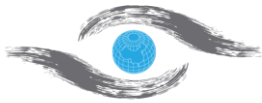




Dennis Lam
& Partners Eye Center
林順潮眼科中心



香港希瑪激光矯視暨眼科手術中心
C-MER (HK) LASIK & EYE SURGERY CENTER

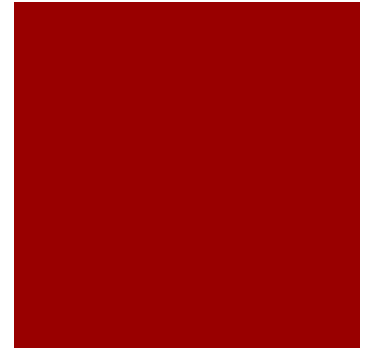
Advances in Management of Macular Degeneration and Cataract in the Elderly (老年黃斑病變及白內障的最新治療)

Dr. David TL Liu 劉大立醫生

FHKAM (Ophthalmology), FCOphth HK, FRCOphth (UK), FRCS (Glasgow),
MRCS (Edinburgh), MSc (CUHK), MBChB (CUHK), BMedSc (CUHK)

Department of Ophthalmology & Visual Sciences,
the Chinese University of Hong Kong, Hong Kong

Financial Disclosure



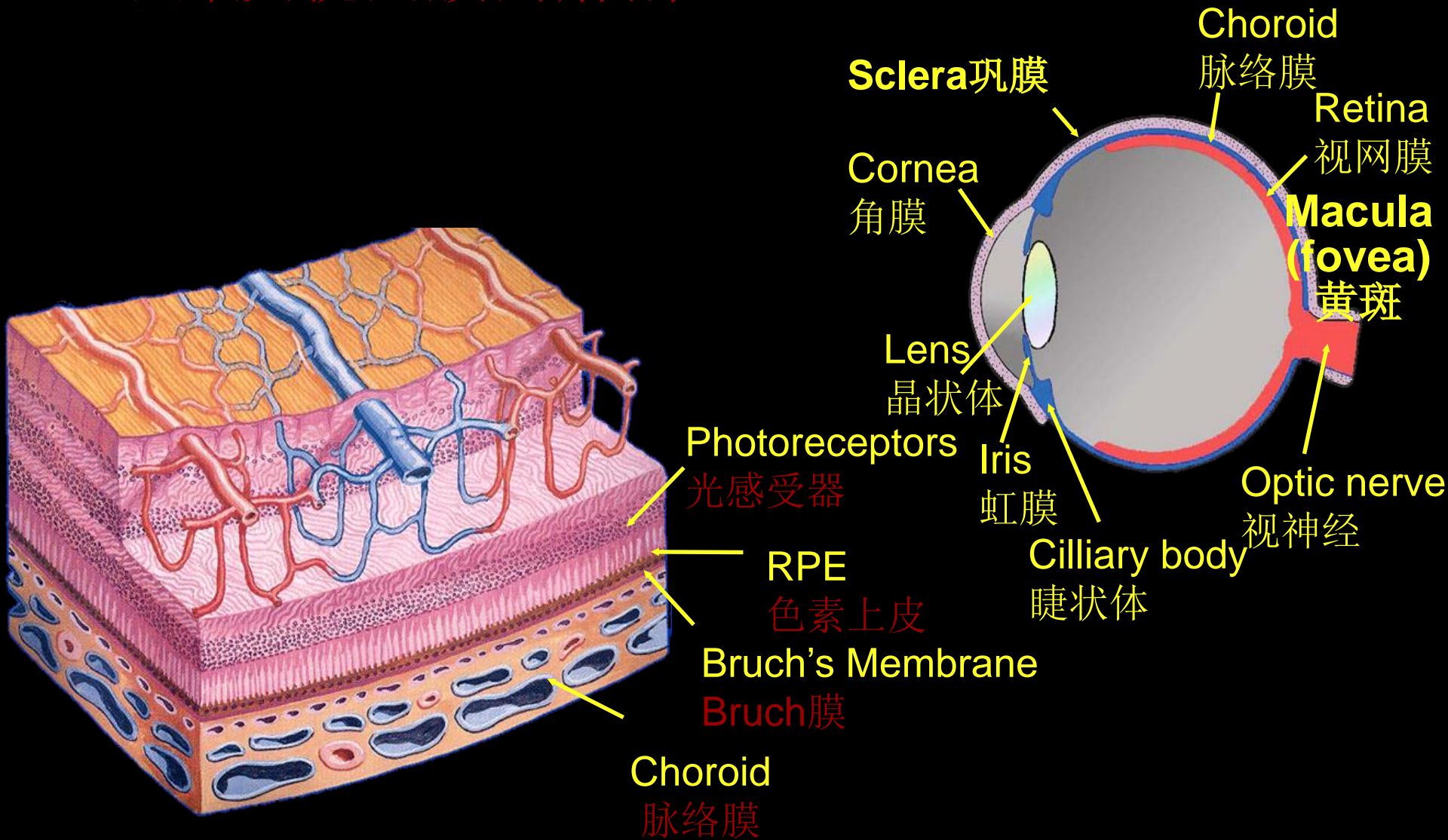
- I have no relevant financial interest or relationship to disclose.



Age-Related Macular Degeneration (AMD) (老年黄斑退化症)

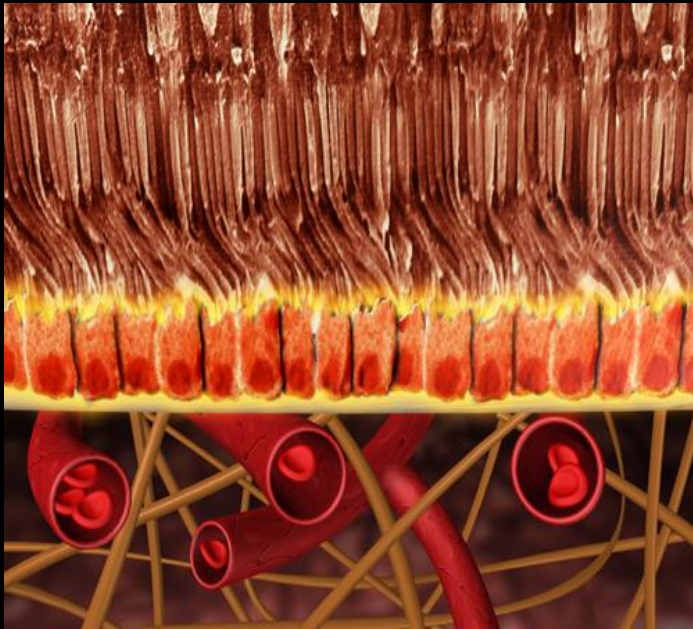
Anatomy of the eye and retina

眼部及视网膜的解剖



Normal retina 正常视网膜

5



schematic 示意图



fundus photograph

眼底照片

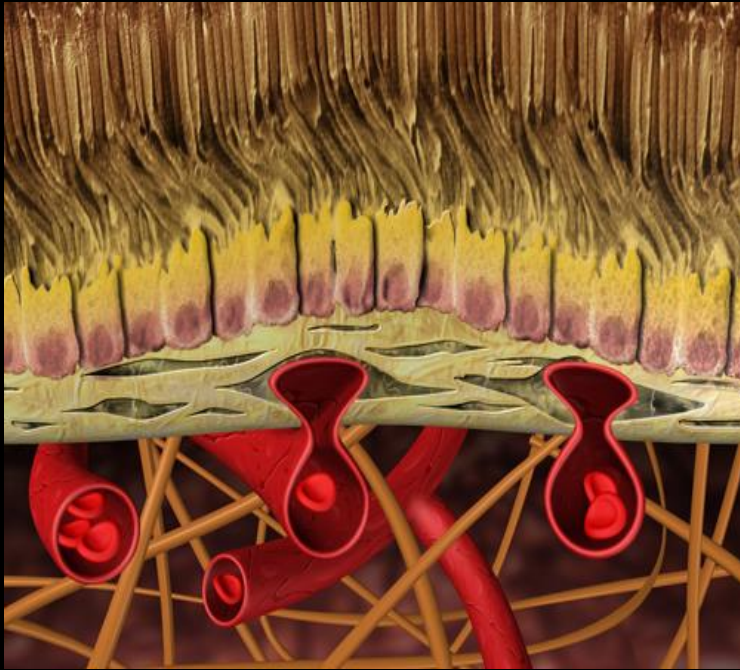
RPE separates choroidal layer from photoreceptors

视网膜色素上皮将脉络膜层与光感受器层分开

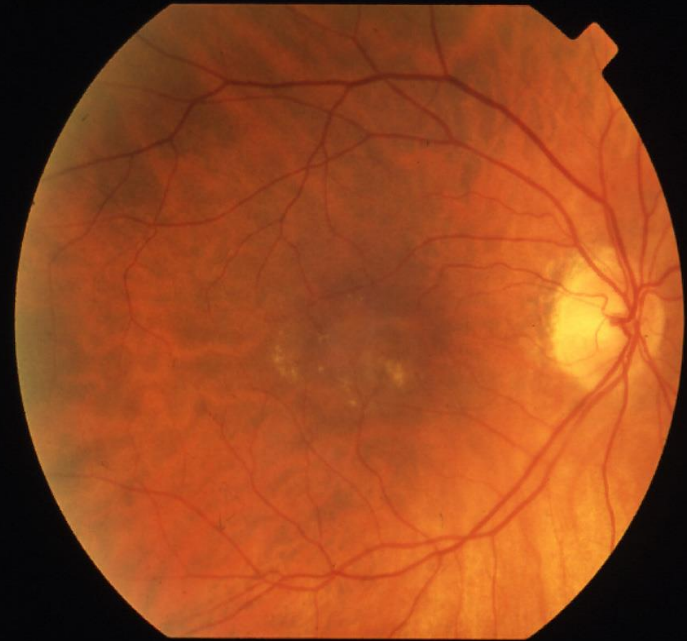
Choroidal neovascularization (CNV)

6

脉络膜新生血管形成 (CNV)



Schematic 示意图



fundus photograph

眼底照片

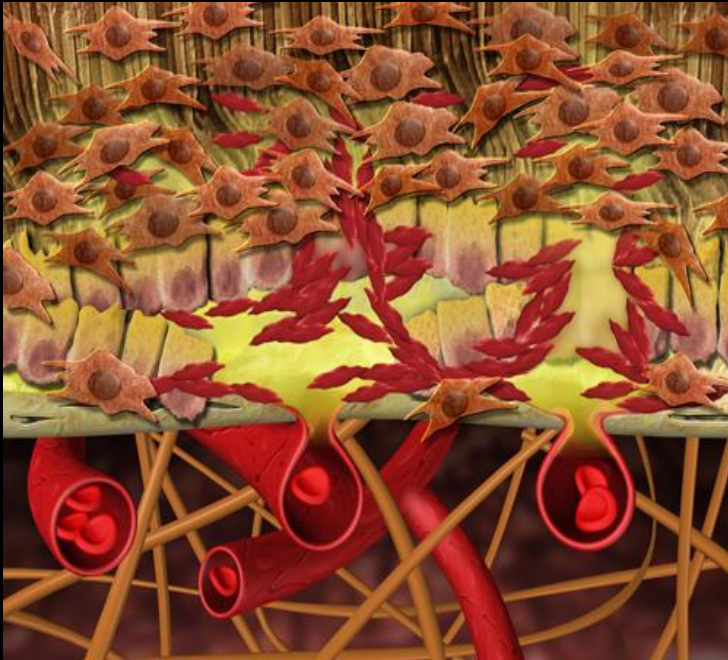
New blood vessels penetrate Bruch's membrane

新生血管穿过玻璃膜

Formation of disciform scar

7

盘状瘢痕形成



Schematic 示意图



fundus photograph

眼底照片

Disciform scars can form in untreated CNV

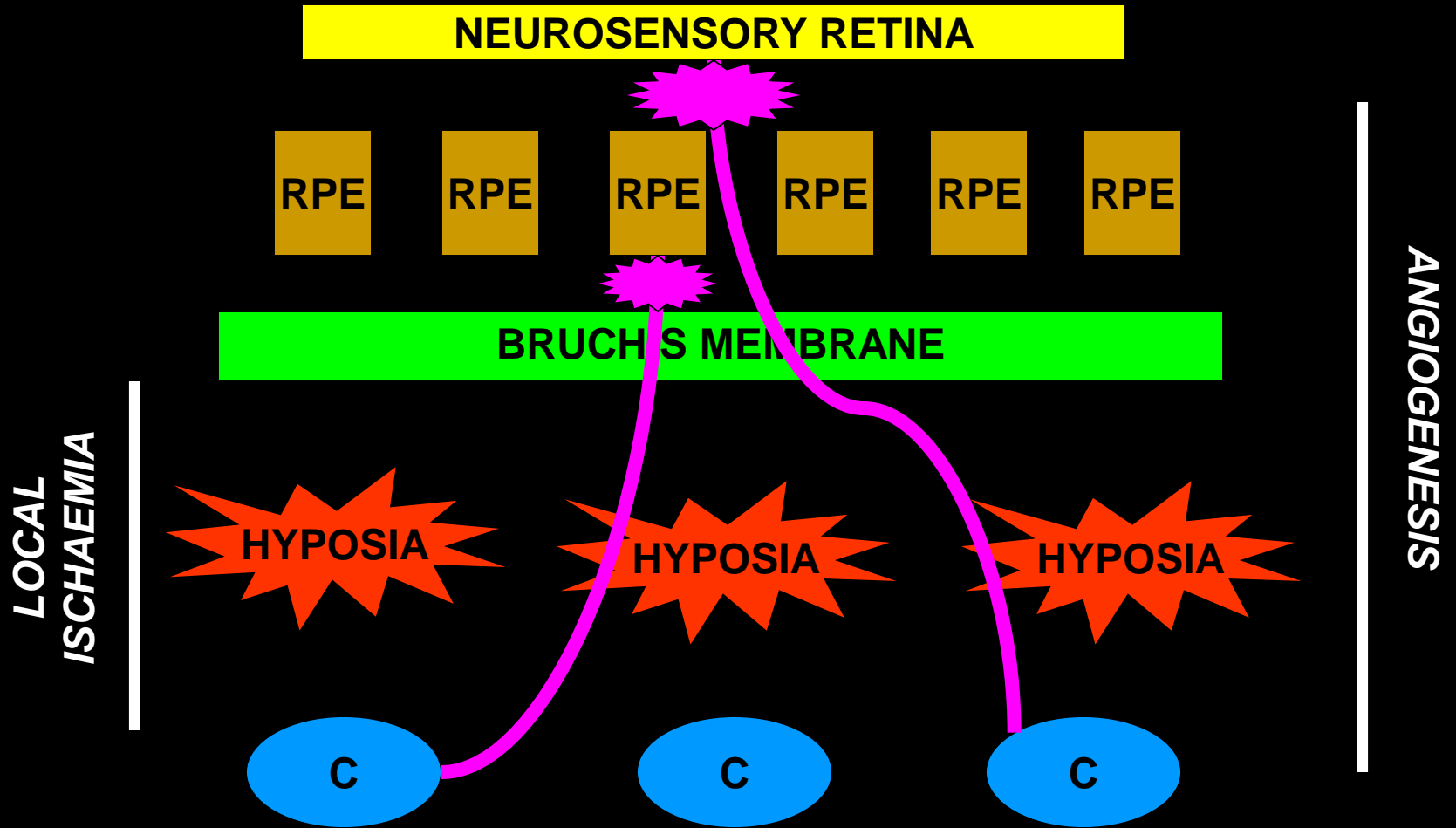
盘状瘢痕可形成于未经治疗的CNV

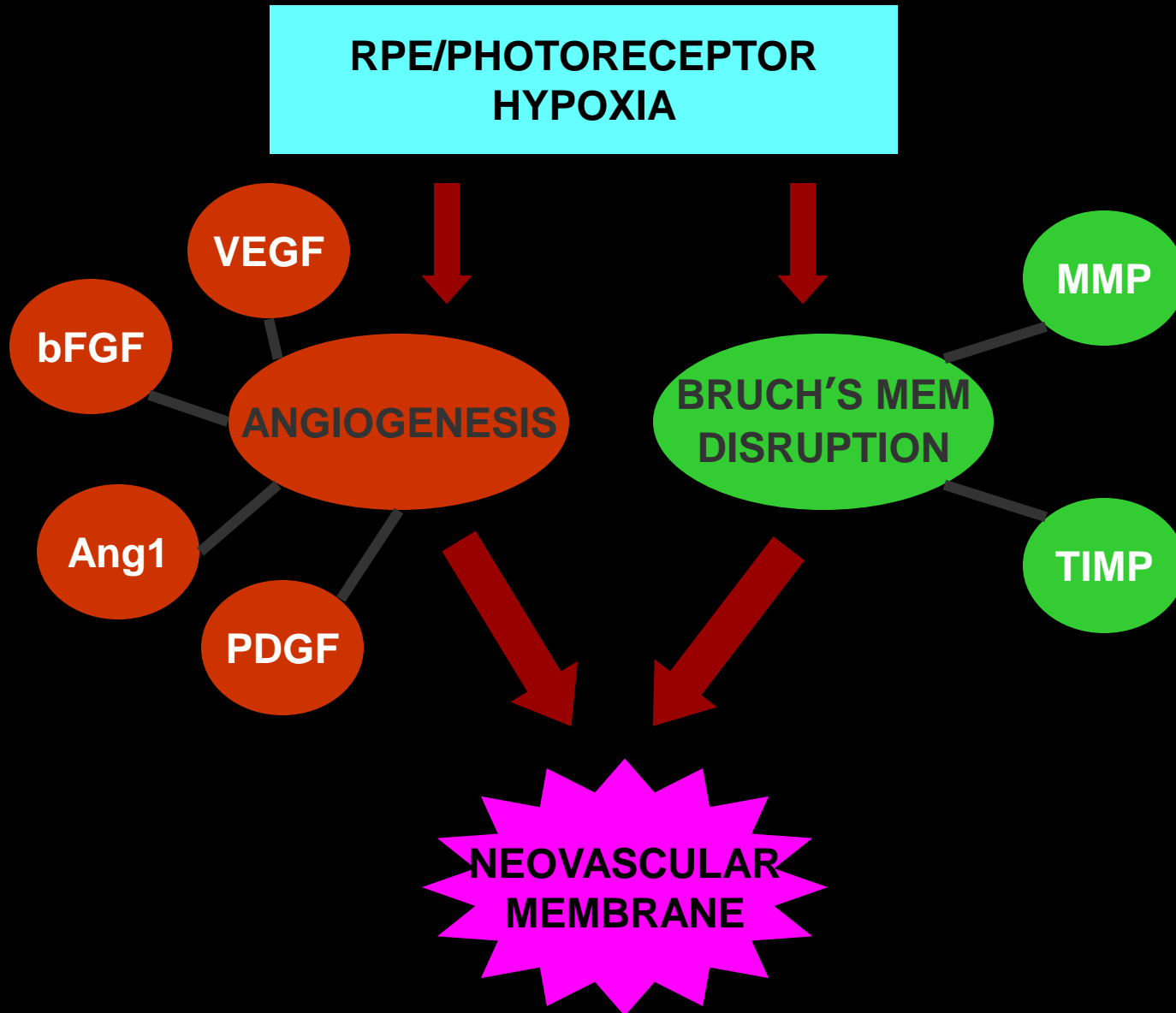


Chocolate Chip

- 1/4 CUP BUCKWHEAT FLOUR
- 1/2 CUP POTATO FLOUR
- 2 TEASPOON BAKING POWDER
- 1/2 CUP PALE ALE BEER
- 1/2 CUP WATER
- 1/4 CUP APPLE CIDER VINEGAR
- 1/2 CUP CHOCOLATE CHIPS







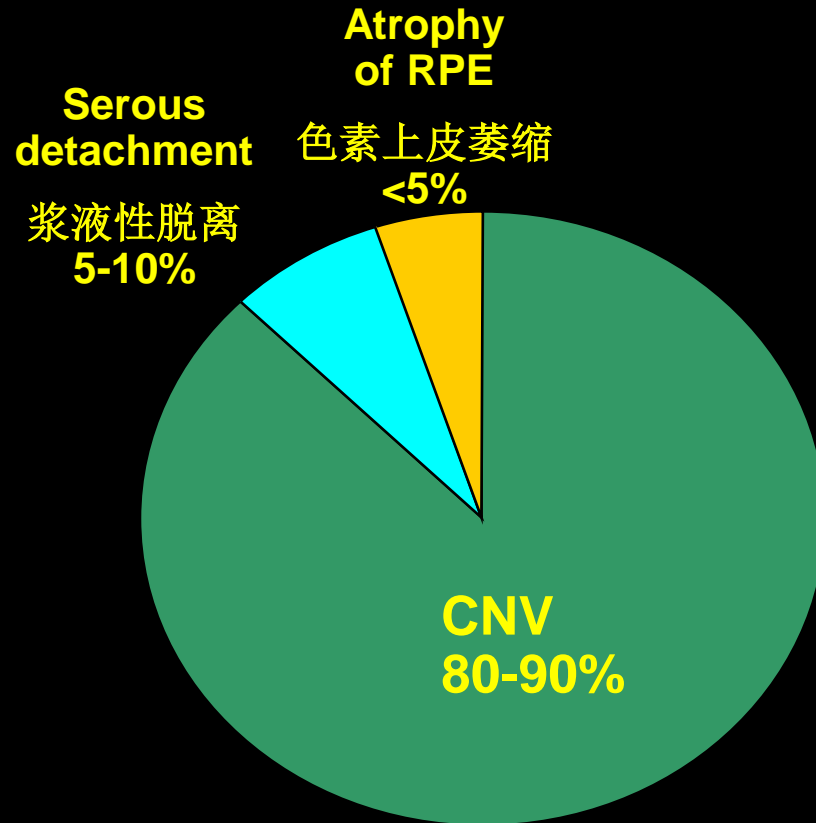
Diseases causing CNV

可导致CNV的疾病

1. Age-related Macular Degeneration 老年性黄斑变性
2. Pathologic Myopia 病理性近视
3. Idiopathic CNV 特发性CNV
4. Choroiditis 脉络膜炎
5. Dystrophy 营养不良
6. Polypoidal choroidal vasculopathy (PCV) 息肉样脉络膜血管病变
7. Trauma 外伤
8. Tumor 肿瘤
9. Central Serous chorioretinopathy (CSCR) 中浆
10. Laser-induced 激光诱导的CNV

Vision loss in AMD

老年性黄斑变性的视觉丧失



Causes of vision loss in AMD

老年性黄斑变性视觉丧失的原因



AMD is a major cause of blindness in the western world

老年性黄斑变性在西方国家时致盲的主要原因

2 Main forms of AMD

AMD二种类型

- **Non-neovascular AMD “DRY” 干性AMD**
 - drusen and abnormalities of RPE 玻璃膜疣及RPE异常
 - usually causes little impact on vision, unless significant RPE atrophy develops
除非RPE萎缩严重，通常对视力影响较小
- **Neovascular AMD “WET” 湿性AMD**
 - new vessel growth from the choroidal layer
来自脉络膜的新生血管
 - usually has a severe impact on vision
通常严重影响视力

AMD - Dry

14

干性
AMD

■ Drusens

玻璃膜疣



AMD - Wet

15

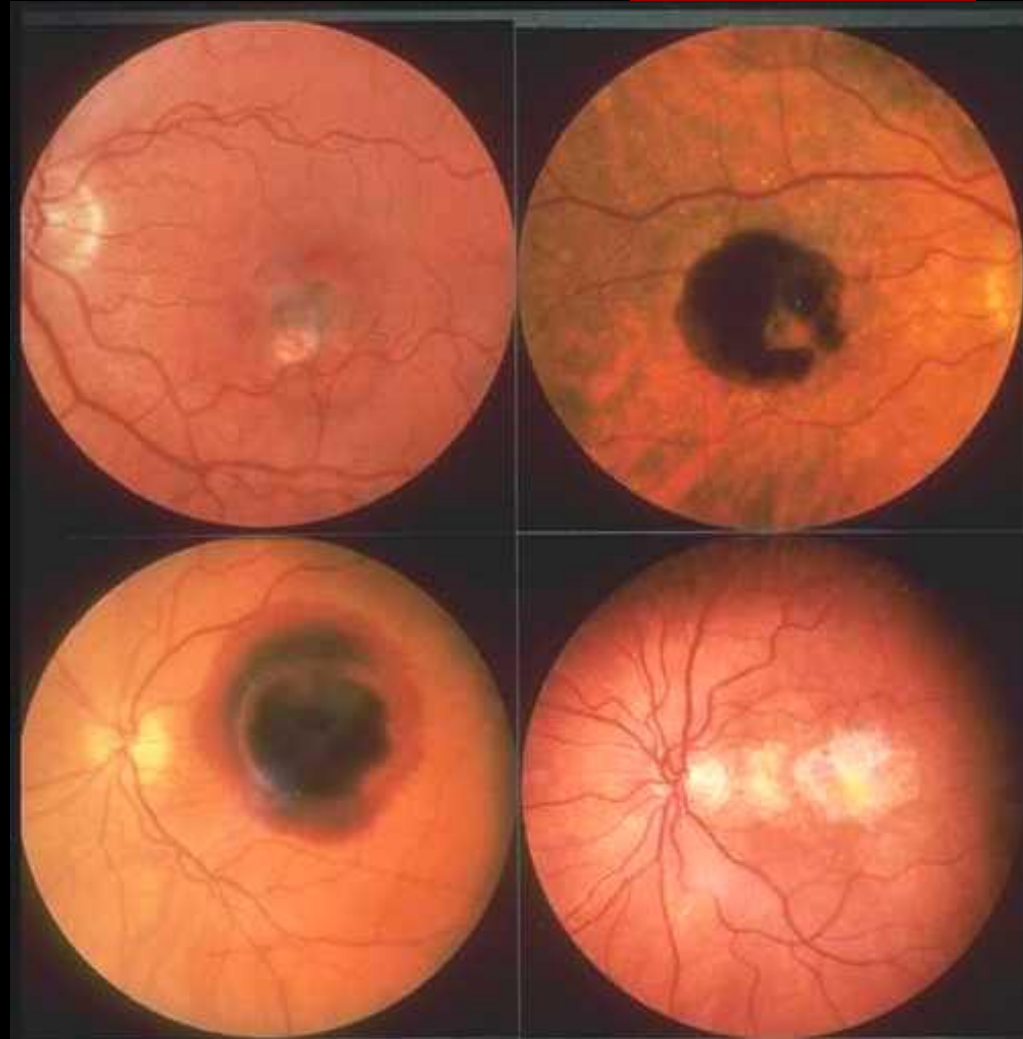
湿性AMD

- Choroidal neovascularization

脉络膜新生血管

- Macular Hemorrhage

黄斑出血



Factors linked to AMD

以下因素与AMD的发生有关

Confirmed

已经证实的因素

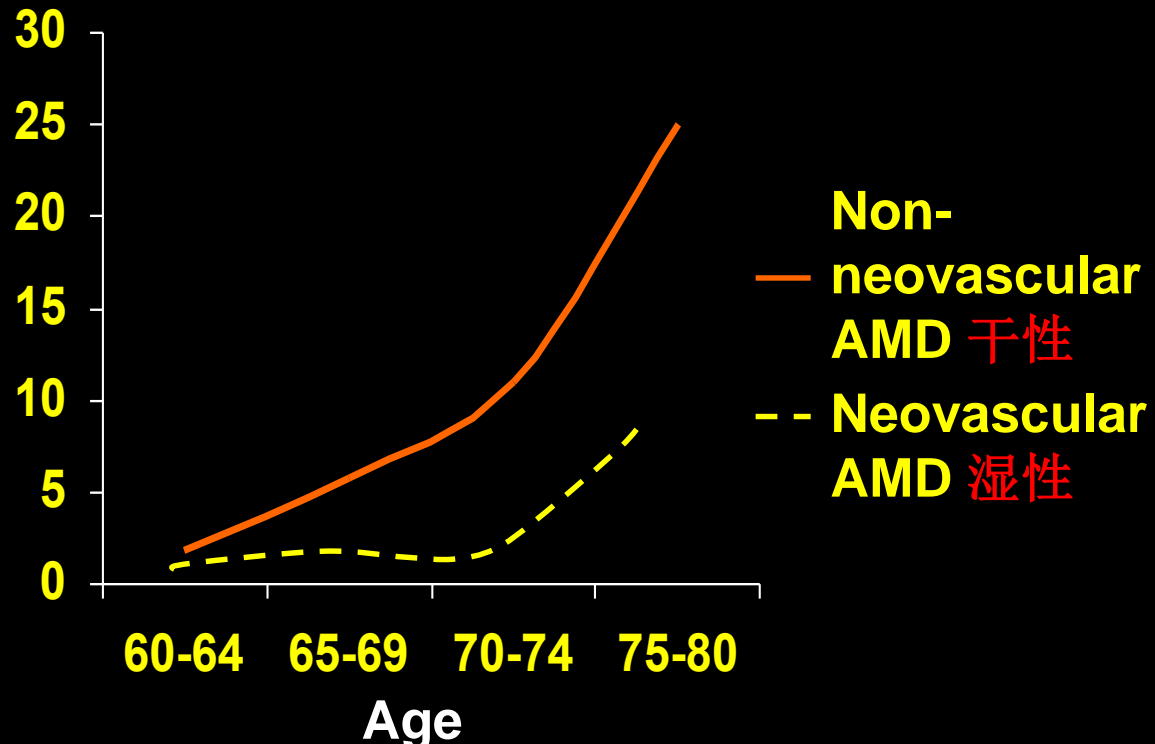
- Age 年龄



- Smoking 吸烟
- Hypertension 高血压
- Cardiovascular disease 心血管疾病
- Nutrition 营养因素
- Neovascular AMD in one eye
一只眼发生新生血管性AMD
- Sex 性别
- Race 种族
- Family history 家族史

Age and AMD 年龄与AMD

% of people



The risk of developing AMD increases with age

随着年龄增长AMD发生的危险性增加

Genetics 遗传学

Genetic and environmental factors

遗传学和环境因素

Approaches 研究方法

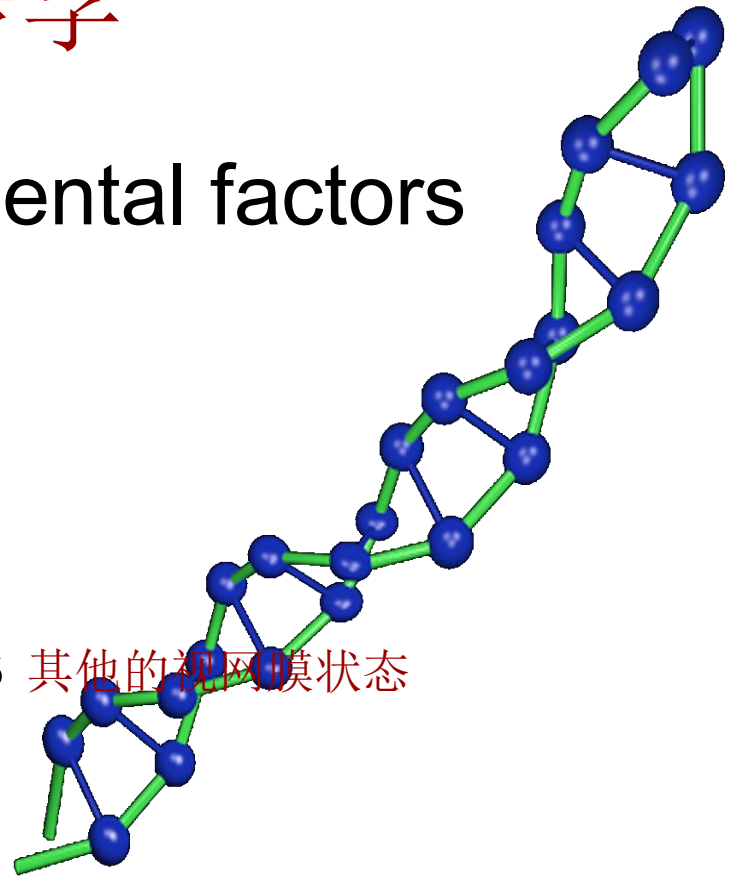
– twin studies 孪生子研究

– other retinal conditions 其他的视网膜状态

Potential uses 可能的策略

– markers / prevention 标记物/阻滞物

– gene therapy 基因治疗

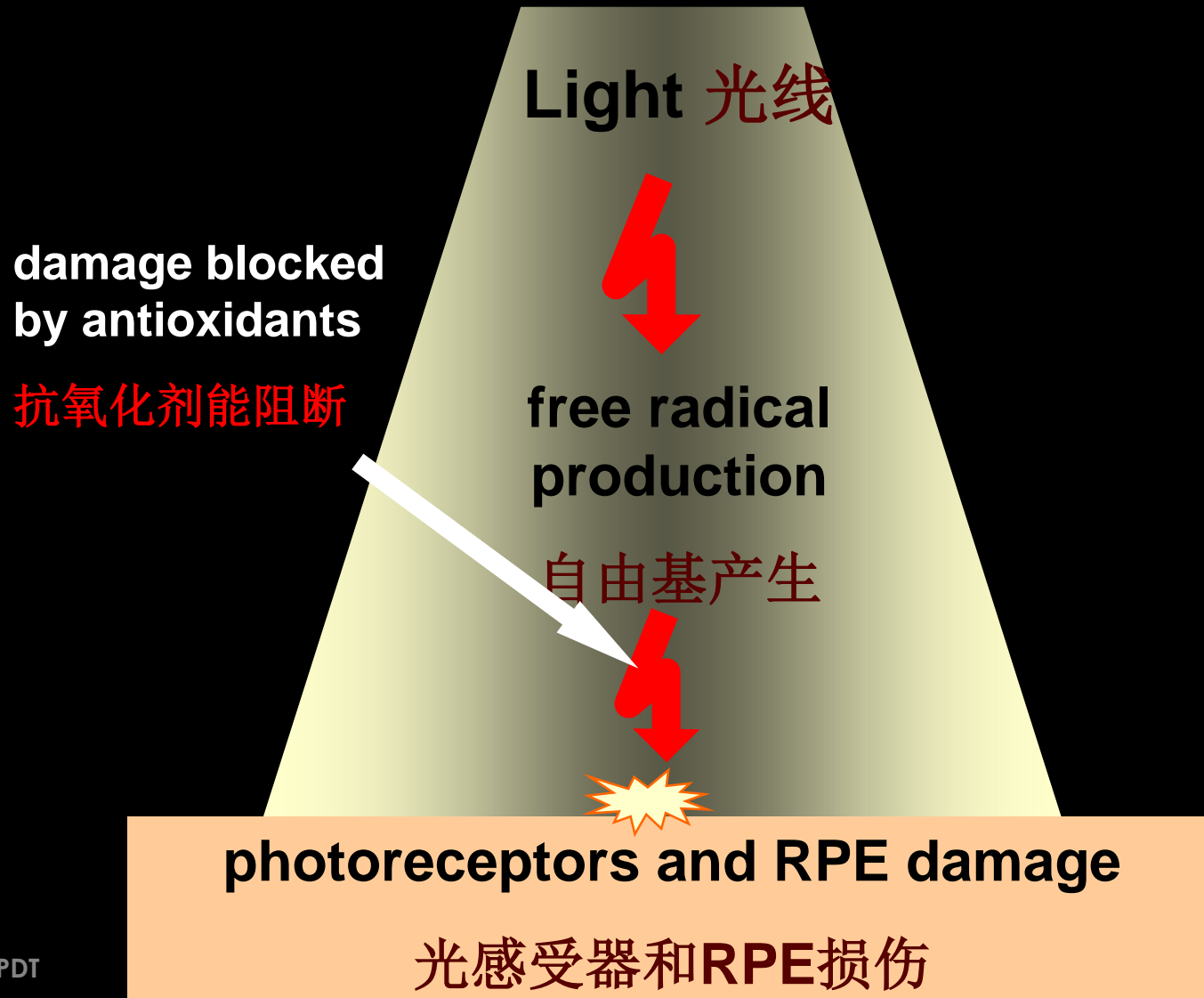


Prevention of AMD



Clues to preventive strategies

预防线索

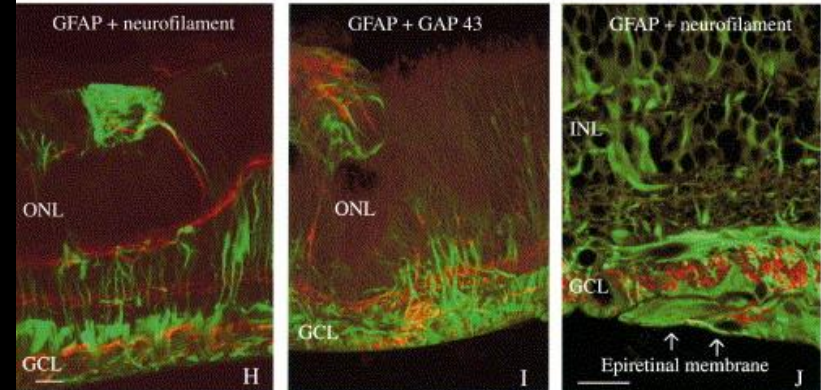
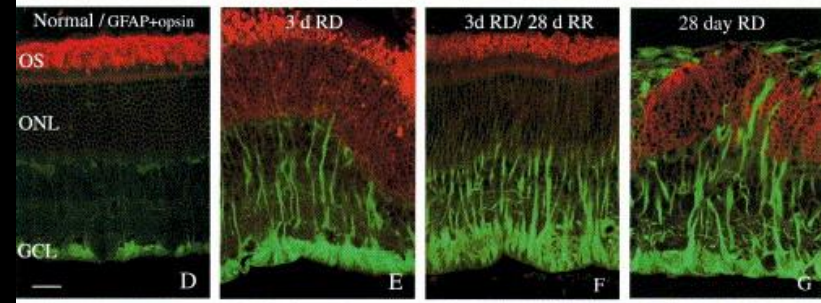
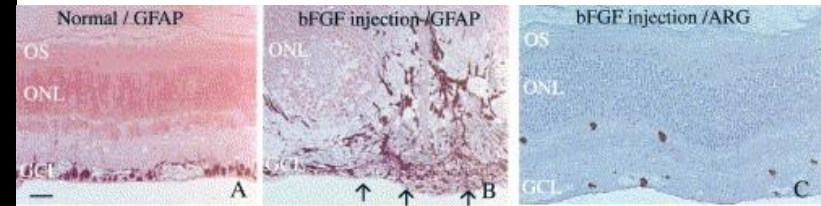


Antioxidants and Vitamins





Ciliary body Neutrophic Factor (CNTF)



Treatment of AMD CNV

DIFFICULT

RPE/PHOTORECEPTOR
HYPOXIA

Thalidomide
Interferon
Troglitazone
Antiangiogenic Ab

Gene Therapy

ANGIOGENESIS

BRUCH'S MEM
DISRUPTION

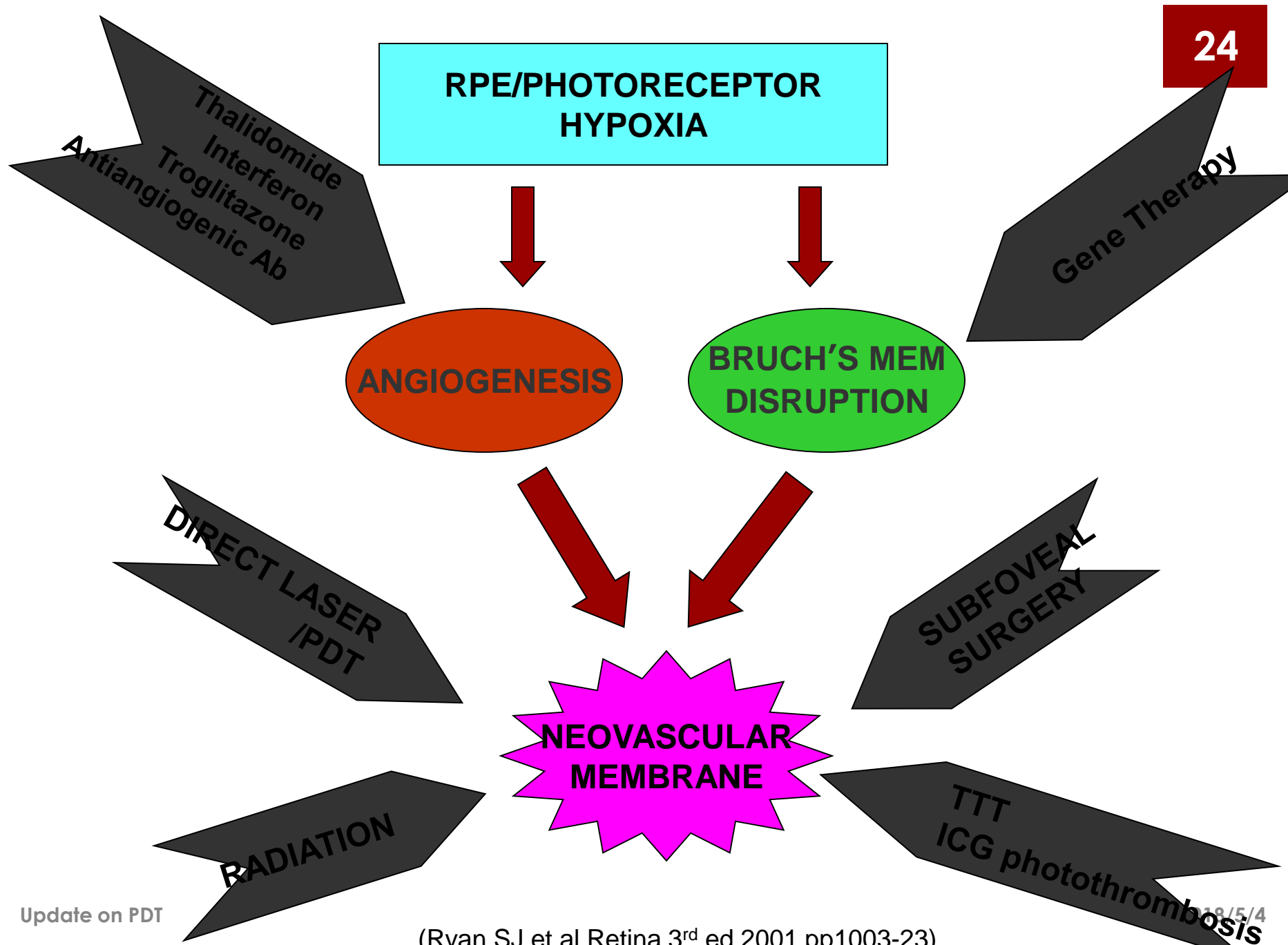
DIRECT LASER
/PDT

SUBFOVEAL
SURGERY

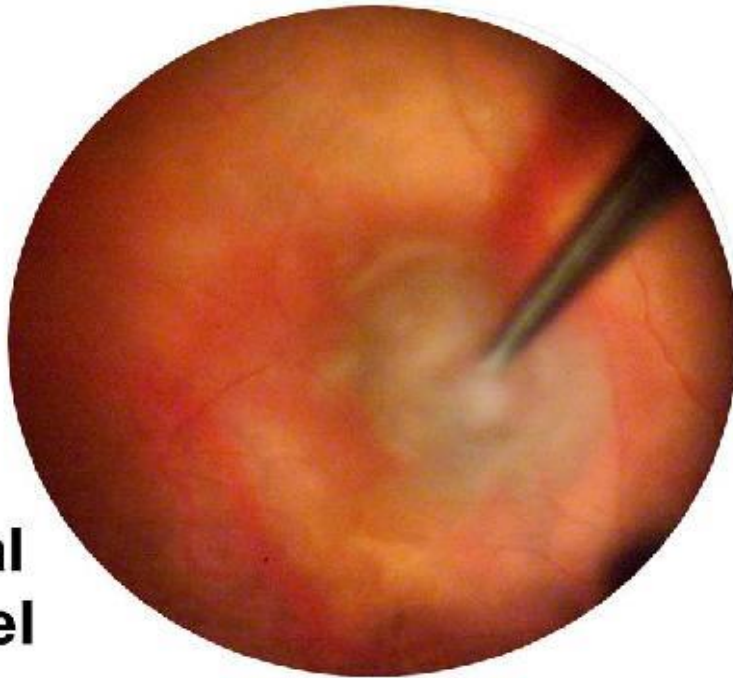
NEOVASCULAR
MEMBRANE

RADIATION

TTT
ICG photothrombosis



Subretinal Surgical Removal



**Removal
sub-retinal
new vessel
with forceps**

- Direct extraction of SR CNV membrane
- Disappointing postop result
 - Foveal atrophic scar [Gasutad et al J Fr Ophthalmol 1999](#)
 - 89% scotoma [TsujiKawa et al Retina 1999](#)

Macular Translocation

- Relocate fovea to new site with good RPEs
- Uncertain [Hamelin et al AJO 2002](#)
 - No RCT
 - Limited case reports
 - Steep learning curve
 - Possible severe complications



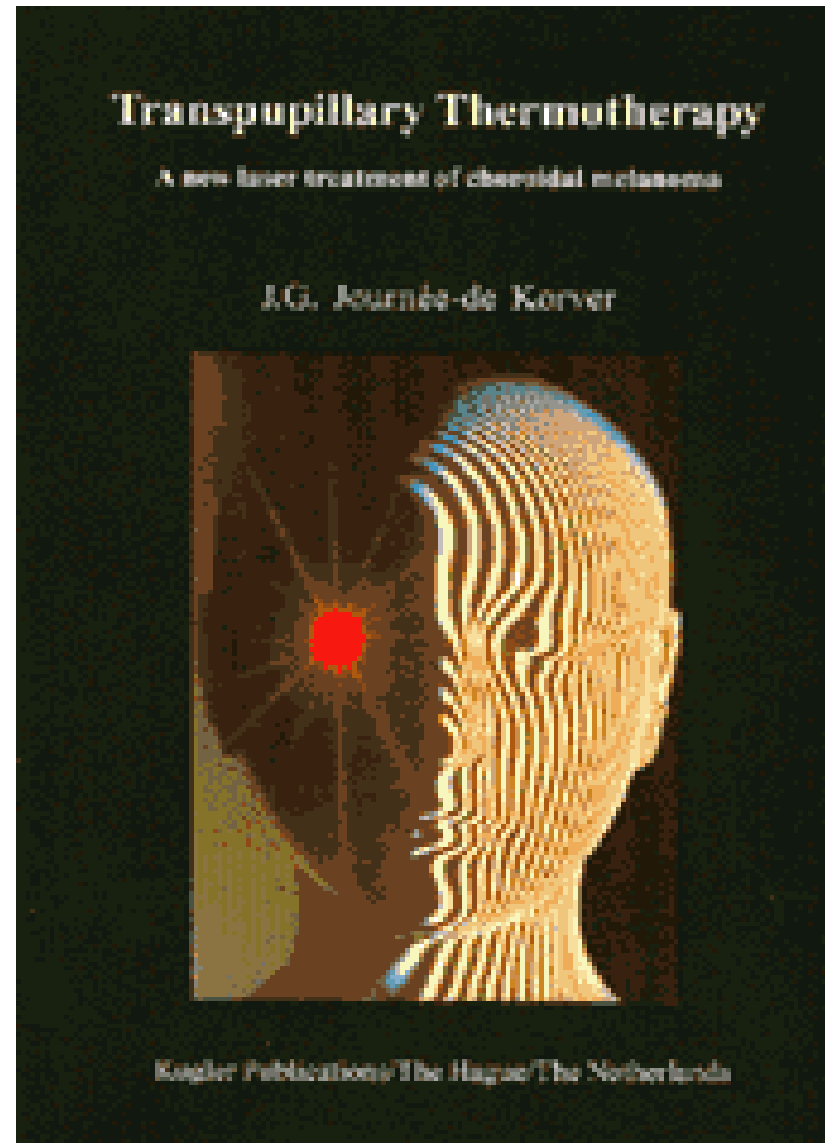
Ionizing Radiation Therapy



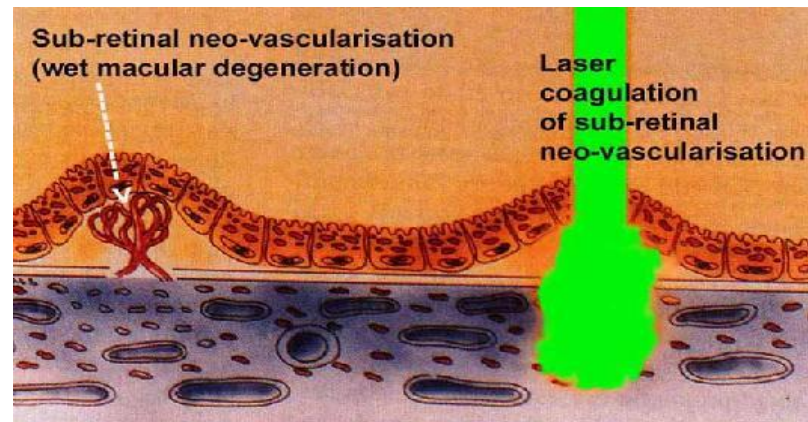
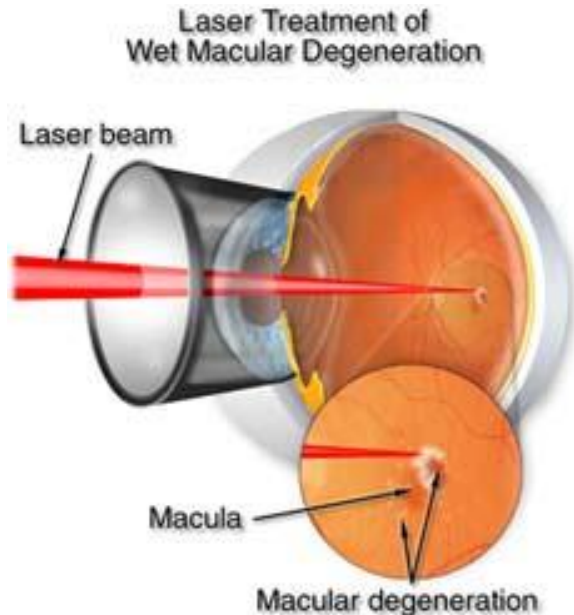
- In AMD_CNV
- Contradictory
 - Bergink et al *Greafes Arch Clin Ophthalmol* 1998, RAD study group
 - Ophthalmol* 1999

Transpupillary Thermotherapy (TTT)

- Infrared laser photocoagulation
- Mainster et al 2000:
 - Lower retinal temp rise (less 20 degree celsius)
- Treatment outcome varied [Piccolino Eur J Ophthalmol 2003](#)
 - Fundus pigmentation
 - Media clarity
- Under RCT evaluation

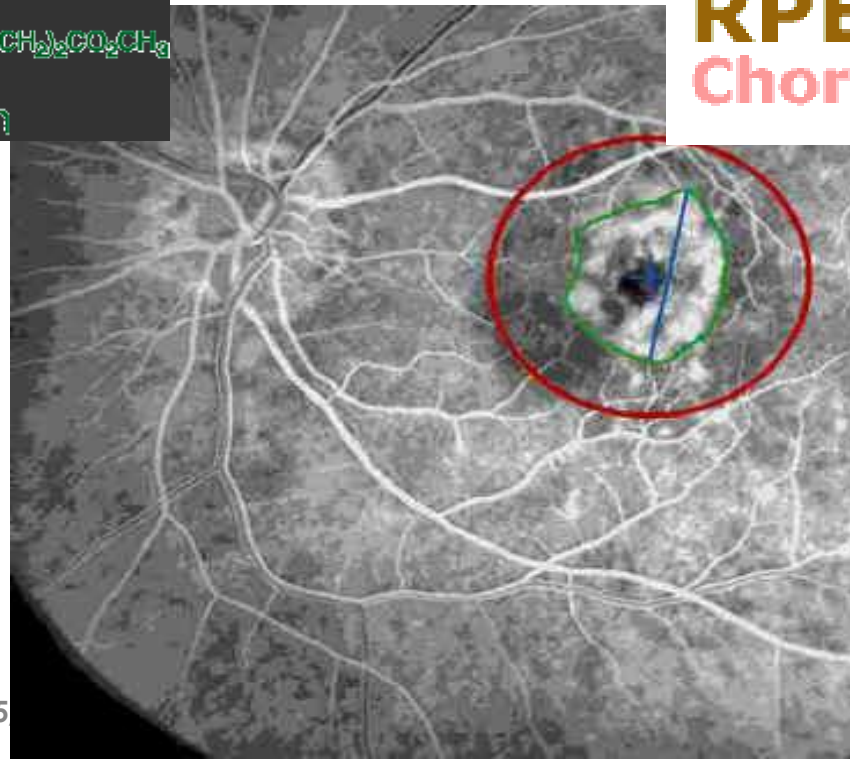
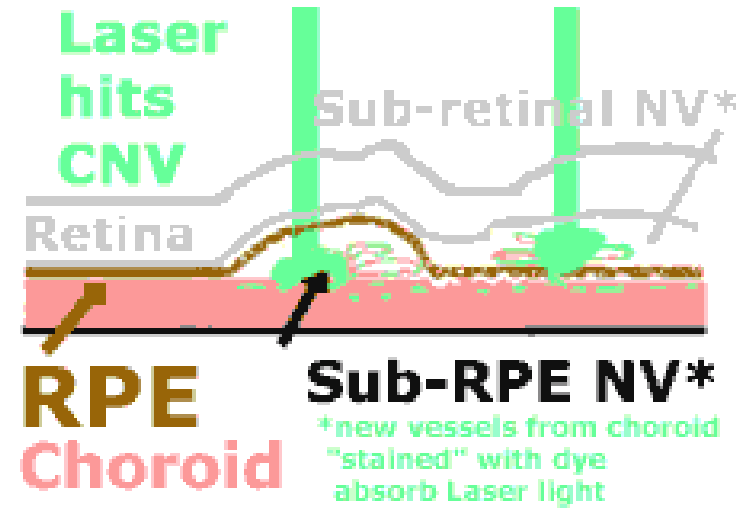
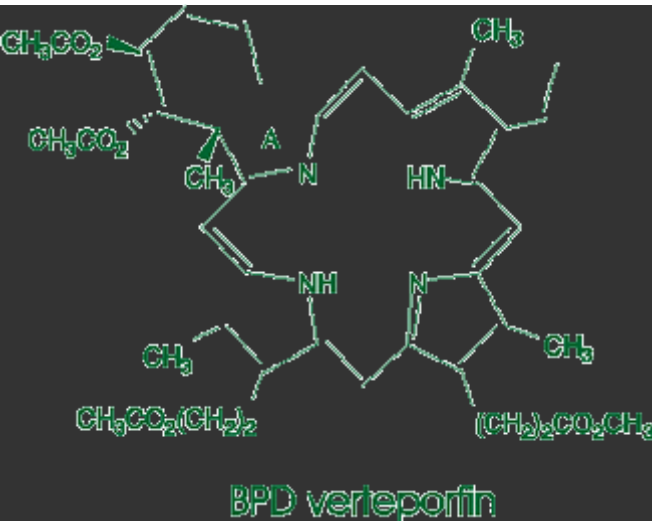


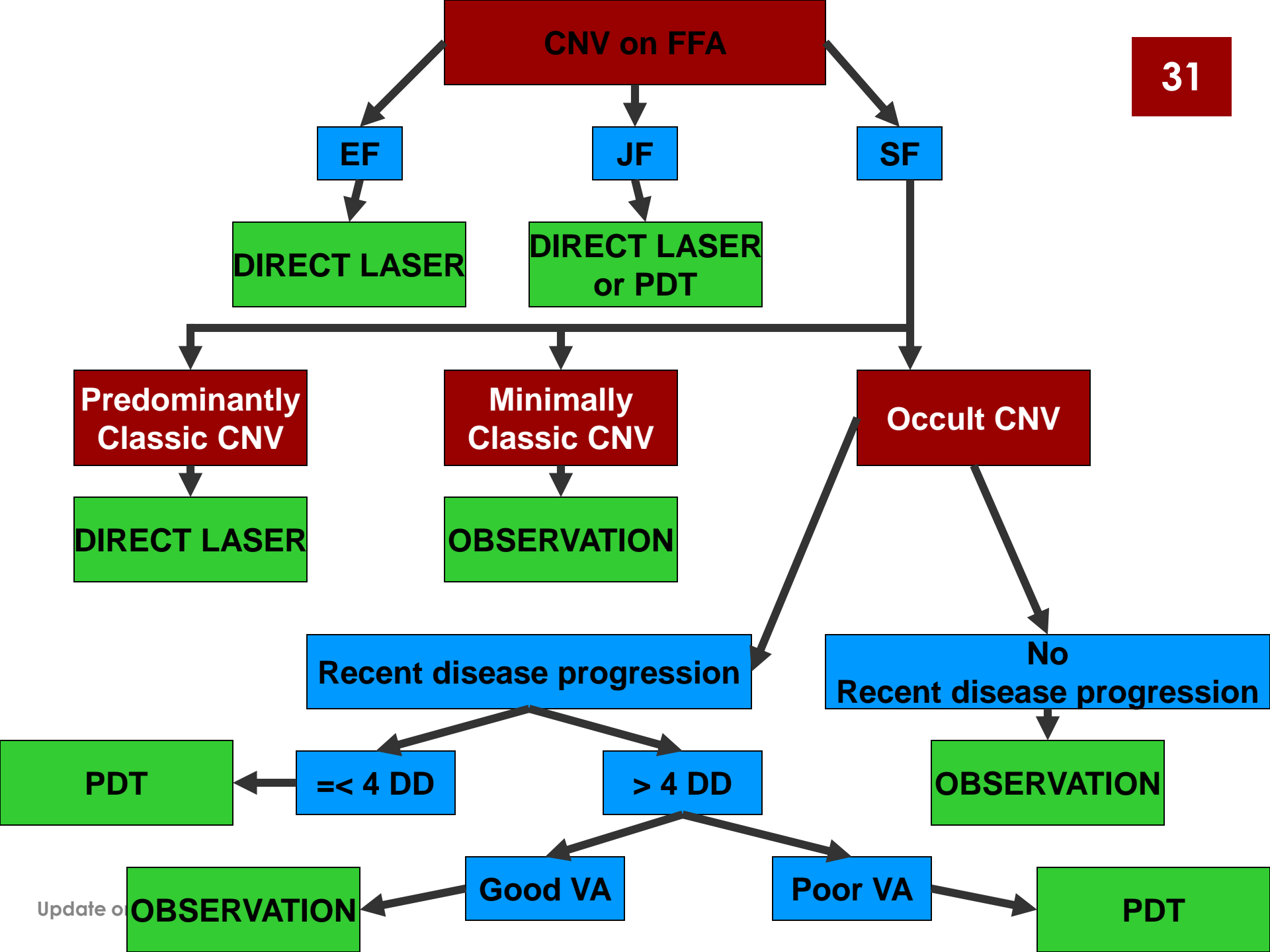
Direct Focal Laser



- Macular Photocoagulation Study (MPS)
 - Primary MPS outcome: severe visual loss (> 6 or more lines loss)
 - Modest treatment benefit

Photodynamic Therapy (PDT)



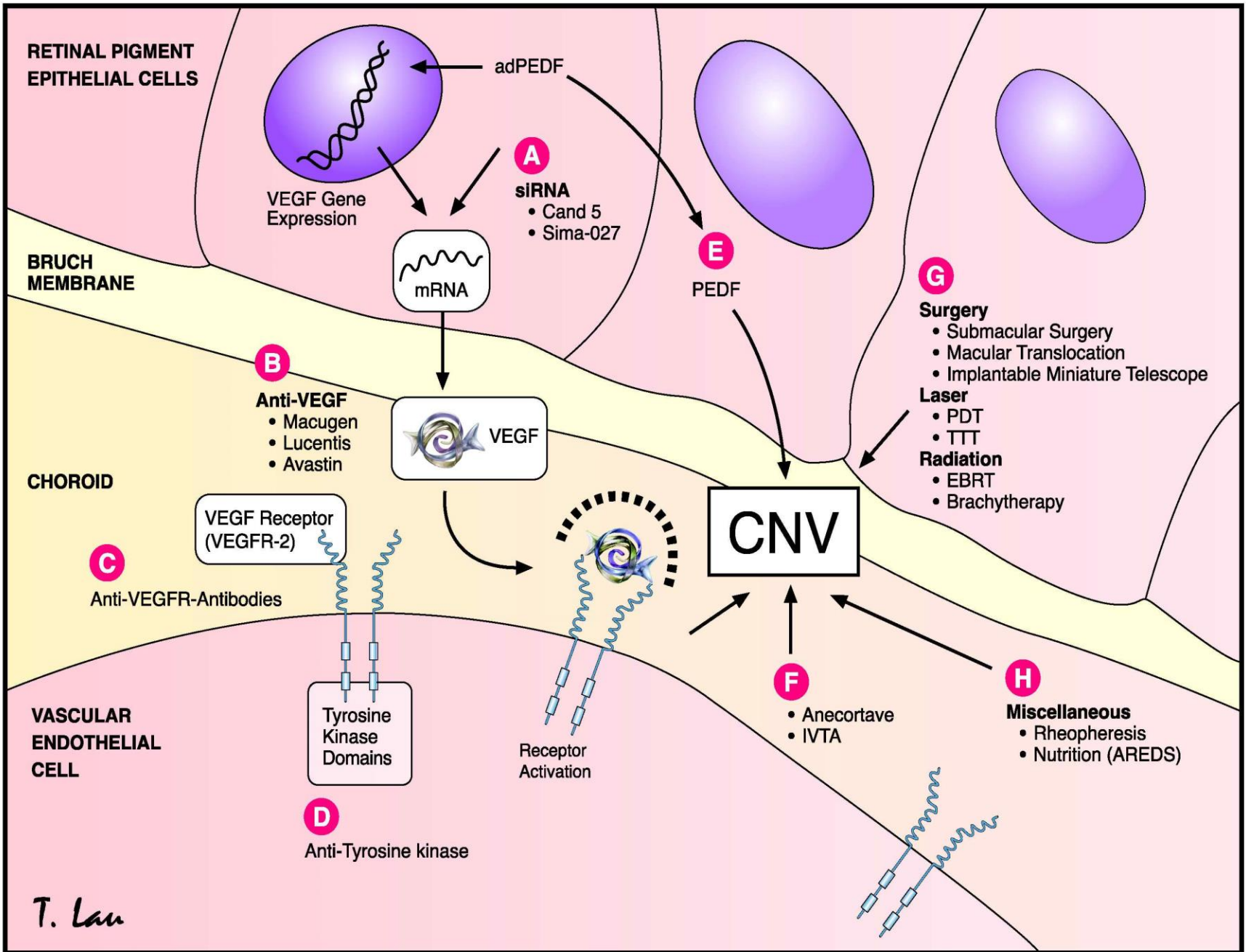


Intravitreal Injection of Drug









Key Studies (Lucentis for AMD)



Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Study Group*

ABSTRACT

BACKGROUND

Ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — has been evaluated for the treatment of neovascular age-related macular degeneration.

METHODS

In this multicenter, 2-year, double-blind, sham-controlled study, we randomly assigned patients with age-related macular degeneration with either minimally classic or occult (with no classic lesions) choroidal neovascularization to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

We enrolled 716 patients in the study. At 12 months, 94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections (P<0.001 for both comparisons). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group (P<0.001 for both doses). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group (P<0.001 for both comparisons). The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

CONCLUSIONS

Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration. (ClinicalTrials.gov number, NCT00056836.)

From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami (P.J.R.); Vitreous Consultants, Methodist Hospital, Houston (D.M.B.); Retina Associates Medical Group, Los Angeles (D.S.B.); the Cole Eye Institute, Cleveland Clinic Foundation, Cleveland (P.K.K.); Ophthalmic Consultants of Boston, Boston (J.S.H.); and Genentech, South San Francisco, CA (C.Y.C., R.Y.K.). Address reprint requests to Dr. Rosenfeld at the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami Miller School of Medicine, 900 NW 17th St., Miami, FL 33136, or at prosenf@med.miami.edu.

*Principal investigators in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1419-31.
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ORIGINAL ARTICLE

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D., for the ANCHOR Study Group*

ABSTRACT

BACKGROUND

We compared ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — with photodynamic therapy with verteporfin in the treatment of predominantly classic neovascular age-related macular degeneration.

METHODS

During the first year of this 2-year, multicenter, double-blind study, we randomly assigned patients in a 1:1:1 ratio to receive monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

Of the 423 patients enrolled, 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost fewer than 15 letters, as compared with 64.3% of those given the verteporfin group (P<0.001 for each comparison). Visual acuity improved by 15 letters or more in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group (P<0.001 for each comparison). Mean acuity increased by 8.9 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group, as compared with a decrease of 9.5 letters in the verteporfin group (P<0.001 for both comparisons). Among 140 patients treated with 0.5 mg of ranibizumab, presumed endophthalmitis occurred in 2 patients (1.4%) and serious uveitis in 1 (0.7%).

CONCLUSIONS

Ranibizumab was superior to verteporfin as intravitreal therapy for predominantly classic neovascular age-related macular degeneration, with low rates of serious ocular adverse events. Treatment improved visual acuity on average 11.3 letters (ClinicalTrials.gov number, NCT00061594.)

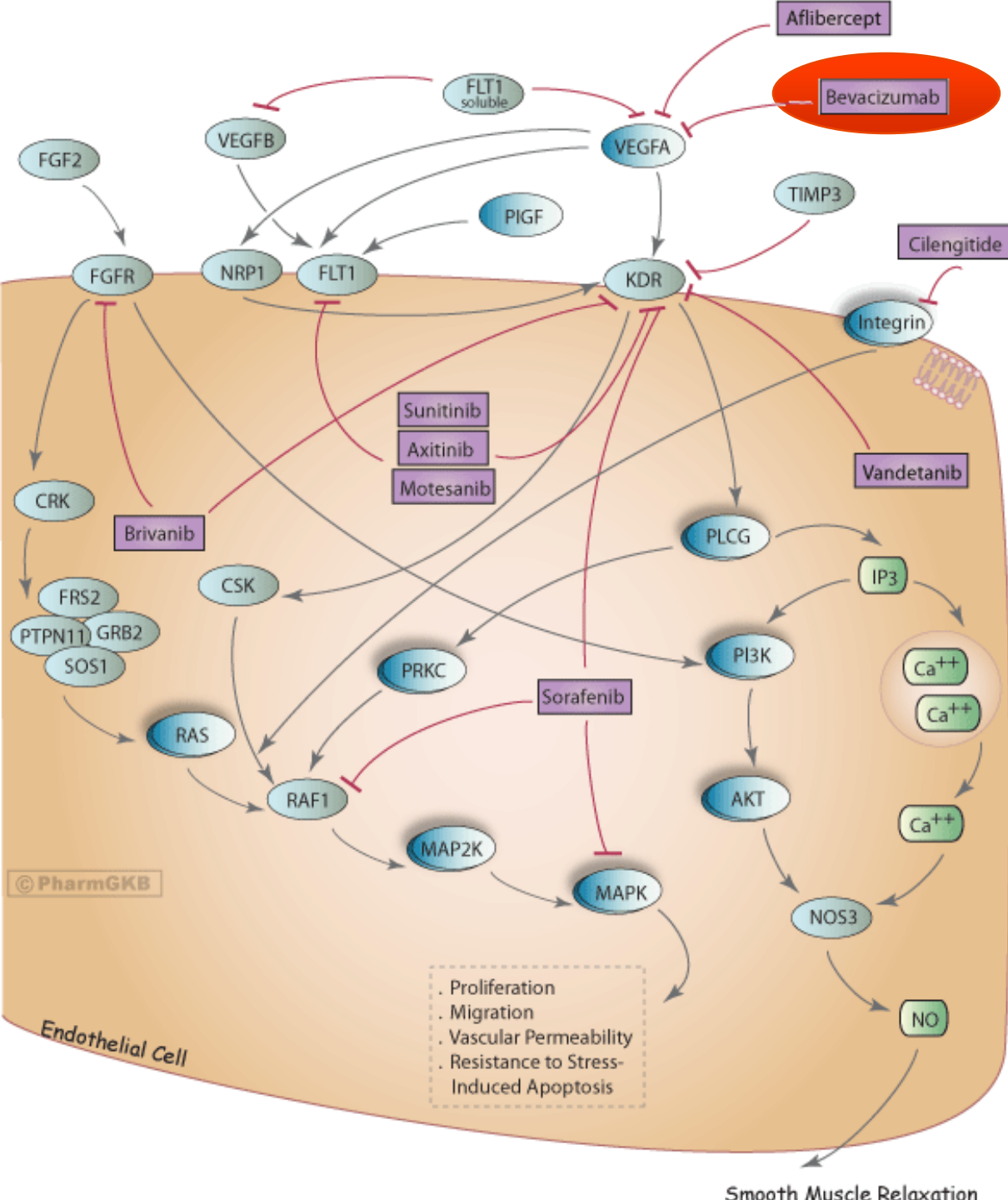
From Vitreoretinal Consultants, Methodist Hospital, Houston (D.M.B.); the Cole Eye Institute, Cleveland Clinic Foundation, Cleveland (P.K.K.); Retina Care Specialists, Palm Beach Gardens, FL (M.M.); the Clinique d'Ophthalmologie, University of Paris XII, Créteil, France (G.S.); Ophthalmic Consultants of Boston, Boston (J.S.H.); and Genentech, South San Francisco, CA (R.Y.K., J.P.S.). Address reprint requests to Dr. Brown at Vitreoretinal Consultants, 6560 Farris St., Suite 750, Houston, TX 77030, or at dmdbmd@houstonmethodist.com.

*Principal investigators in the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (ANCHOR) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1432-44.
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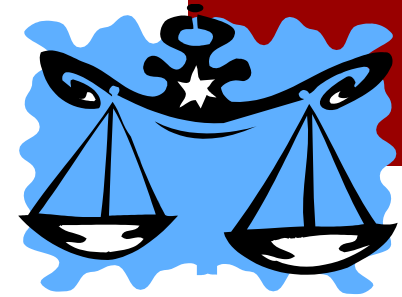
Lucentis= Liquid-Gold ?





Off-label use of Avastin





Is Avastin equal to Lucentis in terms of

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group*

ABSTRACT

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm , $P=0.03$ by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab ($P>0.20$). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.)

The members of the writing committee (Daniel F. Martin, M.D., Cleveland Clinic Cole Eye Institute, Cleveland; Maureen G. Maguire, Ph.D., Gui-shuang Ying, Ph.D., and Juan E. Grunwald, M.D., University of Pennsylvania, Philadelphia; Stuart L. Rina, M.D., University of Colorado Denver, Aurora; and Glenn J. Jaffe, M.D., Duke University, Durham, NC) assume responsibility for the integrity of the article. Address reprint requests to Dr. Maguire at the Scheie Eye Institute, University of Pennsylvania, 3535 Market St., Suite 700, Philadelphia, PA 19104, or at maguirem@mail.med.upenn.edu.

*The members of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) research group are listed in the Supplementary Appendix, available at nejm.org.

This article (10.1056/NEJMoa1102673) was published on April 28, 2011, at nejm.org.

N Engl J Med 2011;364:1897-908.
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CATT Study

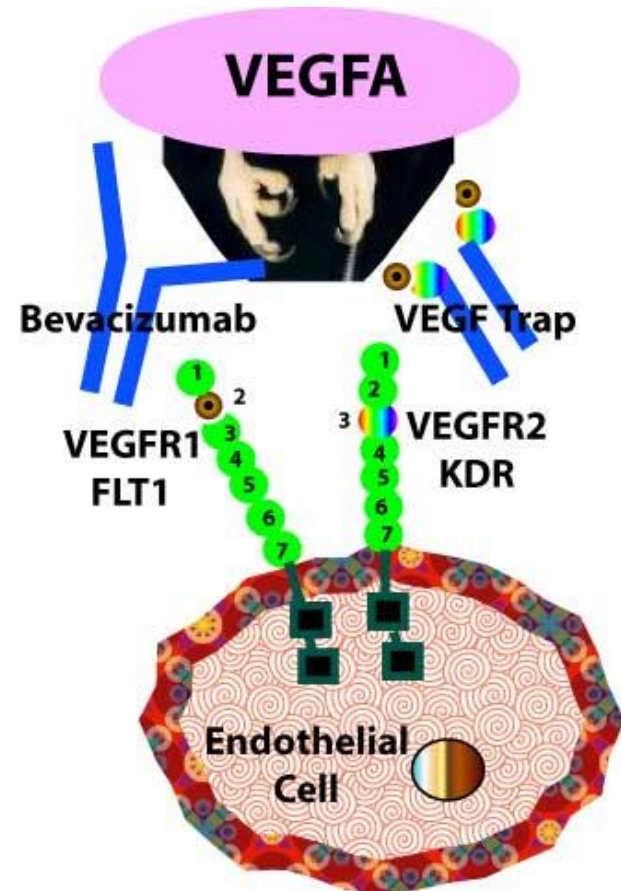
1208 patients

Avastin \approx Lucentis

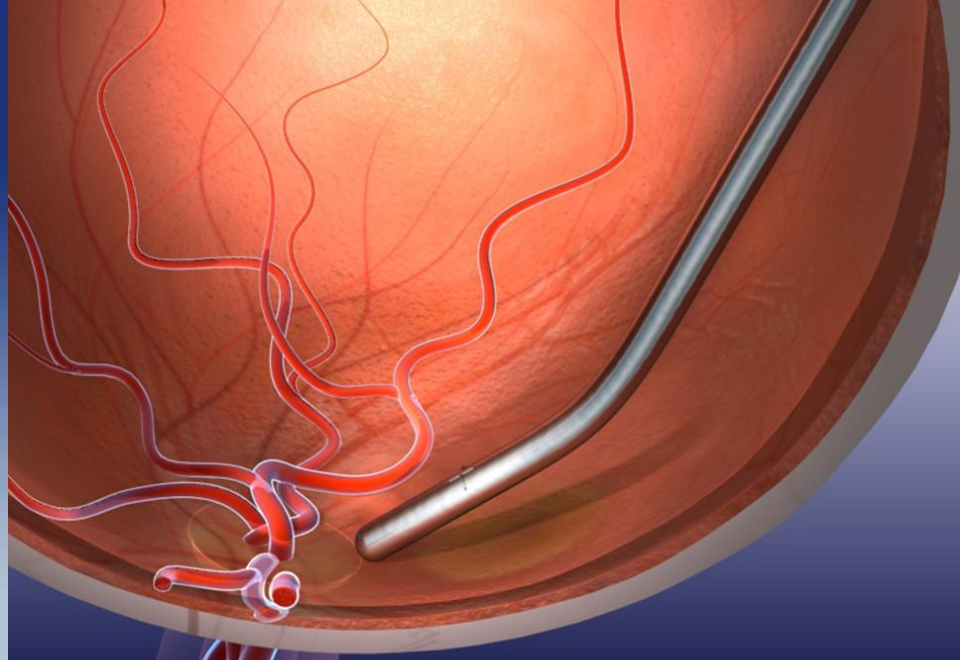
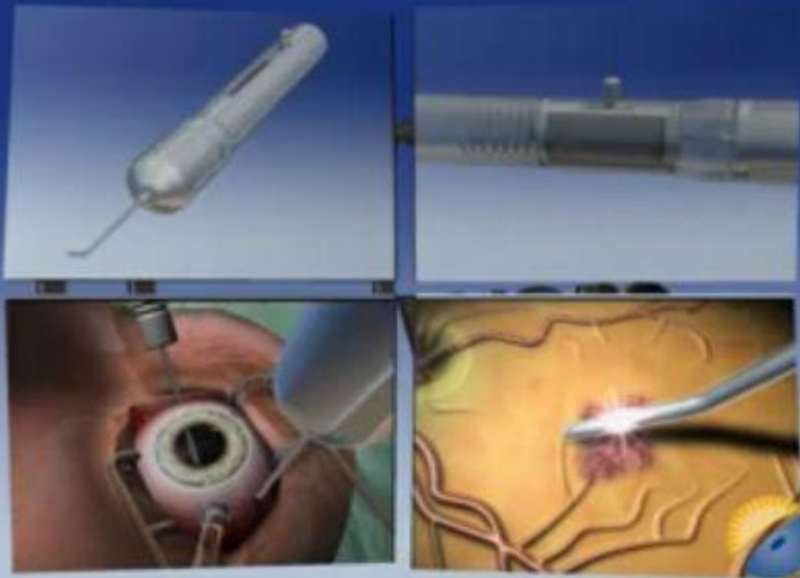
? Difference in SAE

VEGF trap- aflibercept

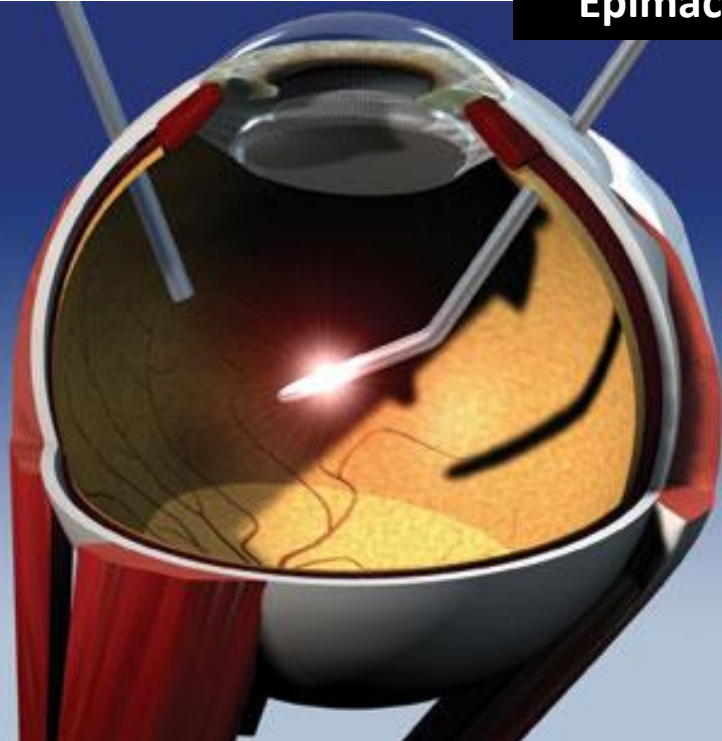
- Fusion protein incorporates the second binding domain of VEGFR-1 receptor and the third domain of VEGFR-2 to the Fc portion of IgG
- Chimeric protein/ fusion protein with higher binding affinity
- Offering a longer interval between doses



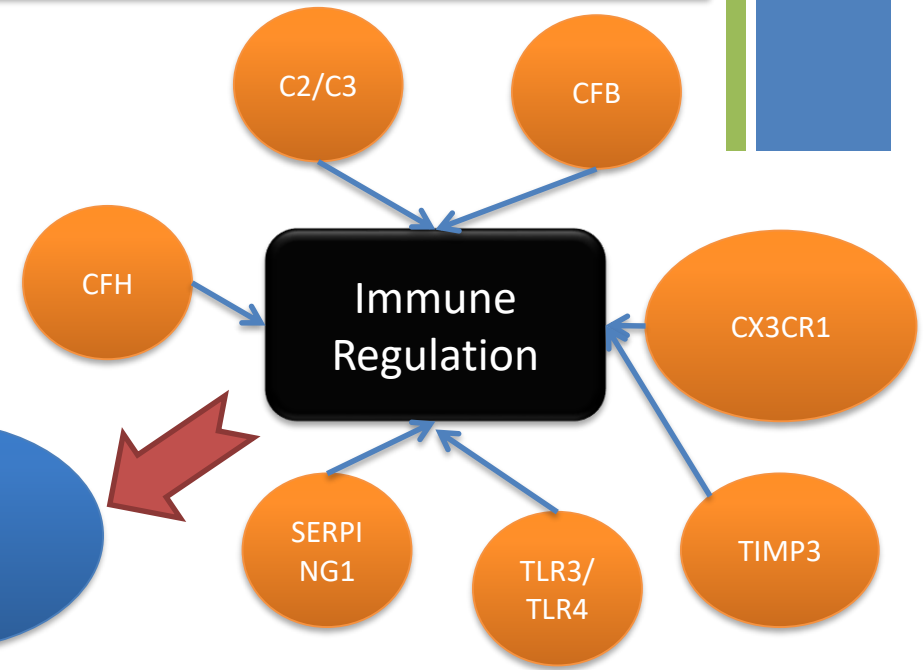
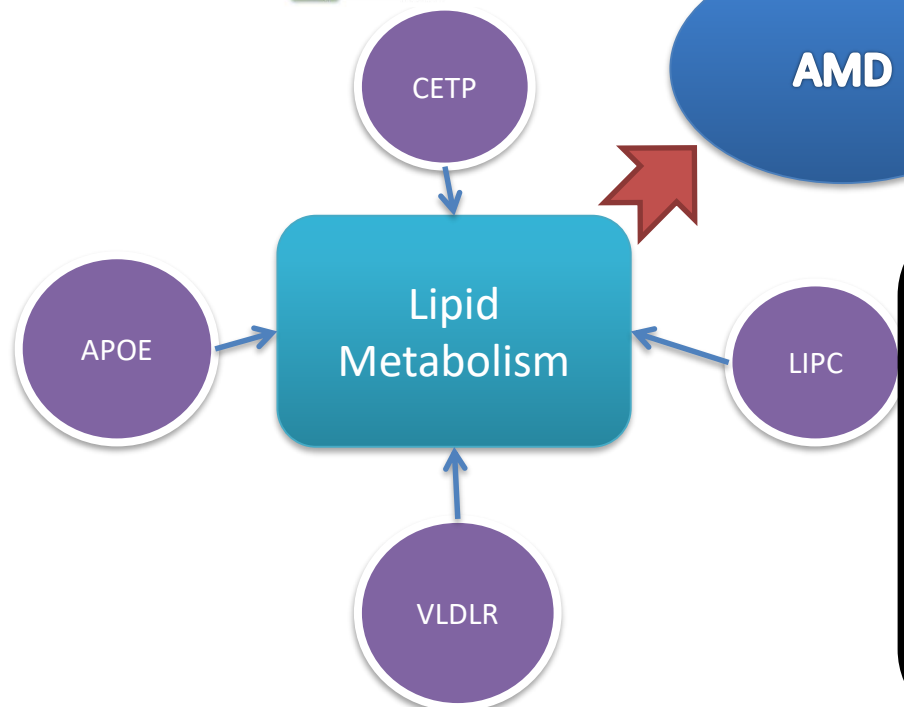
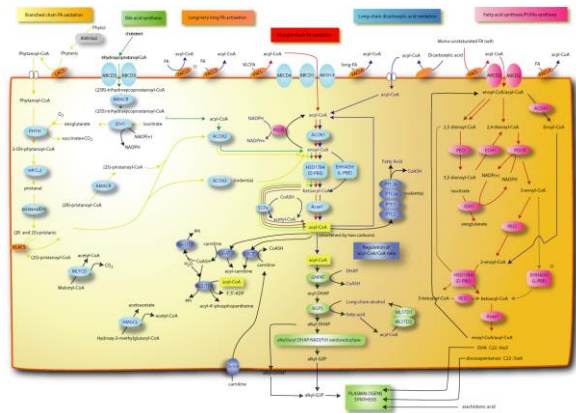
VEGF A- isoform of VEGF can be blocked by bevacizumab



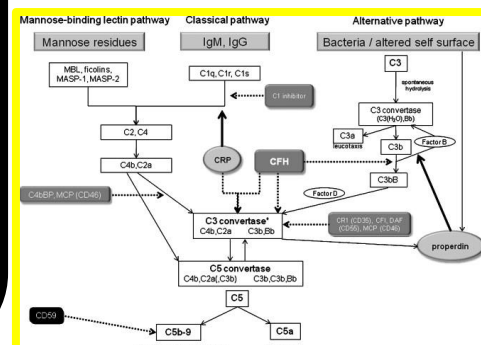
Epimacular Brachytherapy



How genetics improve understanding of AMD pathophysiology ?



- Immune proteins ,complement and lipid in drusen
- Elevated serum complement level in AMD
- Raised C-reactive protein levels in AMD
- Increased CRP showing additive effect on risk of AMD progression if combined with CFH polymorphisms



AMD Pathophysiology

- AMD Pathophysiology
 - Lipid metabolism dysregulation
 - Innate immune system (complement or toll-like receptor) dysregulation

Genetics & Treatment (Pharmacogenetics)¹

- The study of the effects of certain target genetic mutations on response to treatment
- Anti-VEGFs
 - CFH and ARMS2: suboptimal response
- PDT
 - Prothrombin 20210A and factor V 1691A alleles: better response
- Dry AMD
 - CFH: decreased effect of antioxidant therapy

Proteomics ¹

- Study of the molecular phenotype produced by a particular genotype
- Molecular chaperones
- Putative biomarkers for AMD
 - ? Plasma carboxyethylpyrrole (CEP) oxidative protein level
 - ? CEP autoantibody level

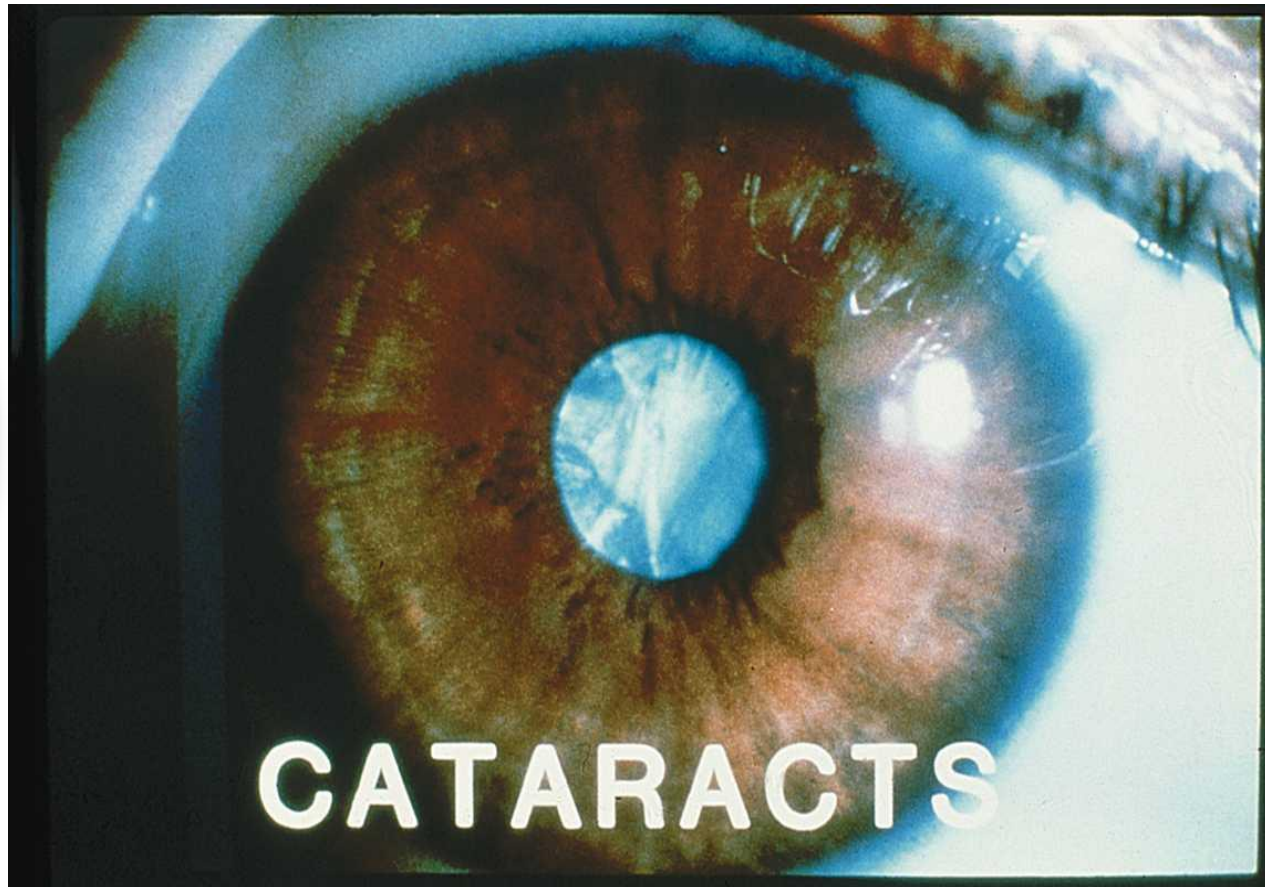
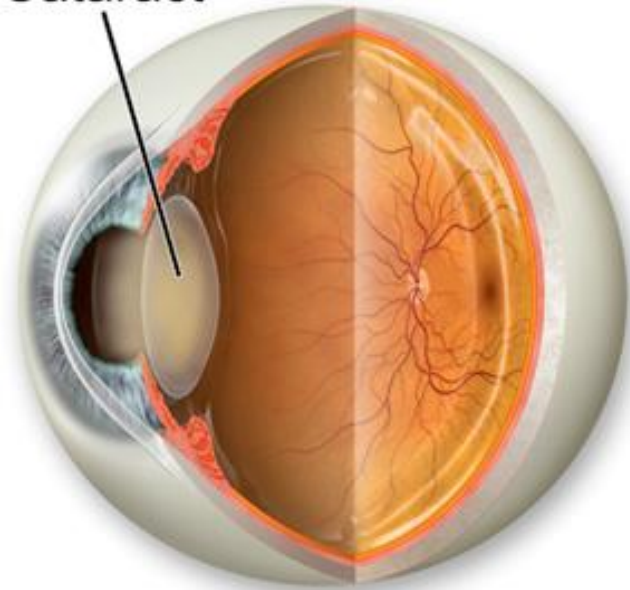
Take Home Message 1

- AMD is the leading cause of irreversible blindness in developed countries. 老年黃斑退化症在發達國家是不可逆失明的主要原因.
- Some visual complaints like distorted central vision necessitate prompt referral to an ophthalmologist. 如果病人發現一些症狀如中央視像扭曲等，必須及時轉診到眼科醫生.
- Anti-VEGF (intravitreal injection) and other upcoming treatments (VEGF trap) are quite promising especially if the disease is tackled at an early stage. 玻璃體內注射抗血管內皮生長因子 (Anti-VEGF) 和其他即將上市的治療如VEGF trap，是相當有前途，特別是如果在疾病早期階段使用.

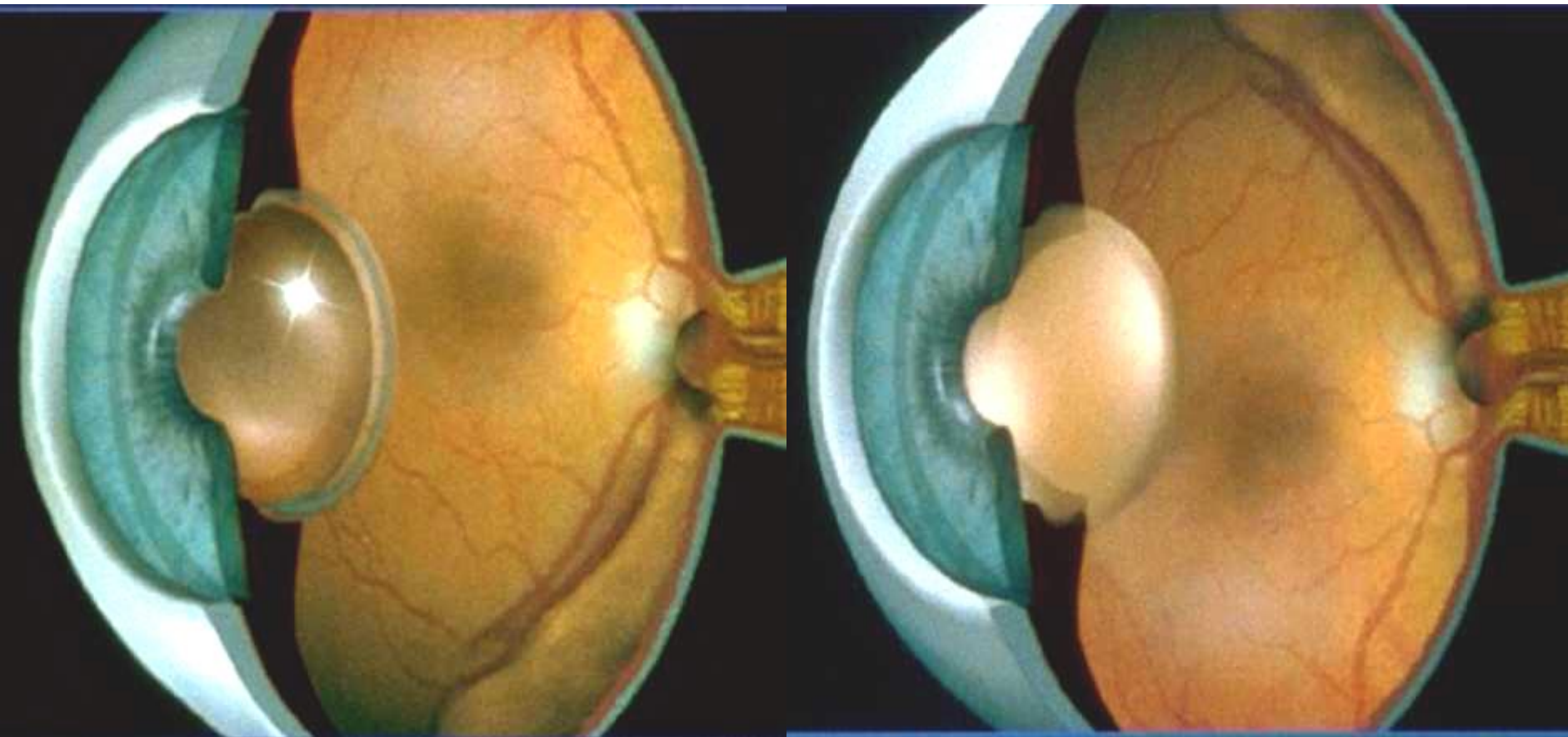
Cataract 白內障

- Due to opacification of the lens (晶體混濁)

Cataract



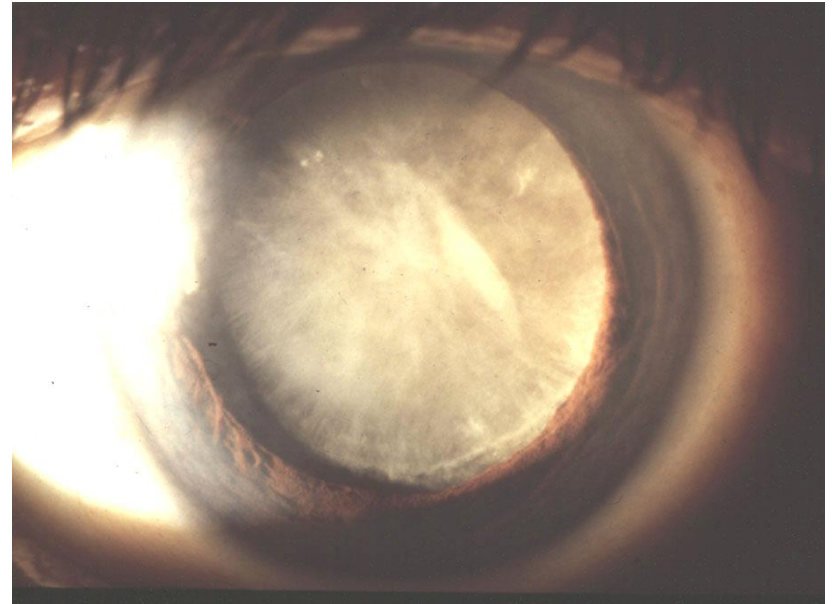
Cataract 白內障



Cataract 白內障

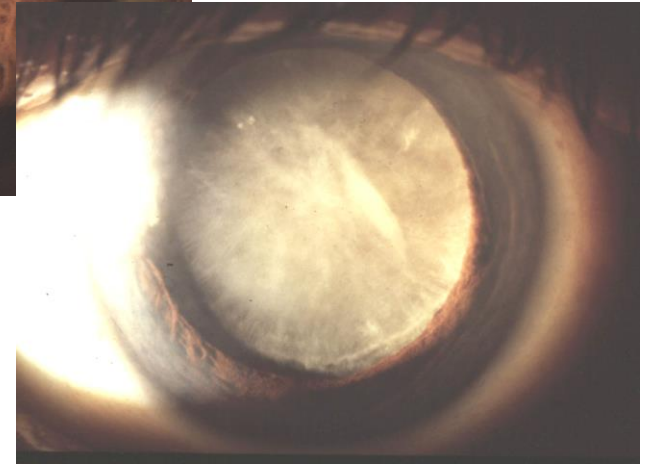
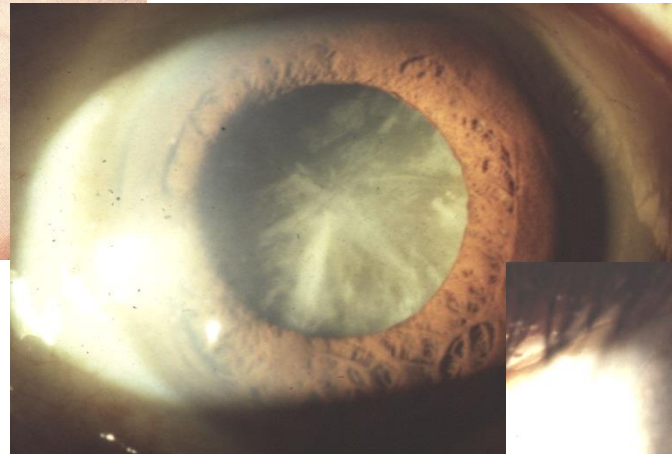
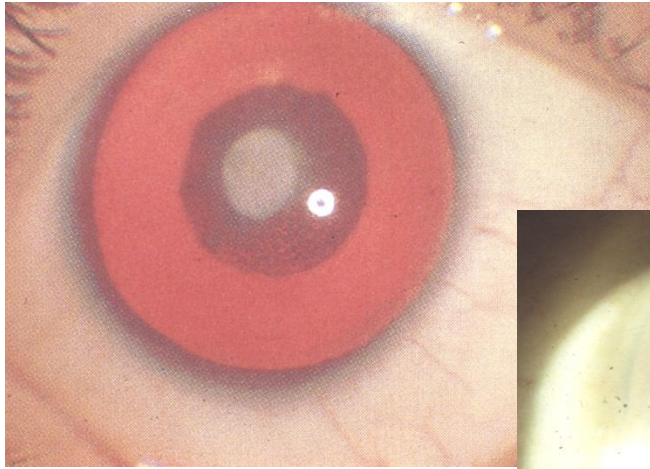
Classification 類別

- Severity 嚴重程度
- Location 部位
- Causes 成因



Cataract 白內障

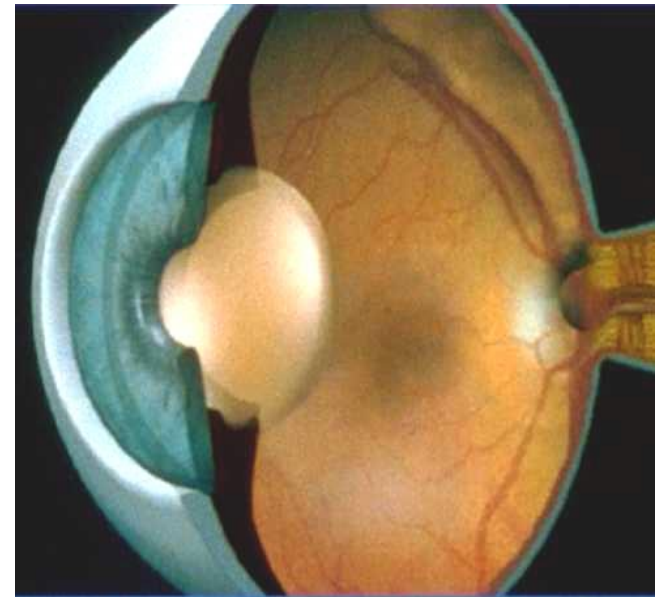
Severity 嚴重程度



Cataract 白內障

Causes of cataract 成因

- Congenital 先天性
- Traumatic 創傷性
- Senile 高齡所致
- Drug induce 藥物所致
- Diabetes 糖尿病
- Others 其它.....



Cataract 白內障

- Congenital Cataract
先天性白內障



Cataract 白內障

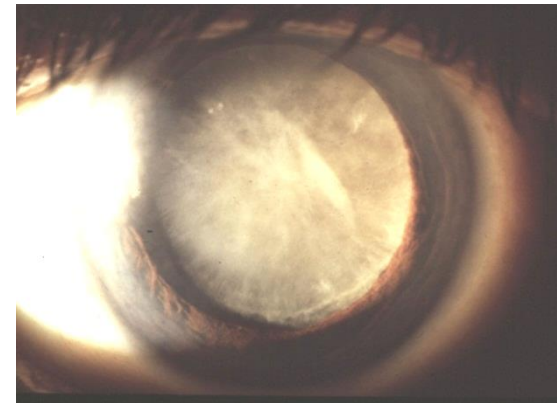
- Secondary Cataract
二次白內障



Cataract 白內障

A major problem in Hong Kong

- Growing population 人口增長
- Longevity 長壽
- Aging population 人口老化



Cataract 白內障

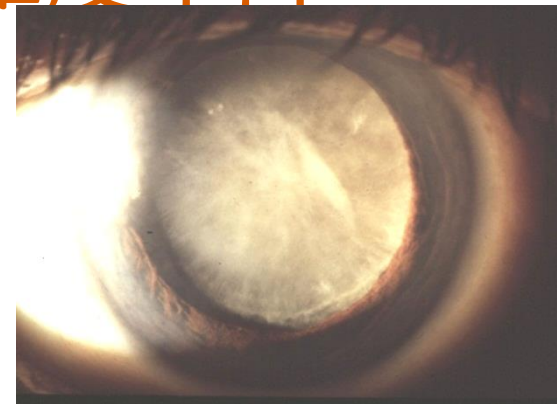
- Commonest eye problem in the elderly

長者最常患之眼疾



Symptoms 徵狀

- Blurring of vision 視力模糊
- Glare 眩光
- Diplopia 重影
- ↓ Color saturation 顏色飽和度下降
- Second sight 再生視力



Symptoms 徵狀

Normal 正常



Cataract 白內障



Cataract 白內障

- Blurring of Vision 視力模糊



Cataract 白內障

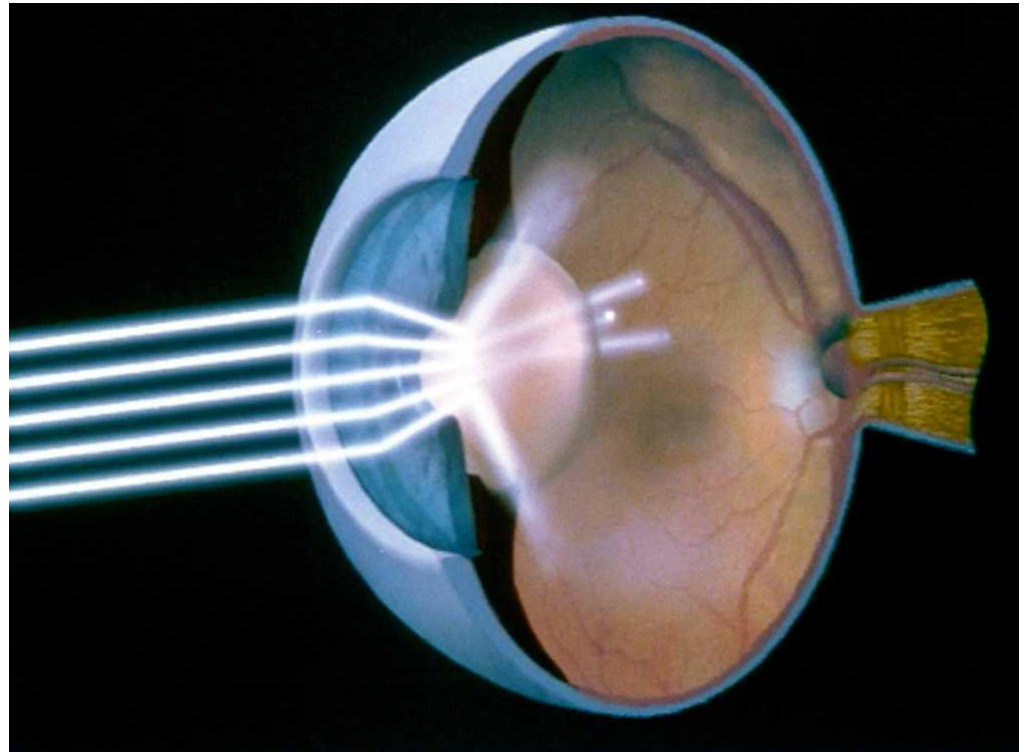
- Decrease color saturation 顏色飽和度下降



Cataract 白內障

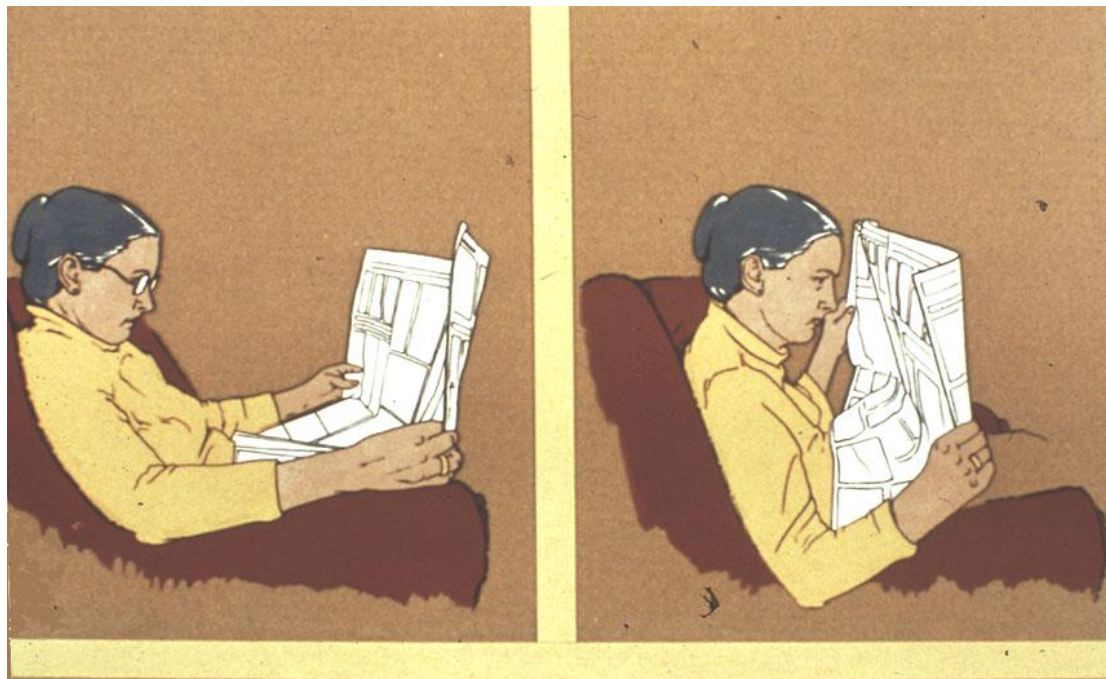
■ Glare 眩光

(Due to light scatter 由光線分散所致)



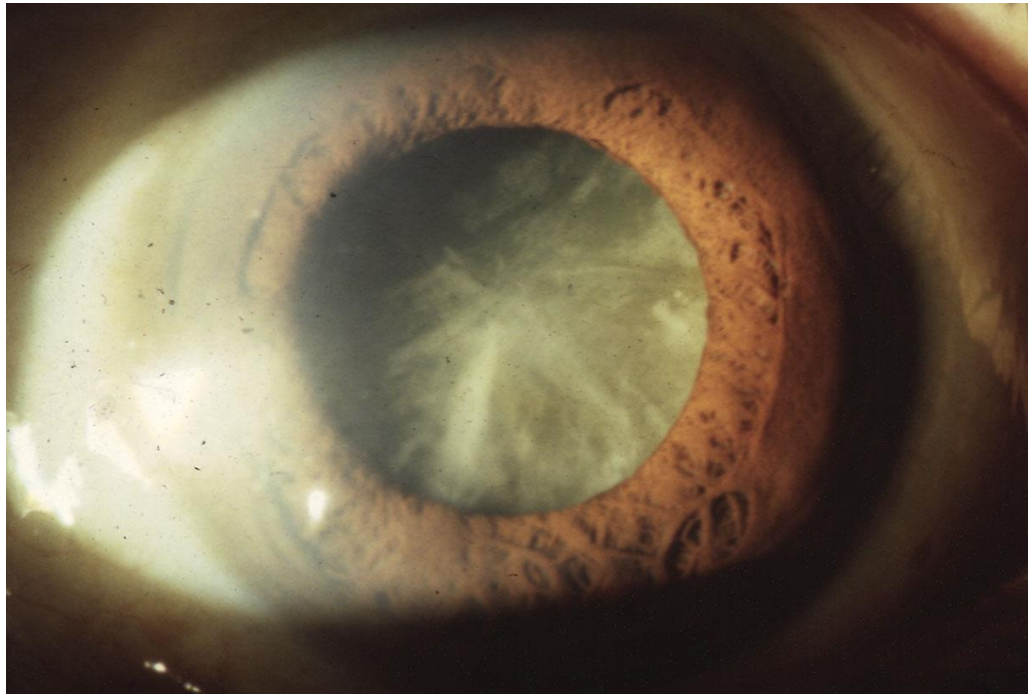
Cataract 白內障

- **Second Sight 再生視力**



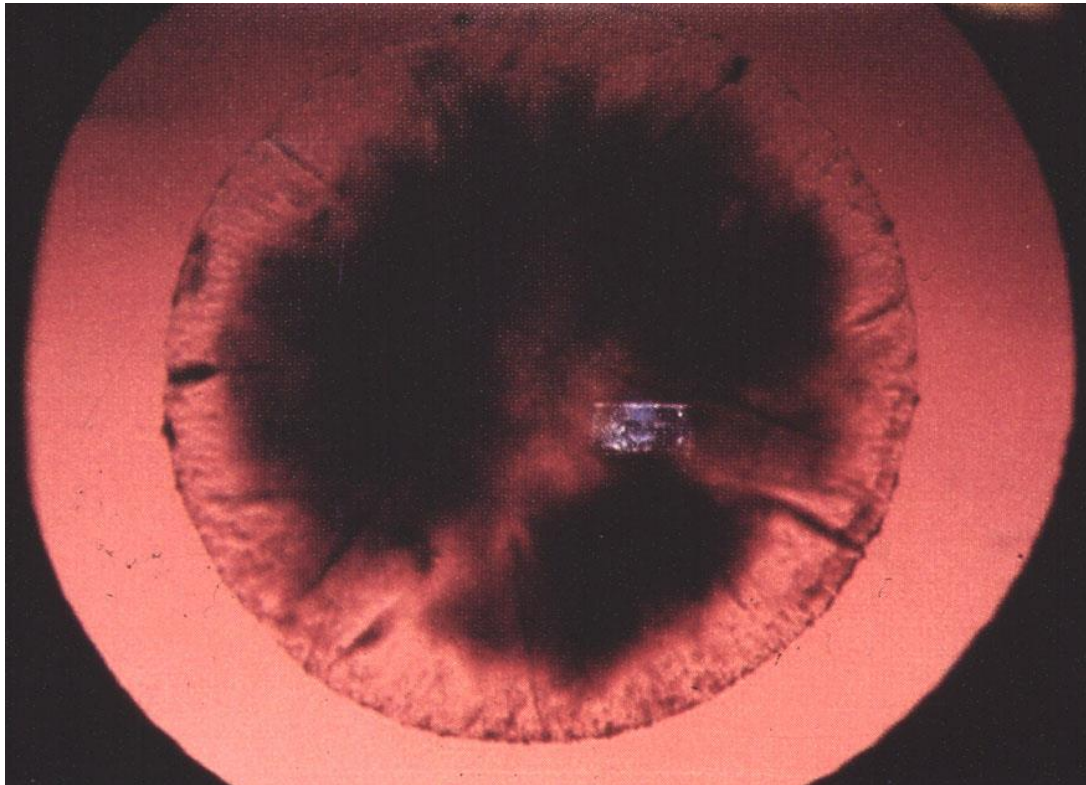
Clinical Feature 臨床特徵

Cataract 白內障



Clinical Feature 臨床特徵

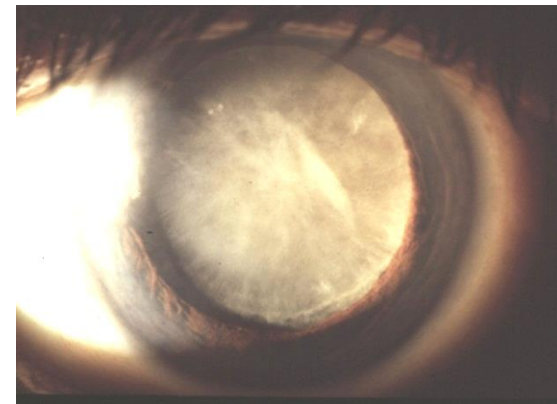
- Loss in Red Reflex 視網膜紅反射



Cataract 白內障

Treatment 治療

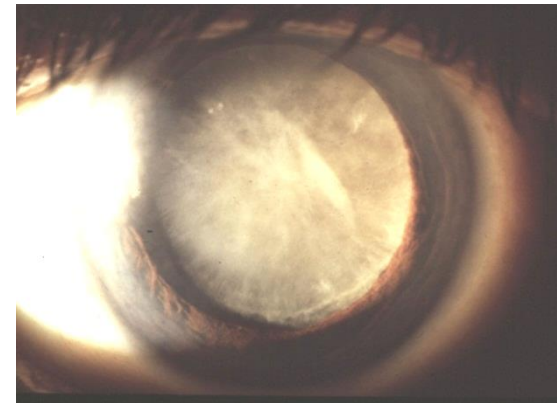
- Observation 觀察?
- Medication 藥物?
- Laser 激光?
- Operation 手術?



Cataract 白內障

Treatment

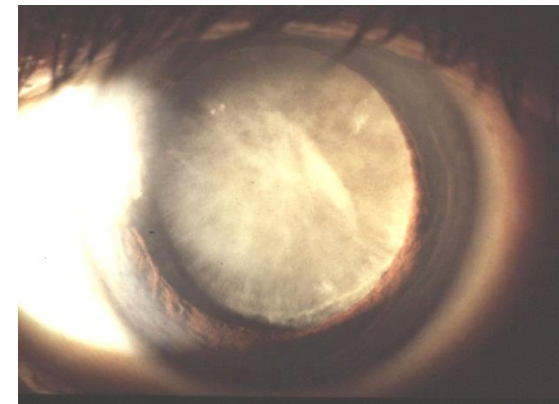
- **Observation 觀察? ✓**
 - For mild cases that visual disturbances do not affect work or daily living
適用於視力受阻不影響工作及日常生活的輕微情況



Cataract 白內障

Treatment

- ~~Medications 藥物~~
- Laser 激光治療
 - X / ✓
 - Not for primary treatment
非首選治療方案



Cataract 白內障

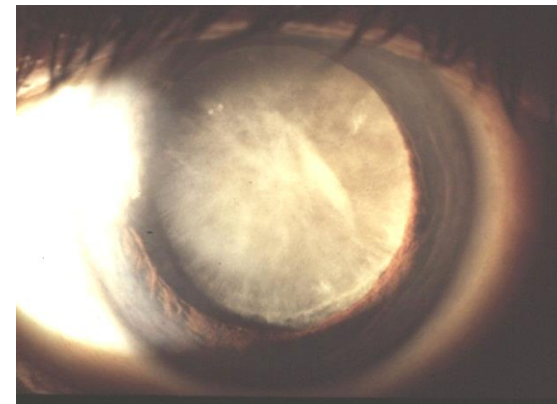
Treatment

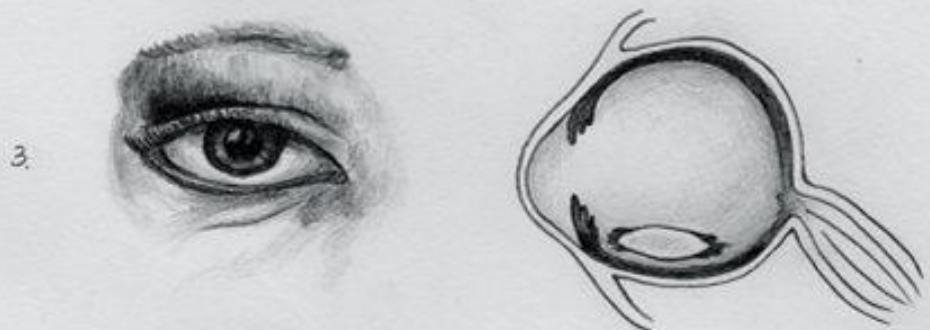
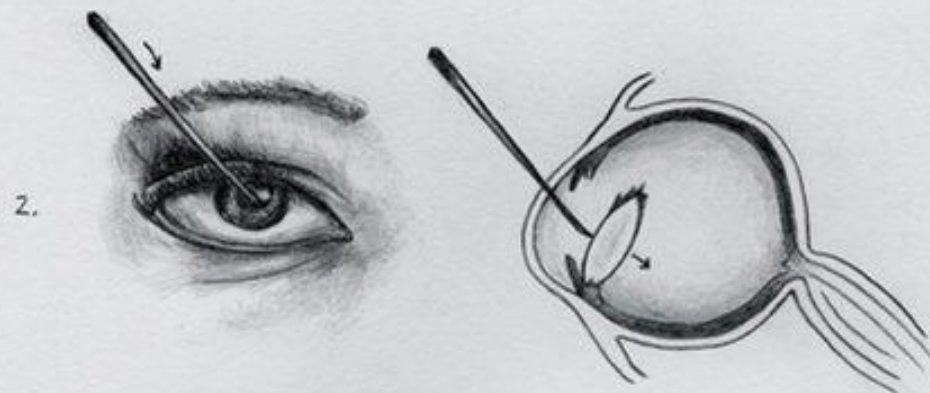
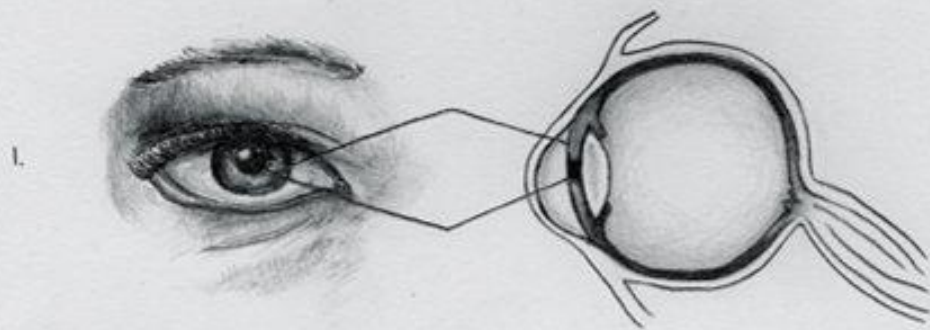
- Operation 手術?



- Only when mature
否待白內障熟透才可做???

是





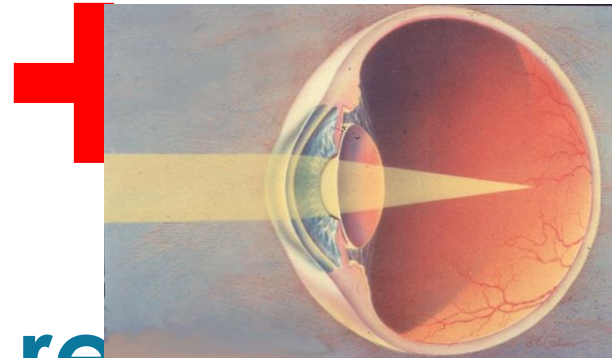
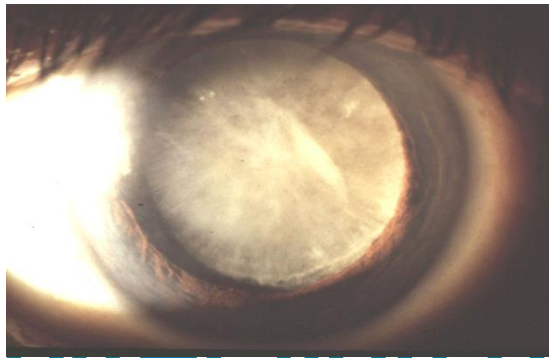
Couching

金針撥障



Treatment 治療

- Removal of the cataract lens
移除白內障晶體



- Correction of refractive error
矯正屈光不正 (+10D = 1,000 度)

Treatment 治療

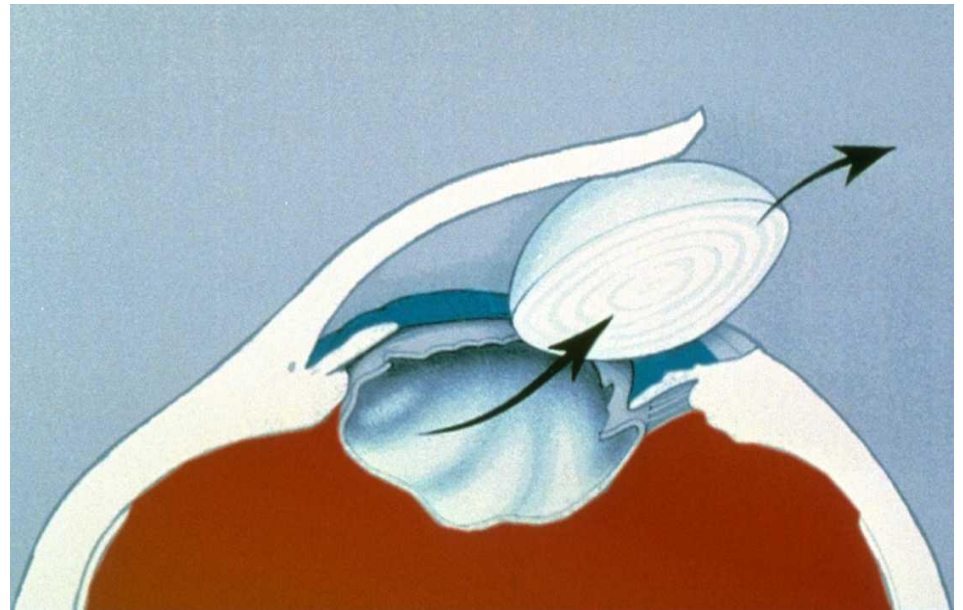
- Extracapsular Cataract Extraction (ECCE) 囊外摘除



Cataract 白內障

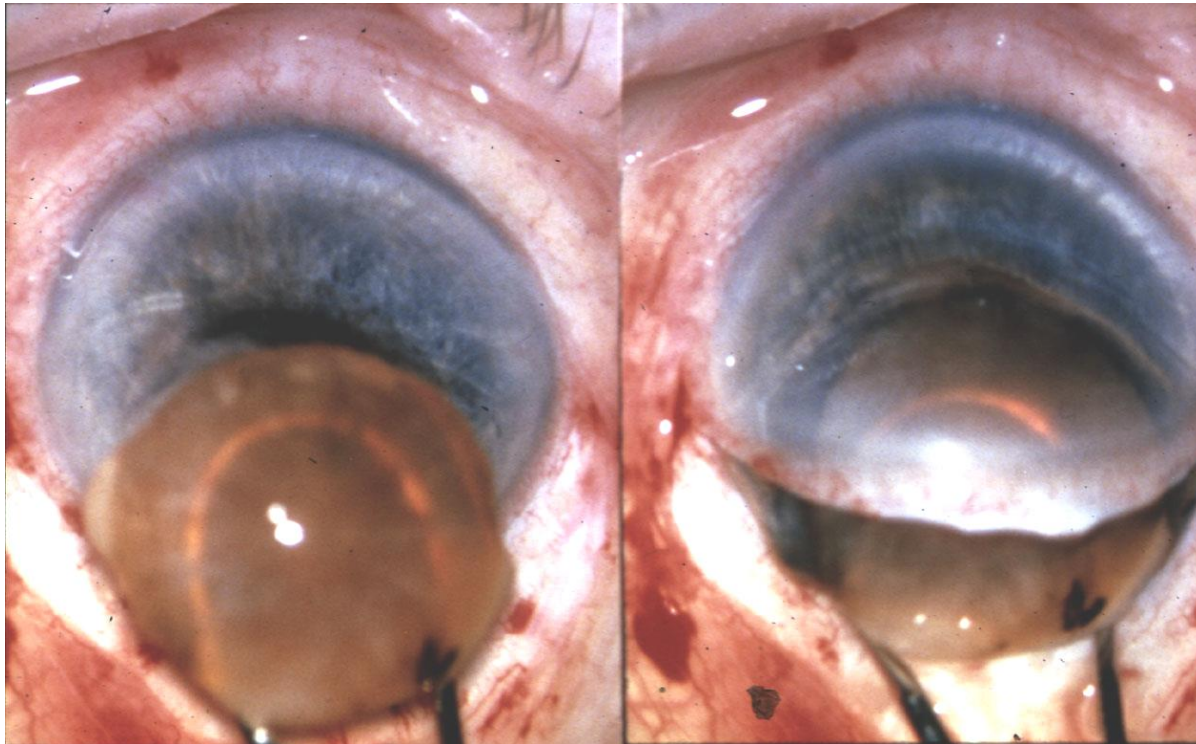
ECCE 囊外摘除

- **Larger Wound** 傷口較大
- **Require Suture** 需要縫線



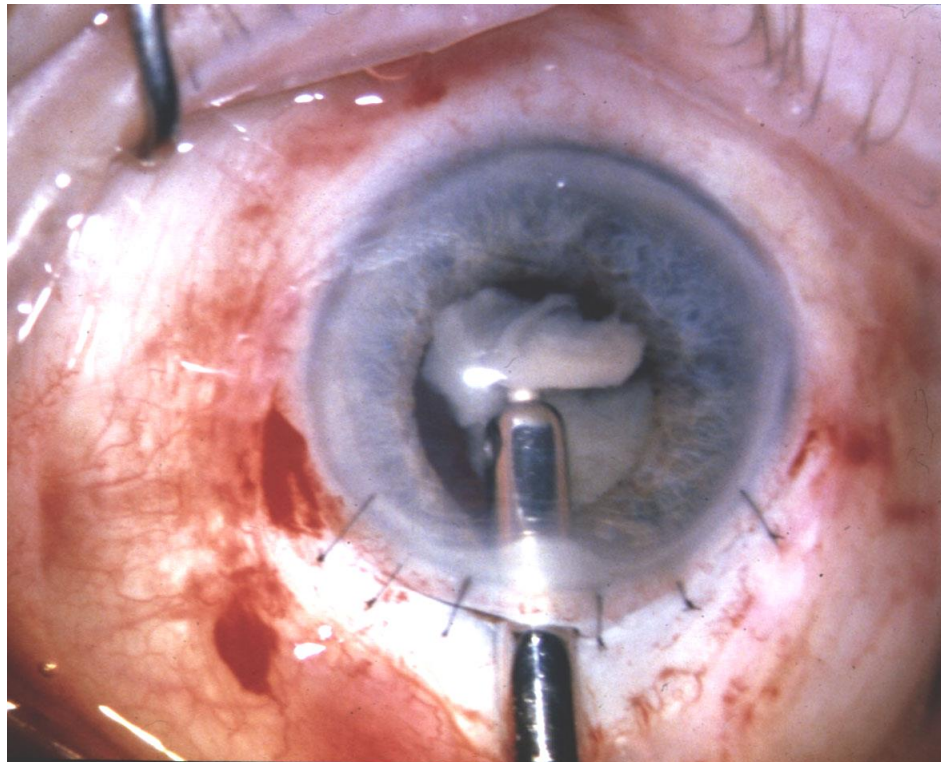
ECCE 囊外摘除

- Cataract Extraction 摘除白內障晶體



Treatment 治療

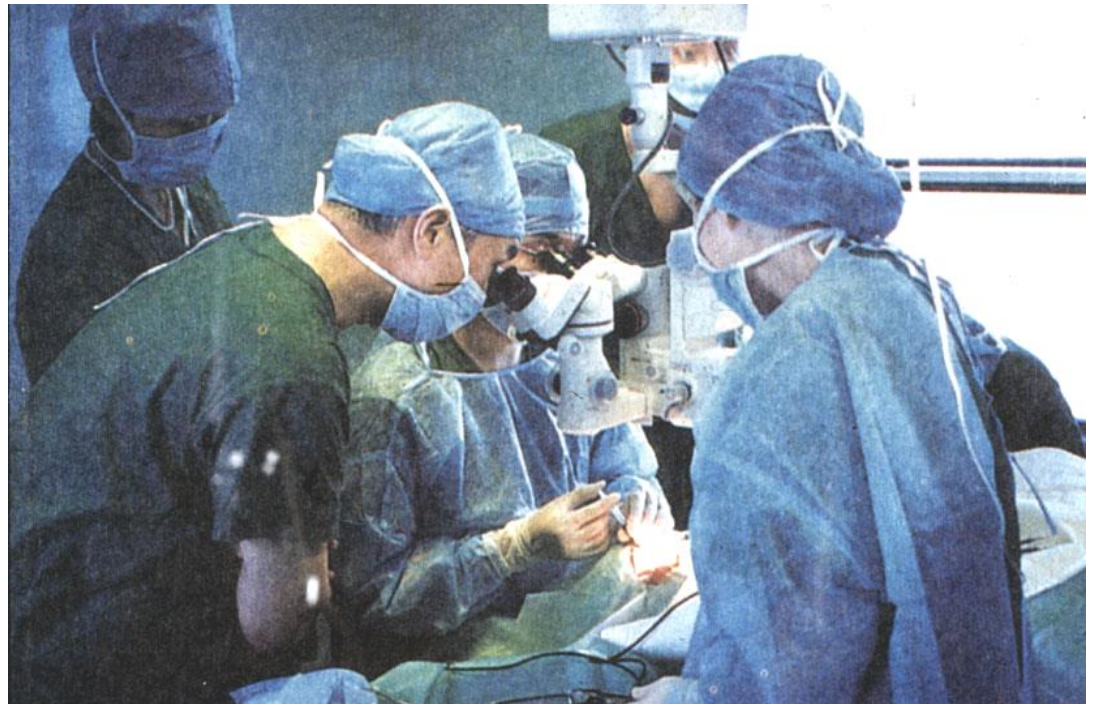
- Removal of Cortex 清除皮質層



Treatment 治療

■ Phacoemulsification

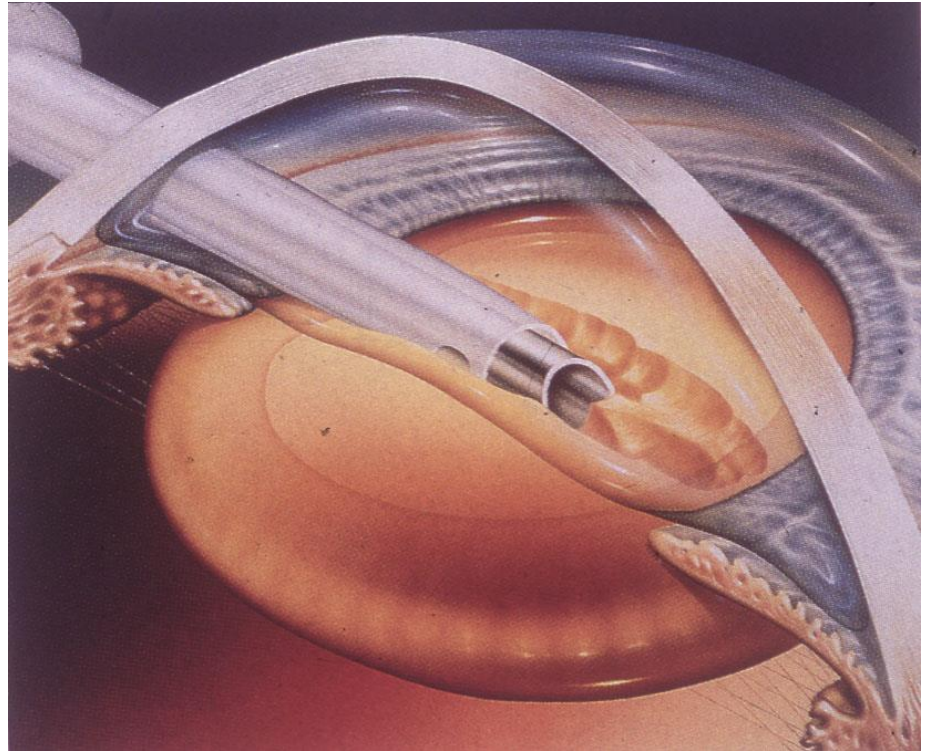
超聲乳化手術



Treatment 治療

* Phacoemulsification

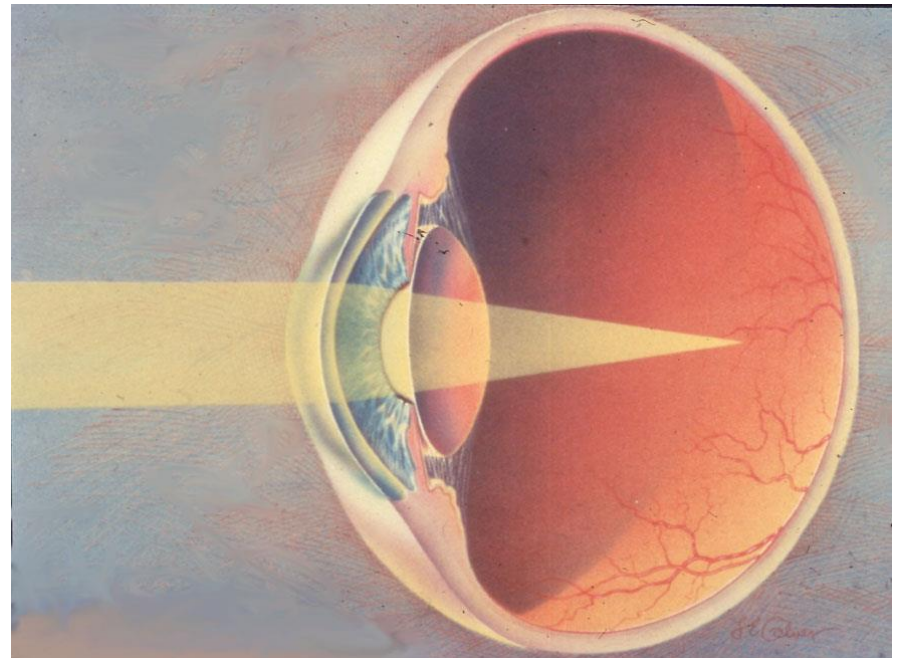
超聲乳化手術



Treatment 治療

- Correction of refractive error

矯正屈光不正 (+10D = 1,000 度)



Treatment 治療

■ Glasses 配戴眼鏡



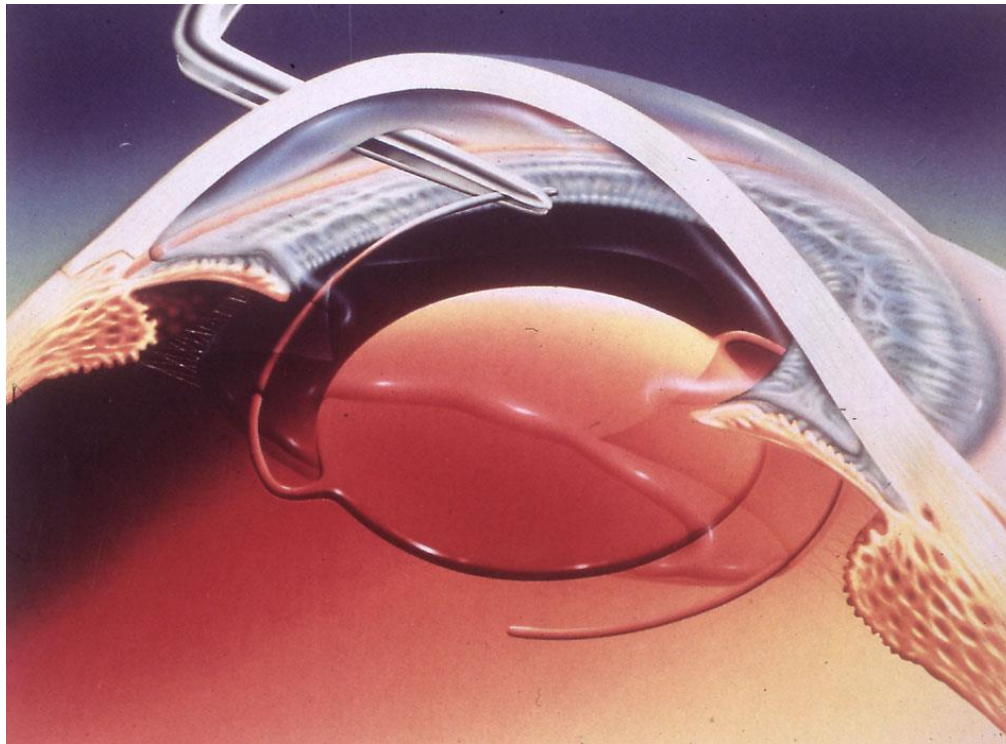
Cataract 白內障

- Intraocular Lens (IOL) 人工晶體



Treatment 治療

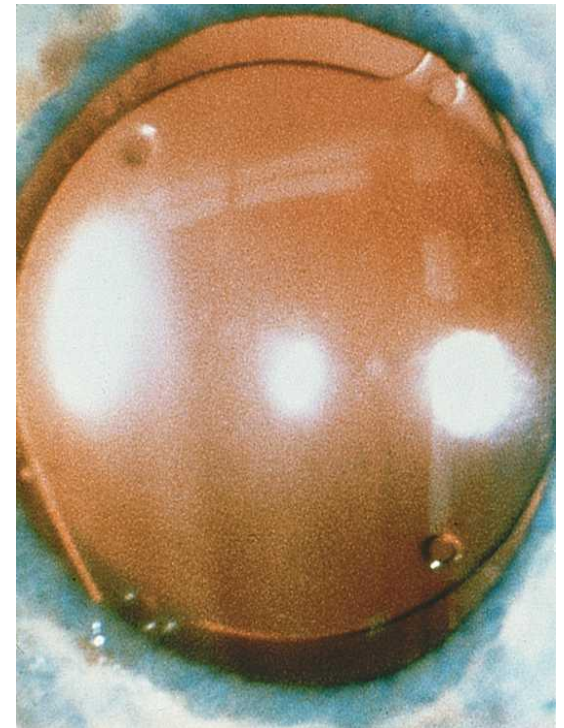
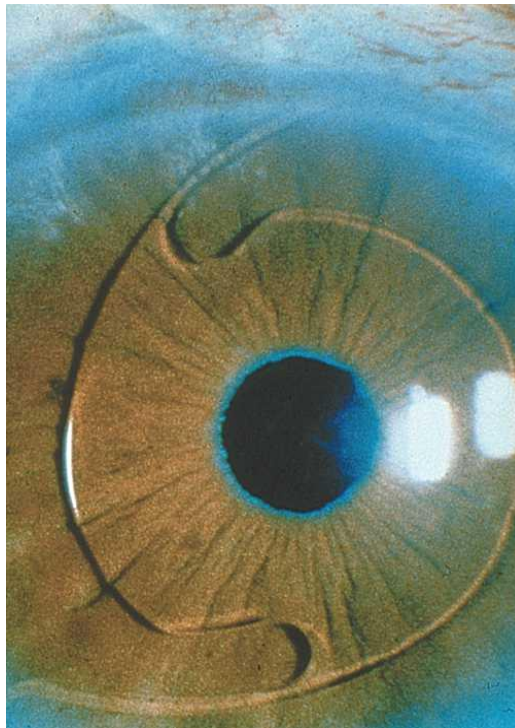
* Intraocular Lens (IOL) 人工晶體



Cataract 白內障

*Types of Intraocular Lens (IOL)

人工晶體的種類



Cataract 白內障

- Treatment

- Surgery

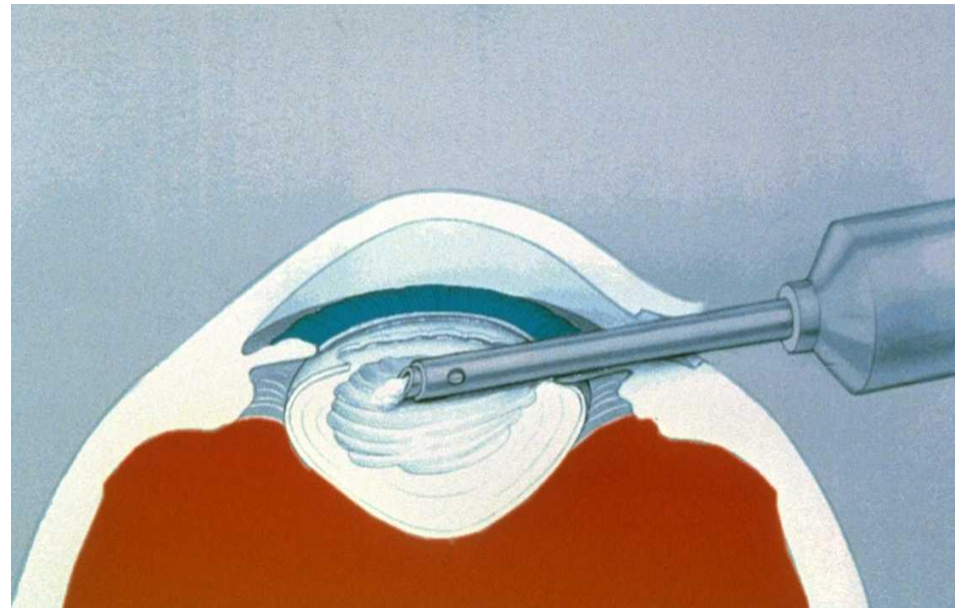
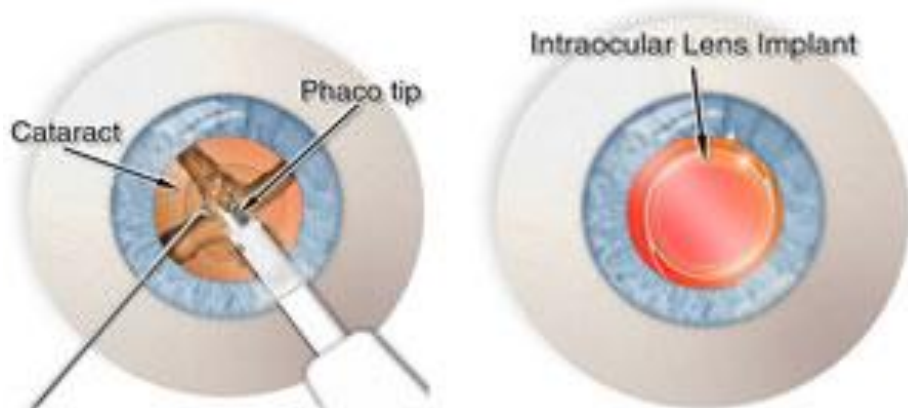
- Extra Capsular Cataract Extraction (ECCE)

- Or Phacoemulsification

- Implantation of Intraocular Lens

Cataract 白內障

- Phacoemulsification 超聲乳化手術
 - Smaller Wound 傷口較小
 - Less astigmatism 出現散光的機會較少



Secondary Cataract

二次白內障

- Posterior capsule opacity (PCO) 後囊渾濁
- ↓ vision after cataract operation 術後視力下降
- Common post-op complication 常見併發症

- Risk factors 風險因素:
 - Diabetic mellitus 糖尿病
 - Young age 年輕

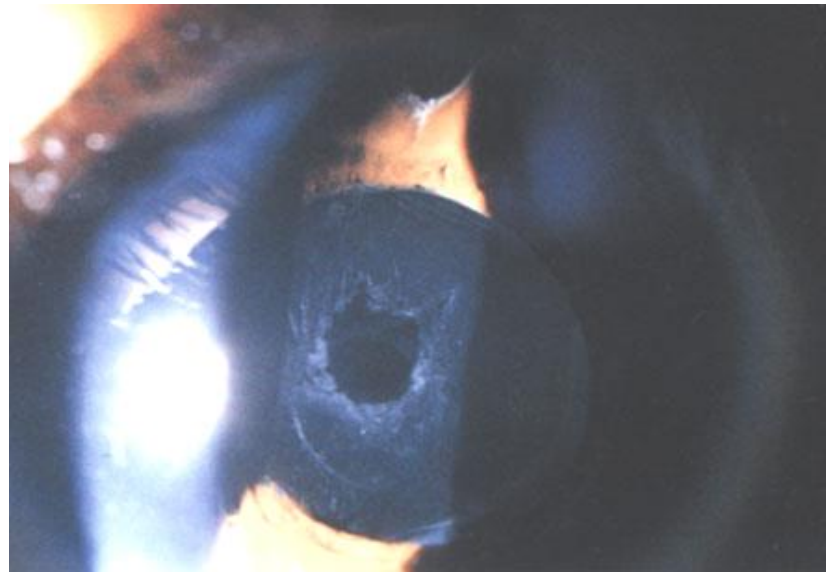
Secondary Cataract

二次白內障

- Nd:YAG laser to create opening in posterior capsule (以Nd:YAG laser 於後囊開孔)

- Clear the visual axis
to improve vision

使視軸更清楚以得到
清晰的視力



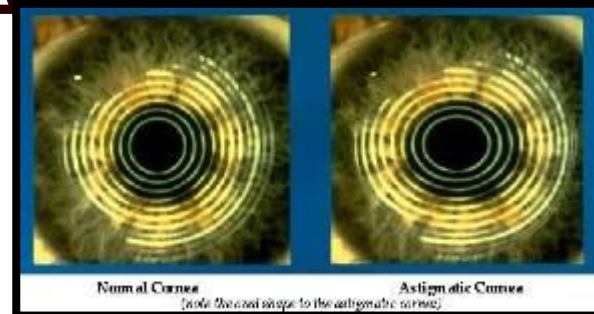
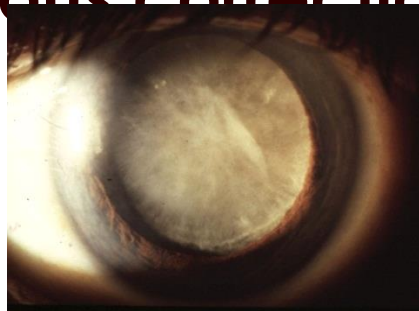
New Development – Cataract

白內障手術最新發展

*Surface anesthesia 表面麻醉 → Needleless 無需打針

*Phaco & foldable IOL → Sutureless
超聲乳化&可摺疊人工晶體 無需縫線

*Simultaneous correction of Astigmatism 同時矯正散光

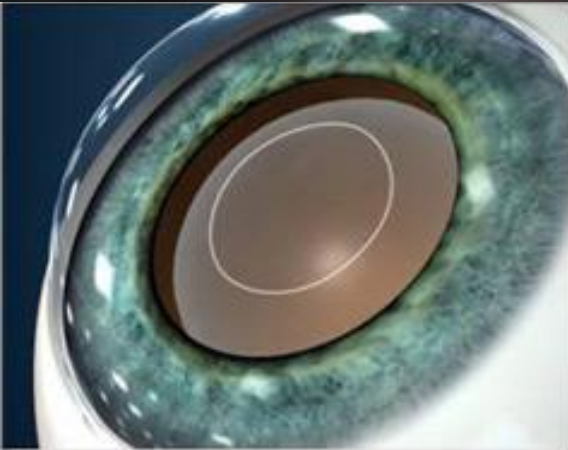
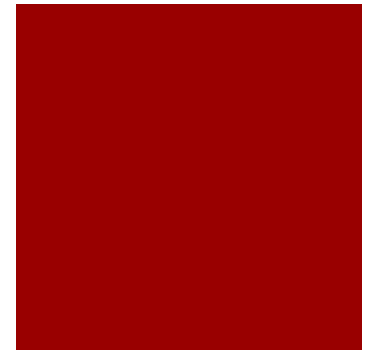


Modern Cataract Operation

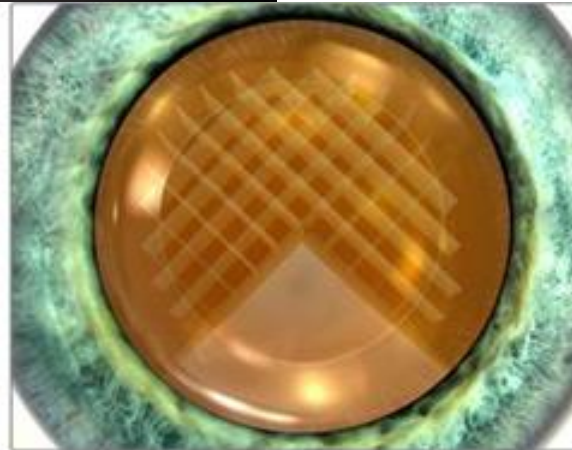
最新白內障手術



LASER REFRACTIVE CATARACT SURGERY (FEMTOSECOND LASER CATARACT SURGERY)



Capsulotomy



Lens Fragmentation



Take Home Message 2



- New advance in cataract surgery is marching towards automation and standardization with lower risk and more predictable visual outcomes. 白內障手術的新進展將邁向自動化和標準化，從而達到更低的風險和更可預見的視覺效果。

