
update

RETINA VITREOUS RESOURCE CENTER

Dr. Norman D. Radtke

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Interchange

Dear Colleagues,

The *Update's* continuing mission is to provide you with the most in-depth and comprehensive review of diagnostic management of vitreoretinal disorders. Our collective charge is to take the most innovative research findings from both laboratory and clinical trials and translate them into the most up to date care for our patients.

With the new NIH roadmap of research funding for the future, additional areas will surface that will be vital for our daily practice. This new approach for research funding by NIH will certainly change how, and what, biomedical research is conducted in the next decade. Because of the scale and complexity of knowledge in science, research teams of the future will require novel approaches. Clinical studies and trials can be connected more effectively through the use of interdisciplinary research teams, public-private partnerships, and linking of existing networks.

An example of this innovative team approach is our work in retinal transplantation. Both east and west coasts have been interconnected by our retinal transplantation work, helping us assess our patients pre-operatively and post-operatively. Our paper published in the August '04 *Archives* and summarized here emphasizes this new approach.

The accelerated pace of discoveries in the retina area requires that they be rapidly translated into practice so our patients can benefit from these new understandings. Therefore, it is important to integrate systems that link information to practice far more effectively than previous approaches. The areas of bench research that will play an important role in this future integration include molecular libraries and imaging of bioinformatics, computational biology, and nanomedicine.

Of course, evaluating research for its most significant application is one of our major emphases. This issue of the *Update* focuses on advances and medical applications of biotechnology, regenerative medicine, tissue engineering, retinal transplantation, and stem cell research. It will also address application of these basic research areas to clinical advances in macular degeneration, diabetic retinopathy, retinal transplantation, and retinal vascular abnormalities. Our discussion will articulate the dynamics of research and its clinical applications.

Our findings continue to evolve, emphasizing the assessment of basic research and clinical trials as they pertain to our daily clinical practice with patients.

Clinical care, surgical care, low vision services, social work services, music therapy, patient education, extensive brochures, videos, lectures, and support groups all help us improve the quality of care for our patients. Together, they build a legacy of excellent care for future generations.

I look forward to one-on-one and group discussion on how we can collectively find ways to provide the best health care possible for our patients, and to promote and support excellent eye care research.

Sincerely,



N. D. Radtke, M.D., F.A.C.S.
Vitreoretinal Surgeon



Dr. Norman D. Radtke

Contents

Retinal Transplantation	2
Sheathotomy for Branch Vein Occlusion	3
Radial Optic Neurotomy for Central Retina Vein Occlusion	3
Risk Factors Associated with Macular Degeneration	3
Risk Factors Associated with Central Serous Retinopathy	4
Transpupillary Thermotherapy for Occult Choroidals Subretinal Neovascular Membrane and Age Related Macular Degeneration	4
Submacular Surgery to Remove Hard Exudates in Patients with Diabetic Retinopathy	4
Effect of Intraocular Gas on Cataract Development in Patients Undergoing Macular Hole Surgery	5
Size of Lesion and Results of Photodynamic Therapy	5
Value of mfERG in Predicting Early Visual Loss in Patients Taking Plaquenil	5
Services Available for Patients	5
Dobelle Artificial Vision Brain Implant	6
Inheritance of Age Related Macular	6
Music Therapy for Our Patients	6
Cholesterol Link to Age Related Macular Degeneration	6
Age Related Eye Disease Study Report No. 13	7
Vitamin Therapy for Retinitis Pigmentosa, Stargardts, and Choroideremia	7
The Visual Short Term Effects of Viagra	7
The Effect of Transluminal YAG Embolysis (TYE) for Retinal Artery Occlusion	7
Update on Gene Therapy	8
Update on Emerging Angiogenesis Pharmacotherapies Hindering Growth	8
Intraocular Lens Telescope, Retinal Photomicrochip Technology, Rheotherapy, Retinal Translocation	8
Longest Duration of Macular Holes That Have Been Repaired	8
Risk Factors and Prevention of ARMD	8

Subject

Advances and Medical Applications of Biotechnology, Regenerative Medicine, Tissue Engineering, Retinal Transplantation, and Stem Cell Research to the Areas of Macular Degeneration, Diabetic Retinopathy, Retinal Transplantation, and Retinal Vascular Abnormalities

Retina Transplantation for Retinitis Pigmentosa and Age Related Macular Degeneration

Where does retinal transplantation research stand at this time?

Retinal transplantation in our laboratory has now progressed to where the FDA has given us approval to do transplantation of sheets of neural retina with retinal pigment epithelium in patients with dry macular degeneration and retinitis pigmentosa with 20/400 vision in one eye. To date our most successful patient with age related macular degeneration has gone from 20/640 to 20/250 in 3 months (See Figures 1 and 2). The most successful patient with retinitis pigmentosa has gone from 20/800 to 20/200 ETDRS in 1 year and at the 2 year follow-up has maintained the 20/200 ETDRS level of vision (See Figures 3-4). We have further information regarding a second retinitis pigmentosa patient and a second patient with macular degeneration, both of whom have undergone retinal transplantation and can preliminarily also see progressive improvement.

The following paper has been published in August 2004 *Archives of Ophthalmology* (112:1159-1165, 2004): "Vision Changes after Sheet Transplant of Fetal Retina with RPE and Retinitis Pigmentosa Patient."

What is the content and clinical message of the article?

This is a first report in humans of combined transplantation of fetal retinal RPE with neural retina with improved vision. After transplantation the patients' vision improved from 20/800 to 20/250 at nine months and to 20/200 at one year and remained there over two years. The vision was tested by Early Treatment Diabetic Retinopathy Study (ETDRS) and scanning laser ophthalmoscope (SLO) testing. The study indicates that fetal retina transplanted together with its RPE can survive one year without apparent rejection and can show improvement in ETDRS visual acuity which remained in follow-up examination after two years.

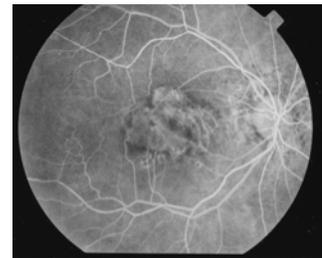


Figure 1: Age related macular degeneration patient pre-operatively. Visual acuity 20/640 ETDRS.

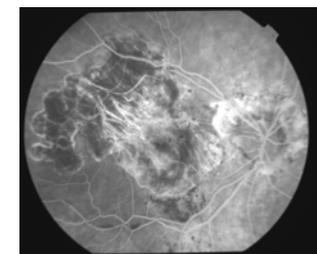


Figure 2: Age related macular degeneration patient three months after implantation of sheets of neural retina with RPE. Visual acuity 20/250 ETDRS.

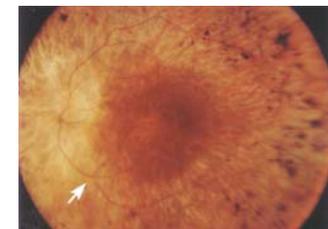


Figure 3: Retinitis pigmentosa patient Preoperative photo prior to retinal transplantation. Visual acuity 20/800 ETDRS.

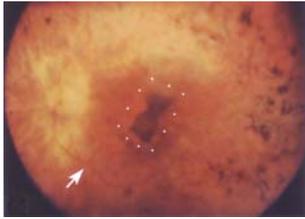


Figure 4: Retinitis pigmentosa patient two years after implantation of sheets of neural retina with RPE. Visual acuity 20/200 ETDRS.

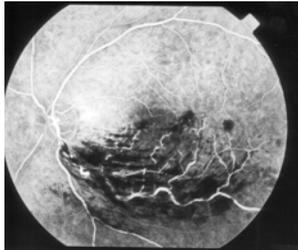


Figure 5: Patient with branch vein occlusion pre-operatively. Visual acuity 20/200.

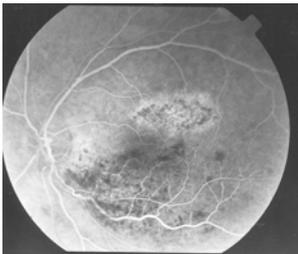


Figure 6: Patient with branch vein occlusion status post sheathotomy. Visual acuity 20/25.

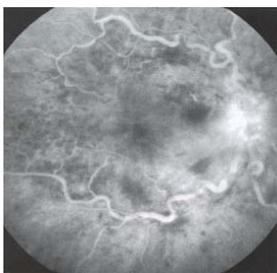


Figure 7: Patient with central retinal vein occlusion pre-operative. Our patient's visual acuity was 20/300.

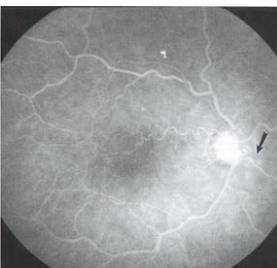


Figure 8: Patient with central retinal vein occlusion status post radial optic neurotomy. Visual acuity 20/30.

Effects of Sheathotomy on Branch Vein Occlusion

What effects of arteriovenous (A/V) crossing sheathotomy are expected in patients with branch vein occlusion?

Yamaji, H., et al (*American Journal of Ophthalmology* 137(5):834-841, 2004) found macular edema and hemorrhage improves in almost all patients. Visual acuity improves 2 or more lines in 83% and did not worsen in any eye. Improvement in perfusion based on pre and post operative fluorescein was 61% (See Figures 5 and 6).

Effect of Radial Optic Neurotomy on Central Retinal Vein Occlusion

Opremcak, E., et al (*Retina* 21(5):408-415, 2001) successfully performed surgical decompression of central retinal vein occlusion via radial optic neurotomy on eleven patients with no complication. They concluded that it was technically feasible and a safe procedure that is associated with rapid perfusion of the retina. Resolution of the intraretinal hemorrhage, edema and ischemia may improve the visual prognosis in patients with this common retinal disorder.

Weizer, JS., et al (*American Journal of Ophthalmology* 135(6):814-819, 2003) concluded that radial optic neurotomy may improve visual acuity in eyes with central retina vein occlusion although choroidovitreous neovascularization from the neurotomy site can occur. They felt that further study was needed to determine its role in the management of central vein occlusion. (See Figures 7 and 8).

Risk Factors Associated with Macular Degeneration

What factors seem to lead to the progression of age related macular degeneration?

Seddon, J., et al (*Archives of Ophthalmology* 121(6):785-792, 2003) indicated that overall an abdominal obesity increased the risks to progression to advance age related macular degeneration and more physical activity tended to decrease the risk. Strangely enough the relative risks for smoking range from 1.48 to 1.99 but were not statistically significant.

Is there an association between cataract surgery and age related macular degeneration patients developing subretinal neovascular membrane after cataract surgery?

Freeman, E., et al (*American Journal of Ophthalmology* 135(6):849-856, 2003), concluded that further research is necessary to determine this. It is not possible to determine whether or not cataract surgery theoretically could predispose to development of subretinal neovascular membrane in patients with age related macular degeneration, possibly related to inflammatory factors or whether exposure of the eye to certain wavelengths of light and higher intensity of light after cataract surgery might provoke growth of subretinal neovascular membranes. At this point, the evidence is not in as to whether or not cataract surgery does make patients who have macular degeneration and cataract surgery at greater risk to developing active subretinal neovascular membrane.

What is the association of sunlight exposure and indicators of sun sensitivity with the 10 year incidence of age related maculopathy (ARM)?

Tomany, S.C., et al (*Archives of Ophthalmology* 122(5):750-757, 2004) found significant association between extended exposure to summer sun and the 10 year incidence of early ARM and increased retinal pigment. A protective effect of hat and sun glasses use by participant while in their teens and 30's against the 10 year incidence of soft drusen and retinal pigment epithelium degeneration was also found. No relationships were found between mean annual ambient UV-B light and incidence or progression of ARM at 10 years. These results support previous findings indicating a possible link between extended sunlight exposure and the incidence of "early" ARM. No conclusion between "late" ARM and sunlight exposure could be reached.

Does fruit intake play a protective role in age related macular degeneration?

Cho, E., et al (*Archives of Ophthalmology* 122(6):883-892, 2004) found that higher fruit intake was related to reduced risk of neovascular age related macular degeneration. Further work is needed to identify the relevant compounds in fruits.

Does age play a role in the development of age related maculopathy?

Mukesh, B.N., et al (*Ophthalmology* 111(6):1176-1182, 2004) described data that suggesting that 1 in 3 persons aged 70 years or older will have age related maculopathy lesions over a 5 year period and that the disease will progress to a more severe form after the age of 80 years. The presence of soft indistinct drusen with pigmentary abnormalities significantly increased the risk for development of age related maculopathy.

Factors Associated with Central Serous Retinopathy

What are some of the factors that appear to be associated with central serous chorioretinopathy?

Tittl, M., et al (*Archives of Ophthalmology* 121(7):975-978, 2003) noted that central serous retinopathy was associated with factors such as mental stress, hyper cortisolism, type A personality, systemic hypertension and increased variable heartbeat. It is believed that psychological stress, especially in men, leads to hyper activation of the sympathetic nervous system with the abnormal neuroendocrine response of endogenous catecholamine concentrations. Their study suggested that choroidal perfusion abnormalities play a role in the pathogenesis of central serous chorioretinopathy.

Baumal, C.R., et al (*Archives of Ophthalmology* 122(6):926-928, 2004) reported a case of central serous retinopathy associated with periocular corticosteroid injection treatment for HLA-B27 associated iritis.

Haimovicci, R., et al (*Ophthalmology* 111(2):244-249, 2004) indicated that in addition to contributing previously recognized risk factors such as the use of systemic steroids in pregnancy, they also found that antibiotics, antihistamines, multi-system autoimmune diseases, untreated hypertension, alcohol use and tobacco use were risk factors.

Transpupillary Thermotherapy for Occult Choroidal Subretinal Neovascular Membrane in Age Related Macular Degeneration

How effective is transpupillary thermotherapy for occult choroidal neovascularization?

Thach, A.B., et al (*Archives of Ophthalmology* 121(6):817-820, 2003) indicated that large spot size transpupillary thermotherapy is effective in stabilizing the visual acuity in those patients who have occult choroidal neovascularization due to age related macular degeneration. The study was uncontrolled.

Submacular Surgery to Remove Hard Exudates in Patients with Diabetic Retinopathy

Does removing the sub macular hard exudates in patients with diabetic maculopathy improve their vision?

Takaya, K. et al (*Retina* 24(1):23-29, 2004) reported that visual improvement could not be obtained after removing sub macular hard exudates in most patients, suggesting that diabetic maculopathy should be treated before massive exudates deposits appear in the macula.

The Effect of Intraocular Gas on the Development of Cataracts in Patients Undergoing Macular Hole Surgery

Does the role of intraocular gas and the age of patient influence the cataract progression after vitrectomy in patients with macular holes and epiretinal membranes?

Thompson, J.T. (*American Journal of Ophthalmology* 137(2):250-257, 2004) indicated that patients older than 50 years of age have a rate of progression of cataracts following intravitreal gas six-fold greater than in patients younger than 50 years of age. Intravitreal gas bubbles, used in macular hole surgery, are associated with a nuclear sclerosis increase of approximately 60% compared with eyes without use of a gas bubble.

Size of Lesion and Results of Photodynamic Therapy

What kinds of lesion size and visual acuity are predictors of good outcome in patients with photodynamic therapy?

Axer-Siegel, R., et al (*American Journal of Ophthalmology* 137(2):258-264, 2004) indicated that a smaller lesion size and better visual acuity at presentation were good predictive signs for improved visual outcome found in photodynamic therapy. Final visual acuity was positively correlated with lesion size and visual acuity at presentation, whereas cystoid macular edema was found to be a poor prognostic sign for visual outcomes following photodynamic therapy.

Value of mfERG in Predicting Early Visual Loss in Patients Taking Plaquenil

How valuable is multifocal electroretinography in the evaluation for early detection of retinal dysfunction patients taking hydroxychloroquine?

Penrose, R.J., et al (*Retina* 23(4):503-512, 2003) reported that asymptomatic patients receiving hydroxychloroquine (Plaquenil) treatment can have substantial local decreases in the retinal function as reflected by the changes in multifocal electroretinogram recordings, possibly indicating a pre-clinical stage of the drug – related toxicity. It appears that patients who have above 6.0 mg/kg/day of Plaquenil therapy are at increased risks for these early findings. It appears that the earliest functional changes in a retina at risk for toxicity are likely to be seen in the impairment of fast adaptive properties. They are reflective predominantly in the second order component of the MFOFO paradigm. Clinically asymptomatic patients receiving hydroxychloroquine treatment can have substantial local decreases in their retinal function, as reflected by the changes in mfERG recordings, possibly indicating a preclinical stage of drug related toxicity.

In addition to the report, observation by Maturi, R.K., et al (*Arch Ophthalmol* 122:973-981, 2004) concluded that long term hydroxychloroquine use may be associated with mfERG abnormalities. The mfERG appears to detect retinal physiological change earlier than visual acuity testing, color vision testing, or Amsler grid testing can. The greatest value of the mfERG is in differentiating a retinal cause and, hence, providing important evidence for hydroxychloroquine toxicity, for whatever visual field loss is apparent on perimetry (See Figures 9-10).

Services Available for Patients Undergoing Macular Hole Surgery

What services and equipment is available for patients who are undergoing macular hole surgery and need help in order to position them in the face down position as required after surgery?

Services booklet for patients undergoing macular hole surgery. Our staff helps the patient obtain the equipment at little or no cost (See Figure 11).

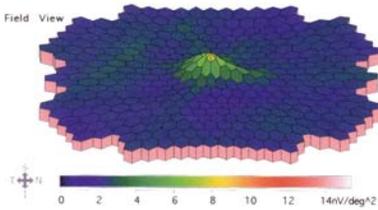


Figure 9: Three-dimensional topographic plot of multifocal ERG for patient with Plaquenil toxicity.

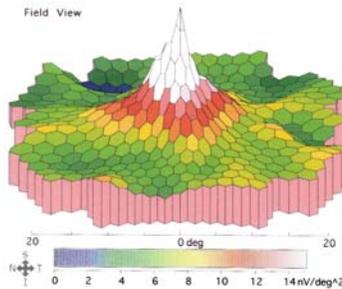


Figure 10: Normal three-dimensional topographic plot of multifocal ERG.



Figure 11: RVRC staff. Technical Staff shown in top picture. Office Staff shown in bottom picture.

Top Picture Back Row (L to R):

Deb Howell, Tammy Weber, Mary Hilliard, Cathy Werner, Tina Borders

Top Picture Front Row (L to R):

Carissa Waldridge, Cynthia Cranmer, Candace McDonald

Bottom Picture (L to R):

Beverly Goatley, Peggy Dennis, Lauren Smith

Dobelle Artificial Vision Brain Implant

What is the status of the Dobelle artificial-vision system that uses the brain implant?

The system includes a glass mounted video camera and computer and battery pack that is attached to the patient's waist and is carried over the shoulder with straps. Video images are simplified by the computer and then transmitted to electrodes that are placed on the brain's vision center. The electrical stimulation of the cortex yields spots of light that can show rough outlines of objects. This is a technique that has not been proven and has not received FDA approval for experimentation in the United States and is being done in Belgium. The overall cost runs around one hundred thousand dollars and has to be paid by the patient. I feel that this is a procedure that is not indicated and shows little promise.

Inheritance of Age Related Macular Degeneration

Is macular degeneration inherited?

Weeks, D.E., et al (*American Journal of Ophthalmology* 132(5):682-692, 2001) indicated that, in summary, three areas of the human genome were found to be shared amongst affected versus unaffected individuals. These are very promising results as two independent research groups have now confirmed these findings. Candidate gene studies have been underway aiming at identifying specific genes. Major challenges in ARM research are determining and defining a continuum of disease and distinguishing alternative causes of macular pathology.

It is important to distinguish between a disease-causing gene and a variation, as well as hereditary versus environmental causes.

The locus on chromosome 1q31 independently confirms a report by Klein, M.L., et al (*Archives of Ophthalmology* 116:1082-1088, 1998) mapping an age related maculopathy susceptibility gene to this region. There was no evidence that other known macular or retinal dystrophy candidate gene regions are major contributors to the genetics of age related maculopathy.

Music Therapy for Our Surgery Patients

How does music therapy help our surgical patients?

Eighty percent of our patients desire to listen to music when having surgery. To relieve anxiety and relax patients they are given their choice of several music types (See Figure 12). We have had patients with high blood pressure have to have the surgery cancelled. On subsequent workup of their high blood pressure, no etiology was found. Our hope is to reduce pain perception and high blood pressure without medications and to relieve the patients' anxiety about surgery preoperatively.

Patients' comments to date are listed (See Figure 13).

Cholesterol Link to Age Related Macular Degeneration

Is there a link between cholesterol and age related macular degeneration?

Van Leeuwen, R., et al (*American Journal of Ophthalmology* 137(4):750-752, 2004) in a brief report concluded that elevated HDL but not total cholesterol is associated with an increased risk of AMD. They concluded that Apolipoprotein E genotype does not explain this association but may be an effect modifier.

Types of Music

- 1) Gospel
- 2) Country
- 3) Jazz
- 4) Contemporary
- 5) Easy Listening
- 6) Easy Listening and Quiet Classical
- 7) Regular Classical
- 8) Ocean Classical
- 9) Popular 60's and 70's

Figure 12: Musical styles offered for patients undergoing music therapy.

Patient Comments on Music Therapy

- Very relaxing.
- Anxiety relieved after music put on.
- I think it is really nice.
- Really helped a lot. It felt like we were at home .
- Very good idea, very soothing. It kept me from thinking about what I was going to face.
- Music kept me from being very nervous and I liked the music selections.
- Helped keep me very calm. I enjoyed it very much and was very soothed.

Figure 13: Comments from patients who underwent music therapy.

Age Related Eye Disease Study Report No. 13

How does high dose of antioxidant or zinc correlate with mortality in Age Related Eye Disease Study (AREDS)?

In the AREDS report, No. 13, the decreased survival of AREDS participants with AMD and cataract suggests that their conditions may reflect systemic rather than only local processes. The improved survival in individuals randomly assigned to receive zinc requires further study.

Vitamin Therapy for Retinitis Pigmentosa, Stargardts and Choroideremia

Are vitamin supplements valuable for patients with retinitis pigmentosa, Choroideremia or Stargardts disease?

Zhao, D.Y., et al (*Archives of Ophthalmology* 121(7):967-972, 2003) while studying the macular keratinoid levels in age matched healthy control subjects, showed that patients with retinitis pigmentosa and choroideremia had normal levels of macular keratinoid suggesting that nutritional supplements of macular keratinoid such as Lutein, Zeaxanthin or both would be unlikely to affect the clinical course. They went on to state that although the number of patients with Stargardts macular dystrophy examination was limited, their macular keratinoid levels were usually lower than those of the subjects of similar age with no macular pathological condition. Therefore, it appears that patients who have Stargardts disease would benefit from additional supplements such as Lutein and Zeaxanthin.

The Visual Short Term Effects of Viagra

What are the short term effects of Viagra on young healthy subjects.

Jägle, H., et al (*American Journal of Ophthalmology* 137(5):842-849, 2004) from Tübingen, Germany, investigated the short-term visual effects of a single 100 mg dose of Viagra (sildenafil citrate) in healthy young men. This led to small but statistically significant transient changes of the outer and inner retinal function as detected by ERG, and psychophysical methods. The acute effects were fully reversible within 24 hours.

The Effect of Transluminal YAG Embolysis (TYE) for Retinal Artery Occlusion

Opremcak M., et al (*Retina* 22(2):213-216, 2002) have shown that breaking up plaques in arterioles in branch retinal artery occlusion or central retina artery occlusion for as long as 6 weeks has been successful. They use the term "retinal coma" for the area affected which will revive itself after the blockage is open. The retina is nourished by the choroidal circulation during the blockage of the arterial, hence the term coma.

Reynard, M and Hanscom, TA (*American Journal of Ophthalmology* 137(1):196-198, 2004) have shown that neodymium:yttrium-aluminum-garnet laser arteriotomy in a patient with central retina artery occlusion resulted in extrusion of the embolus, reopening of the central retina artery and return of vision. This technique warrants further study as a primary treatment for this blinding disorder.

Both authors have shown that TYE resulted in disappearances of the emboli and immediate restoration of the blood flow. The YAG laser photo disrupts the embolus with the lumen of an occluded retinal arteriole without damaging the vessel wall by the rapid deposition of infrared irradiation in the embolus after passing through the vessel wall. Rapid thermal expansion will occur within the embolus until its compression and tensile strengths are excellent. At this point, the embolus will completely or partially shatter, clearing the lumen of the arteriole. The vessel wall is left unharmed because of the greater elasticity and lower absorbing of the infrared irradiation. Energy level of the Nd:YAG were recommended to be below 1 m.

Update on Gene Therapy

Acland, G.M., et al (*Nature Genetics* 28(1):92-95, 2001) made one of the single most important advances in the history of retinal degeneration research by the restoration of vision in a canine model of a severe childhood blindness, known clinically as Leber's congenital amaurosis. This is significant in that it is the first time researchers have successfully restored vision in a large animal model of retinal degeneration.

Update on Emerging Angiogenesis Pharmacotherapies Hindering the Growth of Choroidal Neovascularization

Angiostatic agents exert their therapeutic benefits in age macular degeneration by slowing or stopping the development of abnormal choroidals blood vessels. Three angiostatic compounds are currently in phase III clinical trials for neovascularization age related macular degeneration (See Figure 14).

The results of these trials are pending.

Intraocular Lens Telescope, Retinal Photomicrochip Technology, Rheotherapy and Retinal Translocation

Lane, S.S., et al (*American Journal of Ophthalmology* 137(6):993-1001, 2004) report that success in phase I trials have prompted phase II/III trials which are now in progress. We are still awaiting the results of early studies in retinal photomicrochip technology and rheotherapy. Fang, X., et al (*American Journal of Ophthalmology* 137(6):1034-1041, 2004) concluded that macular translocation surgery with 360 degrees retinopathy results in minimal morphology alteration but significant depression of electrophysiologic function in monkey eyes.

Longest Duration of Macular Hole That Have Been Successfully Repaired

Stec, LA., et al (*Retina*. 24(3):341-347, 2004) concluded that macular holes can be surgically closed with visual improvement in most patients out to 7 years. ILM peeling is an important surgical factor for closure of the macular hole.

Risk Factors for and Prevention of Age Related Macular Degeneration

Several factors have been identified which increase the risk of an individual developing age related macular degeneration (See Figure 15).

What role does vitamin therapy play in preventing age-related macular degeneration?

The National Eye Institute released the latest information from the Age-Related Eye Disease Study which showed that high levels of anti-oxidants and zinc reduced the risk of progression of macular degeneration by 25%. It also reduced the risk of vision loss from age-related macular degeneration by about 19%. The dietary supplements found to be helpful are listed (See Figure 16).

Lutein and zeaxanthin, although not studied in the AREDS, have been shown in uncontrolled scientific data to suggest that they may be helpful in patients with age-related macular degeneration. Beta-carotene is not recommended for smokers, as it has been shown to increase the risk of lung cancer.

Angiogenesis Compounds

Pegaptanib Sodium (anti VEGF aptamer, Macugen™)

Intravitreal injection with interval treatment every six weeks.

Ranibizumab (rhuFab V2 VEGF, Lucentis™)

Intravitreal injection with interval treatment every 4 weeks. Inhibits all 4 known VEGF isomers

Anecortave acetate (Retaane™)

Posterior juxtасcleral depot injection with the interval treatment every 6 months. It inhibits proteases needed for vascular endothelial cell migration and may inhibit several angiogenic stimulators

Figure 14: Angiostatic compounds in phase III clinical trials.

Risk Factors

- 1) Cigarette Smoking
- 2) Dietary Fat
- 3) Obesity
- 4) High Cholesterol
- 5) Hypertension

Figure 15: Risk factors for age related macular degeneration.

Supplements

- 1) Vitamin C (500 mg per day)
- 2) Vitamin E (400 intl. units per day)
- 3) Beta-carotene (15 mg per day)
- 4) Zinc, as zinc oxide (80 mg per day)
- 5) Copper, as cupric oxide (2 mg per day)

Figure 16: Dietary supplements found to be helpful in preventing age related macular degeneration.