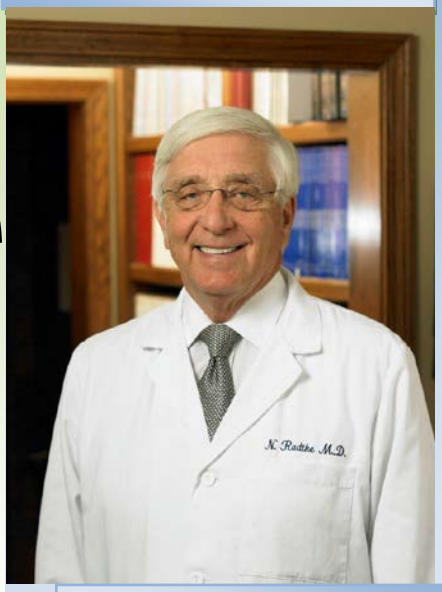
Volume 11, No. 1

Update

Retina Vitreous Resource Center



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INTERCHANGE

Dear Colleagues,

It is the intent of this Update to provide you with information that is practical and useful in answering your patient's questions in your clinical practice. To that end, we present new and emerging data regarding the studies being done with antiangiogenic agents, combination therapies, pharmacological and surgical management of age-related macular degeneration. We will also include review of gene testing and gene therapy, vitamin therapy for age-related macular degeneration, emerging developments in ocular imaging, artificial vision, diabetic retinopathy update, and an induced pluripotent stem cell update.

In addition to cutting edge research information, clinical findings that are important signs to recognize when following up on patients who have had retinal detachment surgery, treatments for age-related macular degeneration, retinal vein occlusions, and other retinal diseases will be discussed. Emphasis will be placed on clinical signs that are important for re-referral to a retina subspecialist.

Practical application to your daily practices will be our focus so we can all provide the most up-to-date information and care to our patients. Additionally, distilling the research frontiers with the greatest potential for clinical applicability will enable us to give hope to our patients with severe debilitating diseases.

We encourage feedback on ways we can improve our effort to meet your educational and practice needs.

For continued updates on these and many other issues, please feel free to call us or visit our website at www.rvrc.com.

Regards,

N.D. Radtke, M.D.

Norman D. Radtke, MD, FACS
Director, Retina Vitreous Resource Center

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SUBJECT

A. Cell-Based Therapy for Retinal Degenerative Disease

Cell-based therapy research is making progress to replace the defective areas of the retina in degenerative diseases and retinal dystrophies, such as dry age-related macular degeneration, retinitis pigmentosa, Stargardt's disease, and geographic atrophy.

Various cell-based therapies are being investigated for reconstruction of defective retinal cells. These include human embryonic stem cells and induced pluripotent stem cells, which attempt to overcome the many challenges facing clinical trials. Early studies will enroll advanced patients with limited opportunity for demonstrating efficacy. Outcome measures are difficult, immunosuppression must be addressed, and funding of trials in our current economic environment is strained. In spite of these obstacles to be overcome, there is a future place for cell-based therapy in the clinical practice.

Our work on cell-based therapy for retinal degeneration was published in the August issue of the AJO (*Am. J. Ophthalmol 2008;146:172-182*). Clinical results showed that 10 patients were tested – six retinitis pigmentosa patients (three improved) and four age-

related macular degeneration patients (all four improved). A total of seven out of ten patients improved. All patients underwent intraocular lens implant and YAG capsulotomies prior to transplantation.

Figure 2

One patient (Figure 2) had retinitis pigmentosa and vision improvement from 20/800 to 20/200 at five years. Subjectively, her first improvement was noted at six months when she could see her grandfather clock; her vision by ETDRS was 20/400 at that time. At two years, two months postoperatively, the patient noted she could see better with her surgery eye and was able to read the large print edition of Reader's Digest.

An eight-minute presentation on this subject, covering fifteen years of ongoing research, can be found in the "Ongoing Research" page on our website (www.rvrc.com) under the "Medical Professionals" section. This material was delivered as an invited speaker at the American Academy of Ophthalmology Meeting in Atlanta on November 7, 2008, as well as in Paris at "Macula of Paris" on January 23, 2009, and the Venezuelan Society of Ophthalmology on June 24, 2009. This work demonstrates successful transplantation of fetal retinal sheets into human patients with retinitis pigmentosa and age-related macular degeneration.

Figure 3

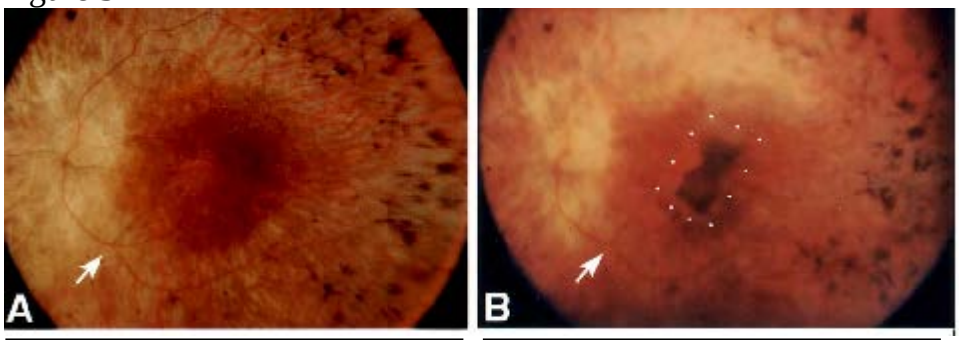


Figure A – Retinitis pigmentosa patient.
Preoperative photo prior to retinal transplantation.
Visual acuity 20/800 ETDRS.

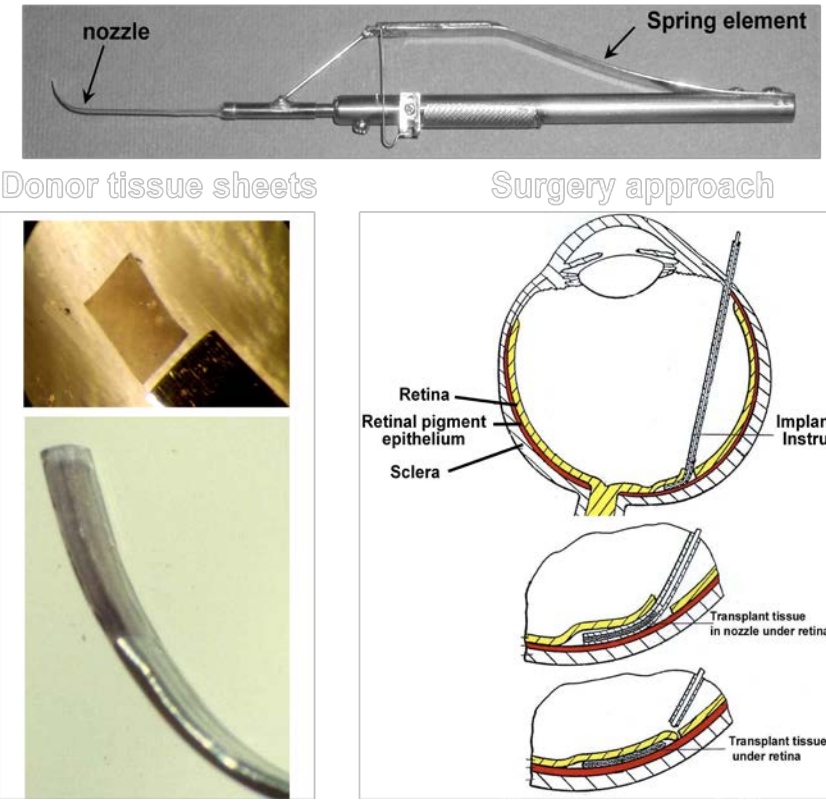
Figure B – Retinitis pigmentosa patient two years after implantation of sheets of neural retina with RPE.
Visual acuity 20/200 ETDRS at four years.

Figure 3 shows transplant recipient fundus photographs (A) preoperatively and (B) two years post operation. The transplants were well tolerated with no signs of clinical rejection as well as no signs of rejection upon histological examination from one patient with age-related macular degeneration at approximately six years post-transplantation. Seventy-percent of the patients showed some visual improvement.

Because of social ramifications with human fetal tissue and human embryonic cells, we have now broadened our efforts to include induced pluripotent stem cell research. Human somatic cells are being genetically reprogrammed by episomal methods to become

induced pluripotent stem cells (iPSC). These have been modulated to become retinal pigment epithelial cells and neural cells. These cells will be put together in layers on a collagen matrix and will then resemble the fetal tissue that we successfully transplanted into humans.

The Foundation for Fighting Blindness acknowledged our work with Dr. David Gamm for our effort in one of six emerging retinal therapies that received foundation funding as part of its Translational Research Acceleration Program (TRAP). The emerging treatments included those using stem cells, gene therapies, and pharmaceuticals.



Many retinal diseases, including Stargardt's disease, dry age-related macular degeneration, and choroideremia, lead to loss of photoreceptors and a supportive layer of cells called retina pigment epithelium (RPE). Dr. David Gamm of the University of Wisconsin is using induced pluripotent stem cells (iPSC) to develop a two-layered cell replacement therapy.

To minimize rejection of this and other treatments, he is also developing lines of iPSC from "super donors," individuals from across the United States whose immune profiles favorably match those of the country's general population. For these efforts, Dr. Gamm is collaborating with scientists from: University of California, Santa Barbara; University of Pennsylvania; Cellular Dynamics International; Retina Vitreous Resource Center in Louisville, Kentucky.

Our work with induced pluripotent stems cells in rats is made possible by surgeries with a special instrument. Paramount to the success of these surgeries was the creation of a patented subretinal transplantation device by Dyson Hickingbotham, an ophthalmic surgical instrument expert. While our rat eye transplantation experiments differ in scale from our previous surgeries in humans, the procedure for loading the tissue into the device and delivering it into the subretinal space of the rat will be similar in our new work with induced pluripotent stem cells and sheets of retina pigment epithelial and neural retina together.

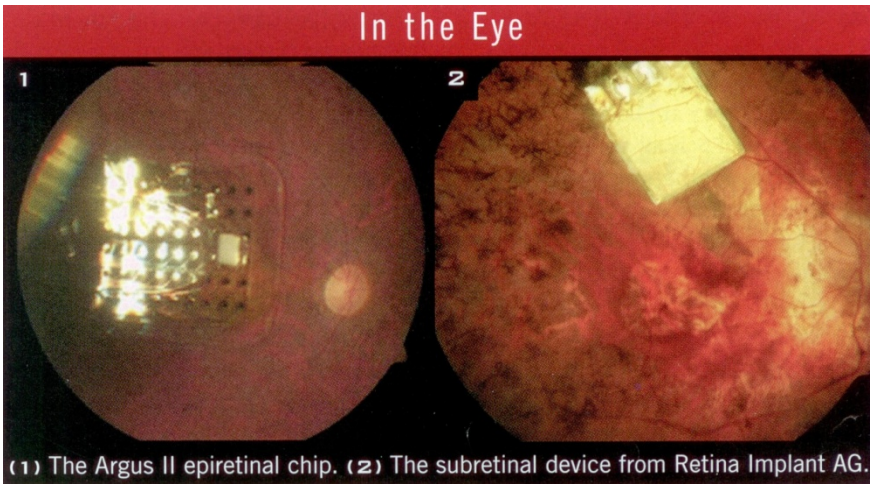
The ultimate goal of this basic research preclinical work is to eventually develop it for use in humans with FDA approval.

B. Artificial Vision

Retinal prostheses have had a long history and now include more than 15 companies and research groups in 6 countries. Those currently in or near human testing include:

- Boston Retinal Implant Project – Boston, Massachusetts
- Second Sight – Sylmar, California
- Retina Implant AG – Reutlingen, Germany
- Intelligent Medical Implant – Bonn, Germany
- Epi-Ret – Bonn, Germany
- Optobionics – Glen Ellyn, Illinois

The two groups that appear to be further along in development are Second Sight and Retina Implant AG.



Weiland et al, Ophthal 2011; 118:2227-2237

SECOND SIGHT ARGUS II RETINAL PROSTHESIS SYSTEM

The Second Sight device uses a camera and transmitter mounted to eyeglasses, an implanted receiver, and an array of electrodes secured to interface epiretinally with retinal ganglion cells. A battery pack worn on the patient's belt powers the system.

The camera captures images as the subject's head moves to view objects and track movement. These images are processed by the transmitter and receiver and turned into electrical impulses on the epiretinal array. These electrical impulses are intended to stimulate the retina's remaining cells and generate corresponding perception of patters of light in the brain, which patients interpret as meaningful images.

RETINA IMPLANT AG PROSTHESIS

The Retina Implant AG prosthesis doesn't have an external camera. Rather, it uses a light-sensitive microchip that is surgically implanted under the retina, in the macular region where photoreceptor cells are located. The implant moves with the eye, which provides for "more natural processing of the image," according to a personal communication with Dr. Robert MacLaren. Aside from the subretinal micro-photodiodes, the only other equipment is a power module implanted behind the ear.

It is my expectation that the Retina Implant AG will probably prove to be the most helpful artificial vision device for restoring useful vision in patients with retinal dystrophies and possible dry age-related macular degeneration. There are multiple reasons for this point of view:

1. The device's imaging functionality of the implant is in the eye, hence being coupled with eye movement.
2. The patients were able to report letter reading, providing strong support for functional vision via electrical stimulants.
3. Personal communication with Dr. Robert MacLaren in Oxford, England, a surgeon who so far implanted six of these devices, stated that, "A great advantage of the subretinal device is that it moves with the eye and is therefore in a more natural position for acquiring a retinal image." He also added, "The use of the bipolar cells also adds an additional level of processing on top of the epiretinal approach developed by Second Sight."
4. It is presently being studied at Wills Eye Institute in Philadelphia, Pennsylvania with Dr. Jay Federman. Its light sensitivity certainly is a great advantage for the Retina Implant AG. Stimulating the bipolar/horizontal cells from the subretinal space rather than ganglion cells from the retinal surface seems more physiological.

There are an estimated 1.2 million people worldwide with retinitis pigmentosa, including 100,000 in the United States. We can give our patients hope for improved vision in the future. The devices are well tolerated in the eye, and as the quality of the devices gets better, we may be able to show that there is real benefit from them for improved vision to change people's lives.

C. AGE-RELATED MACULAR DEGENERATION RISK FACTORS

AGE: Age is an important factor in developing age-related macular degeneration. Anyone over the age of 55 is at risk and the percentage increases with increasing age.

SMOKING: Smoking effects all tissues in the body and the retina is no exception. It is thought that is can increase the chance of developing age-related macular degeneration by 30%.

GENETICS: Family history plays a role in increasing the risk of developing age-related macular degeneration. More genes are being discovered every year that are related to causing this disease.

RACE: Caucasians are more susceptible to developing age-related macular degeneration that any other race.

DIET: Eating foods with high fat, cholesterol, glucose, and low intake of leafy green vegetables are more likely to be affected with age-related macular degeneration.

OBESITY: Overweight individuals are at increased risk for developing age-related macular degeneration. Some studies correlate this with increasing body mass index.

HIGH BLOOD PRESSURE: The effects of high blood pressure on the vessels of the retina lead to decreased blood flow and poor circulation of the retina. This adversely affects the health of the macular area.

PRESENCE OF MACULAR DEGENERATION IN ONE EYE: If an individual has wet age-related macular degeneration in one eye, and dry in the other eye, they are at a 25% risk of developing wet age-related macular degeneration in the second eye within two years.

D. **INHEREITANCE OF AGE-RELATED MACULAR DEGENERATION**

There are five (5) major classes of genes involved in age-related macular degeneration progression:

- Complement pathway genes, CFH, C3, CFB/C2, CFI.
- Cholesterol metabolism genes, APoE, LIPC, CETP.
- Mitochondrial genes, ARMS2, ND2.
- Extracellular matrix regulating genes, TIMP3.
- MicroRNA processing enzymes, DICER1.

E. **TREATMENT OF DRY AGE-RELATED MACULAR DEGENERATION**

The management of neovascular age-related macular degeneration is challenging, but significant progress has been made over the last few years. The development of the new class of intravitreal anti-VEGF agents is in part responsible for the recent advances. Several agents have proven to be effective and safe in this condition and others are showing promising activity in ongoing clinical trials. Other treatments on the horizon may further expand the treatment armamentarium of these diseases.

The only proven therapy to reduce the risk of progression from dry age-related macular degeneration to the wet form of age-related macular degeneration is AREDS vitamins. AREDS stands for *Age-Related Eye Disease Study.* The AREDS was the largest randomized prospective study of macular degeneration ever undertaken. This study was sponsored by the National Eye Institute (a part of the National Institute of Health or NIH) and it evaluated the risk of progression from dry age-related macular degeneration to wet age-related macular degeneration over five (5) and ten (10) years. The AREDS study discovered that a certain formulation of vitamins and antioxidants could reduce the risk of progression to advanced age-related macular degeneration by up to 25% for patients with intermediate and high-risk dry macular degeneration.

A changed formulation of the supplement, AREDS2, has added lutein and zeaxanthin in the first AREDS nutritional supplement for treating age-related macular degeneration.

The new AREDS2 formulations on the market include TOZAL formulation by Focus Laboratories North (Little Rock, Arkansas) and PreserVision AREDS2 Formula (Bausch & Lomb, Rochester, New York).

The new study found that adding omega-3 fatty acids did not improve or harm patients with the disease, while luetin and zeaxanthin was a safe alternative to beta-carotene.

However, the omega-3 in the new study was of the ethyl-esterase form instead of the more effective triglyceride form. Omega-3 in the triglyceride form can be obtained commercially from NORDIC NATURALS with the OMEGA VISION label. This, in my opinion, will be helpful for an anti-inflammatory therapy along with the AREDS2 and would have made a difference in the new study, had it been used instead of the ethyl-esterase form of omega-3. The triglyceride form of omega-3 is similar to eating fish and is a DHA/EPA component which is still important for this patient population.

F. ANTIANGIOGENIC THERAPY FOR NEOVASCULAR ARMD

The management of neovascular age-related macular degeneration is challenging but significant progress has been made over the last few years. The development of the new class of intravitreal anti-VEGF agents is in part responsible for the recent advances. Several agents have proven to be effective and safe in this condition and others are showing promising activity in ongoing clinical trials. Other treatments on the horizon may further expand the treatment armamentarium of the disease.

There are three most commonly used anti-VEGF drugs for wet age-related macular degeneration therapy. These include Avastin (bevacizumab), Lucentis (ranibizumab), and Eylea (aflibercept).

- Avastin (bevacizumab) is an angiogenesis inhibitor used for the treatment of colon cancer, non-small cell lung cancer, and glioblastoma. Dr. Phil Rosenfeld reported successful results using Avastin injected into the eye for the treatment of wet age-related macular degeneration. The “off-label” use of Avastin for the treatment of wet age-related macular degeneration when compared to Lucentis (an FDA-approved drug for the treatment of wet age-related macular degeneration) for the treatment of wet age-related macular degeneration demonstrated that Avastin was not inferior to Lucentis in a National Eye Institute-sponsored study.

  The cost savings associated with using Avastin compared to the other FDA-approved medications has been immense with equal efficacy. Avastin is now the most widely used anti-VEGF drug by retinal subspecialists for the treatment of wet age-related macular degeneration.

- Lucentis® (ranibizumab) has been approved by the FDA for treatment of wet age-related macular degeneration. A dose of 0.5 mg is recommended for intravitreal injection once a month. If monthly injections are not feasible, treatments can be reduced to one injection every three months after the first four monthly injections. Compared to the use of continued monthly dosing, dosing every three months will

lead to an approximate five-letter (one-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly. "Lucentis® provides new hope for patients with wet age-related macular degeneration, because it is the first therapy to provide a benefit in vision for a significant number of patients," said Arthur D. Levinson, Ph.D., Genentech's Chairman and CEO. "We are proud that the seminal work in angiogenesis conducted at Genentech, years of clinical study, and the dedication and commitment of thousands of patients and retina specialists have all contributed to this important approval."

Eugene de Juan, M.D., past President, American Society of Retina Specialists, said: "In my opinion, the Lucentis® approval stands out as one of the most important medical developments in ophthalmology during my 25 years in the field, because it has the potential to reverse vision loss associated with wet age-related macular degeneration.

- Eylea® (aflibercept) is the most recent anti-VEGF drug on the market. It has been approved by the FDA for the treatment of wet age-related macular degeneration and for the treatment of macular edema secondary to central retinal vein occlusion. No studies to date have shown it to be more effective for this use than Avastin. The VIEW Study showed that Eylea® given less frequently was equivalent to Lucentis® given monthly. Eylea® binds anti-VEGF as does Lucentis® and Avastin. Eylea® is a fusion protein, whereas Lucentis® is an antibody fragment and Avastin is a full-length antibody. All bind to and inhibit VEGF.

G. **UPDATE ON DIABETIC RETINOPATHY**

According to the Early Treatment of Diabetic Retinopathy Study (ETDRS), clinically significant diabetic macular edema is one or more of the following:

- Retinal thickening at or within 500 μm of the center of the macula
- Hard exudates at or within 500 μm of the center of the macular if associated within adjacent retinal thickening.
- A zone or zones of retinal thickening one-disc area in size, at least part of which is within one disc-diameter of the center of the macula

Now, with antivascular endothelial growth factor (anti-VEGF) agents and corticosteroids, diabetic macular edema is more appropriately defined as being either center-involved or noncenter-involved.

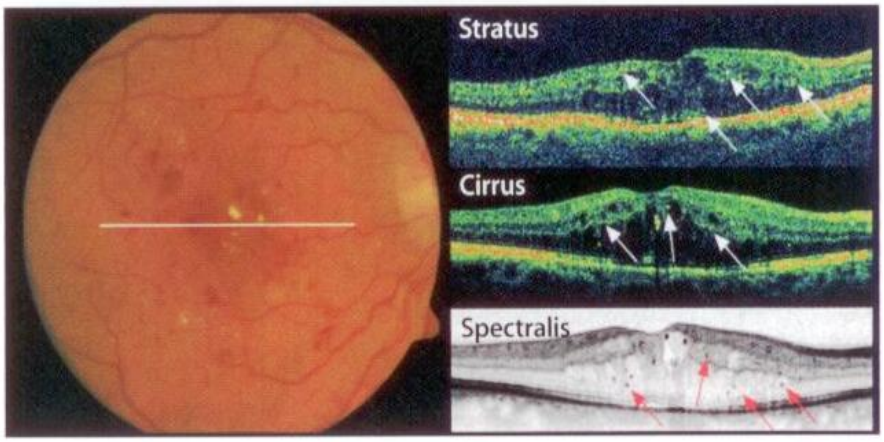
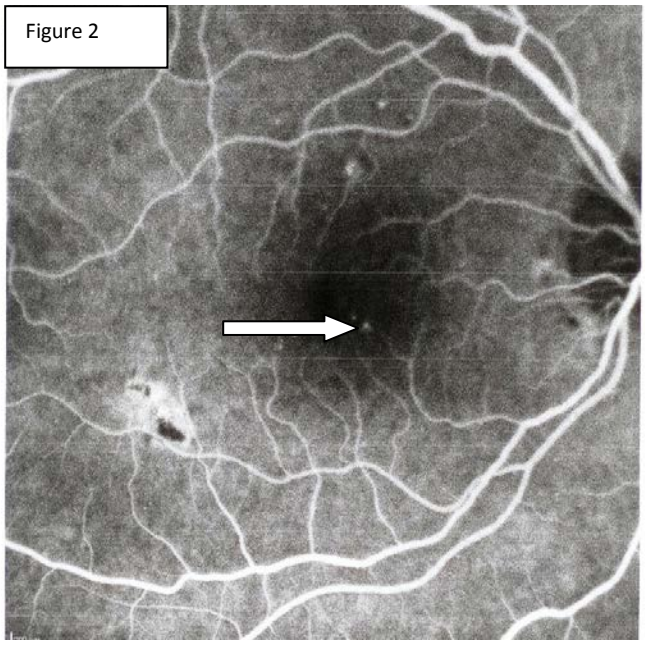


Figure 1. The arrows identify the hyperreflective foci, or black dots, that are seen throughout the retina layers.



If you compare the location on the OCT scans with that of the retina in Figure 1, you will see that most of the foci are hard exudates. Based on this observation, there must be a correlation between exudates and foci.

Assessing extent of leakage of diabetic microaneurysms on fluorescein angiogram can often be helped with an OCT.

The microaneurysm on the fluorescein (Figure 2 at end of arrow) looks harmless, but on the OCT (Figure 3), it is obvious that it is causing clinically significant diabetic macular edema.

The same microaneurysm visualized by spectral-domain OCT (SD-OCT) (Figure 3) along the vertical scanning plane spanning from inner plexiform layer to outer plexiform layer is the microaneurysm shown with the arrow in Figure 2.

Understanding the structural differences between non-leaking microaneurysms and leaking microaneurysms that may lead to clinically significant diabetic macular edema is important. Better understanding of structure and location of non-leaking or leaking diabetic microaneurysms may improve current treatment approaches to macular edema.

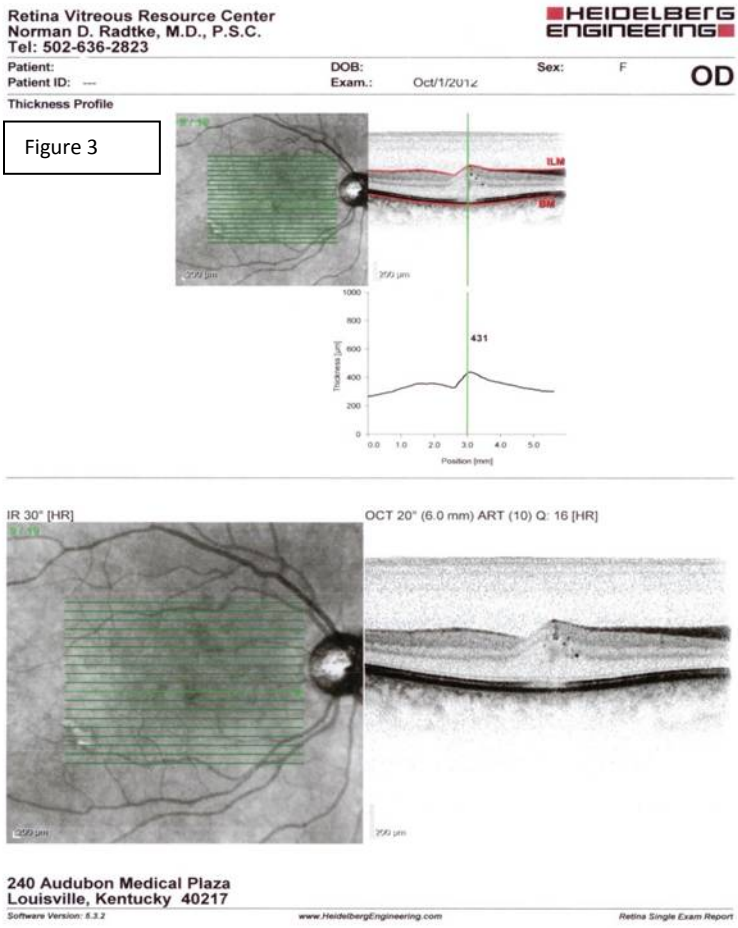


Figure 3

Avastin and Lucentis have been shown in multiple studies, that for an eye with center-involved diabetic macular edema, intravitreal injections improve both functional and anatomic outcomes compared with laser treatment alone.

Therefore, it is our conclusion that the SPECTRALIS OCT is a useful way to screen for advanced vascular damage in diabetic macular edema. This will also allow us to see which patients respond better to therapy for diabetic macular edema in the future.

In the February 10, 2014, issue of Retina Today (*Boyer D. Ozurdex Diabetic Macular Edema Study. Paper presented at: 2013 Annual Meeting of the American Academy of Ophthalmology; November 16-19, 2013; New Orleans, LA),* a Dexamethasone intravitreal implant (Ozurdex, Allergan) provided long-term visual and anatomic improvements for patients with diabetic macular edema (DME), according to David S. Boyer, M.D. He presented results of a 3-year, multicenter, masked, randomized, sham-controlled trial assessing the safety and efficacy of 700-µg and 350-µg dexamethasone posterior segment drug delivery systems.

H. GENE TESTING FOR PATIENTS

The best way to find a laboratory that offers a test for a specific patient's disease is through the ***Genetic Testing Registry of the National Institute of Health.***

www.ncbi.nlm.nihs.gov/gtr

I. EMERGING DEVELOPMENT AND CLINICAL APPLICATION OF OCT IN ANALYZING RETINAL AND CHOROIDAL DISEASES

The first available OCT instruments were based on time-domain technology.

The next breakthrough came with the spectral-domain OCT, which enabled dramatically faster scan acquisition times, therefore allowing for three-dimensional imaging.

Spaide was the first to use enhanced-depth-imaging (EDI) OCT. This effectively focused the OCT scanner on the choroid instead of the retina. Current systems cannot reliably create three-dimensional choroidal maps because the choroidal boundary might not be detected.

The most recent milestone in the development of retina and choroid visualization instrumentation is the swept-source (SS) OCT. The main advantage of the SS-OCT over the EDI-OCT is that the SS-OCT can create retinal thickness and choroidal thickness maps.

The new SS-OCT can show Bruch's membrane, choriocapillaris, Sattler's layer (layer of medium-diameter blood vessels), Haller's layer (outermost layer of the choroid consisting of large-diameter blood vessels), and lamina suprachoroidal.

With this new OCT technology, we can visualize retinal, optic nerve, and choroidal anatomy with a precision not seen before. This allows us to obtain enhanced information about structures of the retina, choroid, and vitreous that guide treatment in common retinal diseases and has enhanced our care of patients tremendously.

J. NANOTECHNOLOGY IN OPHTHALMOLOGY

What is the status of nanotechnology in ophthalmology? According to Paul Sieving, M.D., Ph.D., Director, National Eye Institute (NEI) in Bethesda, MD, the goals of NIH are to characterize the properties of molecules and nanomolecules, to understand the engineering principles that govern the interface between objects and biology, and to apply this knowledge through demonstration projects for repairing tissues, and ultimately to prevent and cure disease. The NEI has funded a number of applications that employ nanomedicine concepts including plasticity and regeneration of the retinal synapses, subconjunctival routes to prolong corticosteroid repair, and effects of substratum topography on corneal epithelium. Nanotechnology yields promise for retinitis pigmentosa, age-related macular degeneration, and ocular infections.

Nanoparticles should possess bio or mucoadhesive properties in order to achieve long precorneal retention time and to improve drug absorption. The intraocular use of biodegradable slow-releasing nanoparticles looks very promising for drug delivery targeted to the tissue of the posterior segment in order to treat chronic diseases or for gene therapy.

K. SEVEN-YEAR OUTCOMES OF LUCENTIS® TRIALS

A recent report study group (*Ophthalmology 2013 Nov; 120(11):2292-9)* AAO assesses the long-term outcomes 7-8 years after initiation of intensive Lucentis® (ranibizumab) therapy in wet age-related macular degeneration patients.

Subject comparisons were obtained from the ANCHOR, MARINA, and HORIZON databases.

The conclusions are:

- One-third of the patients demonstrated good visual outcomes.
- One-third of the patients had poor outcomes.
- Compared with baseline, almost half of the eyes were stable.
- One-third of the eyes declined by 15 letters or more.
- Even at late stage in the therapeutic course, wet age-related macular degeneration patients remain at risk for substantial decline.
- The factor correlating most strongly with poor visual outcome was increased area of macular atrophy.

- Exudative age-related macular degeneration is a chronic disease, and long-term outcomes cannot be extrapolated from the two-year results available from the ANCHOR and MARINA trials.

L. GENE THERAPY RESEARCH DEVELOPMENT

Robert E. MacLaren from Oxford, England has published an article in The Lancet, January 2014, describing the results of six patients who received gene therapy for choroideremia.

The initial results of the retinal gene therapy showed improved rod and cone function. In all patients, six months after gene therapy, there was an increase in retinal sensitivity in the treated eyes that correlated with the vector dose of the gene therapy.

The study assessed the effects of an adeno-associated virus (AAV) vector encoding REP1 (AAV.REP1) in patients with choroideremia. Choroideremia is an x-linked recessive disease that causes blindness due to mutations in the CHM gene, which encodes the Rab escort protein 1 (REP1).

The findings warrant further assessment of gene therapy in choroideremia, age-related macular degeneration, retinitis pigmentosa, and Stargardt's disease.

M. PROS AND CONS OF VITRECTOMY FOR FLOATERS

Up until a few years ago, vitrectomy for floaters would not have been considered because of the high risk for the potential gain that this would involve. However, over the past several years, the sophistication of the instrumentation and the success of the techniques for vitreous surgery have decreased the risk of doing this surgery.

There is no question that the patient can develop an infection, a retinal detachment, and can actually lose the eye because of an initial vitrectomy for floaters. No surgery would be recommended without completely making the patient aware of these facts. However, floaters do bother people and the significance of impaired vision to the patient is on an individual basis.

My initial encounter with this decision to make regarding a vitrectomy for floaters was with a lawyer who was ready to give up his career because he could not see in spite of having 20/20 vision bilaterally. After a thorough workup, the only thing we could find is that he had extensive vitreous floaters. A vitrectomy was done in the right eye, much to the chagrin of my nurse who asked, "Why would you operate on a patient with 20/20

vision, particularly a plaintiff's lawyer?" This lawyer was very adamant about not being able to work well because of the floaters. After we did the surgery, he was so ecstatic that he wanted surgery in the other eye done the next day. This is an extreme example, but many patients complain of floaters and often state they have been told that nothing can be done about them.

I think that vitreous floaters can pose a significant risk to patients. If it is in their visual axis, it could lead to falls and broken limbs. The risk of not doing surgery may be equal to the risk of performing surgery for vitreous floaters.

Full disclosure of risks and counseling the patient as to the pros and cons of a vitrectomy are imperative. The short recovery time and the relatively safe nature of the procedure warrant consideration of a vitrectomy for floaters if the patient is symptomatic enough to warrant such discussions.

N. JAPANESE CLINICAL TRIAL FOR INDUCED PLURIPOTENT STEM CELLS IN WET AGE-RELATED MACULAR DEGENERATION

A Japanese government panel on June 25, 2013 approved the world's first clinical research trial using induced pluripotent stem cells. Massayo Takahoshi, M.D., Ph.D. will serve as head of the clinical study in Kobe, Japan. She will be collaborating with Shinya Yamanaka, M.D., Ph.D., the winner of the 2012 Nobel Prize for Physiology or Medicine for his work with induced pluripotent stem cells.

Six patients with wet age-related macular degeneration will have skin cells taken and genetically reprogrammed to become iPS cells. These cells will be modulated to grow into retina pigment epithelial cells, which will take 10 months. The sheets of the retina pigment epithelial cells will then be transplanted into the eyes under the retina of patients who have had abnormal blood vessels removed.

These patients will then be monitored over the next four years to determine how well the implants have performed and whether the body has accepted them.

We will all benefit from the information obtained about minimizing tumorigenesis from the induced genetic mutations and possible viral contamination, regardless of what level of efficacy is attained.

O. **CONTINUED INFORMATION**

We hope the information presented in this edition of the Update is helpful to you. For more information, please visit our website at **www.rvrc.com** or contact our office at (502)636-2823.

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