Ocular Photodynamic Therapy with Verteporfin for Age-Related Macular Degeneration (AMD)

Coverage and Analysis Group
Division of Items and Devices

MCAC – September 9, 2003

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Review Team

- Marc Stone, MD
- Lead Medical Officer
- Stuart Caplan, RN, MAS
- Lead Analyst
- Michelle Atkinson
- Executive Secretary

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Today's Presentation

- AMD in the Medicare population
- History of Medicare coverage
- MCAC voting and discussion questions
- Clinical presentation:
  - Charles P. Wilkinson, MD
- CMS evidence review and data analysis

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MCAC Panel Materials

- Full-text articles of TAP and VIP trials
- FDA status
- Copies of all articles reviewed
- Evidence summary
- Trial protocols
- Voting and discussion questions for the panel

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AMD in the Medicare Population

- The leading cause of blindness age >65
- Approximate incidence
  - NEI estimates 165,000 new cases/year
- Approximate prevalence
  - 7.1% over age 75
  - 1.2 million

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Age-related Macular Degeneration

- No cure
- Treatments
  - Photodynamic therapy with verteporfin
  - Laser photocoagulation
  - Macular translocation surgery
  - Transpupillary thermotherapy (TTT)
  - Anti-angiogenesis therapies (Phase II/III trails)

FDA Status

- On April 12, 2000, the FDA approved verteporfin for predominantly classic, AMD-related subfoveal choroidal neovasularization (CNV), as determined by fluorescein angiography.
- On August 22, 2001, the FDA approved verteporfin for predominantly classic subfoveal (CNV) related to pathologic myopia and presumed ocular histoplasmosis.

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FDA Status

- The use of verteporfin for occult and no classic AMD-related subfoveal choroidal neovasularization (CNV) is an off-label use.

Clinical Trials of Interest

- TAP: Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group.
- VIP: Verteporfin In Photodynamic Study Group

History of Medicare Coverage

No national coverage determination prior to original verteporfin request

Three Decision Memoranda

- November 8, 2000
- October 17, 2001
- March 28, 2002
- Reconsideration opened July 25, 2003

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Panel Voting Questions

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Panel Voting Question 1

- Is there adequate evidence to draw conclusions about the net health outcomes (that is, whether or not the risks and benefits of treatment outweigh the risks and benefits of non-treatment) of ocular photodynamic therapy (OPT) with verteporfin in routine clinical use in the population of Medicare beneficiaries who have age-related macular degeneration (AMD) and occult with no classic choroidal neovascularization (CNV)?

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Panel Voting Question 2

- If the panel answers the first question affirmatively, does the evidence demonstrate that OPT with verteporfin treatment improves net health outcomes in treating age-related macular degeneration (AMD) and occult with no classic choroidal neovascularization (CNV), and if so, what is the size of the benefit in patients receiving the treatment?

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MCAC Categories of Effectiveness

- Breakthrough technology
- Substantially more effective
- More effective
- As effective but with advantages
- As effective and with no advantages
- Less effective but with advantages
- Less effective and with no advantages
- Not effective

Panel Discussion Questions

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Panel Discussion Question 1

- Neither the TAP nor VIP trials address cessation of verteporfin therapy. Under what circumstances should treatment be discontinued?

Panel Discussion Question 2

- What additional research studies might be useful in clarifying outcome measures, subgroup of patients most likely to benefit, duration of treatment, and other aspects of the use of verteporfin in the Medicare population?

Panel Discussion Question 3

- If the evidence demonstrates that OPT with verteporfin improves net health outcomes, does the size of effect of treatment, from a societal perspective, outweigh the clinical risk and cost its widespread use would create for patients and the Medicare program?

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Charles P. Wilkinson, MD

The Current Dilemma

Since PDT appears to be of some value for “100% Occult” lesions,

Is coverage “reasonable and necessary”?

Presentation

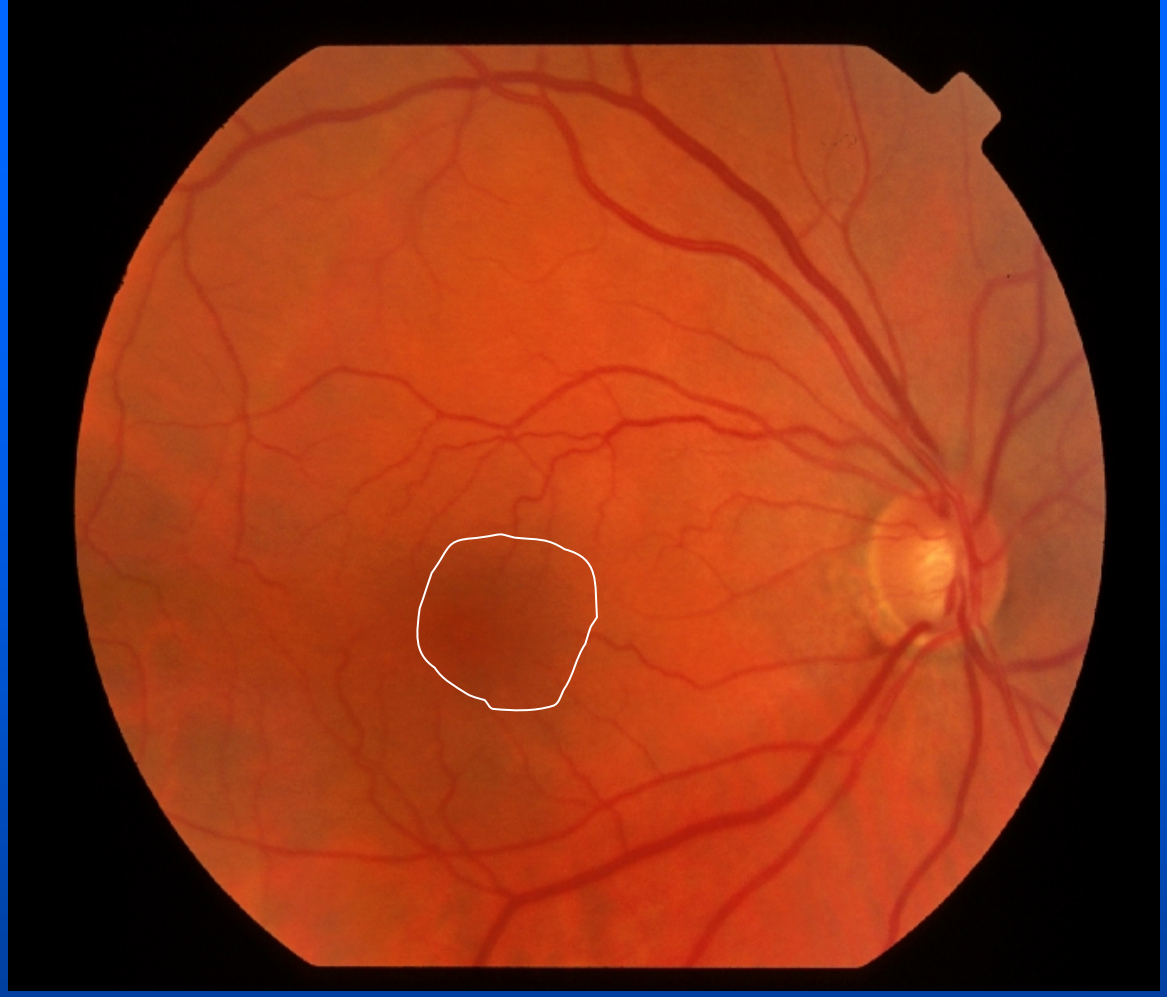
- Brief overview of the disease
- Following Dr. Stone's presentation, a brief overview of the data
- Personal views about the value of PDT for AMD

C.P. Wilkinson, MD : "Conceivable Potential Conflicts"

- ASRS: Member & BOT member
- Retina Society: Member & President-elect
- Macula Society: Member
- AAO "Preferred Practice Patterns": Chairman, Retina Panel, 1992-2001
- "NAPP Trial" (Steroids + PDT for AMD – (Privately-funded): Member, Safety/Data Monitoring Committee

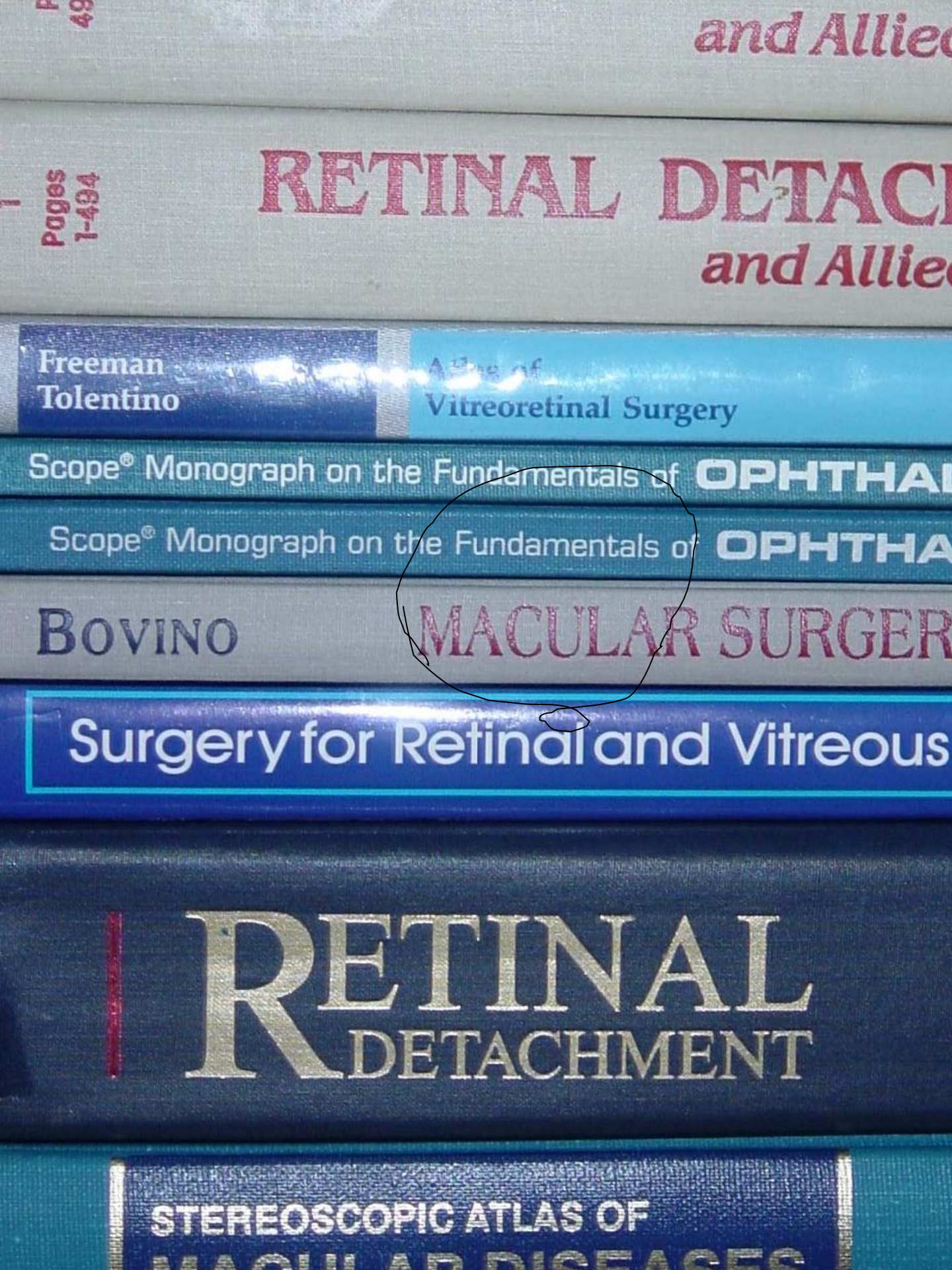
AMD OVERVIEW (1)

- Aging changes are ”normal”
- Few > 85 have perfect vision
- AMD onset difficult to define
- “Early AMD” might, by some, be considered “normal aging”
- Notable loss of vision due to macular changes = AMD

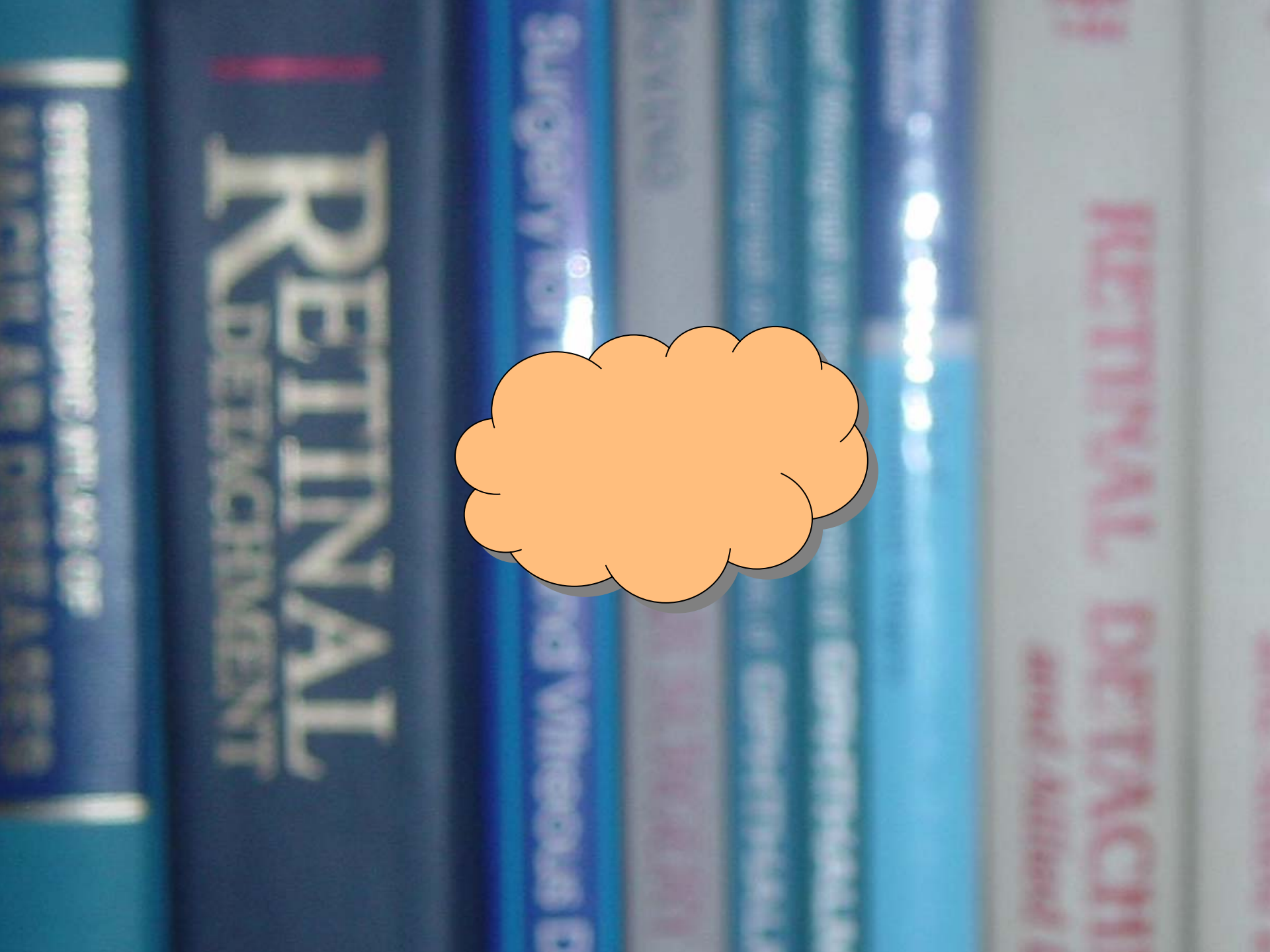


Macular function produces the normally sharp central image.

Vision peripheral to the center is never as good as the precise center of vision.


and Allied
Pages 1-494
RETINAL DETACH
and Allied
Freeman
Tolentino
Vitreoretinal Surgery
Scope® Monograph on the Fundamentals of OPHTHAL
Scope® Monograph on the Fundamentals of OPHTHA
BOVINO
MACULAR SURGER
Surgery for Retinal and Vitreous
RETINAL
DETACHMENT
STEREOSCOPIC ATLAS OF

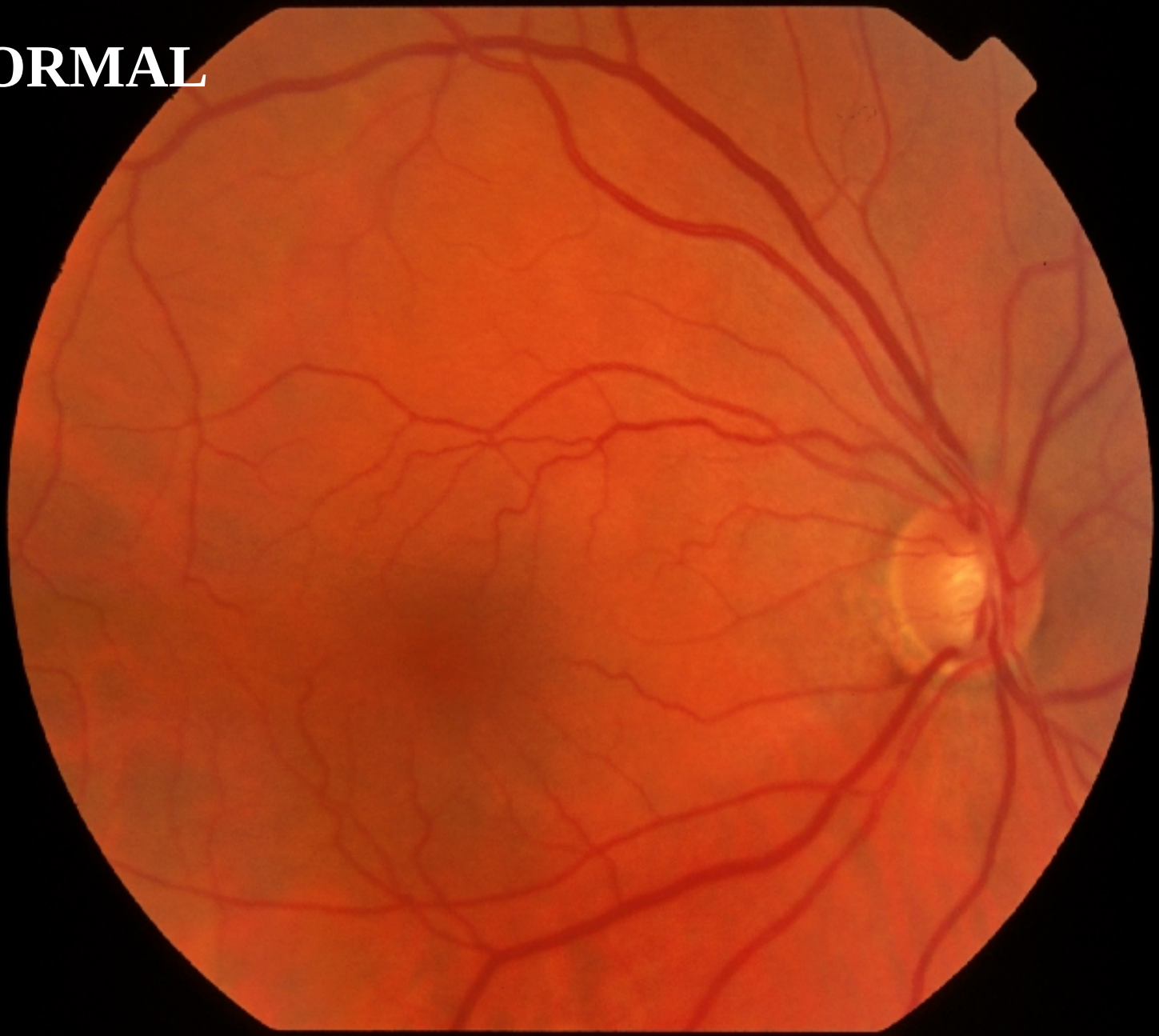
RETINAL


RETINAL

AMD OVERVIEW (2)

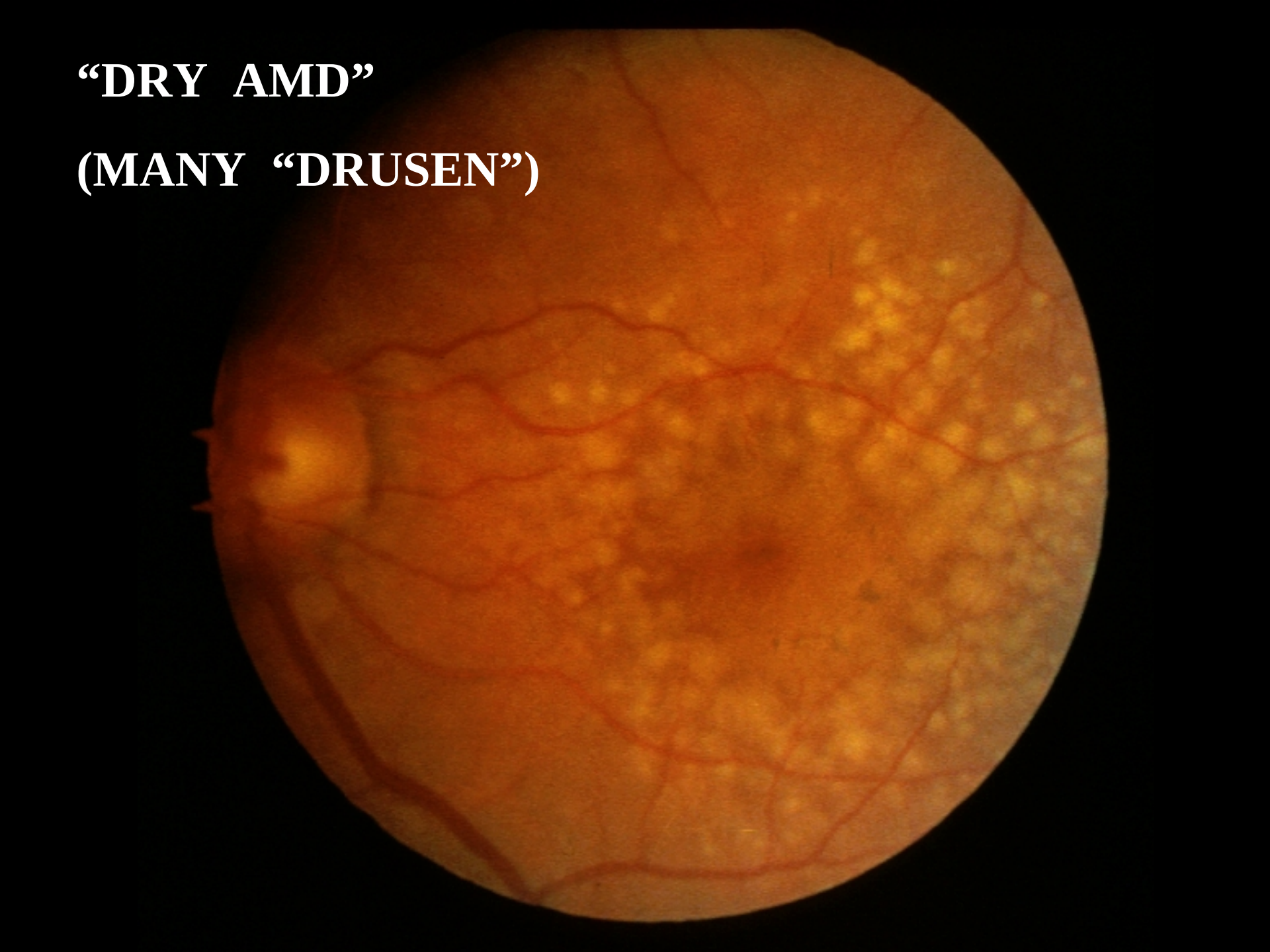
- AMD Categorized as "DRY" or "WET"
- "DRY" = Changes in pigmented layer of retina that cause loss of vision.
- Most (90%?) of AMD is "DRY"
- "DRY" usually precedes "WET"

NORMAL



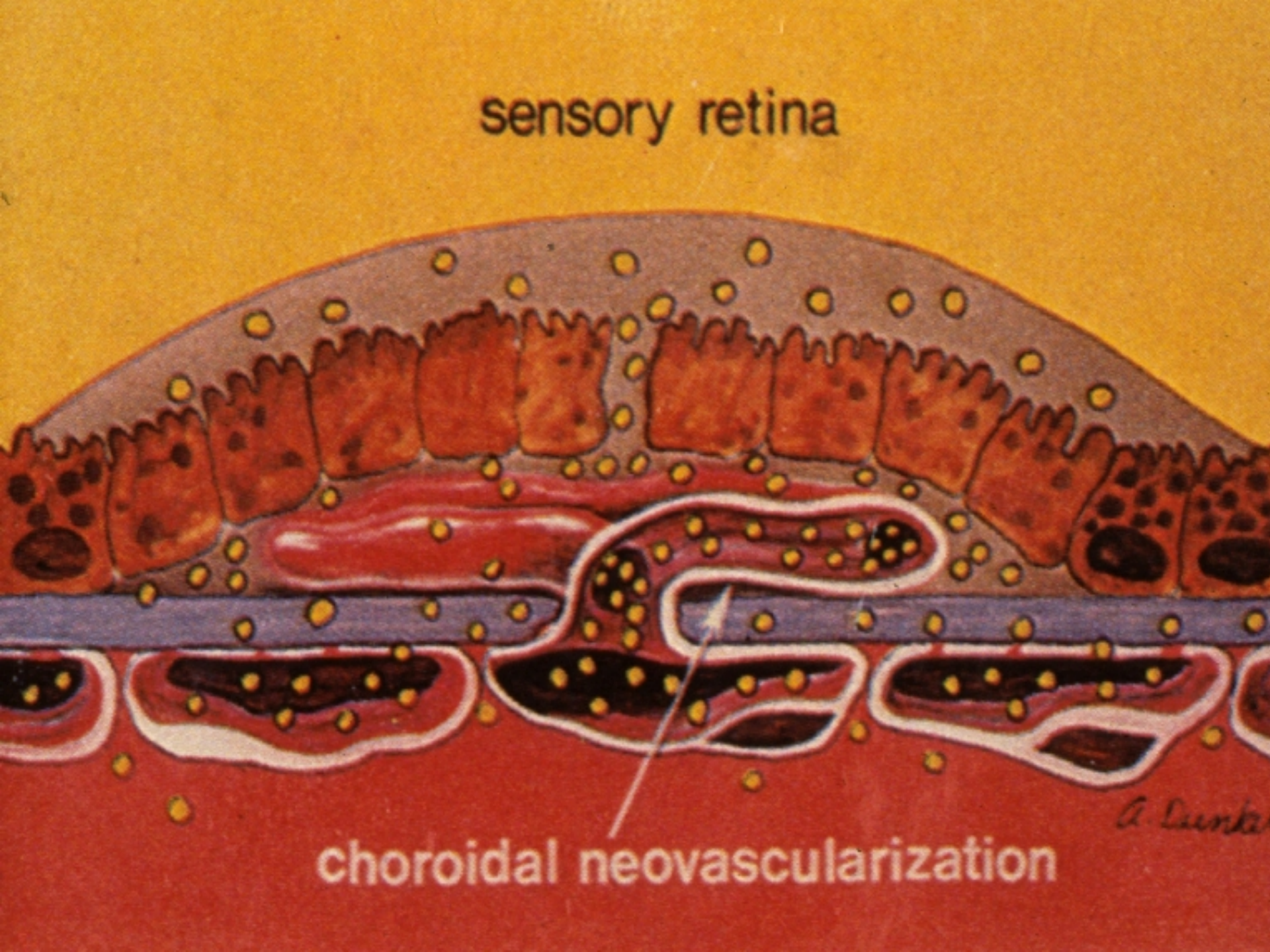
“DRY AMD”

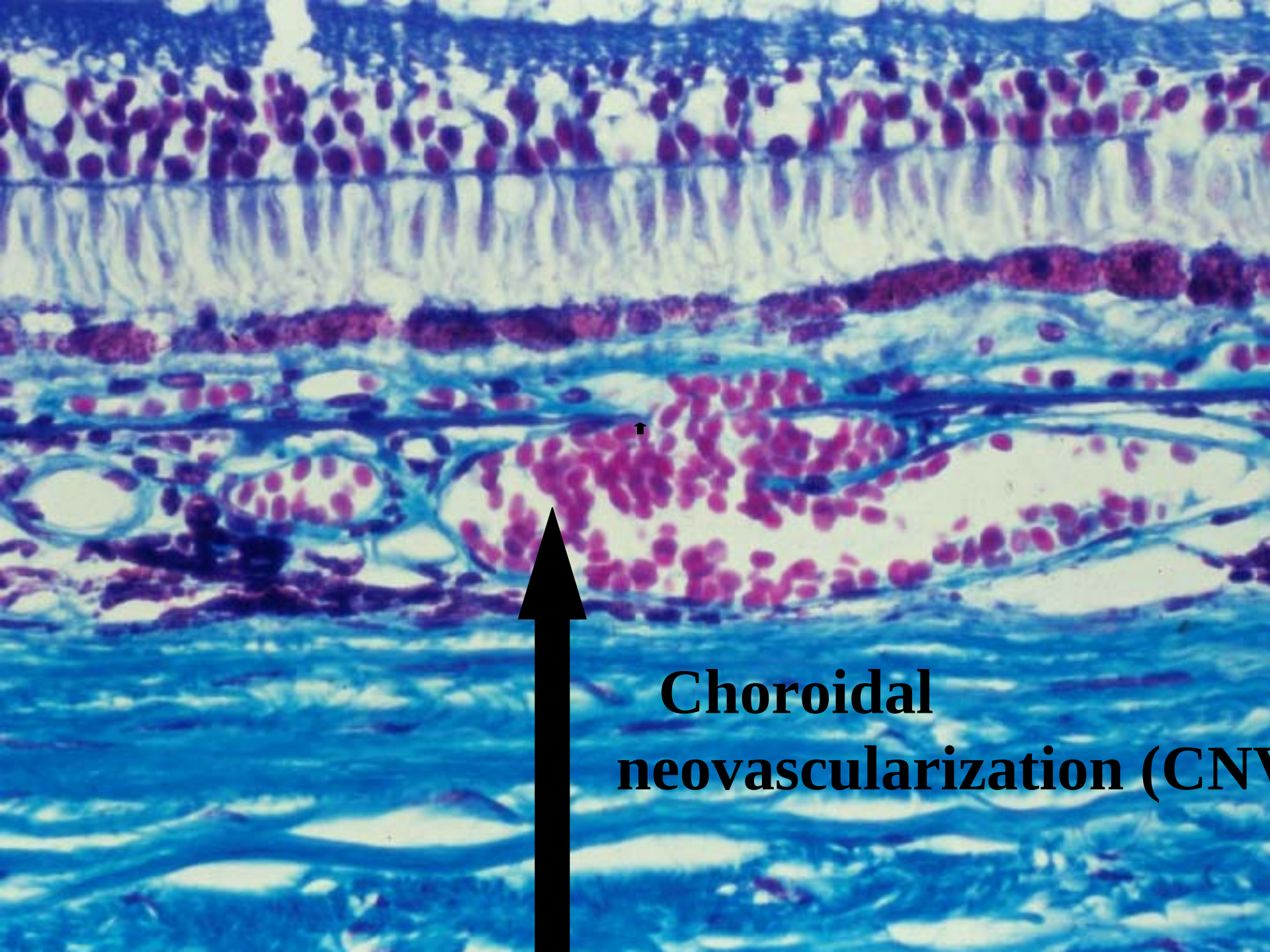
(MANY “DRUSEN”)



AMD OVERVIEW (3)

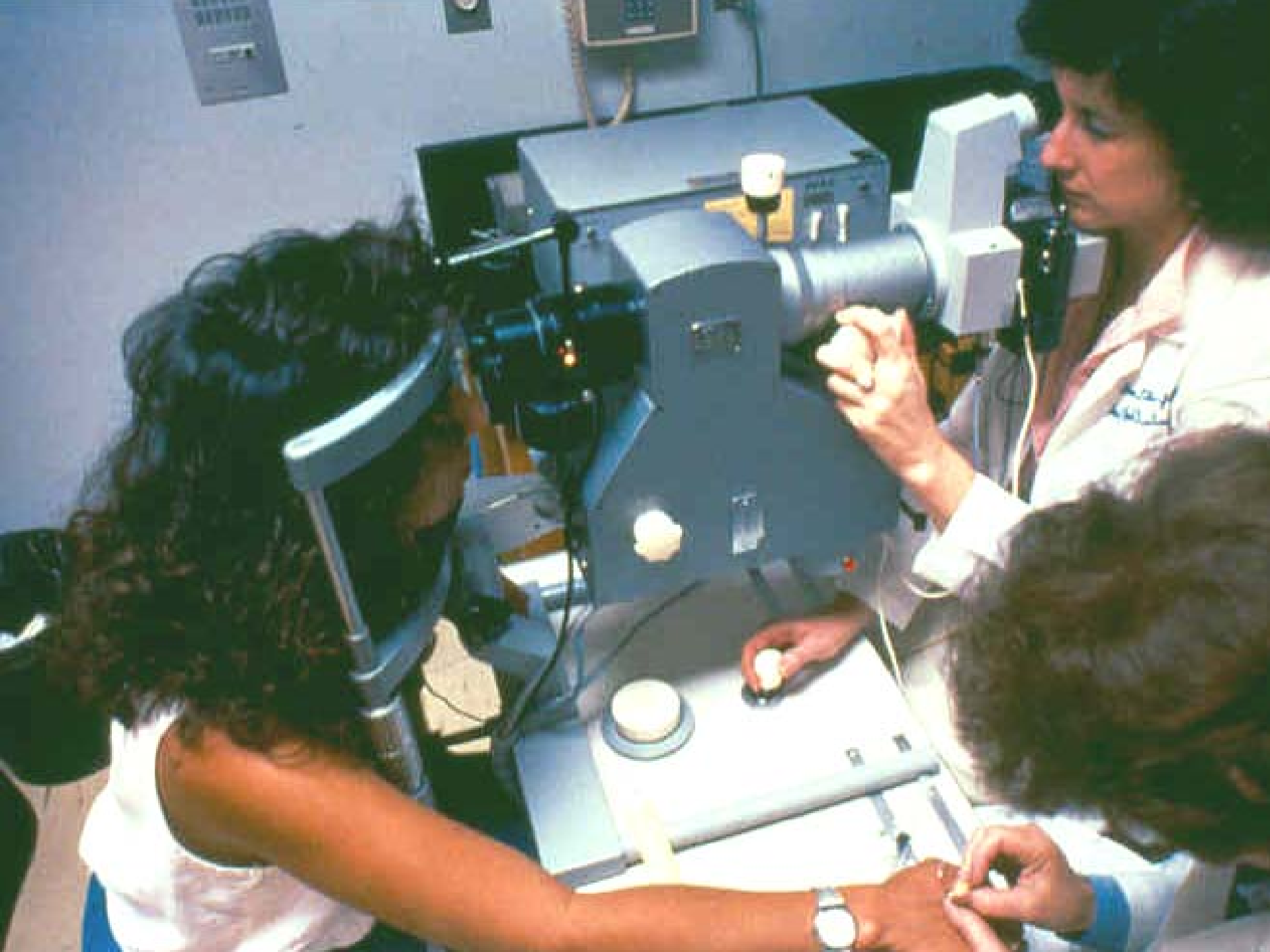
- "WET" = Leakage from beneath retina, usually from abnormal blood vessels from the choroid
- These abnormal vessels = CNV "Choroidal neovascularization"
- "WET" usually termed "Neovascular"
- 90% of legal blindness due to "neovascular"

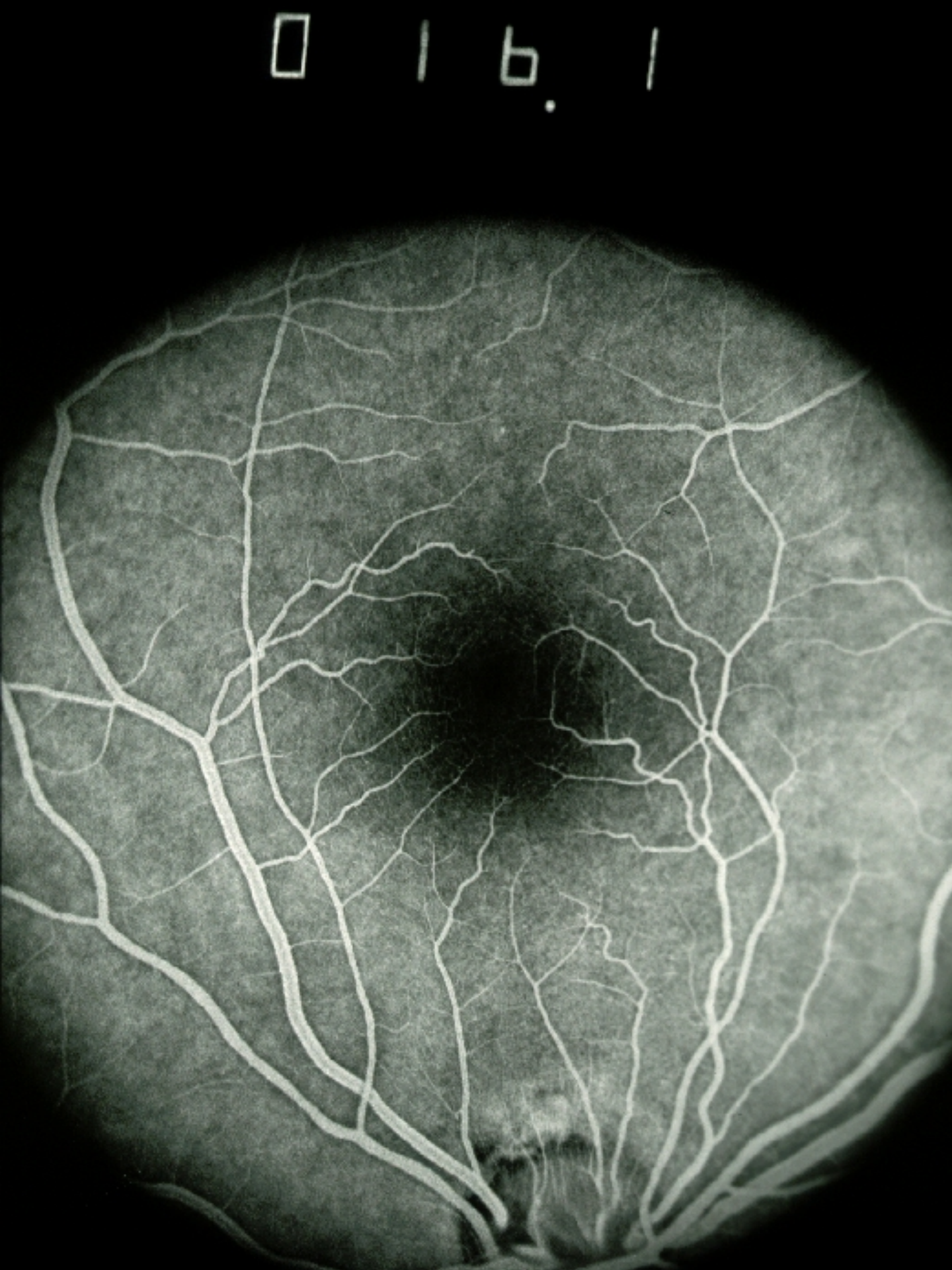

sensory retina
choroidal neovascularization


Choroidal
neovascularization (CNV

CNV : DEFINED BY FLUORESCEIN ANGIOGRAM

- “Classic” CNV
- “Occult” CNV
- Both “Classic” AND “Occult”
- > 50% “Classic” = “Predominately Classic” lesion

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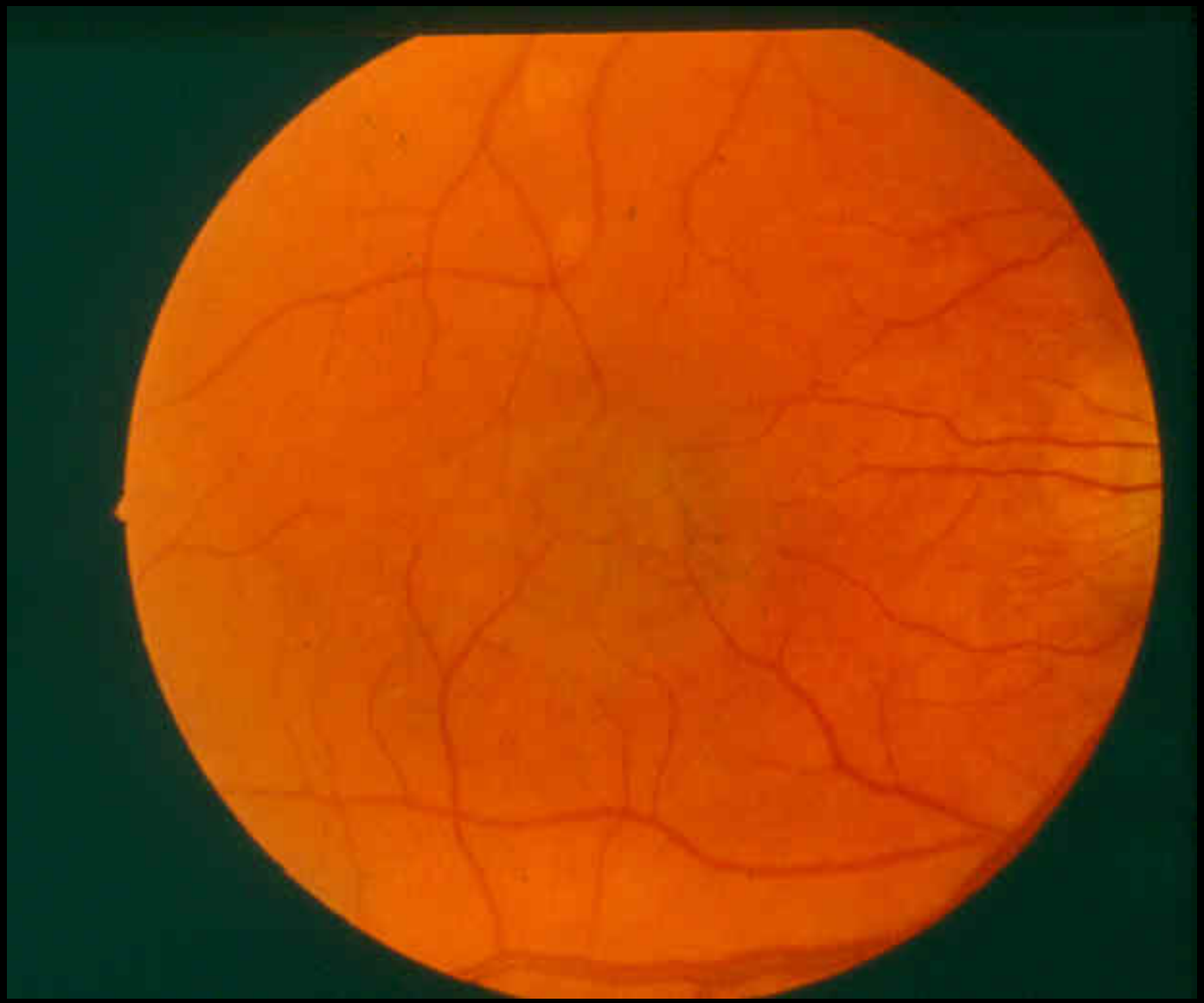
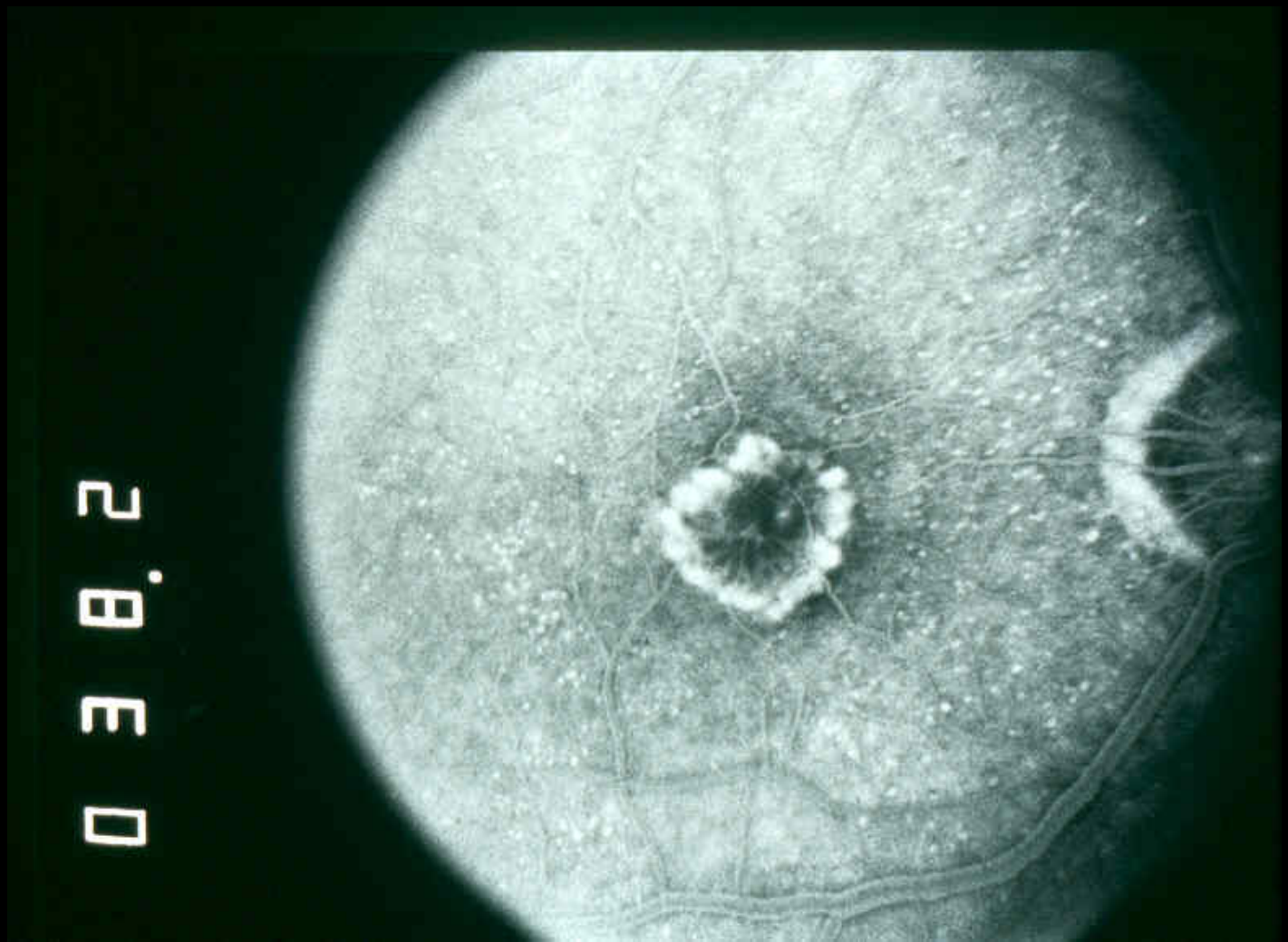
“ CLASSIC “ ANGIOGRAPHIC FEATURES

- Early Hyperfluorescence
- Well-defined site
- Visible margins
- Progressive leaks
- Characteristic pattern

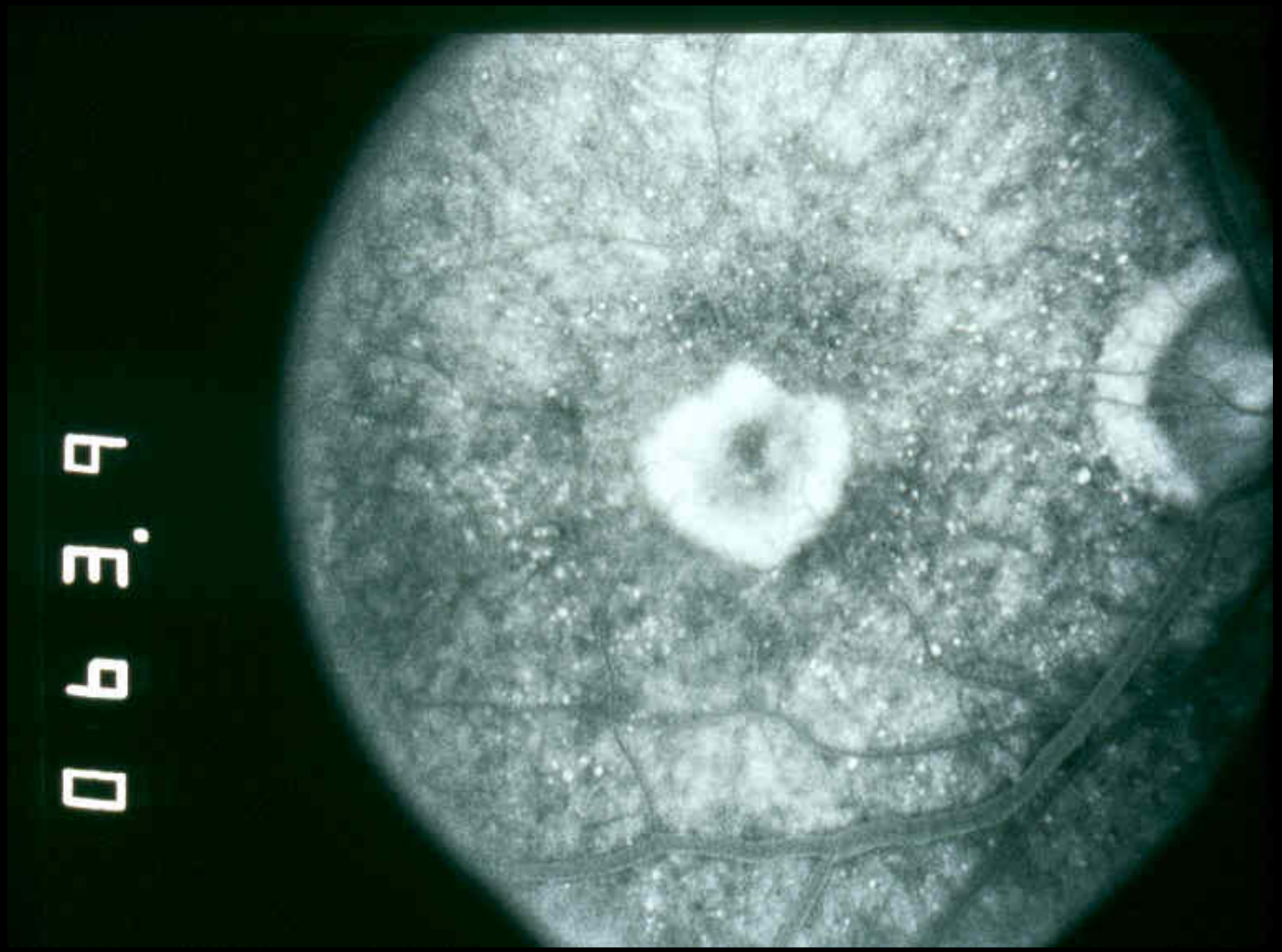
AMD

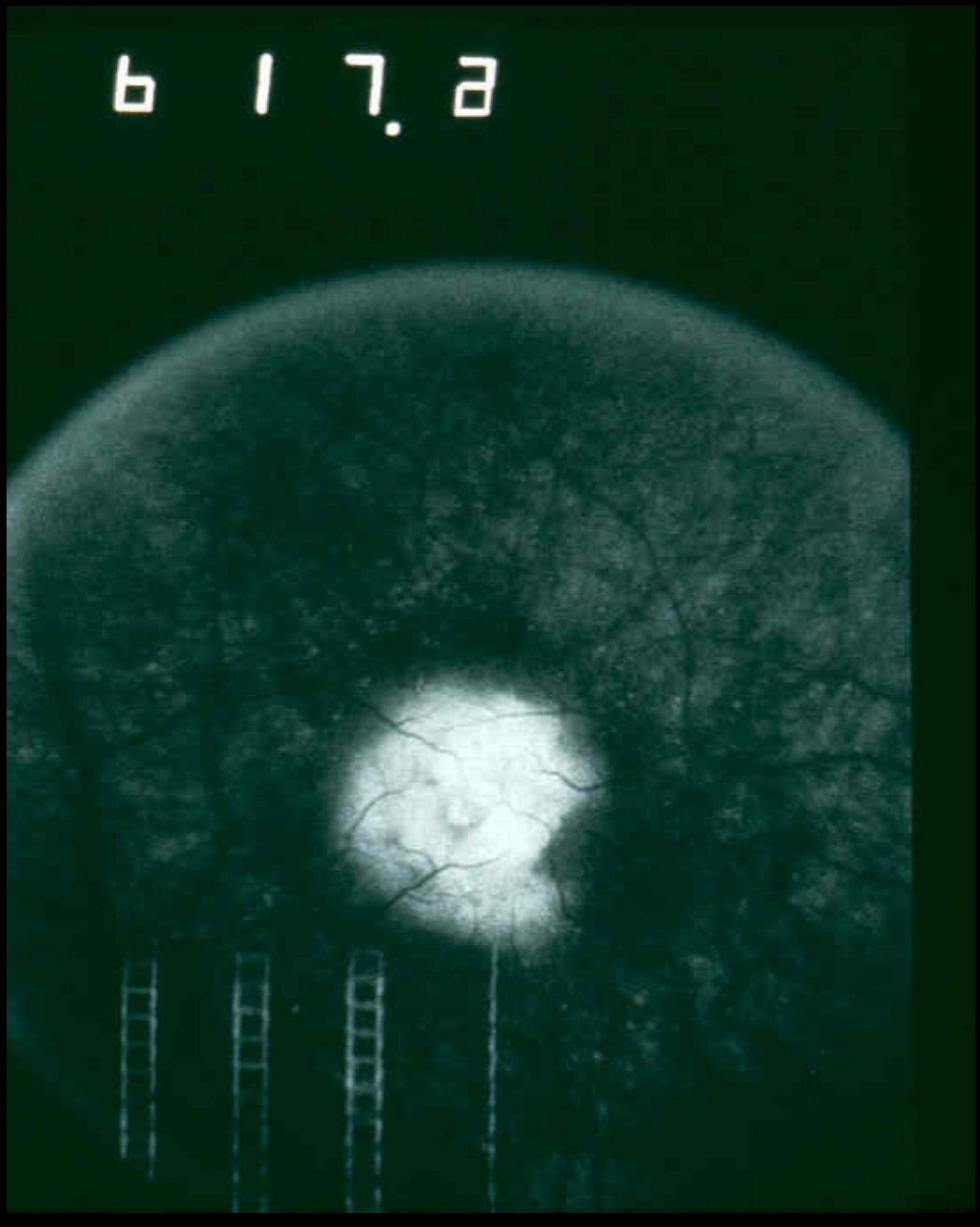


“CLASSIC”: Well-demarcated hyperfluorescence (Early Phase)



“CLASSIC”: Progressive pooling of dye

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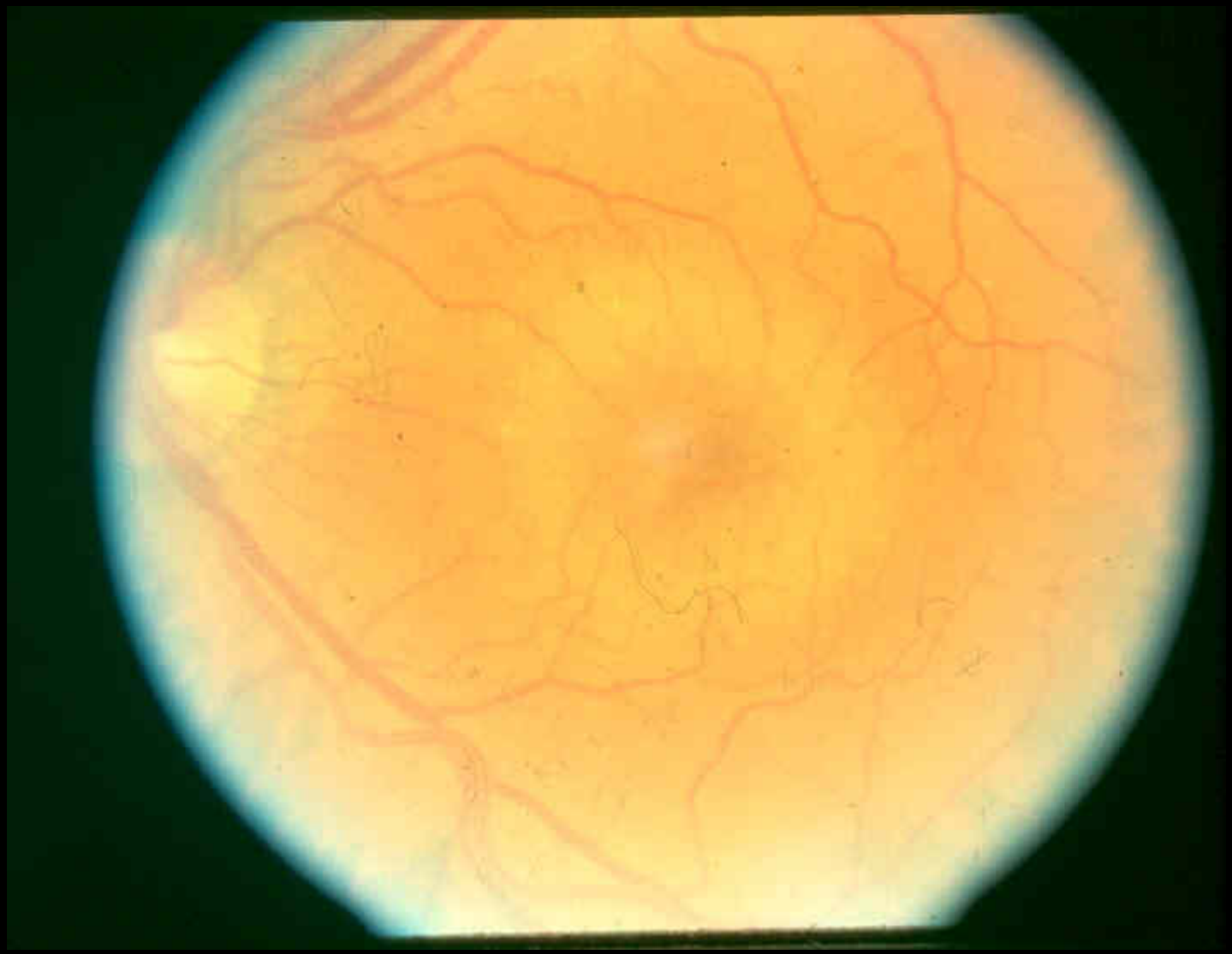
Age-related macular degeneration (AMD)



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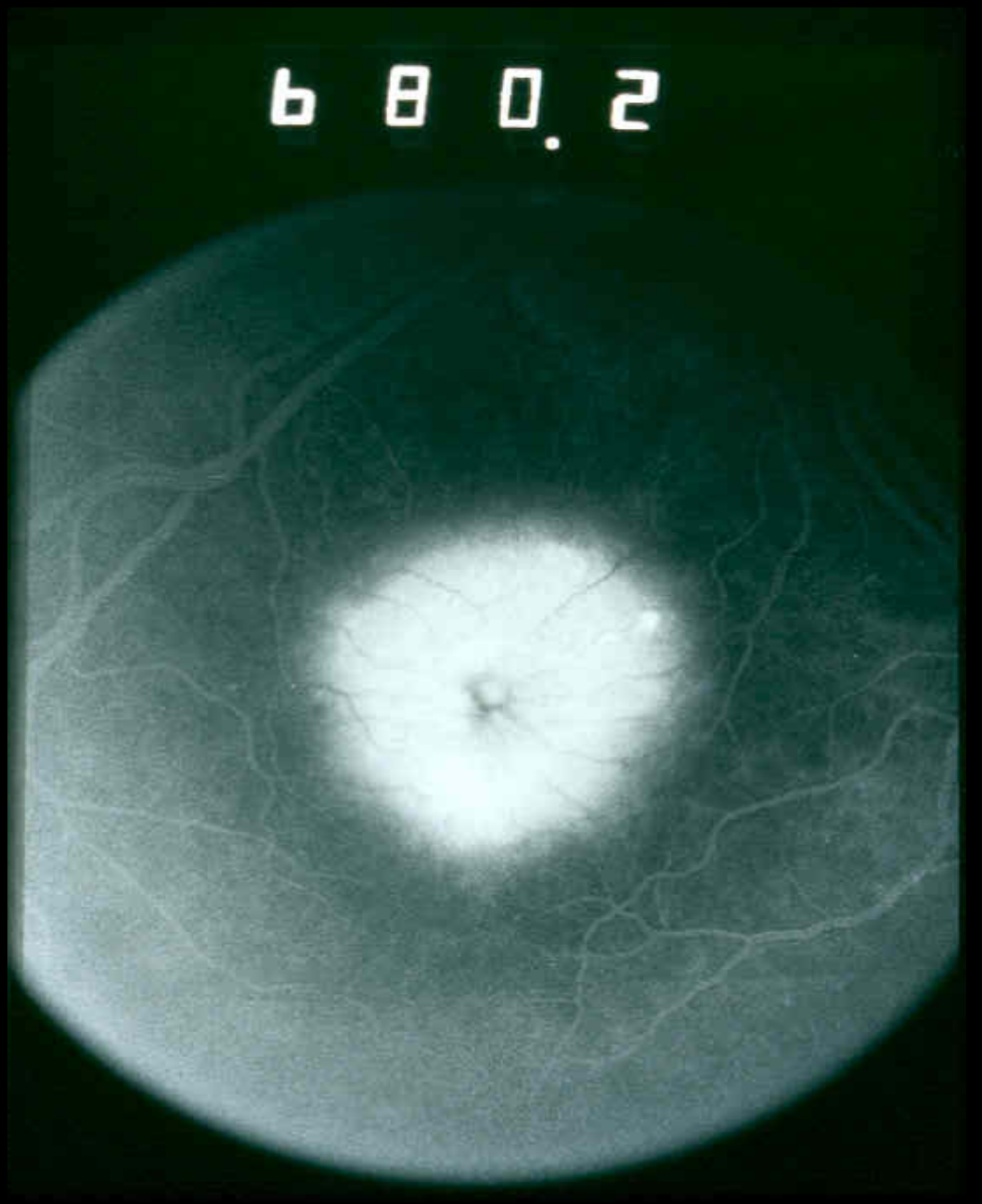
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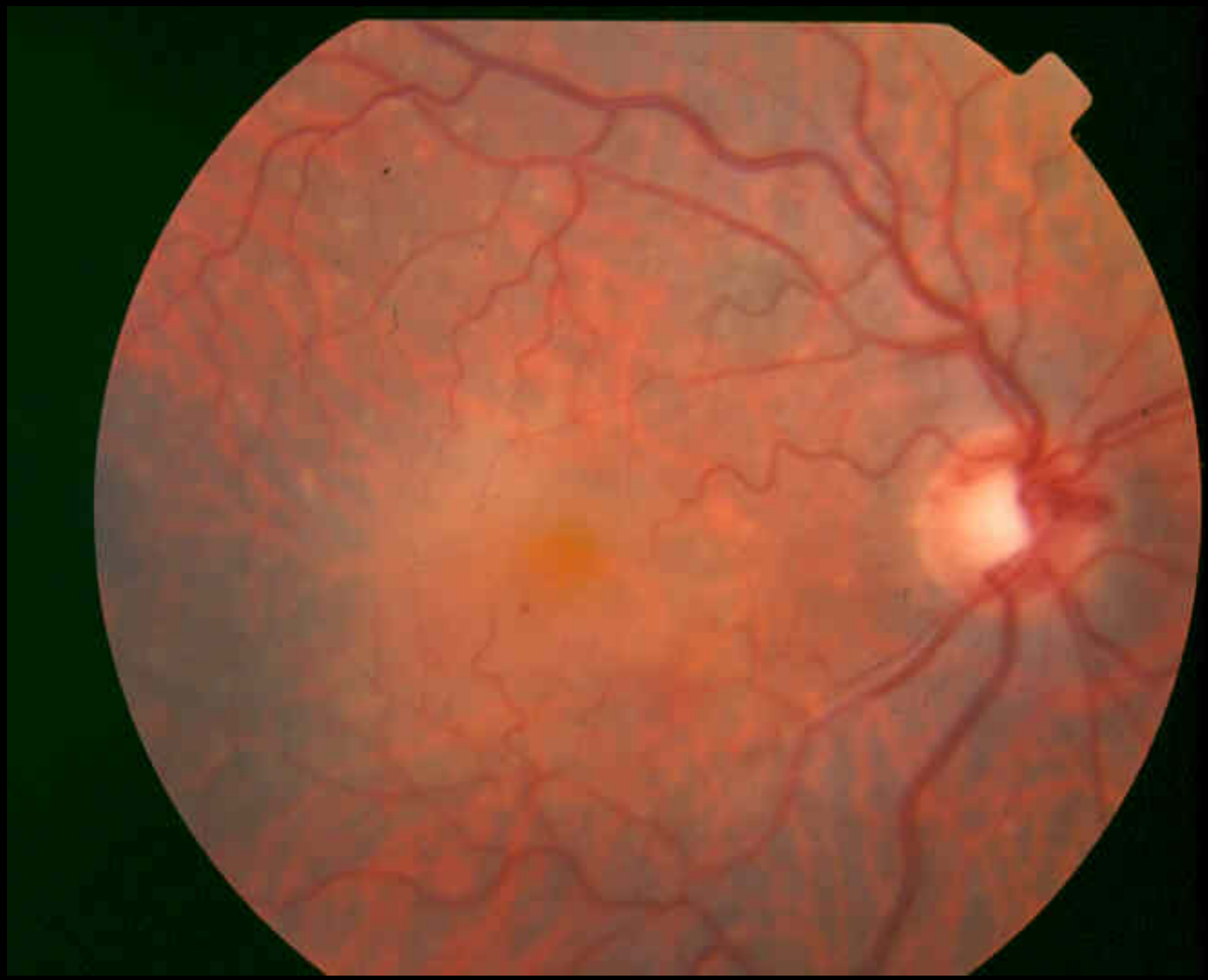
OCCULT CNV

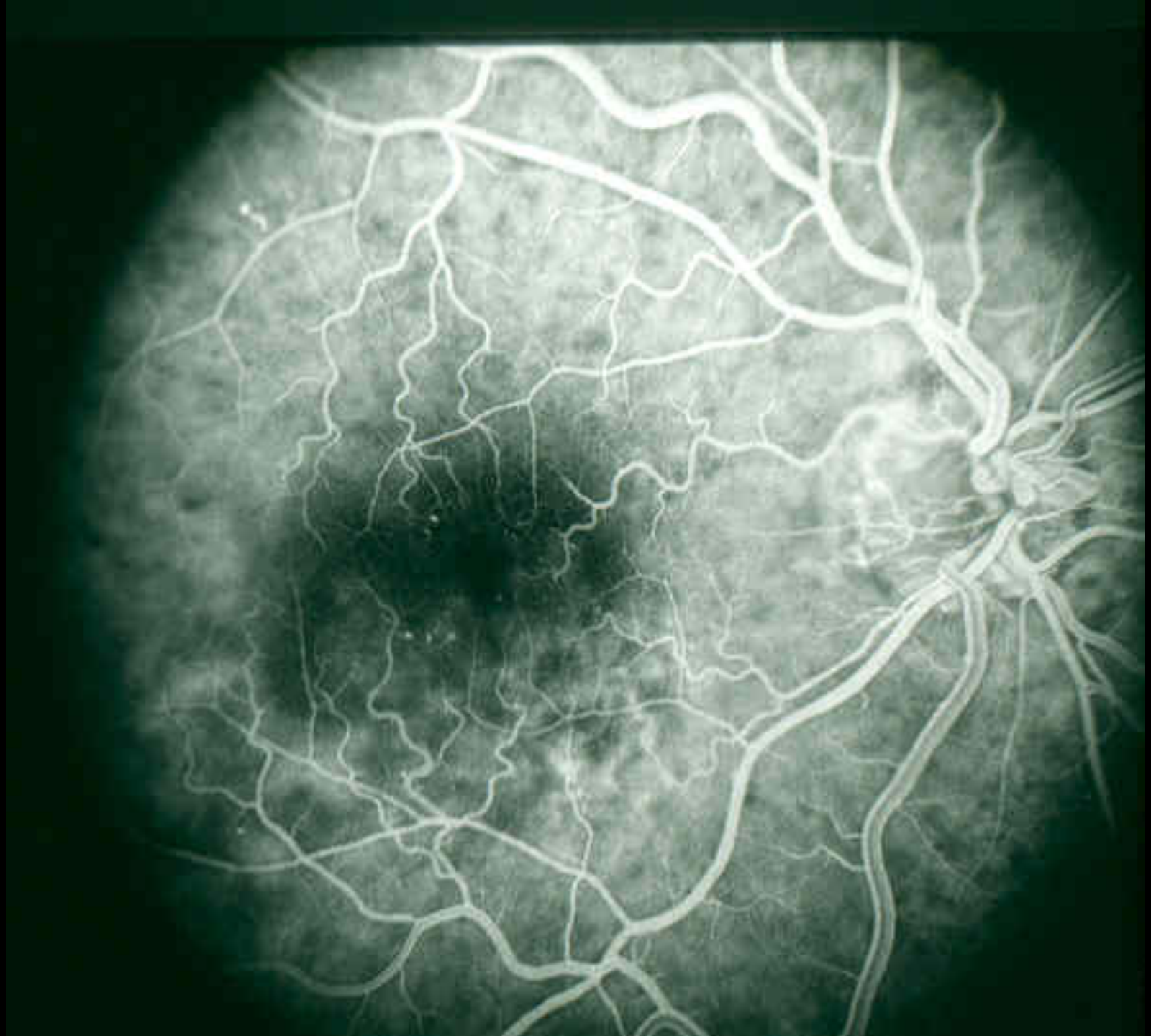
Because of F.A. features, I know CNV is there, but I can't identify the precise location and boundaries of the lesion.

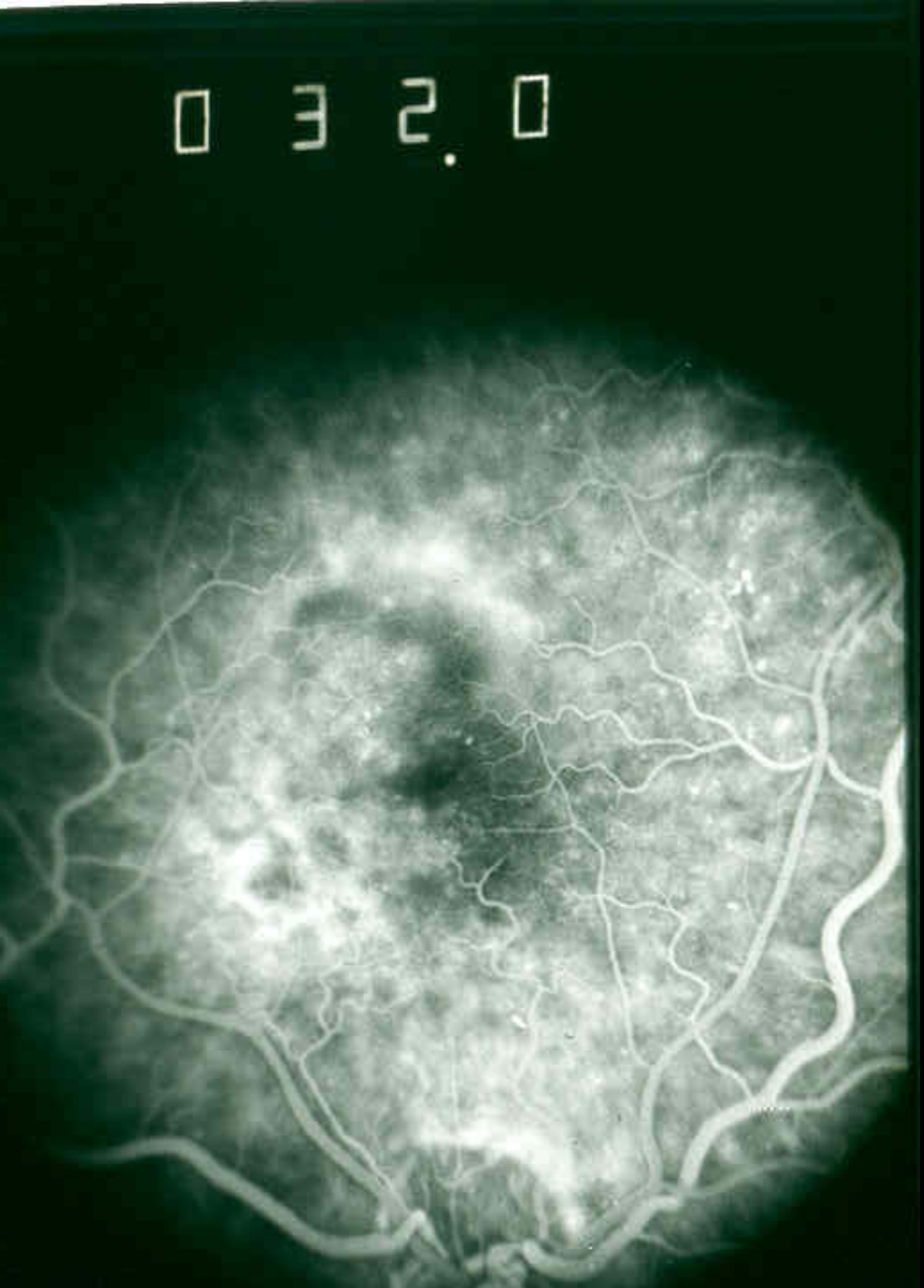
Limitations of F.A. :

- Permeability characteristics
- Other ?? Characteristics
- Dye Filling sub-RPE space
- Other matter in SUB-RPE SPACE

AMD



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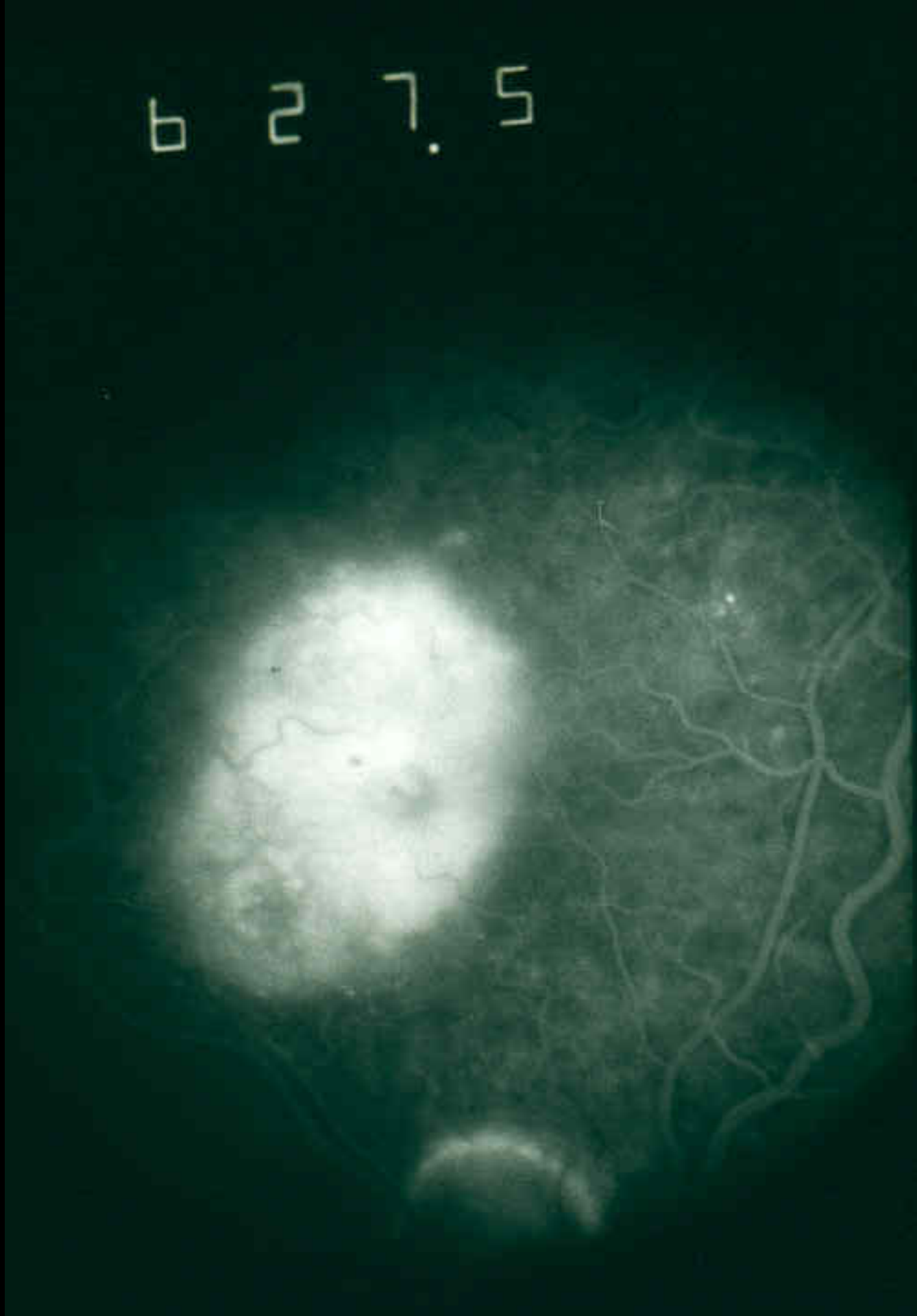
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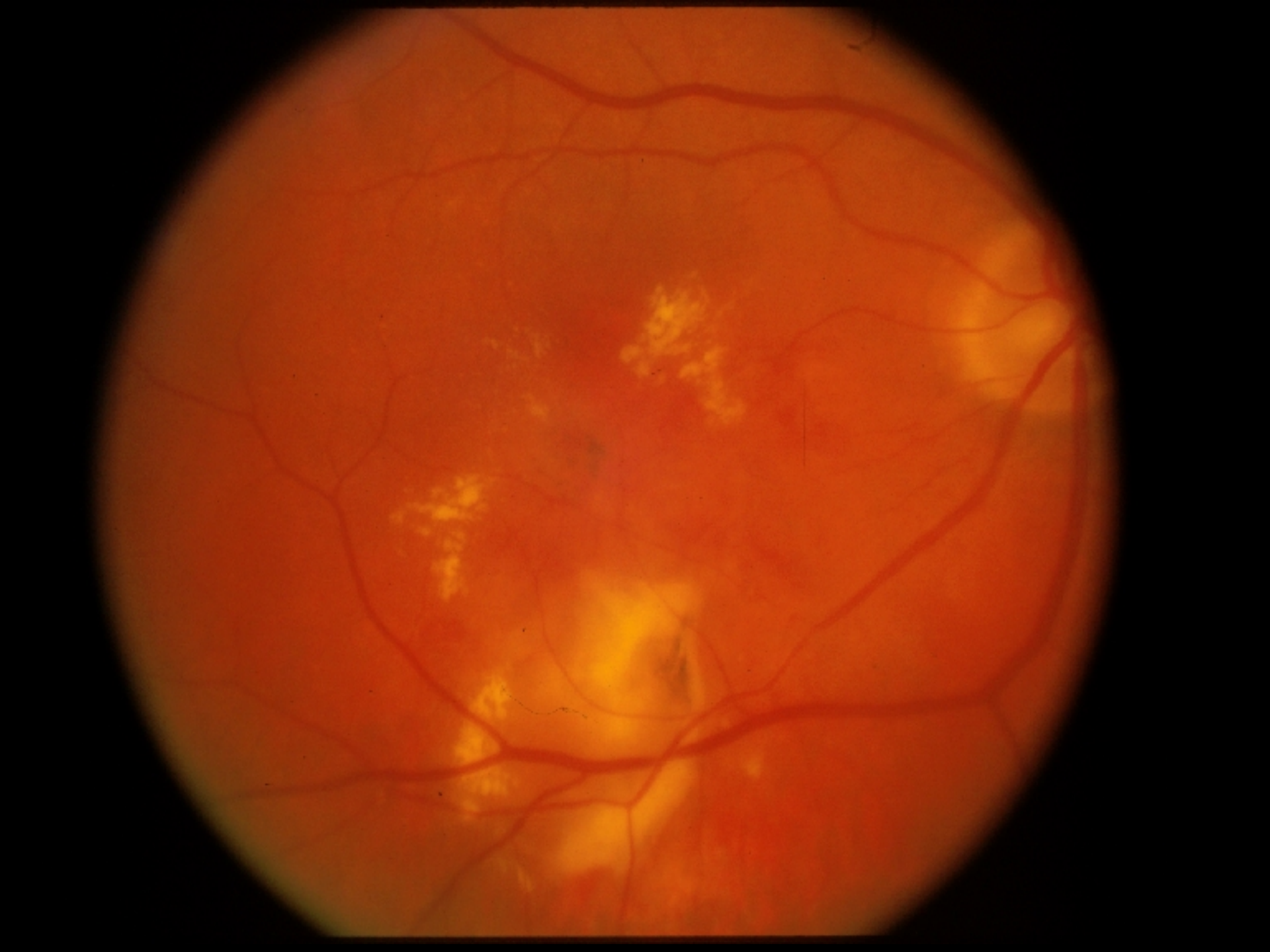

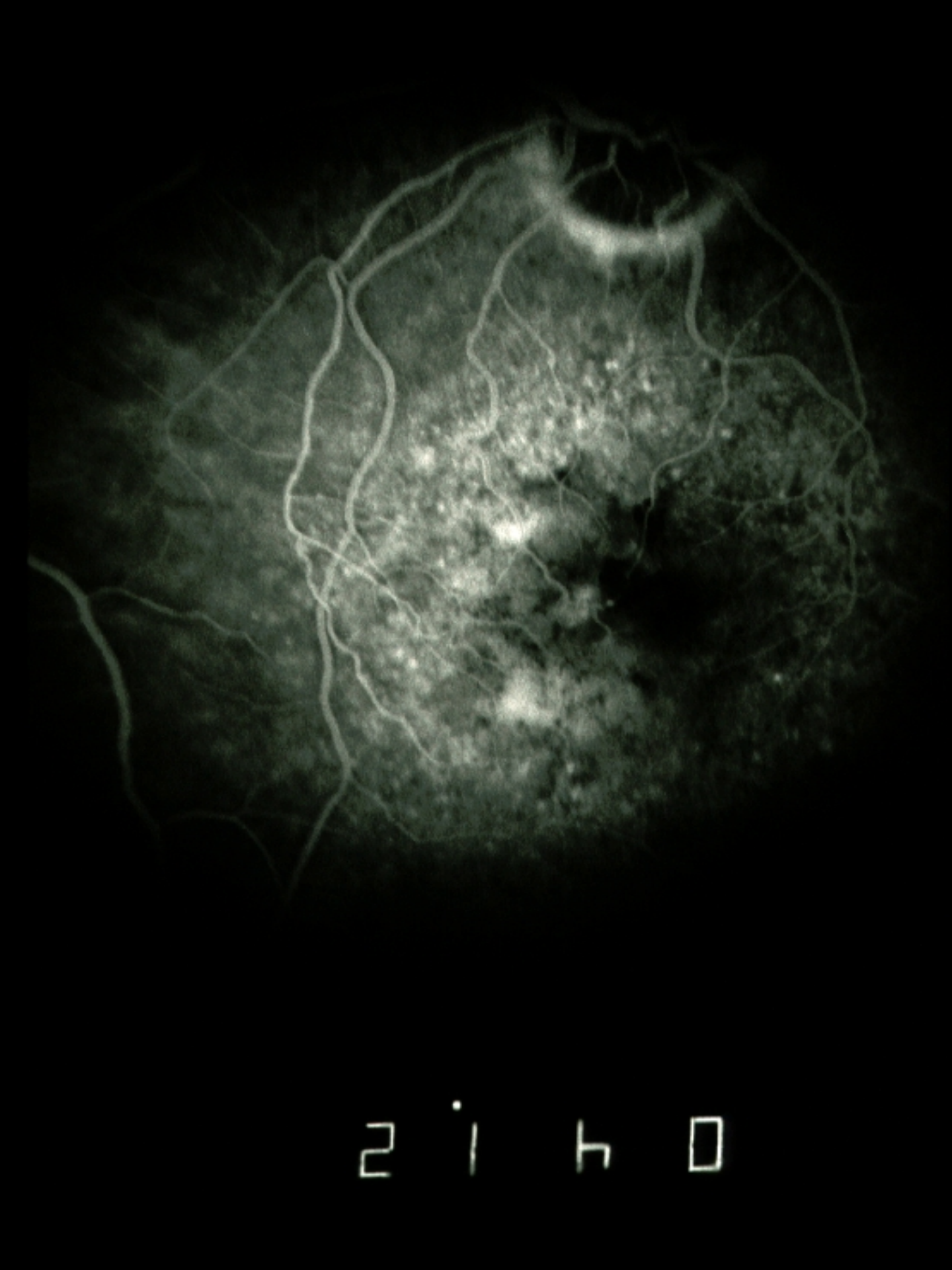
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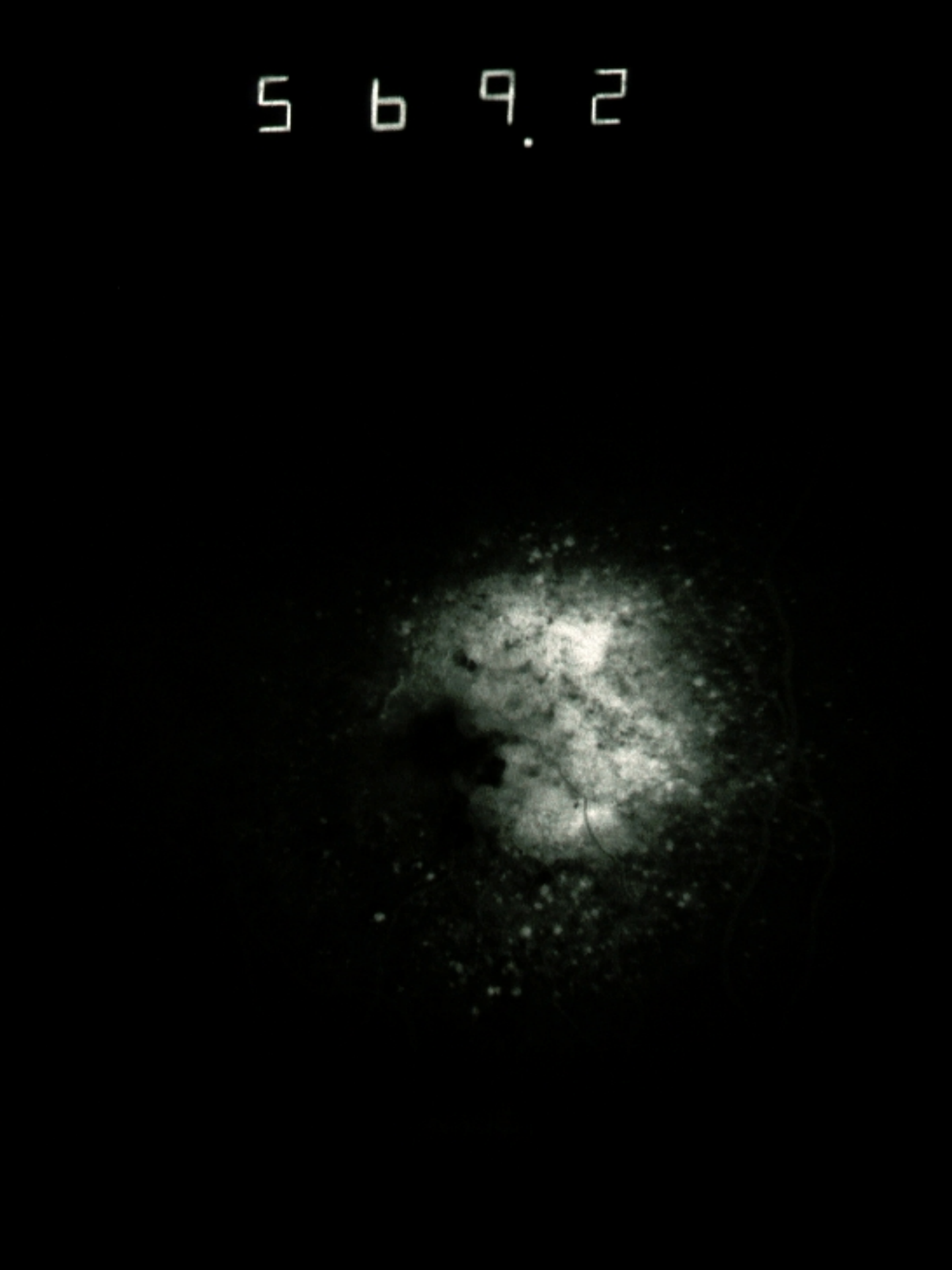
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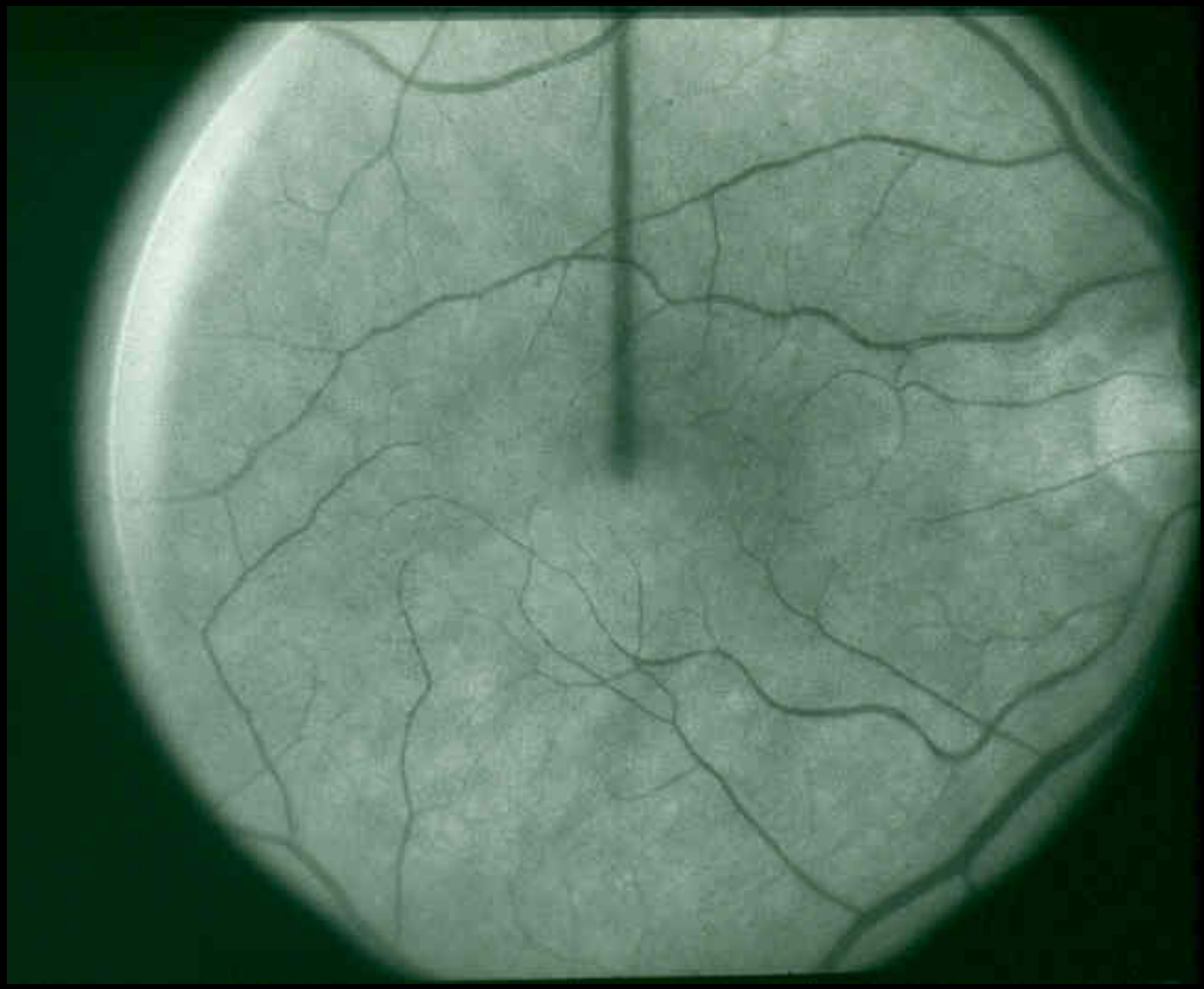
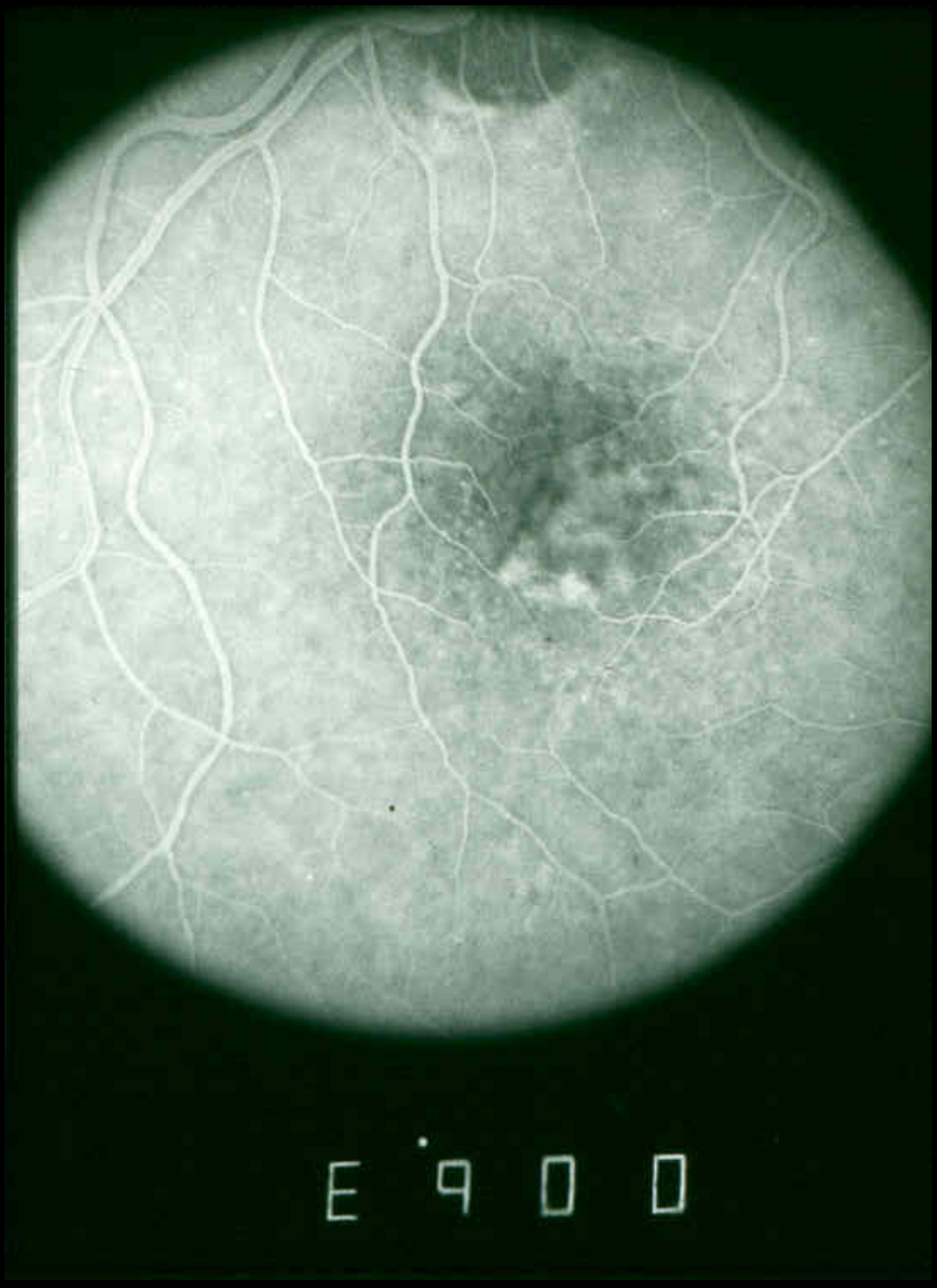
AMD

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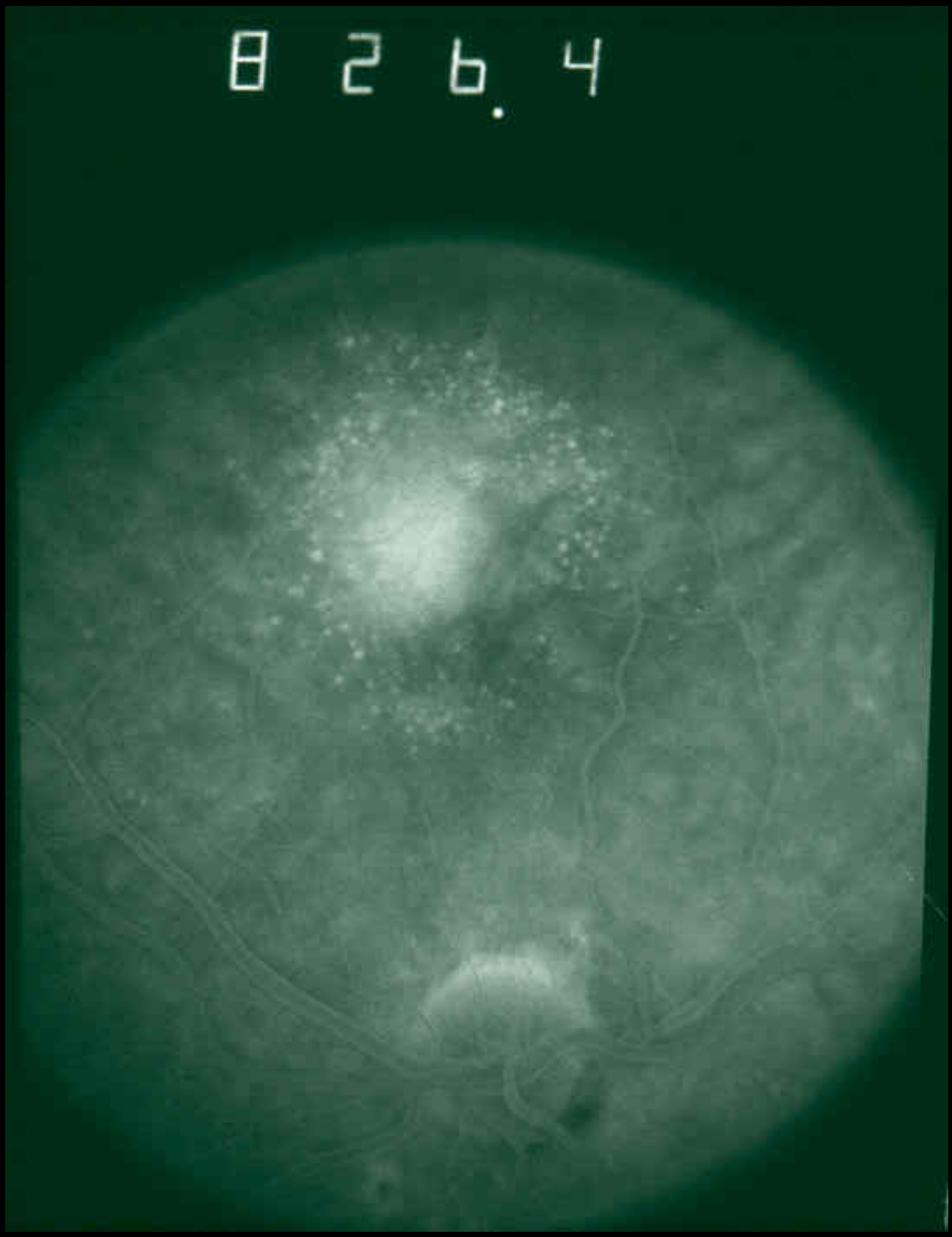
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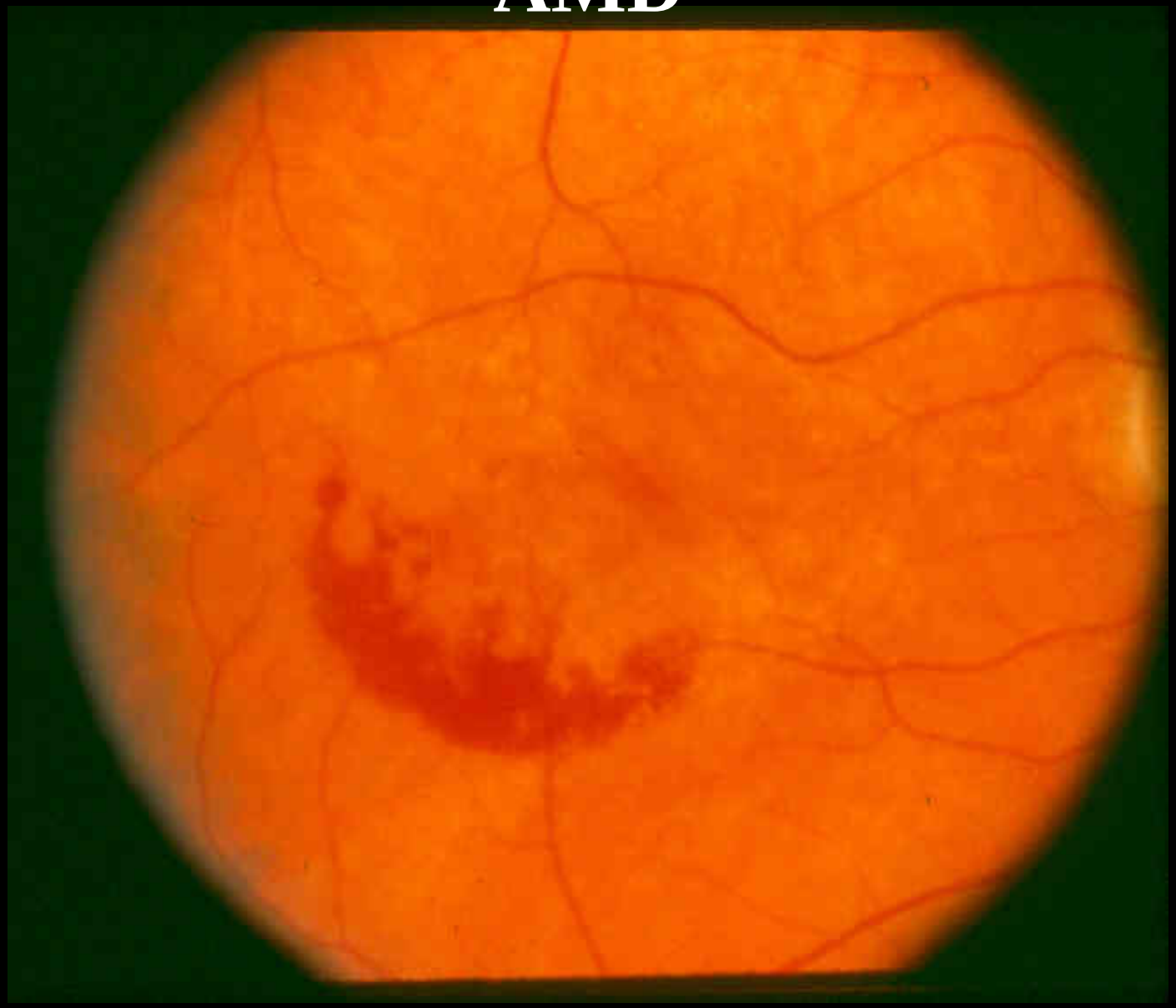
SOME OF BOTH…..

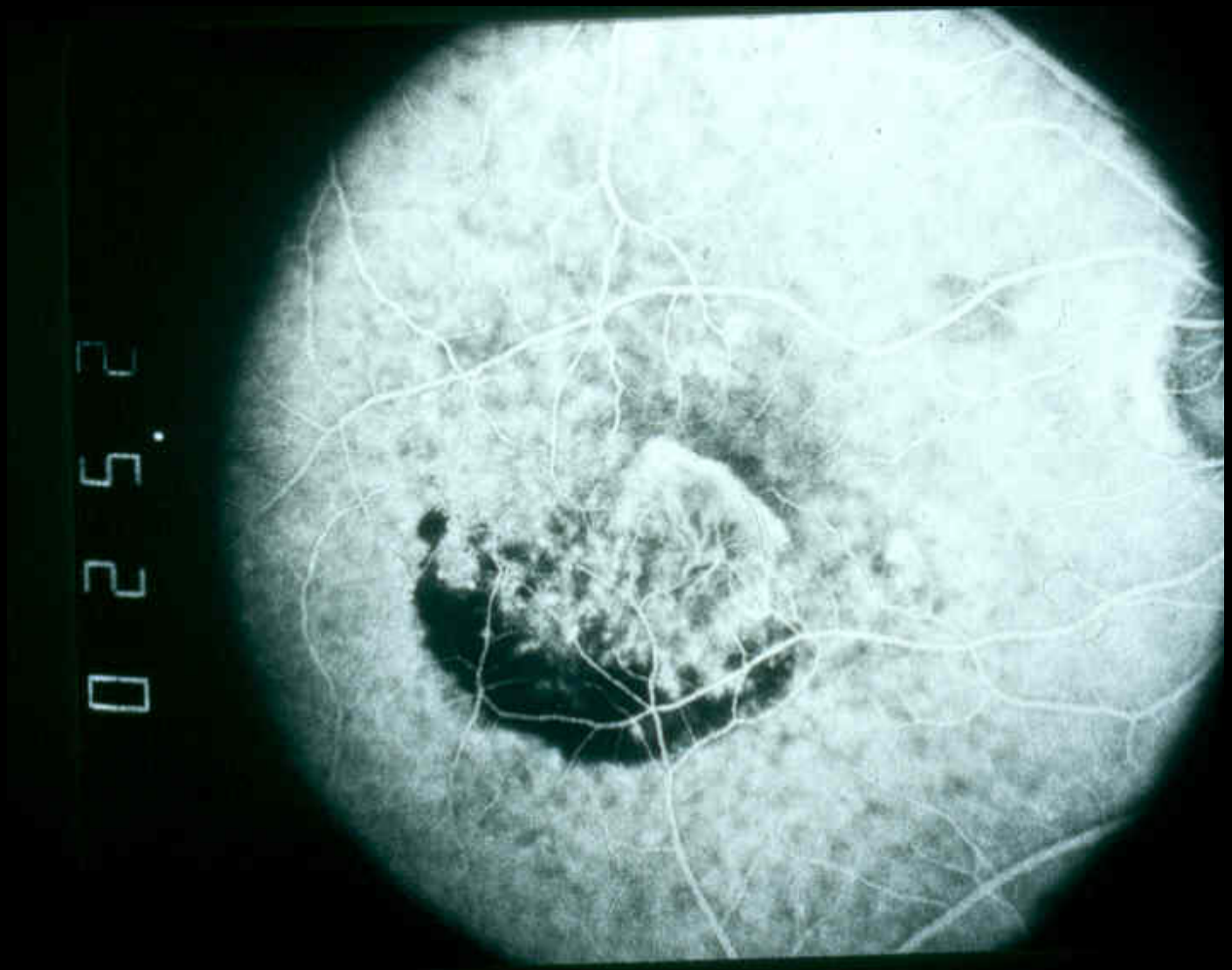
- Lesion = CNV Composed of both Classic & Occult CNV
- Lesion composed of > 50% classic = “Predominately classic” CNV

AMD

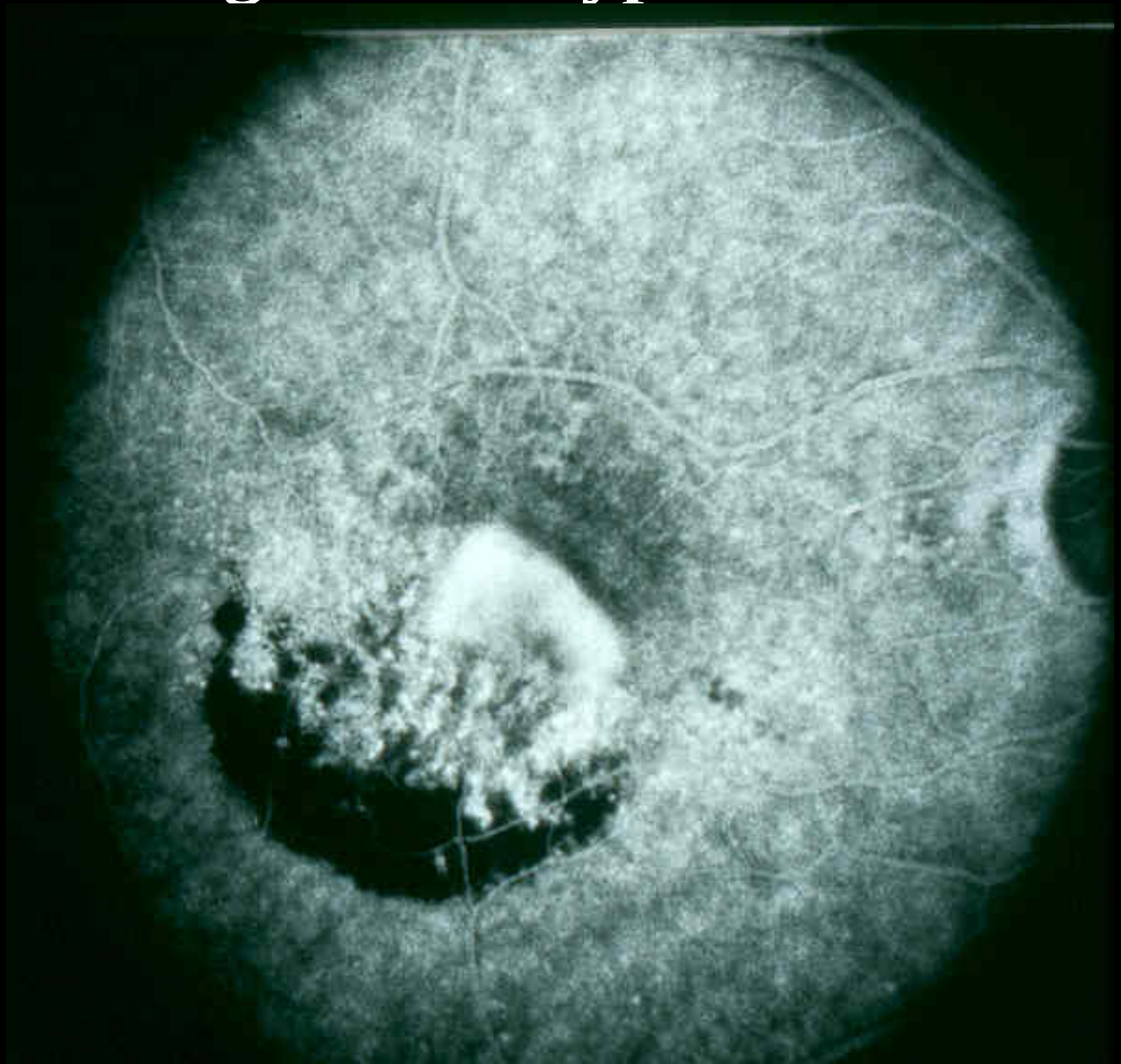


“Occult”(+ Classic)

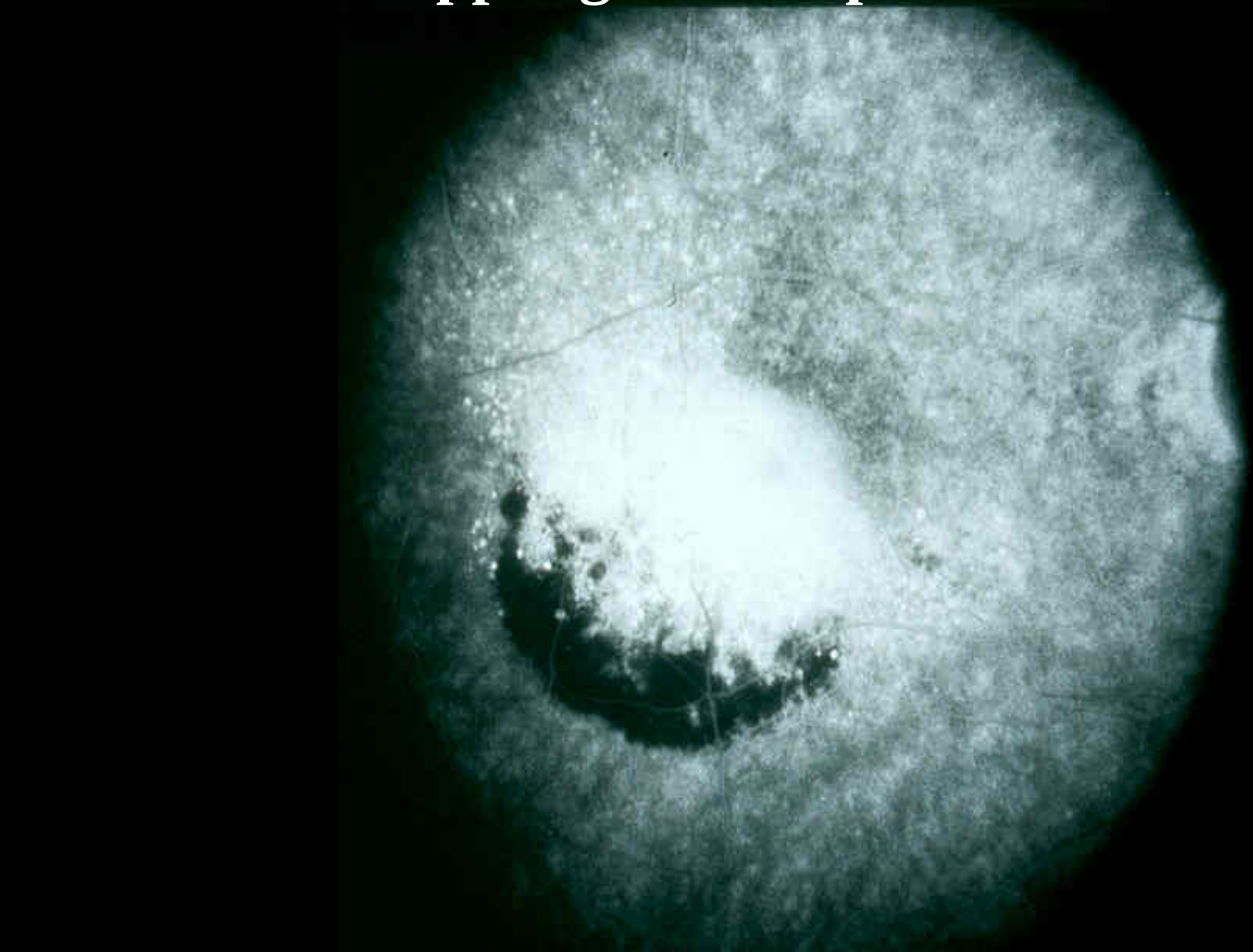
OCC = Less well-defined area of hyperfl.



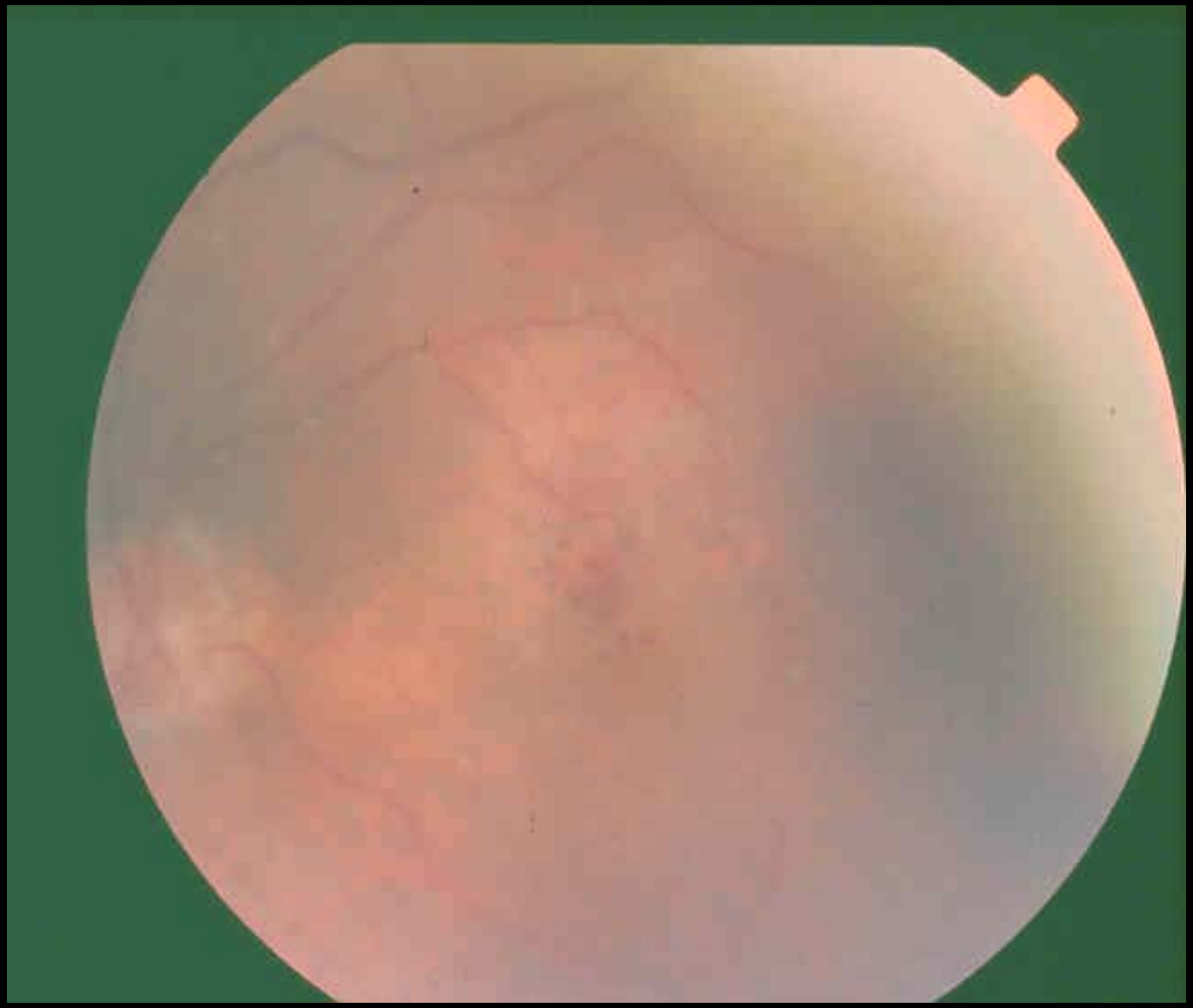
“Occult” Progressive Hyperfluorescence

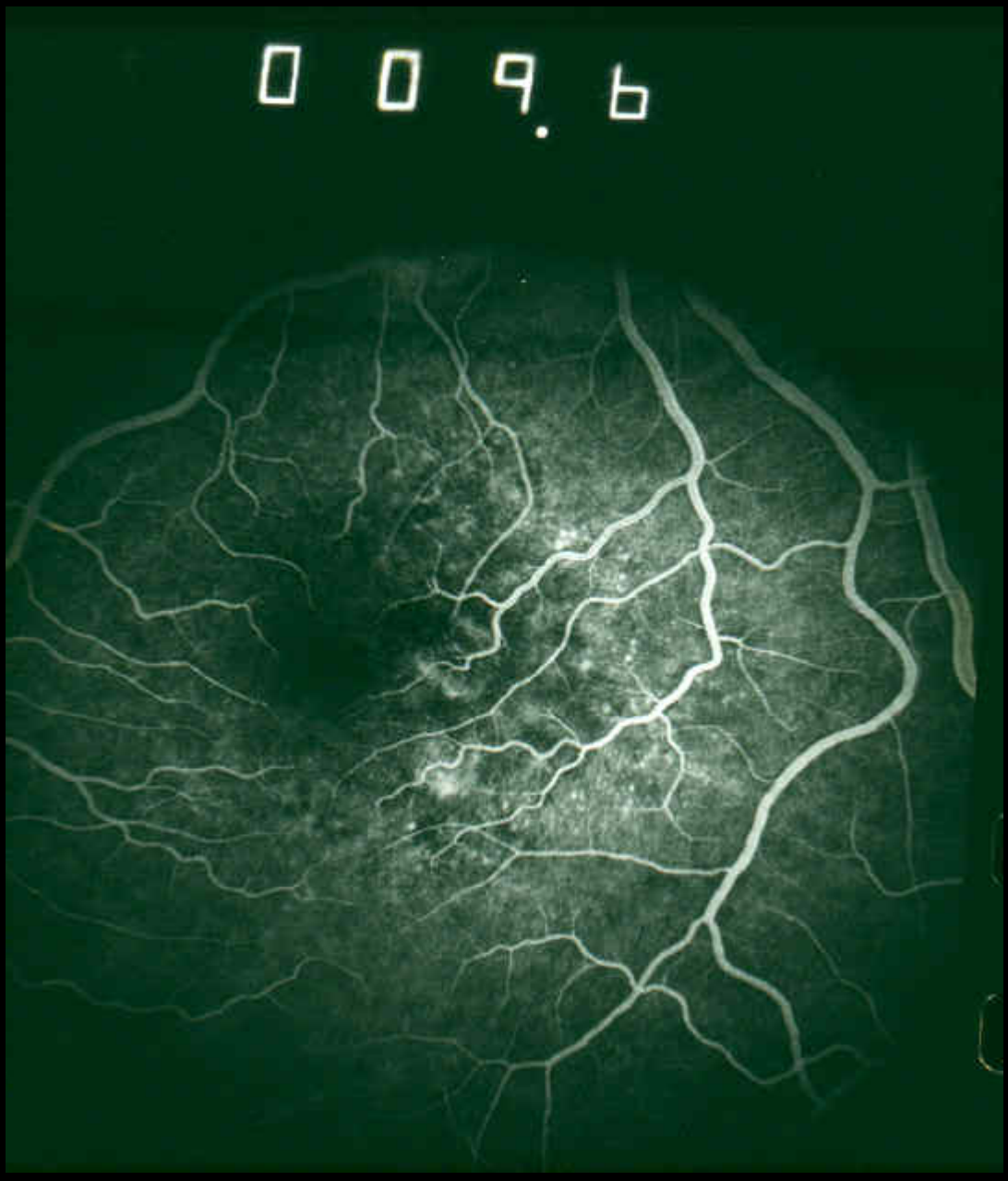


“Occult” “Stippling” in late phases



AMD

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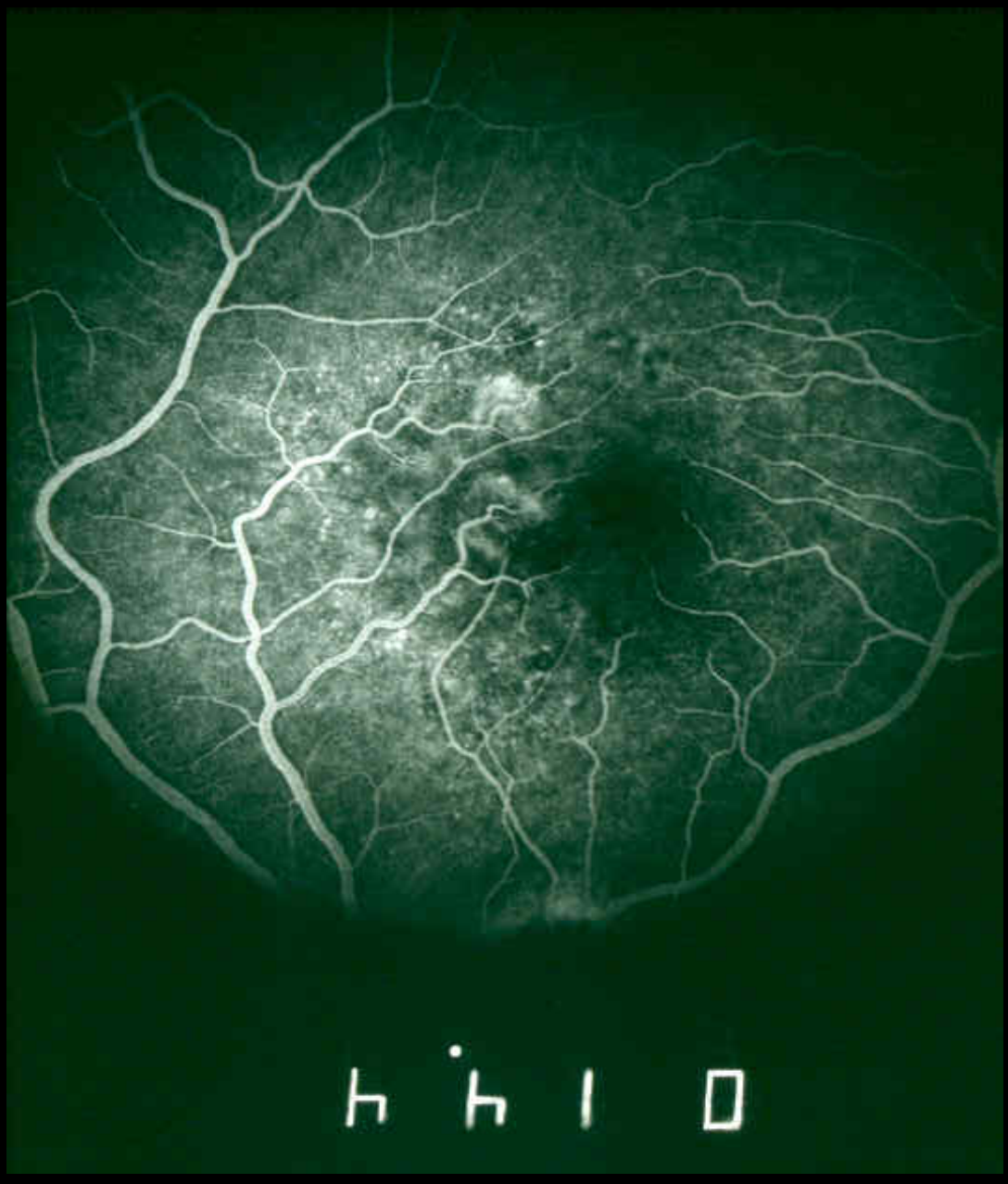
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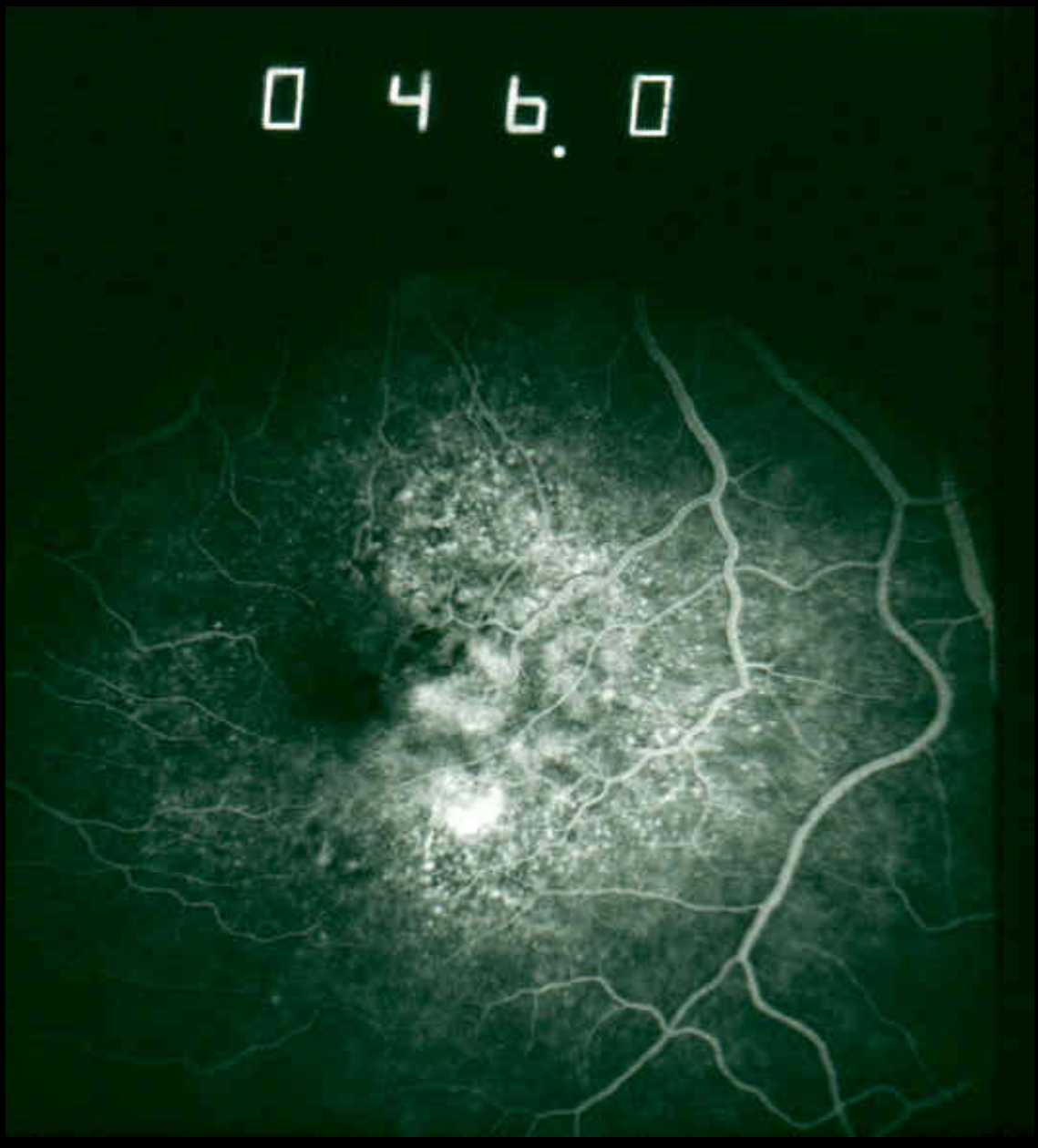
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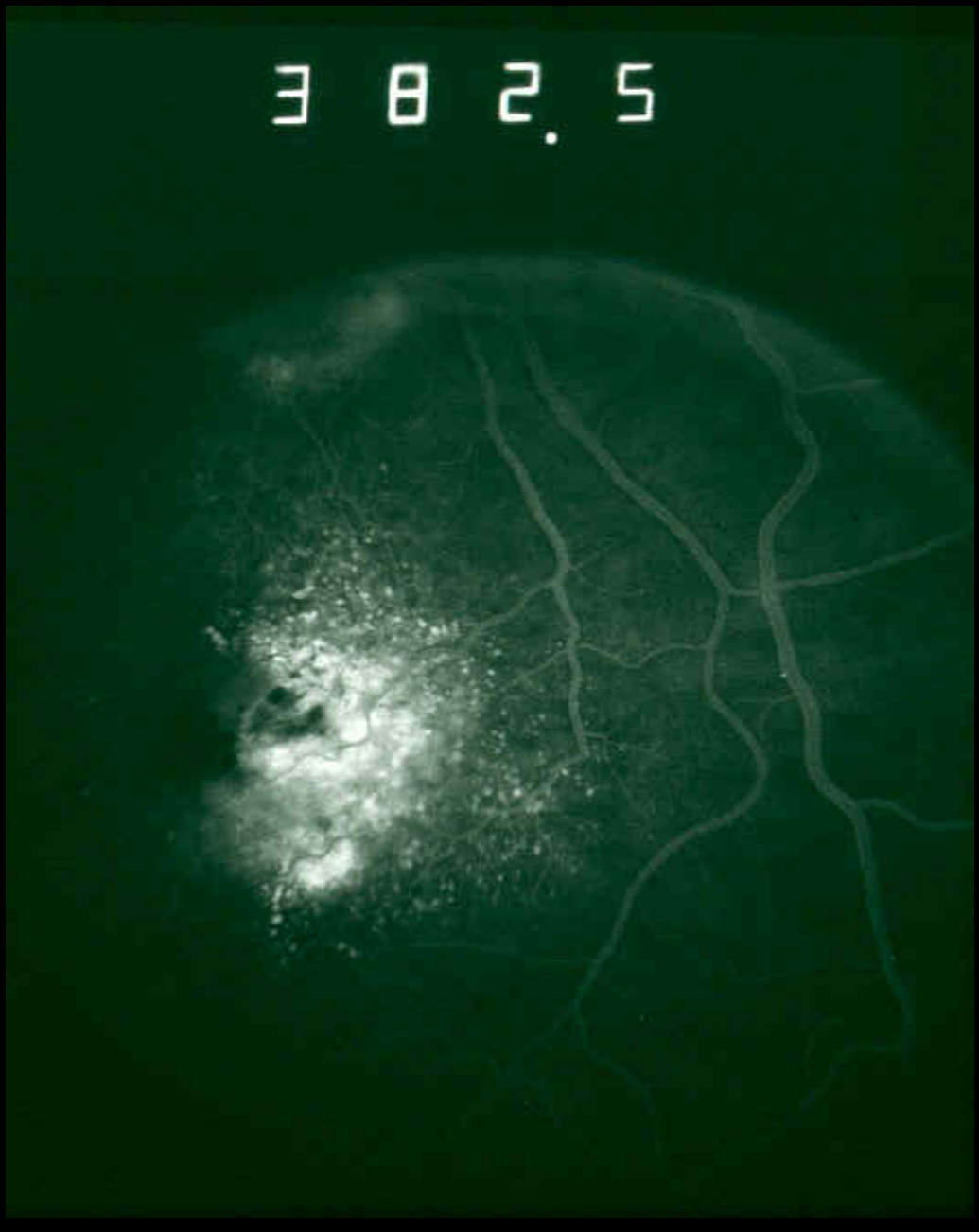
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Usual therapy for “wet” CNV AMD is destruction of CNV.

This is admittedly far from optimal Rx.

Future = More novel ways to prevent, modify, destroy CNV.

Elimination of CNV with conventional laser is of limited value if lesions are subfoveal, because therapy destroys what one is trying to save (the central macula).

Photodynamic therapy (PDT) with verteporfin offers a potential means of “destroying” CNV’s without major damage to the overlying macula.

Photodynamic Therapy (PDT)
is a photochemical reaction, not a routine thermal effect (i.e., a burn)

Marc Stone, MD

Lead Medical Officer

Verteporfin Clinical Trials

TAP Trial
Treatment of AMD with PDT

AMD Subjects with

some degree of classic CNV

AND

Visual acuity between 20/40 and 20/200

TAP Trial
Treatment of AMD with PDT

- 609 Subjects enrolled (split into two trials)
- Randomized at 2:1 ratio of PDT to placebo (stratified by visual acuity and center)
- Assignment masked from patients, doctors, vision examiners, angiogram readers

TAP Trial
Published Results – 12 months

Loss of fewer than 15 letters of Visual Acuity *All subjects*			
Verteporfin	246/402	61.2%	p <.001
Placebo	96/207	46.4%	

Arch Ophthalmol. 1999;117:1329-1345

TAP Trial
Published Results – 12 months

Loss of fewer than 15 letters of Visual Acuity *Subgroup: Predominantly Classic CNV*			
Verteporfin	107/159	67.3%	p <.001
Placebo	33/84	39.3%	

Arch Ophthalmol. 1999;117:1329-1345

TAP Trial
Published Results – 12 months

Loss of fewer than 15 letters of Visual Acuity *Subgroup: Minimally Classic CNV*			
Verteporfin	112/202	55.9%	p =.92
Placebo	56/103	55.3%	

Arch Ophthalmol. 1999;117:1329-1345

TAP Trial
Published Results – 24 months

Loss of fewer than 15 letters of Visual Acuity *All Subjects*			
Verteporfin	213/402	53.0%	p <.001
Placebo	78/207	37.7%	

Arch Ophthalmol. 2001;119:198-207

TAP Trial
Published Results – 24 months

Loss of fewer than 15 letters of Visual Acuity *Subgroup: Predominantly Classic CNV*			
Verteporfin	94/159	59.1%	p <.001
Placebo	26/83	31.3%	

Arch Ophthalmol. 2001;119:198-207

TAP Trial
Published Results – 24 months

Loss of fewer than 15 letters of Visual Acuity *Subgroup: Minimally Classic CNV*			
Verteporfin	96/202	47.5%	p =.58
Placebo	46/104	44.2%	

Arch Ophthalmol. 2001;119:198-207

VIP Trial
Verteporfin In Photodynamic Therapy

AMD Subjects with

No Classic CNV (Occult CNV only)
and visual acuity 20/100 or better

OR

Classic CNV

with visual acuity better than 20/40

VIP Trial

Subjects with pathological myopia were studied simultaneously in an essentially separate trial.

VIP Trial

- 339 AMD subjects enrolled
- Randomized at 2:1 ratio of PDT to placebo (stratification by center only)
- Assignment masked from patients, doctors, vision examiners, angiogram readers

VIP Trial
Published Results – 12 months

Loss of fewer than 15 letters of Visual Acuity *All Subjects*			
Verteporfin	111/225	49.3%	p =.52
Placebo	52/114	45.6%	

Am J Ophthalmol 2001;131:541-560

VIP Trial
Published Results – 24 months

Loss of fewer than 15 letters of Visual Acuity *All Subjects*			
Verteporfin	104/225	46.2%	p =.023
Placebo	38/114	33.3%	

Am J Ophthalmol 2001;131:541-560

VIP Trial
Published Results – 24 months

Loss of fewer than 15 letters of Visual Acuity *Subgroup: Occult with no Classic CNV*			
Verteporfin	75/166	45.2%	p =.032
Placebo	29/92	33.3%	

Am J Ophthalmol 2001;131:541-560

VIP Trial
Published Results – 24 months

Loss of fewer than 30 letters of Visual Acuity *Subgroup: Occult with no Classic CNV*			
Verteporfin	118/166	71.1%	p =.004
Placebo	49/92	53.3%	

Am J Ophthalmol 2001;131:541-560

PDT works for lesions that are “classic” or “predominately classic”.

But NOT for lesions which are < 50% “Classic Features”.

PDT also appears to be of some value for 100% “OCCULT” lesions.

HUH ??!!

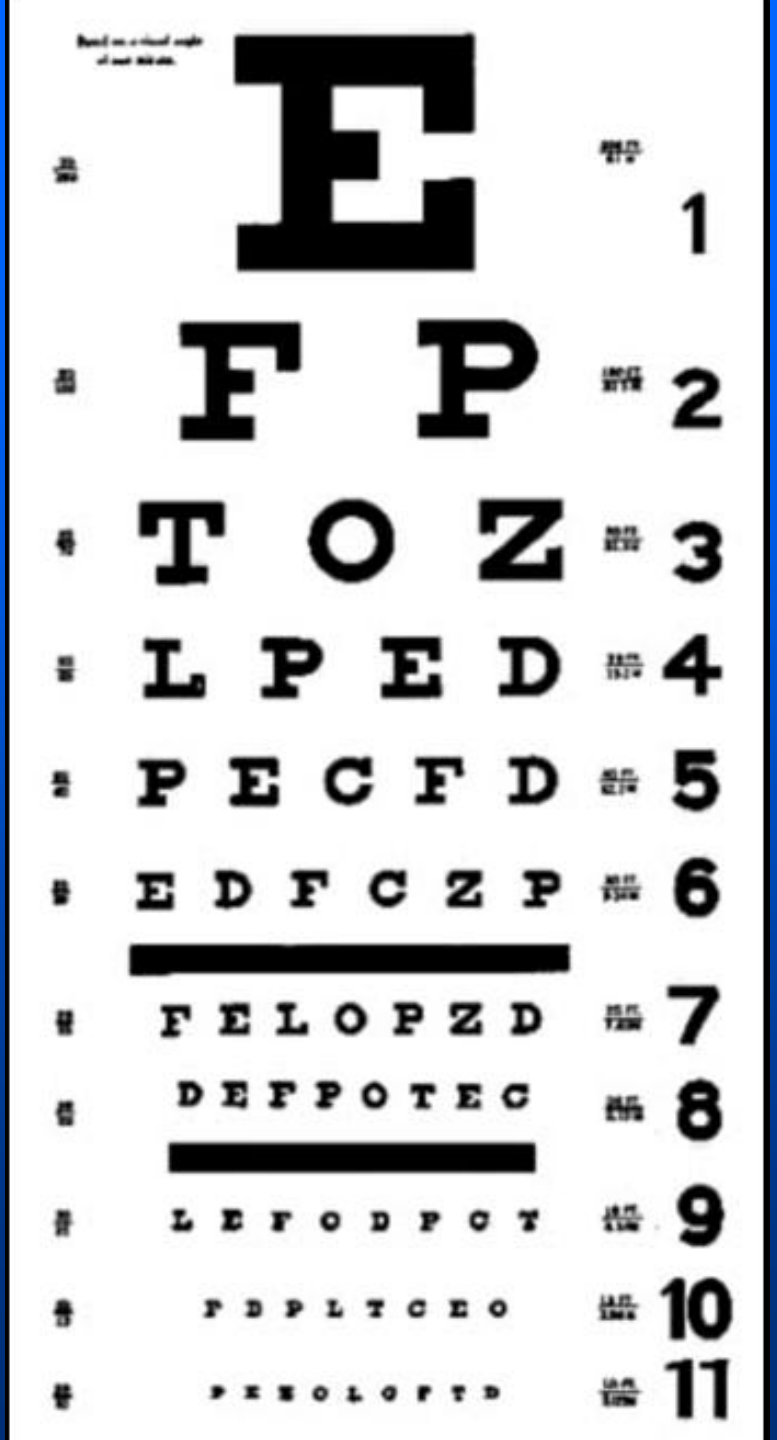
(NOT effective for lesions with > 50% “Occult” but some “Classic”)

THE KEY DATA FOR CLINICIANS

TABLE 2: Moderate and Severe Vision Loss at 12 and 24 month F-U, Occult no Classic Subgroup

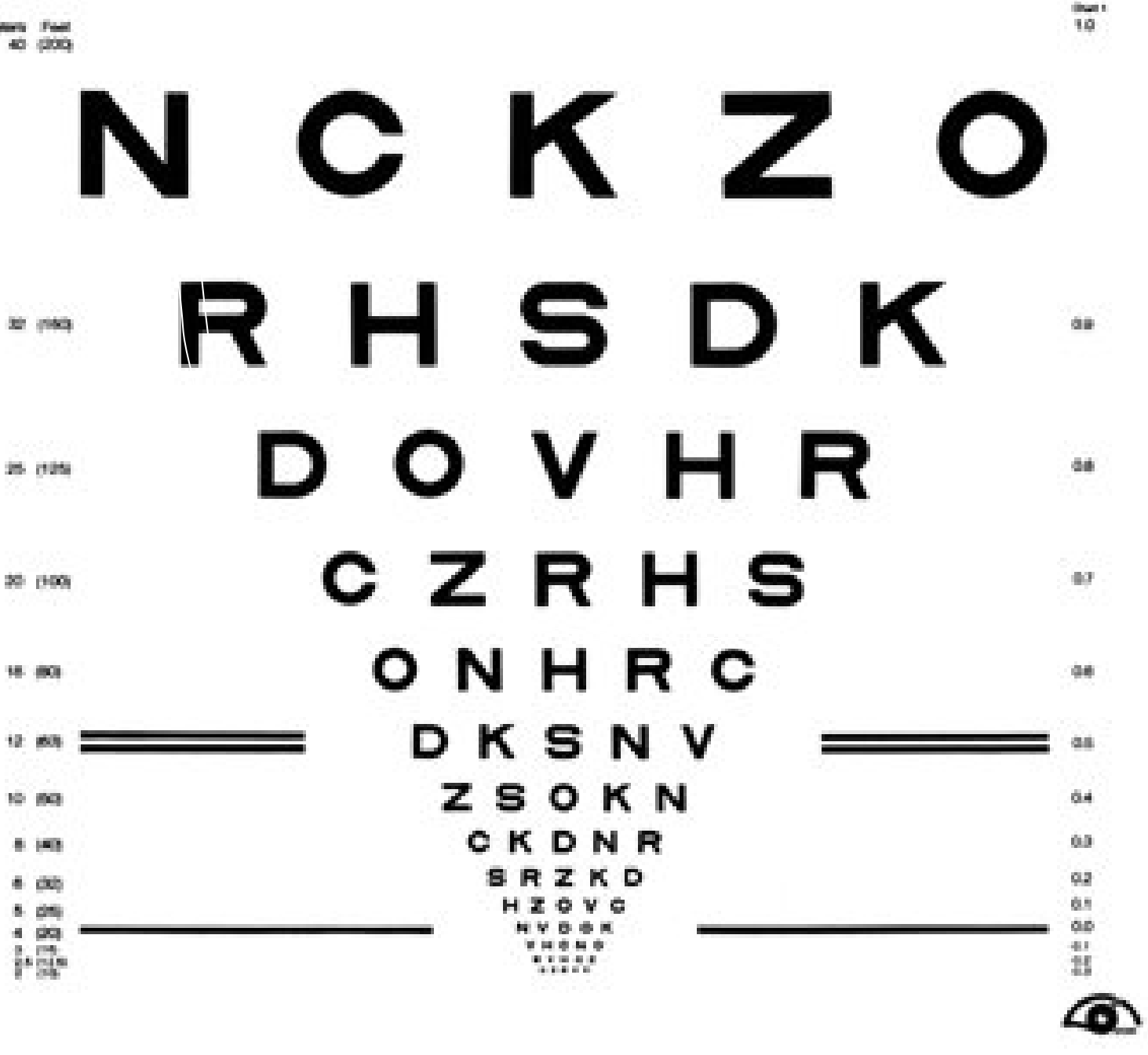
	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss
Verte-porfin	51% (84/166)	22% (36/166)	55% (91/166)	29% (48/166)
Placebo	55% (51/92)	33% (30/92)	68% (63/92)	47% (43/92)
	P=0.51	P=0.07	P=0.032	P=0.004

CLASSIC SNELLEN EYE CHART



ETDRS

CHART “1”

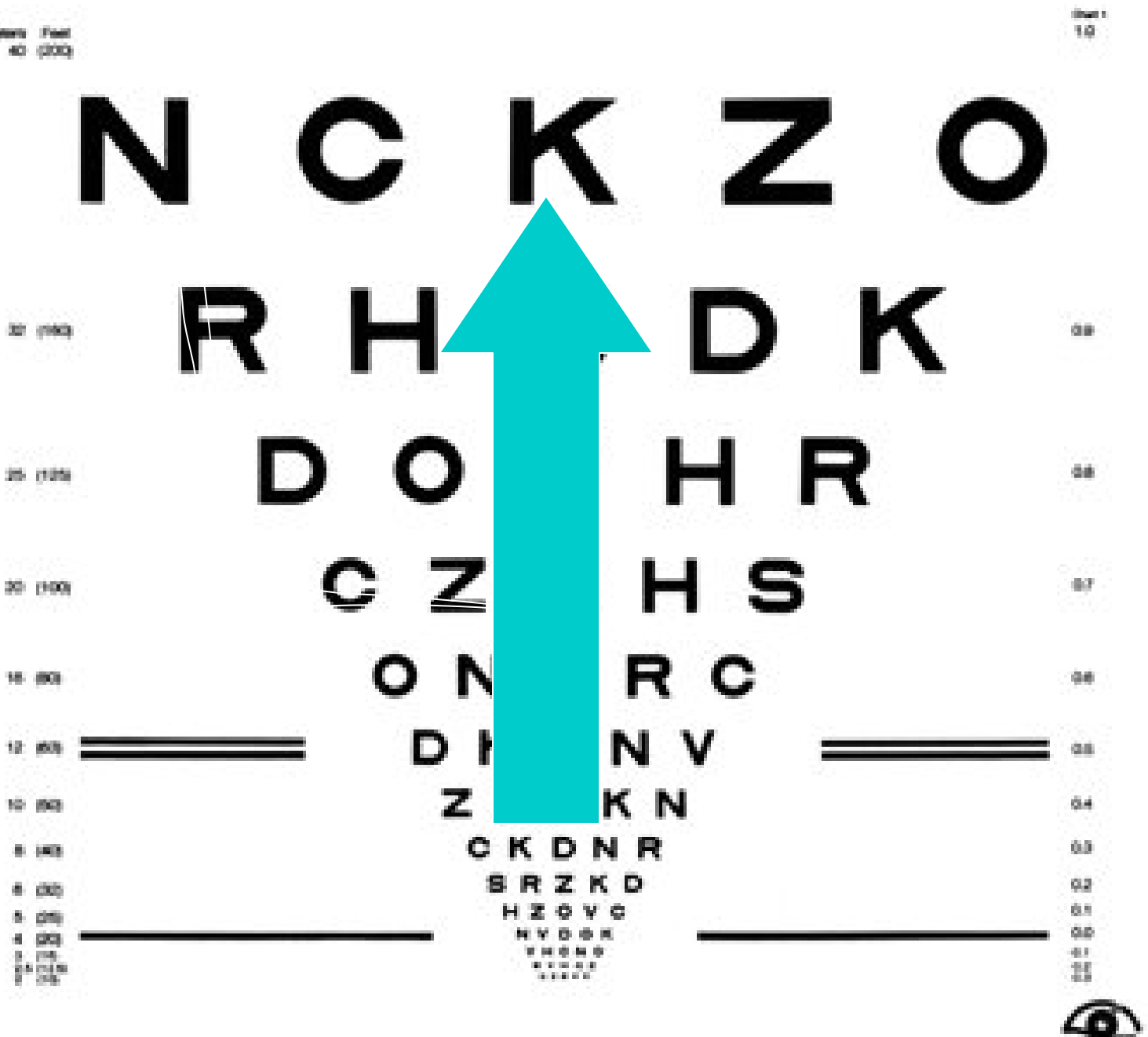


3-LINE

LOSS

IS

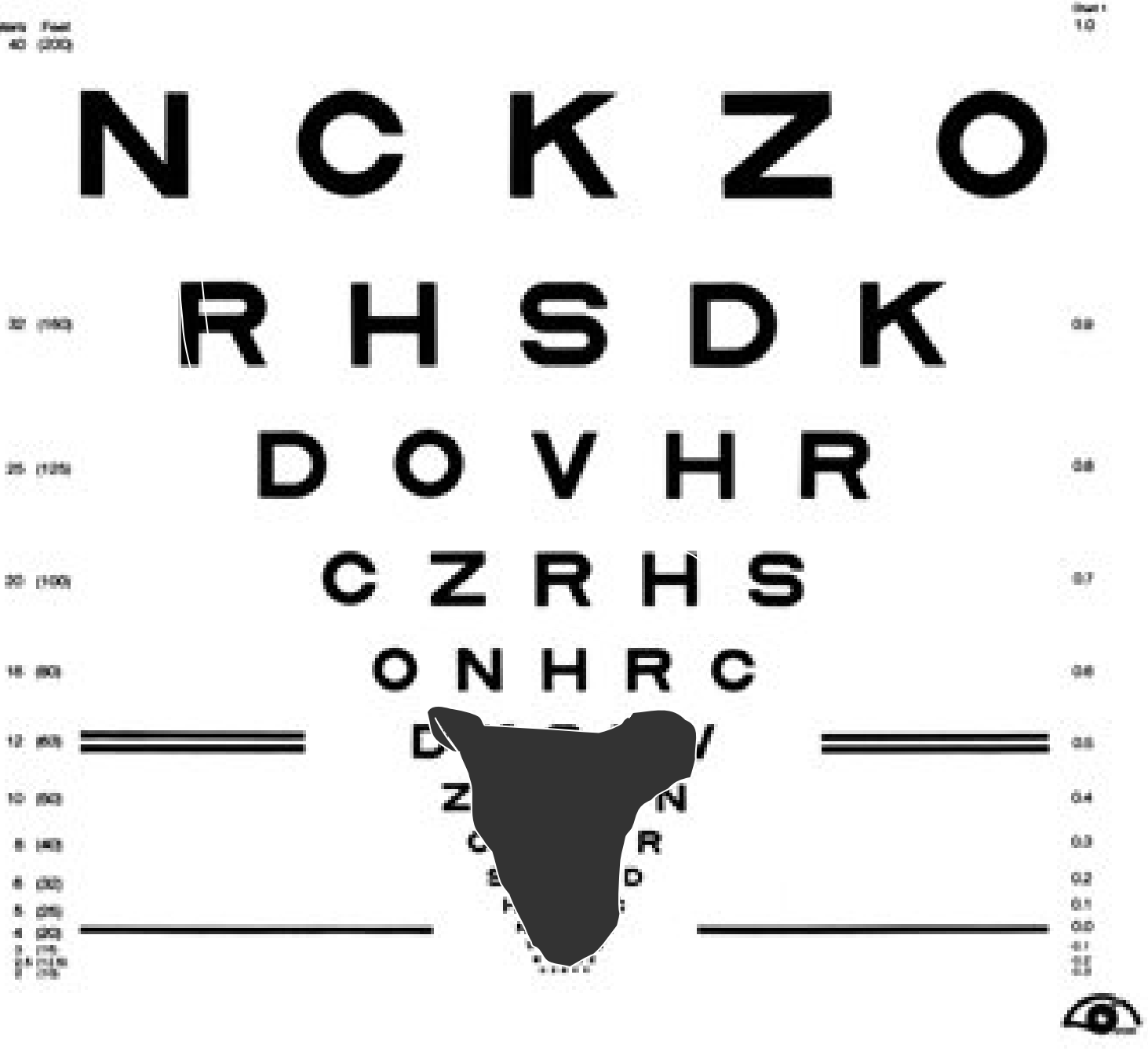
“MODERATE”



6 – LINE LOSS

IS

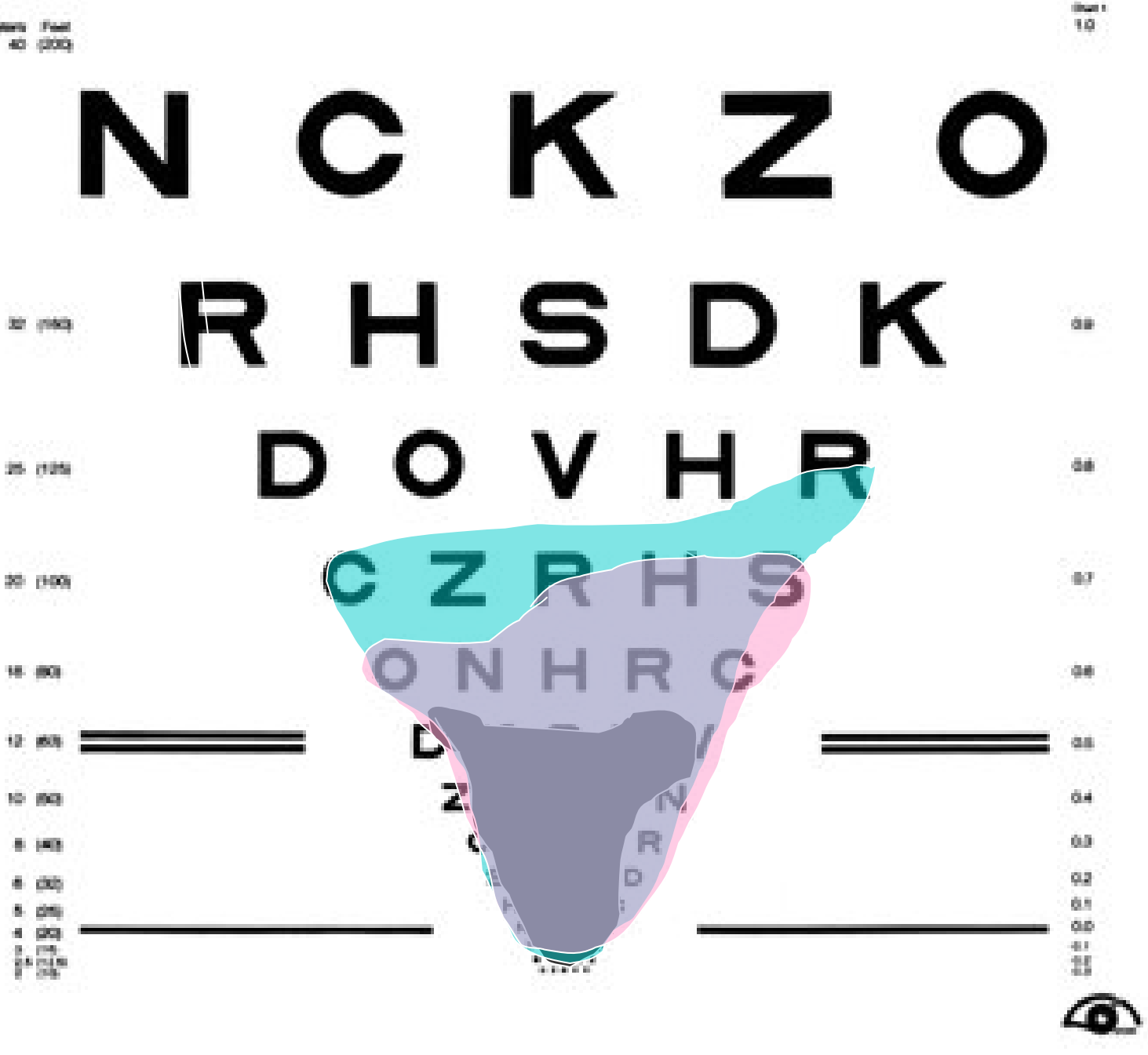
“SEVERE”



AVERAGE ENTRY;

V.A. = 65 LETTERS

CHART WAS HELD CLOSER, SO THESE LETTERS = 50 % TRUE #



AVERAGE ENTRY

V.A. = 65 LETTERS

12 MONTHS

RX = 50

NO = 44

AVERAGE

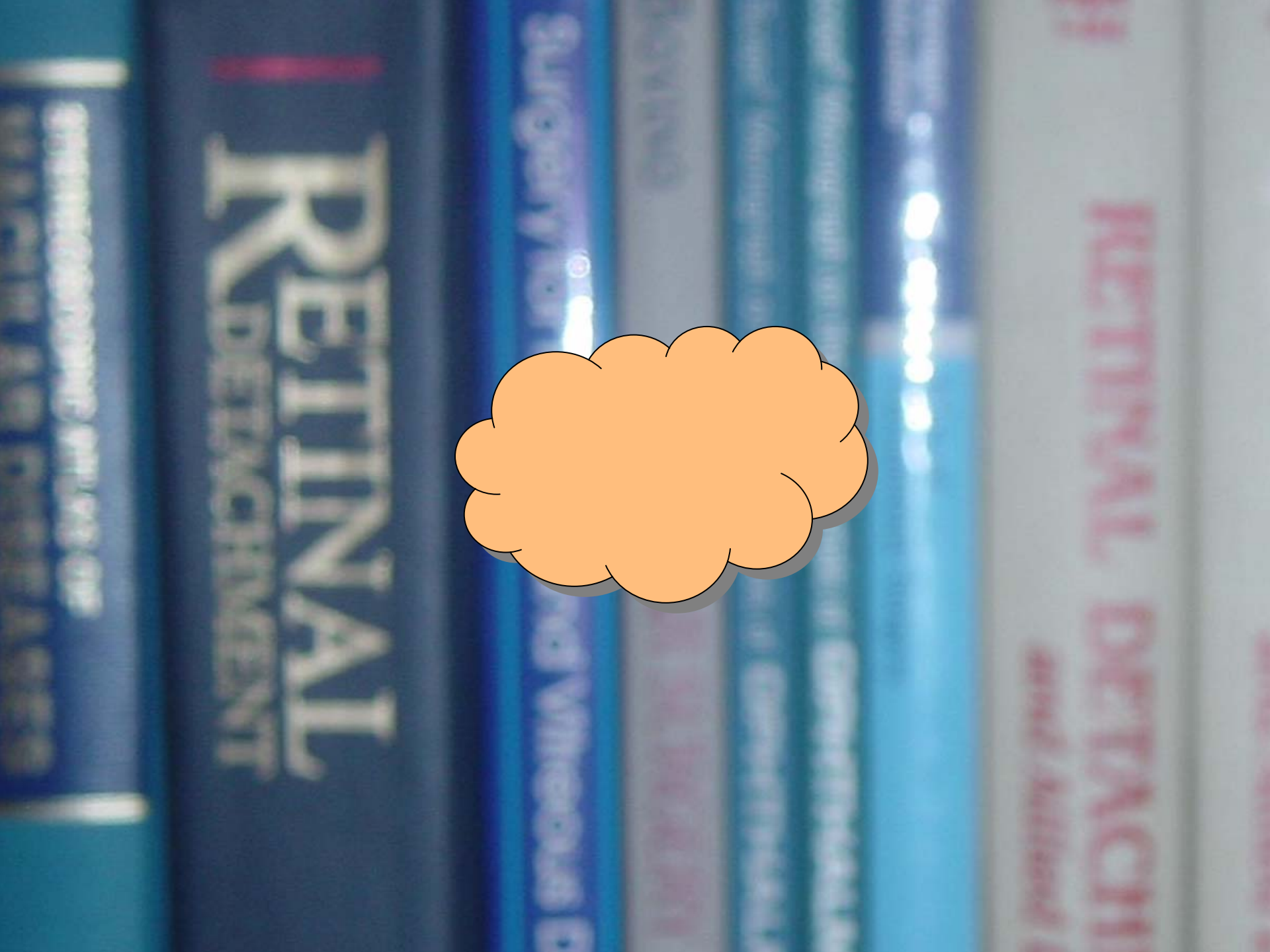
ENTRY

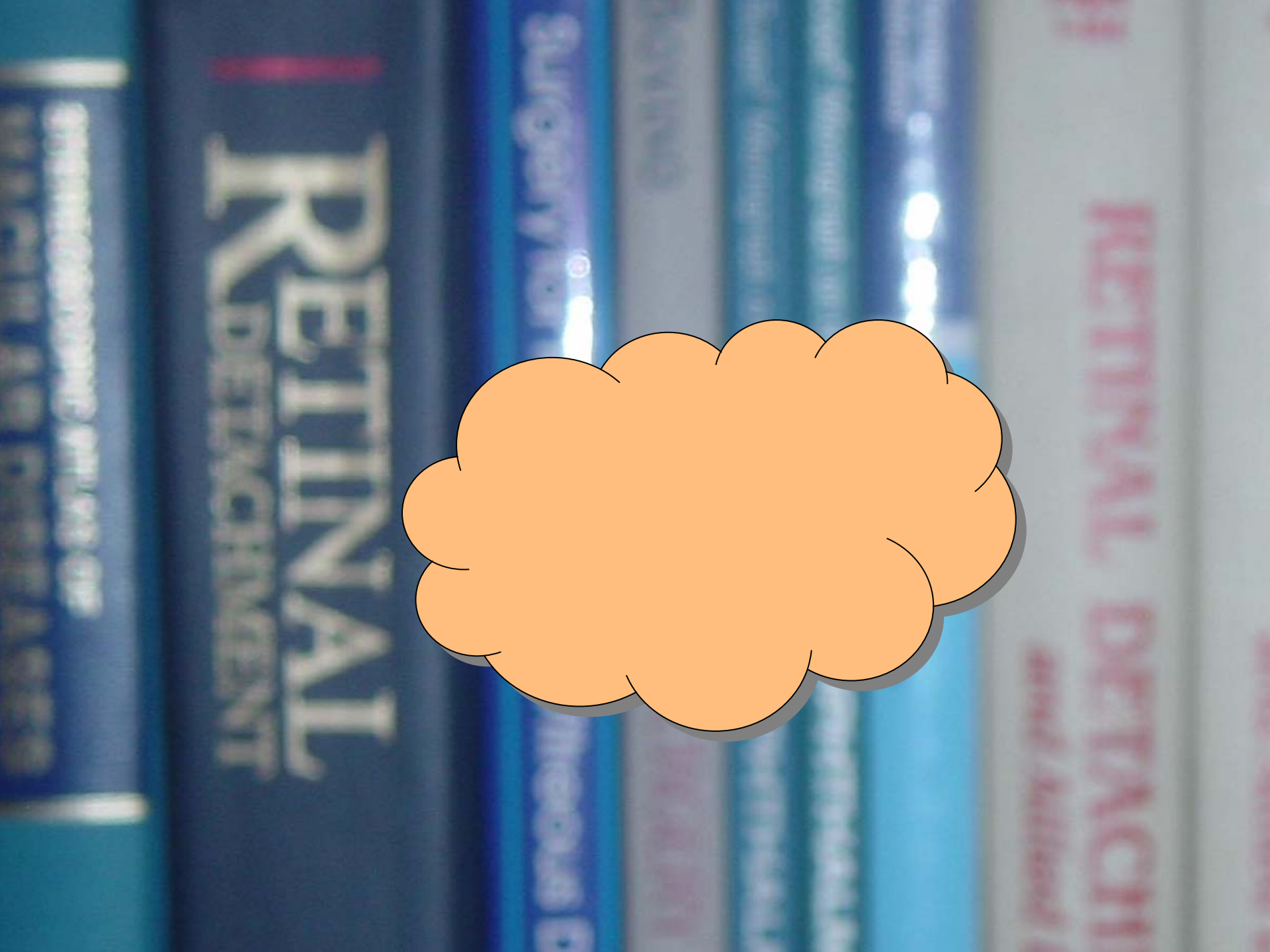
V.A. = 65
LETTERS

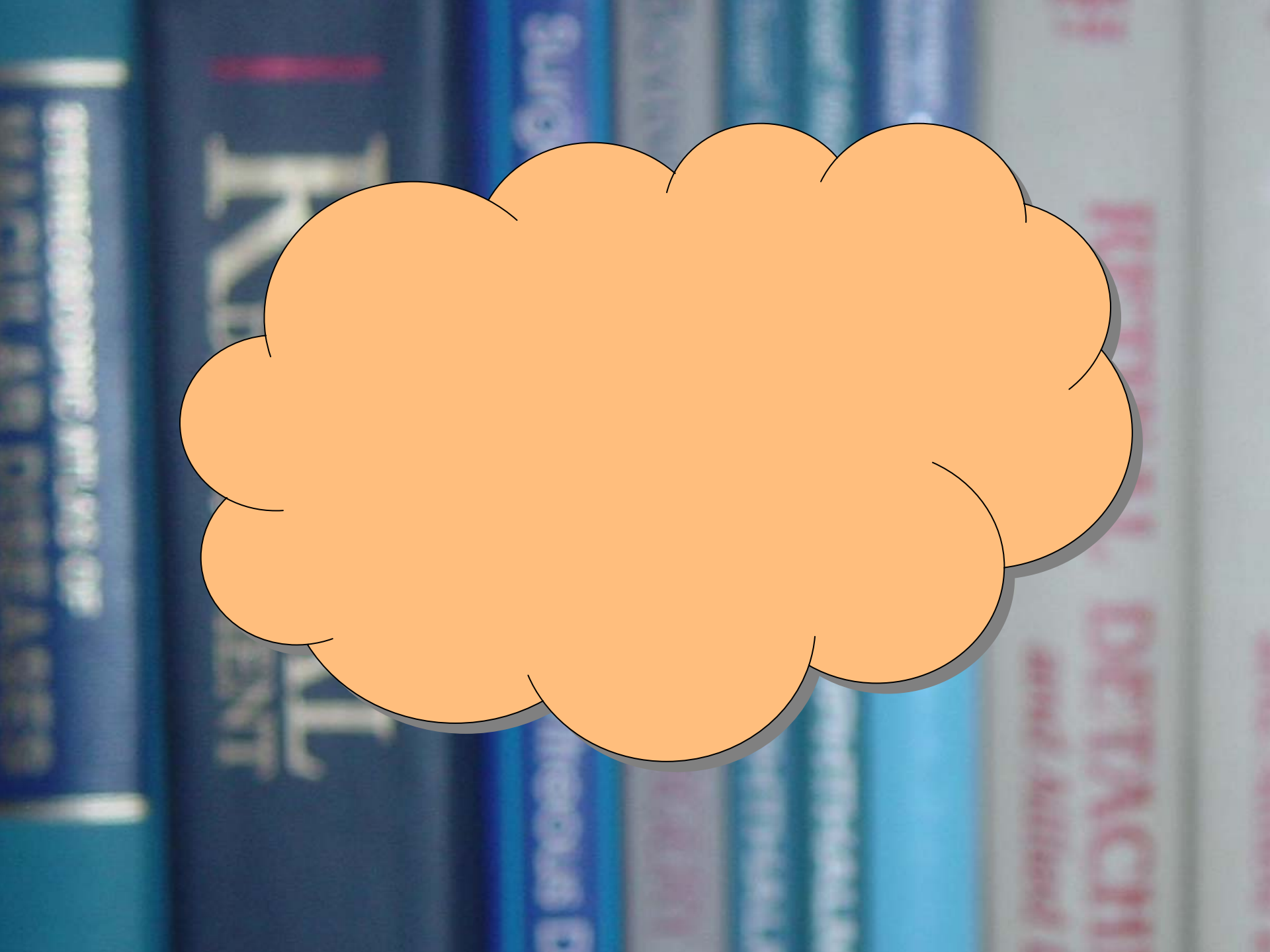
24 MONTHS

RX = 47

NO = 40


RETINAL


RETINAL



THE KEY DATA FOR CLINICIANS

TABLE 2: Moderate and Severe Vision Loss at 12 and 24 month F-U, Occult no Classic Subgroup

	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss
Verte-porfin	51% (84/166)	22% (36/166)	55% (91/166)	29% (48/166)
Placebo	55% (51/92)	33% (30/92)	68% (63/92)	47% (43/92)
	P=0.51	P=0.07	P=0.032	P=0.004

CONSENSUS "COMMUNITY" OPINION :

PDT is currently recommended for Rx of "appropriate" Subfoveal Occult CNV.

"NOT VERY GOOD, BUT BETTER THAN NOTHING"

THE CURRENT DILLEMA:

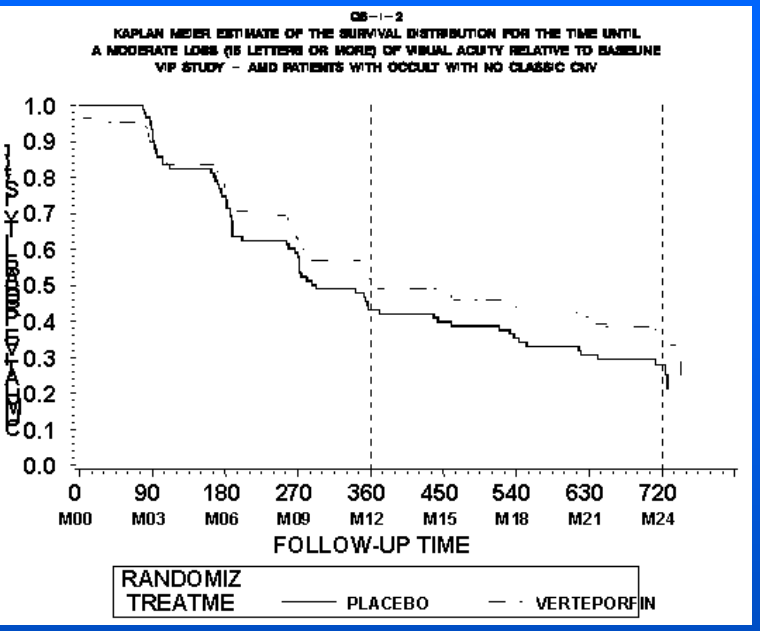
Since PDT appears to be of some value for "100% Occult" LESIONS,

Is Coverage for this "reasonable and necessary"?

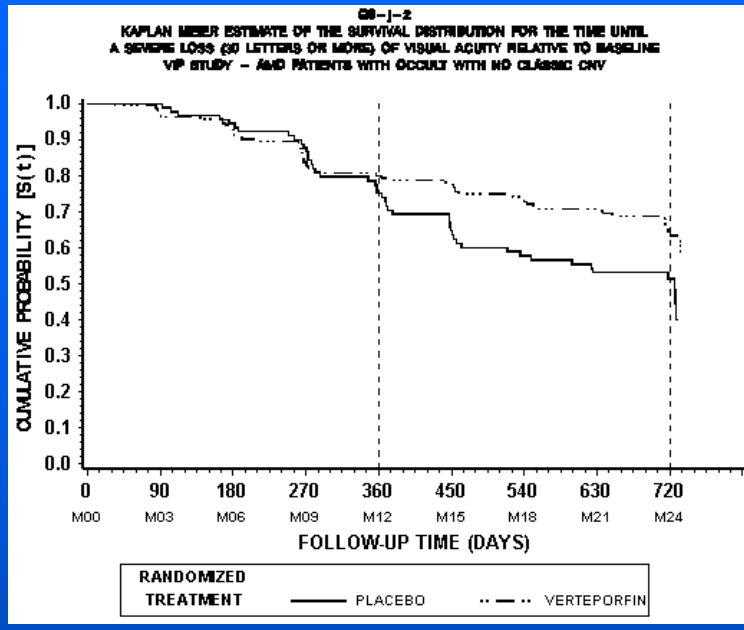
CMS REQUESTED ADDITIONAL LOOKS AT THE DATA

- What is the observed effect?
- Is the observed effect truly due to effects of photodynamic therapy?
- Others:
  - " Effect of attrition" ?
  - " Benefit of Occult > Classic" ?

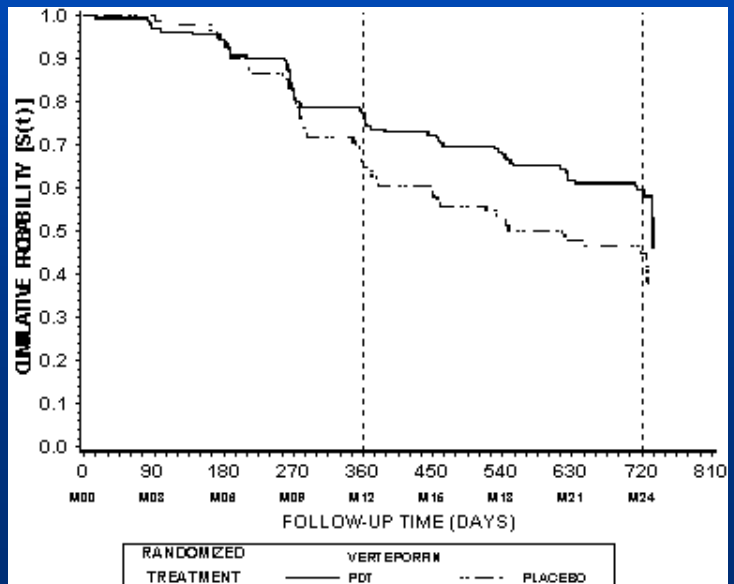
KAPLAN-MEYER SURVIVAL CURVES



MODERATE VA LOSS P = 0.130



SEVERE VA LOSS P = 0.022



TIME UNTIL 20/200

p = 0.02

TABLE 4: Moderate and Severe Vision Loss at 12 and 24 month Follow-Up Without the Last Observation Carried Forward

	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss
Verte-porfin	53% (83/157)	23% (36/157)	55% (79/143)	29% (41/143)
Placebo	54% (45/83)	34% (28/83)	69% (56/81)	48% (39/81)
	P=0.84	P=0.07	P=0.04	P=0.0035

PERSONAL COMMENTS

1. These new CMS data interpretations do not appear to result in significant changes in outcome analysis.

2. PDT with verteporfin is admittedly of rather limited value, especially in occult lesions.

PERSONAL COMMENTS

3. PDT does (sometimes) do something to alter the expected course of occult neovascular CNV.

4. The fact that a greater effect is not seen at 12 months is consistent with with the fact that the value of PDT is limited.

PERSONAL OPINIONS

5. Progression continues in Rx'd eyes, and most become legally blind.

6. There are very few "contented" Rx'd patients.

7. Still, a small benefit appears to exist for this subset of patients.

PERSONAL OPINIONS

8. Although pure PDT will not remain the best remedy, it currently appears to represent the best we have.

9. Physicians are obligated to employ the best current methods for their patients.

"If a doctor fails to prescribe XXX to a patient, despite the compelling evidence that this interaction reduces YYY, questions must be raised." **

** Carolyn Clancy
Thomas Scully

" Perspective: A Call to Excellence "
Health Affairs, Volume 22, #2, 2003

PERSONAL OPINIONS

10. This discussion would not be as important if the costs of PDT with verteporfin were not so high!!

- $131,000,000 projected in 2002

  (But Payment to physicians is barely adequate to cover their costs for the drug!)

PERSONAL OPINIONS

11. This issue of medical costs and charges vs. benefits will become an increasingly critical contemporary issue for our society.

PERSONAL OPINIONS

12. The issue of "genuine practical value" (i.e., "bang for the buck") is only beginning to emerge as an important variable in discussions of health care for afflicted patients.

"VALUE-BASED MEDICINE "
IS A WORTHY CONCEPT.

Verteporfin Clinical Trials

Methodological Questions

The Issue

"…one must distinguish between a weak study showing a modest effect and a strong study showing a modest effect."

-Letter from the Vitreous Society (Drs. Kirk Packo and Neil Bressler) to HHS Secretary Tommy Thompson, February 25, 2002

Problem Areas

- Prespecification of the Analysis
- Definition of Study Population in VIP Trial
- Masking Method
- Approach to Missing Data
- Choice of Primary Outcome
- Interpretation of Control Group in VIP Trial

Verteporfin Clinical Trials

Prespecification of the Analysis

The Standard

International Conference on
Harmonisation
of Technical Requirements for
Registration of Pharmaceuticals
for Human Use

ICH Harmonised Tripartite Guideline

Statistical Principles for Clinical Trials
E9

Recommended for Adoption

at Step 4 of the ICH Process

on 5 February 1998

by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Statistical Principles for Clinical Trials

For each clinical trial … all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins.

TAP Trial

Original protocol approved	10-25-1996
First subject treated	12-6- 1996
Last subject 12 mo. visit (Results unmasked to sponsor)	10-3-1998 (9-25-1998)
Revised statistical analysis plan (Dated September 25, 1998)	Approved 11-24-1998

VIP Trial

Original protocol approved	12-19-1997
First subject treated	3-6-1998
Last Subject 12 mo. Visit (Results unmasked to sponsor)	10-18-1999
1st revised statistical analysis plan	10-19-1999
2nd revised statistical analysis plan	1-11-2001

Trial Context

Confirmatory (Hypothesis-Testing) Trial

As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete.

Trial Context

Confirmatory Trial

…in most confirmatory trials the data are also subjected to exploratory analyses which serve as a basis for explaining or supporting their findings and for suggesting further hypotheses for later research. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

Statistical Principles

Primary and Secondary Variables

The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables.

Statistical Principles

Categorized Variables

Dichotomisation or other categorisation of continuous or ordinal variables may sometimes be desirable.

The criteria for categorisation should be pre-defined and specified in the protocol, as knowledge of trial results could easily bias the choice of such criteria.

TAP Trial: Initial Analysis Plan

- Primary efficacy analysis at 12 months
- Two primary outcomes: loss of visual acuity of 15 or 30 letters
- Two analyses of each outcome
- Split into two separate trials
- No specified adjustment for multiple comparisons

TAP Trial: Initial Analysis Plan

- Analysis of both “intention–to-treat” (full analysis) and “evaluable” (per protocol) patients
- No analyses specified for 24 month data
- “…the trial will be continued to 24 months to provide additional data on long-term safety and efficacy”
- Except for the primary analysis, no analysis is described as testing a hypothesis

TAP Revised Analysis Plan

- Primary efficacy analysis at 12 months
- One primary outcome: loss of visual acuity of 15 letters – One analysis
- Split into two separate trials
- No specified approach for interpreting results

TAP Revised Analysis Plan

- Analysis of both “intention–to-treat” and “evaluable” patients?
- Significance of 24 month data:

  “The 15-letter response rates at the 24-month visit will be used for confirming the durability of effect.”

  Implication: 24-month analysis is contingent upon finding an effect at 12 months.

TAP Trial: Analysis Plans

	Initial	Revised
Primary analyses	8	2
Secondary analyses	7	7
Confirmatory analyses	4	2
Subgroup analyses	6	13
Subgroups defined?	No	Yes
Total Month 12 analyses	>420	520
Total Month 24 analyses	?	520

VIP Trial: Initial Analysis Plan

- Primary efficacy analysis at 12 months
- Primary efficacy criterion: loss of visual acuity of 15 letters
- Secondary efficacy criterion: loss of visual acuity of 30 letters
- Thirteen additional secondary efficacy “variables” (outcomes)

VIP Trial: Initial Analysis Plan

- Analysis of both “intention–to-treat” (full analysis) and “evaluable” (per protocol) patients
- Except for the primary analysis, no analysis is described as testing a hypothesis
- No analyses specified for 24 month data
- “…the trial will be continued to 24 months to provide additional data on long-term safety and efficacy”

VIP First Revised Analysis Plan

- Primary efficacy analysis at 12 months
- Primary outcome: loss of visual acuity of 15 letters
  - Intention to Treat
  - Last Observation Carried Forward
  - Confirmatory analysis w/o LOCF

VIP First Revised Analysis Plan

- Analysis of both “intention–to-treat” and “evaluable” patients
- Logistic regression model “to explore”

VIP First Revised Analysis Plan

Additional analyses for classic and occult subgroups of all secondary outcomes

- Classic: Any or Questionable
- Occult: None

VIP First Revised Analysis Plan

24 month analysis is contingent upon finding an effect at 12 months.

"The respective responder rates at the 24-month visit will be used for confirming the durability of effect. Therefore, if the difference in responder rates at the 12-month visit is statistically significant … then the study will be judged as having provided pivotal evidence of efficacy …"

VIP Trial: Analysis Plans

	Initial	1st Revision
Primary analyses	1	1
Secondary analyses	1 + 13	11
Confirmatory analyses	3	1
Subgroup analyses	12	20
Subgroups defined?	No	Yes
Total Month 12 analyses	>864	70
Total Month 24 analyses	?	70?

VIP Second Revised Analysis Plan

Revised definition of classic and occult subgroups

- Classic: Any
- Occult: Questionable, can’t grade, or none

VIP Second Revised Analysis Plan

Additional subgroup analyses of 24 month data for subjects with baseline

- No Classic CNV
- Lesion size of =<4 MPS disk areas, and
- Visual acuity score between 73 and 34 letters

Prompted by *ad hoc* analysis of TAP and VIP 12 month data

TAP Trial

Explicit Hypotheses for the Experiments

The corresponding null (H0) and alternative (H1) hypotheses to be tested for the primary efficacy variable are as follows:

H0: The proportion of patient responders for visual acuity is the same for verteporfin PDT and placebo.

H1: The proportion of patient responders for visual acuity is different between verteporfin PDT and placebo.

TAP Trial

Explicit Conclusion for the Experiments

Revised Plan

- Primary efficacy criterion: loss of visual acuity of 15 letters
- Primary efficacy analysis at 12 months

H1: The proportion of patient responders for visual acuity is different between verteporfin PDT and placebo.

(p=.02 or p=.01 (two trials))

VIP Trial

Explicit Hypotheses for the Experiment

The corresponding null (H0) and alternative (H1) hypotheses to be tested for the primary efficacy variable are as follows:

H0: The proportion of patient responders for visual acuity is the same for verteporfin PDT and placebo.

H1: The proportion of patient responders for visual acuity is different between verteporfin PDT and placebo.

VIP Trial

Explicit Conclusion for the Experiment

- Primary efficacy criterion: loss of visual acuity of 15 letters
- Primary efficacy analysis at 12 months

H0: The proportion of patient responders for visual acuity is the same for verteporfin PDT and placebo. ($p > 0.5$)

Verteporfin Clinical Trials

Definition of Study Population in VIP Trial

TAP Trial Exclusions

AMD with No Classic CNV

"Visual acuity may deteriorate more in patients with lesions containing classic CNV than in patients with lesions containing occult with no classic CNV"

Classic CNV with visual acuity > 20/40

"With limited safety data at the initiation of the TAP trial, the investigators were unwilling to apply this therapy to affected eyes with excellent visual acuity"

VIP Trial

These groups were treated as homogeneous:

- Randomization *not* stratified
- Single primary hypothesis applied to entire population

Problems with VIP Trial

- Recruitment patterns may differ by center
- Mix of groups may not reflect the target population
- Natural histories of groups may be different

Problems with VIP Trial (continued)

- Treatment effects on groups may be different.
- Reliance on *post hoc* statistical adjustment to account for differences
- There may be inadequate statistical power to recognize these differences

Verteporfin Clinical Trials

Masking Method

Masking Method

- Repeated disclosure of treatment assignment on site:

  Study coordinator or designate must look up subject's treatment arm every time the subject is treated (up to eight times) in order to prepare treatment.
- High risk of inadvertent hinting or unmasking

Masking Method Alternatives

- Prepare a placebo (dextrose “cake”) centrally that looks like and is reconstituted in the same manner as verteporfin
- Provide sites with vials of drug/placebo labeled only with subject number

Verteporfin Clinical Trials

Approach to Missing Data

Approach to Missing Data

Last Observation Carried Forward

- Treats dropouts as successes
- Favors trial arm with more dropouts

Approach to Missing Data

Last Observation Carried Forward

Not a conservative choice

- More adverse effects likely with active treatment
- No reason to expect more dropouts in placebo arm from disappointment
  - » Improvement not expected
  - » No alternative therapies

Approach to Missing Data

Alternatives

- Assume dropouts to be failures
- Extrapolate individual trends
- Choose different primary outcome (time-to-failure) that makes more reasonable(?) assumptions about censored data (life table)

Verteporfin Clinical Trials

Choice of Primary Outcome

Choice of Primary Outcome

What is the Goal of Treatment?

Is there a critical time or end point?

Choice of Primary Outcome

Unique Time Point

- Example: maximize FVC before surgery

Functional Threshold

- Example: death

Choice of Primary Outcome

In AMD

- No unique time point
- Vision level in one eye cannot determine a functional threshold
- Total vision loss is rare
- No quantity of vision loss is uniquely important

Choice of Primary Outcome

Primary Outcome for Verteporfin Trials

- Specified threshold: loss of 15 letters
- Specified time point: 12 months

Alternative Primary Outcomes

Difference in numbers of letters lost

- Specified threshold: None
- Specified time point: 12 months

Alternative Primary Outcomes

Time until 15 letters lost

- Specified threshold: 15 letters lost
- Specified time point: None

Alternative Primary Outcomes

Loss of visual acuity over entire trial

Area under the curve

- Specified threshold: None
- Specified time point: None

Verteporfin Clinical Trials

Interpretation of Control Group in VIP Trial

VIP Trial

AMD Subjects with No Classic CNV (and visual acuity 20/100 or better)

OR

Classic CNV with visual acuity better than 20/40

VIP Trial

Natural History (Placebo Control Group)

AMD Subjects with No Classic CNV

- *At least* 60% met TAP enrollment criteria during trial
  - 39 of 92 developed Classic CNV by Month 12
  - 55 of 92 developed Classic CNV by Month 24
- Subjects presented with a history of Classic CNV on approximately 1/3 of possible treatment visits

VIP Trial

Natural History (Placebo Control Group)

AMD Subjects with Classic CNV and visual acuity better than 20/40

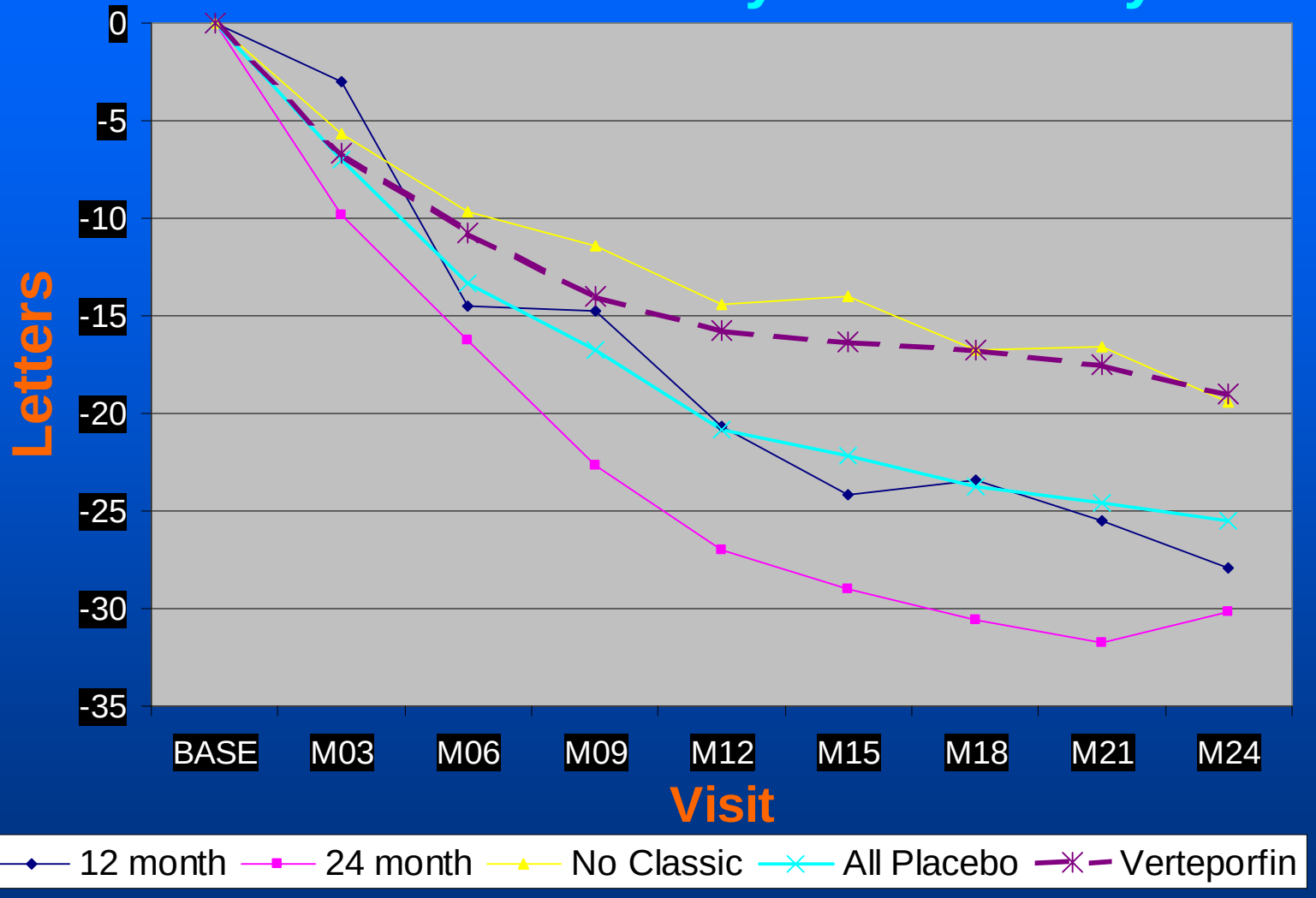
- 100% met TAP enrollment criteria during trial
  - 18 of 22 had visual acuity 20/40 or worse at baseline visit
  - Remainder had visual acuity 20/40 or worse at 3 month visit
- Subjects eligible under TAP for 98% of possible treatment visits

Is VIP a repetition of TAP?

Is PDT essentially effective only for patients who have or are developing classic CNV?

VIP Trial

Loss of Visual Acuity: Occult Only



VIP Trial

ALL of the difference between treatment arms is attributable to placebo subjects who developed classic CNV.

however…

VIP Trial

Some of the difference may have occurred in these subjects before they developed classic CNV…

VIP Trial

How significant is that difference?

TAP Trial

Loss of Visual Acuity at 24 months

Verteporfin	13.4 letters
Placebo	19.6 letters

32% reduction ($p<.0001$)

VIP Trial
Occult Only

Loss of Visual Acuity at 24 months

Verteporfin	19.0 letters
Placebo	25.5 letters

25% reduction (p=.017)

VIP Trial

Occult Only

Effect of treatment of newly developed classic CNV in placebo subjects

Reduction in TAP Trial	32% x
Proportion of Time Treated	33%
Expected reduction in VA Loss	11%

VIP Trial

Occult Only

Adjusted Loss of VA at 24 months

Verteporfin	19.0 letters
Placebo	22.7 letters

16% reduction (p=.14, NS)

VIP Trial

Assuming a true benefit over placebo, is

- Immediate treatment of all patients with occult CNV

superior to

- Watchful waiting until classic CNV develops?

Watchful Waiting Advantages

- Fewer patients treated
- Fewer treatments for treated patients
- Fewer patients with side effects
- Lower cost

Summary

How “strong” are these studies?

Report Card

	TAP	VIP
Prespecification of the Analysis: Conclusions based on prespecified primary outcome?	B-	F
Definition of Study Population	A	D
Masking Method	C	C
Choice of Primary Outcome	C	C
Approach to Missing Data	C	C
Interpretation of Control Group: Appropriate for stated conclusion?	A	C
Reliability and Accuracy of Patient Assessments	A-	A-
Overall	B-	C-

VIP Trial and Occult CNV

Does the VIP trial show PDT as effective in occult CNV?

- Had a negative principal result
- Was not designed to answer this question
- Has methodological weaknesses
- Exploratory (secondary and subgroup) analyses give varying results
- Not clear that any effect is not equivalent to treatment of early classic CNV
- Showed significant severe side effects

Panel Voting Question 1

- Is there adequate evidence to draw conclusions about the net health outcomes (that is, whether or not the risks and benefits of treatment outweigh the risks and benefits of non-treatment) of ocular photodynamic therapy (OPT) with verteporfin in routine clinical use in the population of Medicare beneficiaries who have age-related macular degeneration (AMD) and occult with no classic choroidal neovascularization (CNV)?

Panel Voting Question 2

- If the panel answers the first question affirmatively, does the evidence demonstrate that OPT with verteporfin treatment improves net health outcomes in treating age-related macular degeneration (AMD) and occult with no classic choroidal neovascularization (CNV), and if so, what is the size of the benefit in patients receiving the treatment?

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

THANK YOU