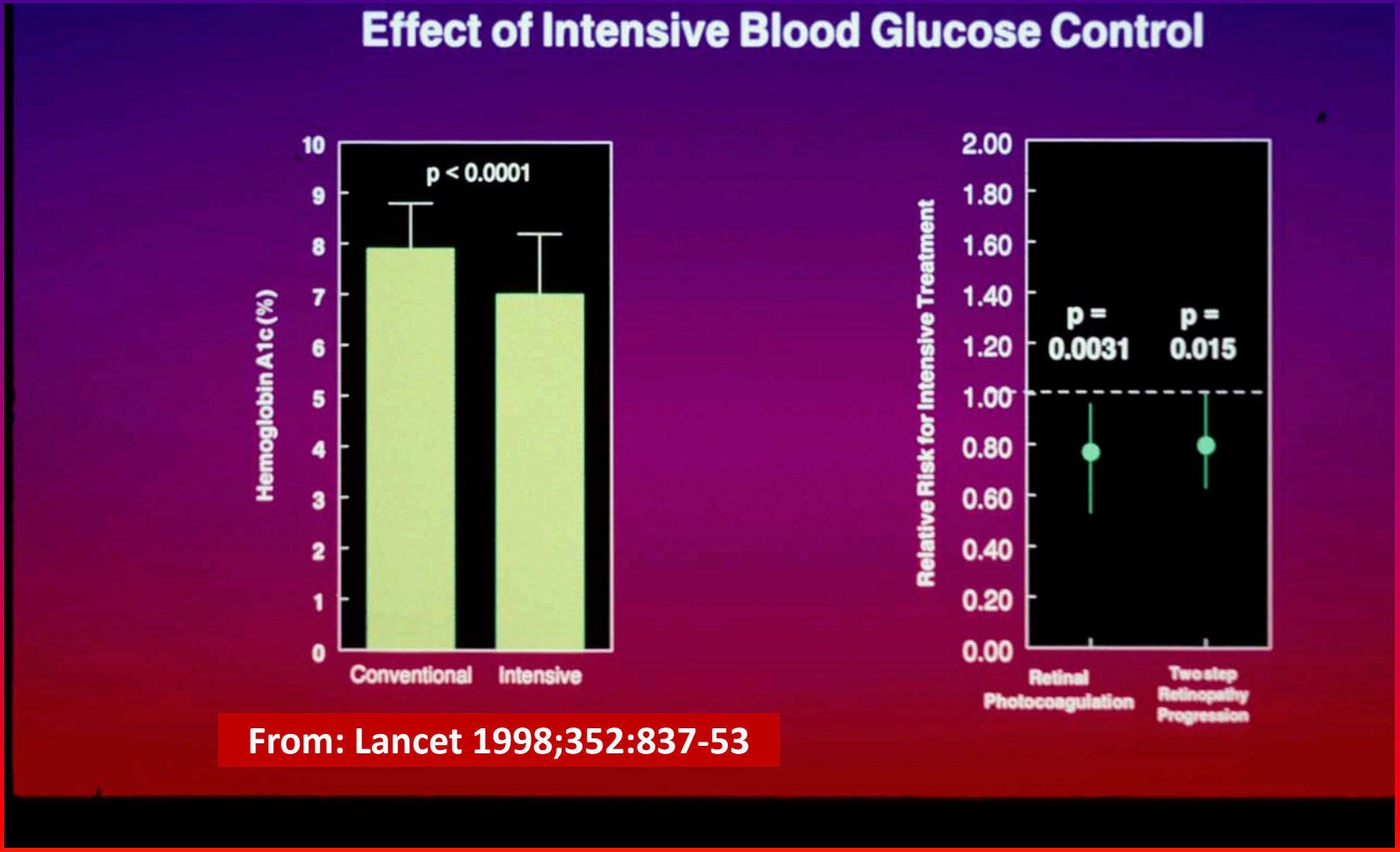
- What is known about prevention of diabetic retinopathy?

- What is known about prevention of diabetic macular edema?

DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT): Type 1 Diabetes



UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS): Type 2 Diabetes



From: Lancet 1998;352:837-53

These studies do not specifically discuss macular edema.

“Progression of retinopathy” refers to:

- **The advancement of pre-specified retinopathy stages or**
- **The decision by individual ophthalmologists to perform laser photocoagulation.**

TREATMENTS FOR MACULAR EDEMA

QUESTIONS:

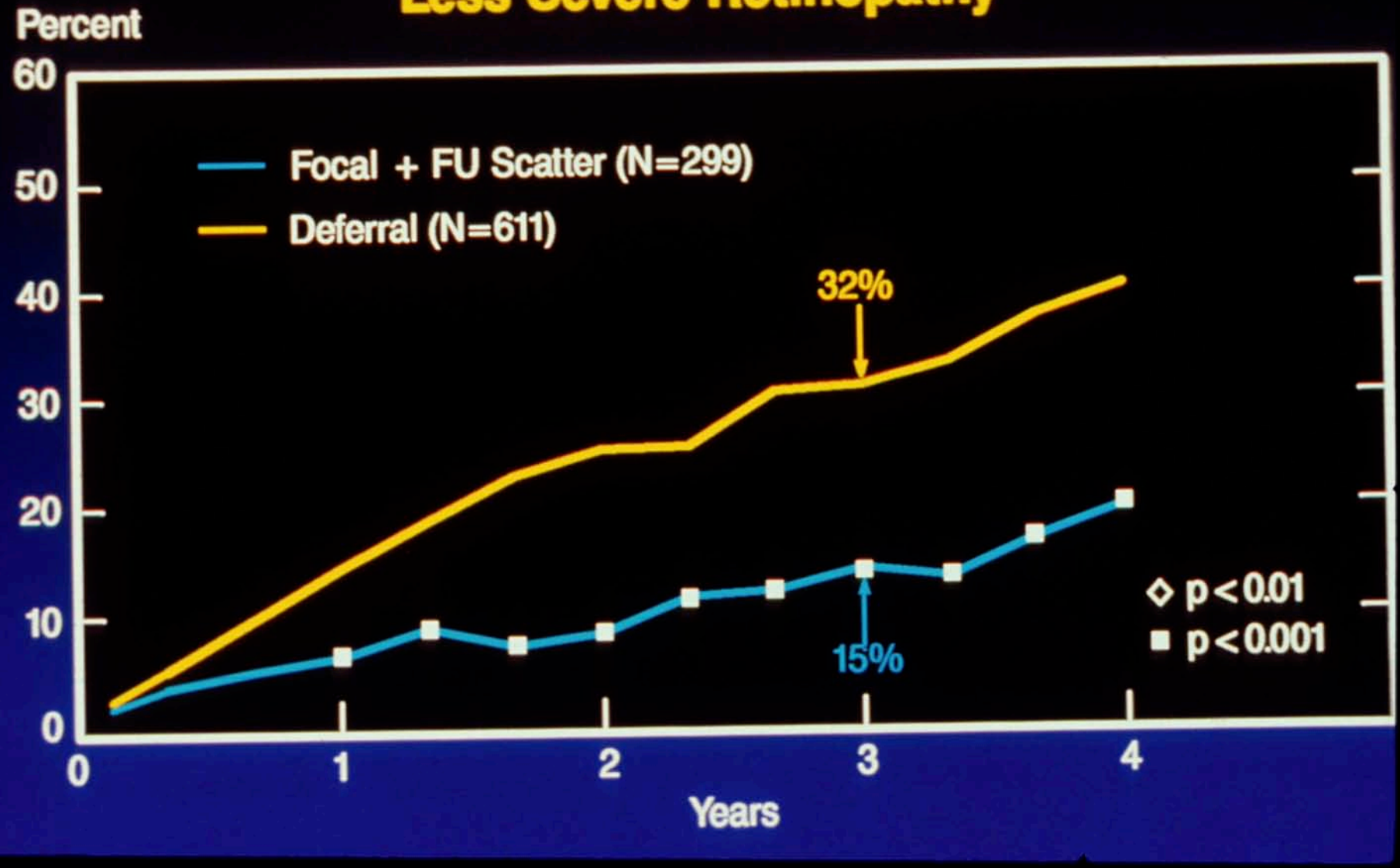
- What are the mechanisms of DME?
- What are the efficacies of various treatments for DME?

TREATMENT - 1

Until recently, focal (vs pan-retinal for PDR) argon laser photocoagulation was the preferred treatment for diabetic macular edema [Early Treatment Diabetic Retinopathy Study (ETDRS), an RCT, 1985, 1991].

Moderate Visual Loss

Clinically Significant Macular Edema - Center Involved
Less Severe Retinopathy



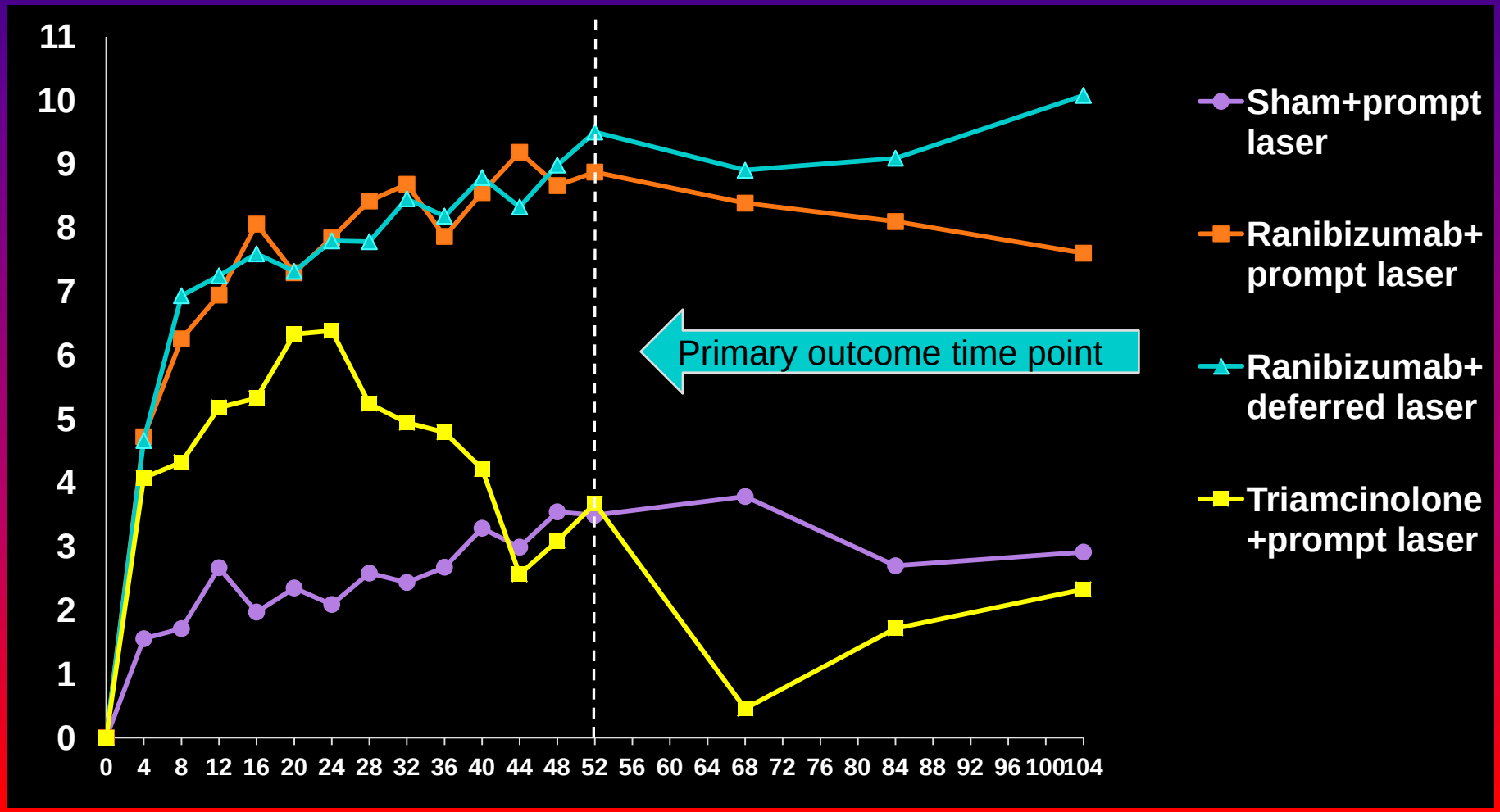
TREATMENT - 2

- Triamcinolone acetonide (a corticosteroid), injected intraocularly, is also highly effective for CSDME, but causes cataracts in nearly all subjects and elevated intraocular pressure in about 30%.
- Ranibizumab (Lucentis, a humanized Fab fragment of the full-length anti-VEGF antibody; Genentech/Roche), injected intraocularly once/month, is highly effective for DME.

TREATMENT - 3

- Pegaptanib (Macugen, an older anti-VEGF aptamer; Eyetech/Pfizer) is a less viable alternative because it blocks only the most prevalent VEGF isoforms , 165aa form.
- Bevacizumab (Avastin; the full-length anti-VEGF antibody) may be effective as suggested by extensive anecdotal clinical experience and the small BOLT study (n=80) in the UK. A large RCT by the Diabetic Retinopathy Clinical Research Network (DRCR.net) comparing ranibizumab and bevacizumab is pending.
- Aflibercept (Eylea, a soluble anti-VEGF receptor fusion protein; Regeneron/Bayer), shows promise, but an RCT for CSDME hasn't been published. Need long-term comparative RCT for this agent with ranibizumab, bevacizumab.

Mean Change in Visual Acuity* at Follow-up Visits

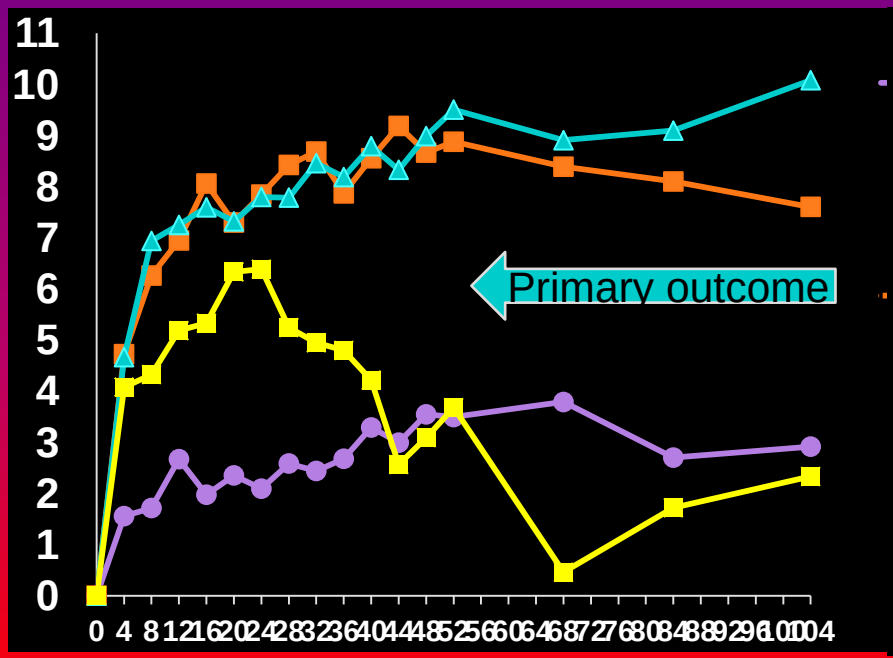


* Values that were 30 letters were assigned a value of 30

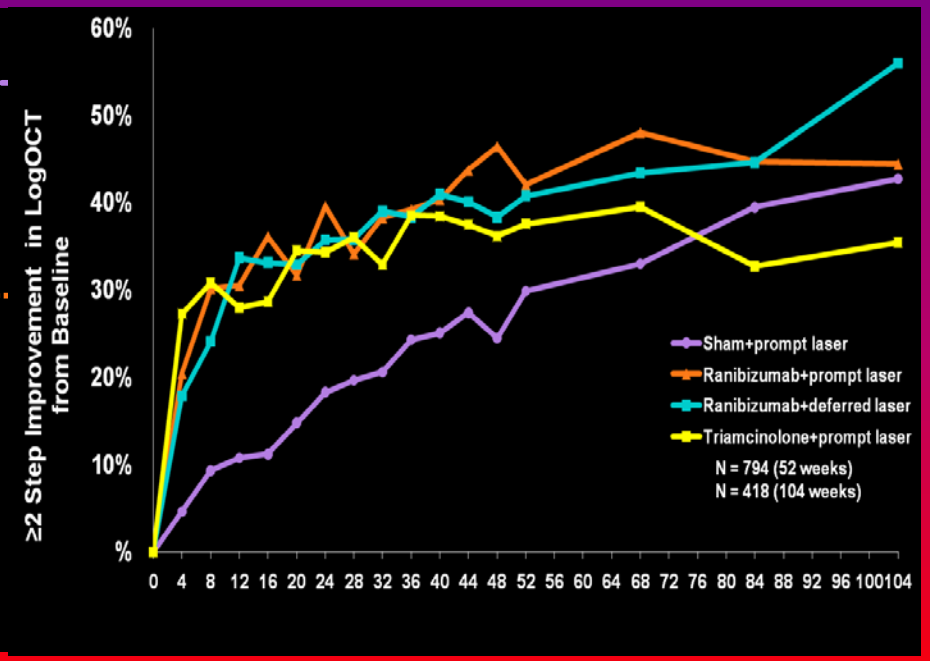
P-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.

Comparison of Visual Acuity and OCT Central Subfield Thickness

Mean Change in Visual Acuity



≥2 Step Improvement in Log OCT



- Reduction in macular thickness @ 2 yrs similar in ranibizumab, focal laser groups, but VA results much better with anti-VEGF antibodies. Suggests metabolic, neurologic effects of anti-VEGFs not present with laser.
- Median number of injections in 2 ranibizumab cohorts: 8 & 9 of max. 13 in year 1; 11 & 13 of max. 25 in year 2. In triamcinolone groups, 3 of 4 in Year 1, 4 of 8 in Year 2.
- Decreasing number of ranibizumab injections in late year 1, still less in years 2, 3: Anti-VEGF therapy is more than “fighting smoke instead of fire.” Other mechanisms involved?

WHAT ELSE IS RESPONSIBLE BESIDES VEGF?

- VEGF increases vascular permeability, induces endothelial fenestrations.
- VEGF is increased in diabetic retina, vitreous.

BUT

- Patients may have PDR but no macular edema, AND others may have macular edema but no PDR.
- Study of VEGF gene polymorphisms in DCCT/EDIC cohort found 18 informative SNPs strongly associated ($p = 6.8 \times 10^{-5}$) with severe NPDR, PDR but ***not*** with macular edema, renal failure (Al-Kateb H, et al. *Diabetes* 2007;56:2161-8).

VEGF UPREGULATION IN OPTIC NERVE GLIA OF DIABETIC HUMAN WITHOUT RETINOPATHY

TREATMENT - 4

- Topical non-steroidal anti-inflammatory medications (NSAIDs)
  - Effective for cystoid macular edema following cataract surgery (Irvine-Gass syndrome).
  - DRCR.net is now testing one such drug, nepafenac, in non-DSDME.
- The immunosuppressive antibiotic sirolimus (rapamycin)
  - To be tested, using sub-Tenon's capsule injection, in a clinical trial for CSDME by the DRCR.net.
- Topical carbonic anhydrase (CA) inhibitors
  - Available CA inhibitors are most effective against CA-2 & CA-4 isoforms.
  - Efficacy limited in diabetic patients because CA-1 is the predominant isoform in the vitreous proteome .
  - Effective for cystoid macular edema in some patients with retinitis pigmentosa.
  - Often tachyphylaxis, with resumed efficacy after several months delay.

TREATMENT - 5

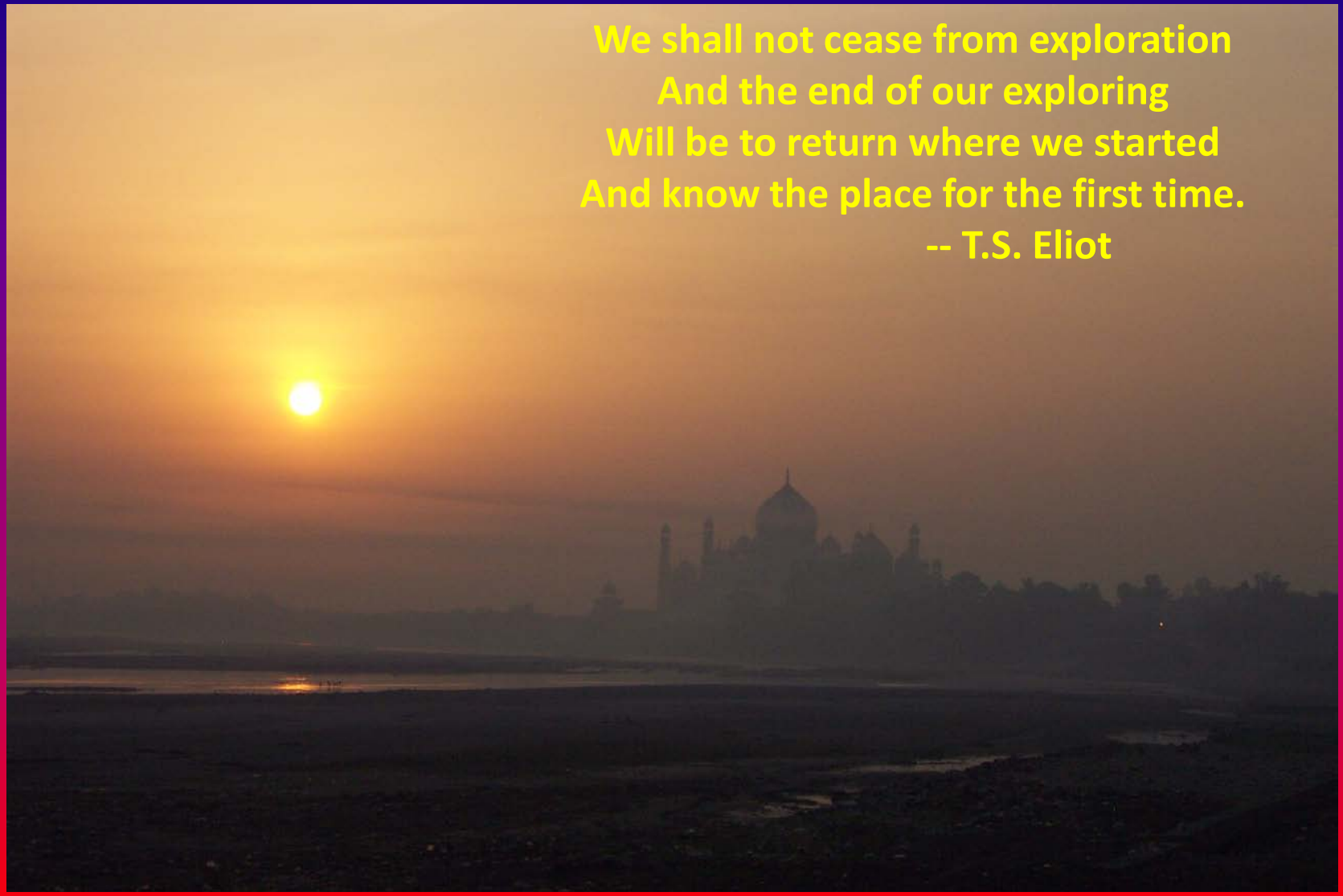
- Drugs that have been tested, unsuccessfully, in RCTs for diabetic retinopathy include:
  - Aldose reductase inhibitors (Pfizer, Wyeth-Ayerst)
  - A protein kinase C, β–isoform inhibitor (Eli Lilly)
  - Aminoguanidine
  - Aspirin (650 mg/day)
- Possible roles for:
  - High-dose antioxidants, successful in the Age-Related Eye Disease Study Part 1 (AREDS-1)
  - Omega-3 fatty acids (known antiproliferative effects)
  - Lutein, currently being tested in AREDS-2

- Lipids: ETDRS retrospective analysis: more macular lipid = higher plasma lipids. ACCORD prospective RCT: statin + fenofibrate, significantly less retinopathy progression than statin alone.
- Blood pressure: UKPDS, treatment of systolic hypertension effective; ACCORD and forthcoming Cochrane review, further BP lowering in normotensive diabetics of no benefit.
- Nonenzymatic protein glycation: no good prevention other than maintaining normoglycemia, since no safe blocking agent known.

OTHER MECHANISMS, OTHER TREATMENTS - 2

- Inflammation: suggested by laboratory studies. Aspirin, however, of no benefit in ETDRS.
- Genetic, epigenetic abnormalities. Still under investigation (cf. FIND study).
- Other cytokines: still being investigated.

This is the present state of knowledge about the mechanisms, and treatment, of diabetic macular edema. Further explorations continue.


We shall not cease from exploration
And the end of our exploring
Will be to return where we started
And know the place for the first time.
-- T.S. Eliot