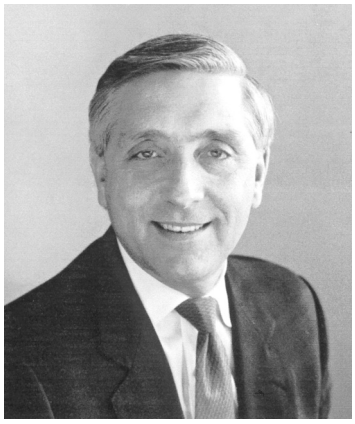
update

RETINA VITREOUS RESOURCE CENTER

Dr. Norman D. Radtke | July, 2002 | Volume 8, No. 1



Dr. Norman D. Radtke

Interchange

Dear Colleagues,

Update was initiated with a mission to provide you with the most in-depth and comprehensive review of the diagnosis and management of vitreoretinal disorders.

Our collective charge is to focus on taking the most innovative, new bench research findings from the laboratory and from clinical trials to translate it into new treatments for our patients. Evaluating what has the most significant clinical application is a major emphasis. This issue is focused on Advances in Macular Degeneration, Diabetic Retinopathy, and Central Retinal Vein Occlusion. This overview articulates the dynamics of research and its clinical application. Our findings continue to evolve, emphasizing the assessment of basic research and clinical trials as they pertain to our daily clinical practice with patients. Molecular medicine and genomics are the keys to the future of medicine and certainly to our understanding of age-related macular degeneration.

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

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

Sincerely,

N. D. Radtke, M.D.

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

Subject

Advances and Potential Treatments in Macular Degeneration, Diabetic Retinopathy, and Central Retinal Vein Occlusion

- Retinal transplantation
- Gene therapy and Genetics of Age-Related Maculopathy Study
- Vitamin therapy
- Radial optic neurotomy for central retinal vein occlusion
- Radiation therapy
- Laser therapy to drusen
- Membrane differential filtration
- Transpupillary thermal therapy
- Submacular surgery
- Retinal translocation
- Photodynamic therapy
- Feeder-vessel therapy
- Anti-angiogenesis therapy
- Vitrectomy indications for diabetic macular edema
- Implantable miniaturized telescope
- Low-vision aids

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 central areolar choroidal atrophy patients with macular degeneration, retinitis pigmentosa, and a vision of 20/800 in one eye. The following paper has been accepted for publication by the American Journal of Ophthalmology, Transplantation of Intact Sheets of Fetal Neural Retina with its RPE in Retinitis Pigmentosa Patients, Vol. 133, No. 4, pgs. 544-550, April 2002.

What is the content and clinical message of the article?

This is the first report in humans of combined transplantation of fetal RPE and neural retina. After six months in this safety study, two transplants increased in size and all five showed no clinical evidence of macular edema or tissue encapsulation.

What were the comments of the scientific review committee regarding the article?

"These authors are the first to report combined transplantation of fetal RPE and neural retina in an otherwise untreatable disease, and thus, the results are extraordinarily important." Another reviewer stated, "My sense is that the authors are on the verge of something important here, and while there will undoubtedly be many blind alleys and failures in between, the field is well served by incremental additions to the state of the art in the development of such potentially sight-restoring therapies as retinal transplantation."

What were the results of this study?

No evidence of rejection was observed. Out to six months, there was no evidence of tissue disintegration, retinal edema, scarring, or encapsulation. There was no change in the vision, by both ETDRS acuity and with multifocal ERGs. Growth of the transplant was noted in two of five patients at six

Responsible for retinal transplantation: Norman D. Radtke, M.D., Magdalene J. Seiler, Ph.D., and Robert B. Aramant, PhD.

Responsible for electrophysiology: Heywood M. Petry, PhD.

Responsible for immunologic studies: Diane J. Pidwell, PhD.

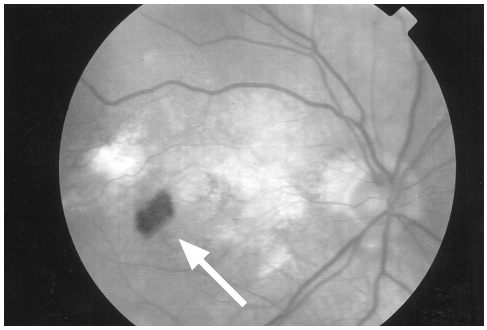


Fig. 1: Retintis pigmentosa patient with LP vision two weeks after implantation of sheet of fetal neural retina an RPE (arrow).

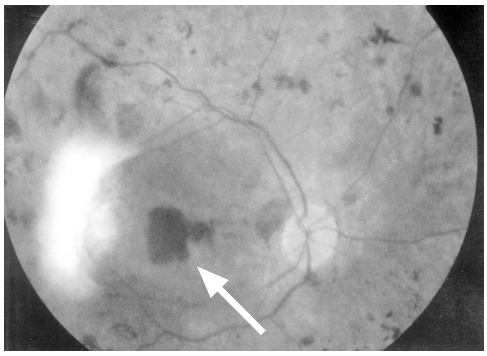


Fig. 2: Retintis pigmentosa patient with LP vision six months after implantation. Note growth of transplanted sheet of fetal neural retina and RPE as compared to same area in Fig. 1 (arrow).

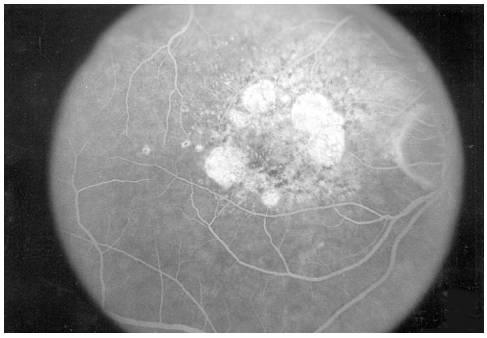


Fig. 3: A patient with central areolar choroidal pigment epithelial atrophy.

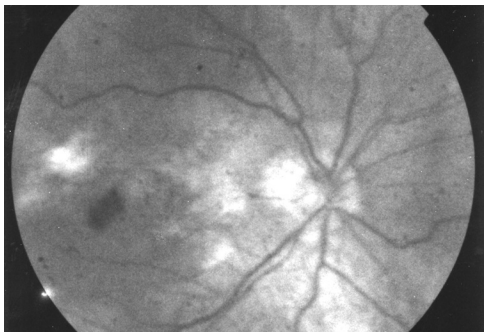


Fig. 4: Clinical picture of first patient with central areolar choroidal pigment epithelial atrophy who had a retinal transplantation. This transplant is out one year at this time with no signs of rejection.

months versus two weeks (Figs.1 and 2). All patients typed were HLA mismatched with donor tissue.

What were the conclusions of this study?

The study indicates that fetal retina can be transplanted together with its RPE and survive for at least six months without rejection. However, no improvement in vision was observed, possibly due to the severe retinal degeneration of the patients.

What is the next step in our retinal transplantation research?

The FDA has given us permission to do transplantation in patients with a vision of 20/800 in one eye with central areolar pigment epithelial dystrophy. Figure 3 shows a patient with central areolar choroidal pigment epithelial atrophy. A patient with macular degeneration in the form of central areolar choroidal pigment epithelial atrophy was successfully transplanted with RPE and neural retina and is one year post surgery (Fig. 4).

Is it possible to make a bionic retina with photomicrochip diode/retinal chips?

Several research groups, two in Germany and at least three in the U.S., are working on implanting light-sensitive microchips into the eye. Lately, additional research groups have started in other countries. This research still needs more time for development before it can be applied to patients.

There are two different approaches to the implantation of microchips into the eye. The simplest approach is to implant it under the retina to replace lost photoreceptors. This approach is being developed by Dr. Alan Chow in Chicago and Dr. Zrenner in Tubingen, Germany. The other groups in the U.S. and Germany (Eckmiller, Bonn, Germany; Rizzo at Harvard-MIT, Boston; Humayun at Johns Hopkins University, Baltimore) are trying to bypass the photoreceptors and stimulate the ganglion cell that transfers visual information to the brain. This is done by a 2-component system: a light detector in front of the eye that sends signals to a microchip placed on the surface of the retina and, in that way, stimulates the ganglion cells. The two units can be connected by inductive link telemetry, allowing the intraocular unit to derive both power and data signals from the extraocular unit wirelessly. The extraocular unit includes a video camera and a video processing board, a telemetry encoder chip, a radio frequency amplifier, and primary coil. The intraocular unit consists of a secondary coil, rectifier and regulator, retinal stimulator with a telemetry protocol decoder, stimulus signal generator, and an electrode array.

Humayun's group has tested blind patients with chips temporarily placed onto the retinal surface and reported some visual sensation after stimulation. News of these first surgeries, however, is a sign that artificial retinas are advancing toward clinical trials.

Dr. Normann at Utah University follows a completely different approach: to stimulate the brain directly with a microphotodiode array without stimulating the eye.

What is the "Genetics of Age-Related Maculopathy Study"?

The GARM study is a research effort to identify genetic factors that increase an individual's risk of developing macular degeneration. It was initiated in 1989 by Dr. Michael Gorin at the University of Pittsburgh and involves a number of ophthalmologists and their practices, such as ourselves, throughout the United States.

What are the genetics of macular degeneration?

Previous studies have shown that age-related macular degeneration can run in families. Children, brothers, sisters, nieces, nephews, and grandchildren of a person who has age-related macular degeneration may have an increased risk to develop this condition as they become older. The annotation of all human genes should result in rapid advances in the determination of which genes are

involved in the pathogenesis of age-related macular degeneration. Age-related macular degeneration will prove to be a multifactorial and multigenetic disease and will also prove to have a complex inheritance pattern involving multiple genes. The challenge is converting the tremendous amount of data gathered into useful information and knowledge.

Who can participate in the GARM Study?

Individuals who have macular degeneration and have a living relative who also has this condition are eligible for this study. It is necessary for at least two individuals in a family who have macular degeneration to participate. If an individual is selected to participate, he/she will be asked to provide a small blood sample. They do not have to travel anywhere other than their primary care physician or local clinic or hospital for this blood draw. No patient will be charged for any aspect of this study.

Why is the blood sample necessary?

The blood is used to isolate the genetic information to determine if a specific part of that genetic information is associated with the risk of developing age-related macular degeneration.

What genes have been recently discovered related to macular degeneration?

Kang Zhang, M.D., Ph.D., at Cleveland Clinic Cole Eye Institute has identified and cloned a major gene that causes Stargardt's like macular dystrophy and autosomal dominant macular dystrophy, two inherited forms of macular degeneration. His research is the first to implicate the biosynthesis of polyunsaturated fatty acids and the pathogenesis of inherited macular degenerations. A retinal photoreceptor-specific gene, called ELOVL4, has had bio-informatic analysis, and it revealed its significant function in a biosynthesis of very long chain fatty acids. ELOVL4 is the first gene involved in lipid metabolism implicated in macular degeneration. His results are the first to implicate the biosynthesis of fatty acids in the pathogenesis of at least two related forms of macular degeneration. His research appears in the January 2001 issue of Nature Genetics.

What is the most recent advance in gene therapy?

One of the single most important advances in the history of retinal degeneration research has been the restoration of vision in a canine model of a severe childhood blindness, known clinically as Leber's congenital amaurosis, as was published in the May issue of Nature Genetics by researchers at Cornell University, University of Pennsylvania, and University of Florida, lead by Drs. Gregory Acland and Gustavo Aguirre. This is significant in that it is the first time researchers have successfully restored vision in a large animal model of retinal degeneration.

What is Leber's Congenital Amaurosis (LCA)?

LCA is the name given to a group of severe early-onset forms of retinal degeneration, and researchers have discovered that mutations in the RPE65 gene causes a form of LCA. The RPE65 gene product supports the phototransduction cycle, the biochemical process that turns light into an electrical signal. Twelve weeks after a subretinal injection containing the RPE65 gene and a viral vehicle to deliver the gene to RPE cells, the ERG test revealed the treated eyes had a remarkable improvement in retinal function. By contrast, untreated eyes had almost no detectable ERG function. Behavioral testing also revealed that these canines had regained ambulatory vision.

Has this gone into clinical trials at this time?

At the present time, steps are being taken to advance this gene therapy treatment to human clinical trials. The significance of this is that if vision can be restored in this type of disease or retinal degeneration, other diseases may also be possibly treated, such as autosomal recessive Stargardt's disease, fundus flavimaculatus, cone-rod dystrophy, and autosomal recessive retinitis pigmentosa. A clinical trial in humans has begun at Johns Hopkins to treat a complication of macular

degeneration, new blood vessel growth under the macula, by gene therapy. Another trial of gene therapy for a form of retinitis pigmentosa, Leber's amaurosis, has been approved by the National Eye Institute, providing a $10 million grant to the University of Florida in Gainesville for the project. This form of Leber's amaurosis is due to a defect in the retinal pigment epithelium (RPE). The epithelium rapidly picks up viral vectors, which facilitates transfer of genes into these cells. This strategy has worked in a dog model of this retinal degeneration. This is a landmark event in the history of hereditary photoreceptor degeneration, gene therapy being tested in a clinical trial! We have along way to go but it's an important first step.

What can't gene therapy do?

If the photoreceptors have degenerated, gene therapy cannot help. In this case, one must depend on other breakthroughs, transplantation of photoreceptors or the use of an electronic substitute for photoreceptors. Both techniques are being studied. They are more difficult than gene therapy but they are rational and therefore do-able.

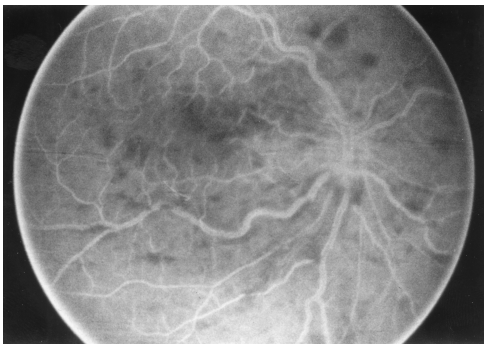


Fig. 5: CRVO patient with count fingers vision.

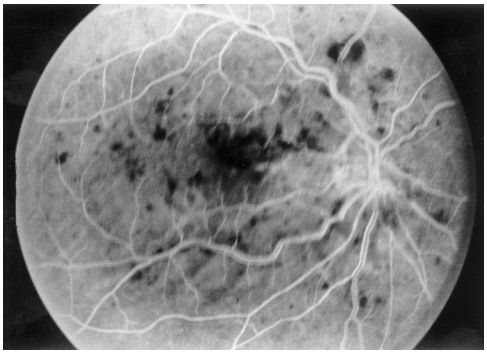


Fig. 6: Same CRVO patient with 20/50 vision following radial optic neurotomy.

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 below:

- Vitamin C 500 mg per day
- Vitamin E 400 international units daily
- Beta-carotene 15 mg daily
- Zinc, as zinc oxide, 80 mg daily
- Copper, as cupric oxide, 2 mg daily

Lutein and zeaxanthin, although not studied in the AREDS Study, 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.

What is the newest clinical treatment for central retinal vein occlusion?

Radial optic neurotomy for central retinal vein occlusion has been shown, in a retrospective pilot study of 11 consecutive cases by Dr. E. Mitchel Opremcak from the University of Ohio, to improve the vision in patients who are 20/400 or better - such that their postoperative visual acuities were equal to or improved in 82% of the patients. Eight of the patients (73%) had rapid improvement of visual acuity with an average gain of five lines of vision. Many anecdotal follow-up reports subsequent to this publication have indicated other surgeons have gotten improved visions from 20/400 or count fingers to ranges going from 20/20 to 20/60. This certainly appears to be a very positive report and has been substantiated in the hands of other surgeons as well. Our own results indicate that we have had patients who have gone from count fingers (CF) or worse to 20/50. (Figs. 5 & 6) It is definitely a procedure which I think has value, and I would recommend it to patients who would qualify with a preoperative visual acuity of 20/400 or less.

Are any other therapies for central retinal vein occlusion available at this time?

Dr. Jeffrey M. Weiss has presented work of a prospective study of 46 eyes that were given a tissue plasminogen activator injection into the central retinal vein. He noted that 53% recovered at least three lines and eight eyes gained at least six lines. His theory is that, because the problem is decreased retinal perfusion, his technique is an effective treatment to re-establish perfusion. He feels that vascular thrombosis causes poor perfusion, and therefore, thrombolysis is a potential strategy to improve this. T-PA is a fibrin-specific enzyme that lyses plasminogen to plasma. A retinal vein cannula allows surgeons to administer t-PA directly to the site of the thrombus in central retinal vein occlusion. Dr.

PA directly to the site of the thrombus in central retinal vein occlusion. Dr. Leon A. Bynoe, in the practice with Dr. Weiss, initially presented the results of the human patient at the Annual Meeting of the American Academy of Ophthalmology. At this time, the only way that their research will know for certain about the relative contribution of t-PA is to randomize patients to either t-PA or normal saline injection. This work is presently ongoing.

What trials are ongoing for radiation treatment?

Trials are ongoing but results are very unequivocal at this time.
Despite negative results in early trials, efforts are continuing to determine whether external beam irradiation can slow visual loss caused by subfoveal choroidal neovascularization in age-related macular degeneration. The take-home message stated by Dr. Dennis M. Marcus, who is at the Medical College of Georgia and is involved in a multi-center randomized pilot study financed by the National Eye Institute Clinical Trial Planning Grant, says that the study of external beam irradiation for treatment of subfoveal choroidal neovascularization in age-related macular degeneration is continuing. Three of five studies have shown promise. One year pilot results will be available in six months to a year.

What studies are ongoing for laser therapy to drusen?

Studies are ongoing but the results to date are very unequivocal.

What is the role of atherosclerotic process in age-related macular degeneration?
Usually macular degeneration and atherosclerosis might share mechanisms of extracellular cholesterol deposition. Friedman's vascular model proposes that it is the combination of high choriocapillary pressure, breaks in calcified Bruch's membrane, and vascular endothelial growth factors that are responsible for the growth of new vessels into the subretinal space and macular degeneration.

The vascular model suggests that the decisive development in the pathogenesis of age-related macular degeneration is elevated choriocapillary hydrostatic pressure.

The therapeutic implication is that membrane differential filtration or Rheofilter System to remove high molecular weight lipoproteins to thin the blood and increase capillary blood flow, thereby increasing oxygen delivery to the tissue, increasing metabolism, increasing elimination of cellular waste products, and improving cell function, would help prevent macular degeneration.

This is being tested in a very good study by Dr. Ron Davis at Indiana University/Perdue University at Indianapolis. His phone number is 317-274-3821. Other studies being done in Germany, requiring extensive cash outlays by patients, are not being done under the close control of the study by Dr. Davis. Additional information will be forthcoming, I am sure, but patients are going to Germany for this now. I have seen this in my practice happen already where my patients have had great expense in travel and treatment cost for a procedure that is still being investigated scientifically. Although this procedure has some theoretical basis, there is a long way to go before clinical application should be widespread.

How effective is TTT?

Transpupillary thermal therapy (TTT) may be useful in treating occult choroidal neovascularization, but it is felt at this time that it is probably not useful for treating predominantly classic choroidal neovascularization. This therapy involves using a 60 second laser exposure with a 3.0 mm or greater spot size and a power of 300 to 800 milliwatts. Theoretically, in TTT, you see no visible retinal change because of the low temperature rise induced by the treatment.
At present, a large multicenter trial is underway to help determine if TTT stabilizes vision in these occult lesions.

What is the theory of treatment with submacular surgery in macular degeneration?

The theory behind the surgery is that by removing the choroidal subretinal neovascular membrane you can halt the lesion's growth and the enlargement of the central visual defect. Unlike the laser procedure, submacular surgery may

spare photoreceptors in the region of the neovascular membrane. The problem with that is that you do take out the RPE with these nets.

Although results have been promising for ocular histoplasmosis and somewhat promising in age-related macular degeneration, recurrence rates are very high. Most recurrences, especially in age-related macular degeneration, are beneath the fovea. The question in this situation is how to proceed. Is a repeat of the surgery indicated, is a performing of photodynamic therapy, or is laser photocoagulation necessary? At this time, it may also be valuable to perform the surgery after photodynamic therapy when this fails, but at this time, no substantial information is available about this technique.

What is the status of retinal translocation?

Retinal translocation is being developed and involves performing a large retinal detachment and suturing the sclera, repositioning the retina with a gas bubble, then lasering the neovascularization.

Six-month data is now showing some promise, but surgical complications are significant. At this point, no data is available on the exact rate of recurrence after laser treatment and whether recurrent lesions will be subfoveal. Translocation surgery works best in patients who have a small, well-defined lesion of recent onset, good vision, no previous laser treatment, and healthy retinal pigment epithelium. It appears, however, that the lesions that do best with the surgery are the same ones that do best with photodynamic therapy. Complications are great with this treatment and include a high retinal detachment rate, inadequate retinal shift, and torsion diplopia.

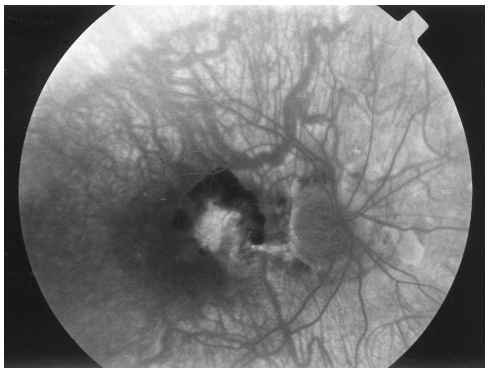


Fig. 7: Patient with a SRNVM in the fovea, secondary to myopic degeneration, and a vision of 20/200.

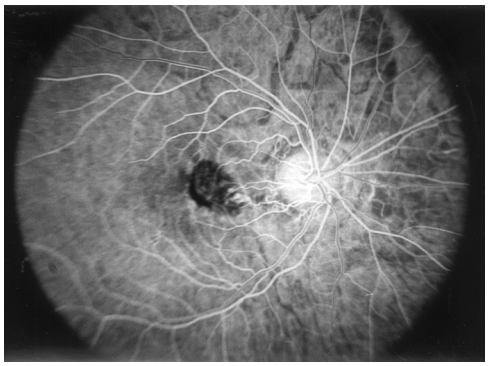


Fig. 8: Same patient as above with a SRNVM in the fovea, following PDT, and a vision of 20/25.

What are the recent findings in photodynamic therapy?

It seems at this time that researchers have found that verteporfin therapy works best when the lesions are less than 4 MPS disc areas or vision is 20/50 or worse. Additional clinical evidence indicates that the average visual acuity remains stable during the third year of verteporfin therapy.

As studies continue, new information will come to light regarding this new therapy, and it does seem to help in many patients which were otherwise untreatable with present therapies. Approved last year by the FDA, PDT is a two-step process: administration of a photosensitizing dye, followed by application of low-intensity laser light for activation of the dye. The recent randomized multicenter clinical trial in the U.S. and Europe, of which we were a part, found this was a significant treatment benefit. The ratio is almost two to one for preservation of vision with Visudyne compared to placebo.

Dr. Corrado Balacco Gabrieli from Rome University stated that, although visual results are still poor, patients experience improved retinal sensitivity, better perception of colors and less visual field distortion. There is a noticeable improvement of other functional parameters which improve the quality of the patient's life. Our results in a patient with a subretinal neovascular membrane (SRNVM), secondary to myopic degeneration, went from 20/200 to 20/25 (Figs. 7 & 8).

What is the technique for feeder-vessel therapy?

Feeder-vessel therapy involves using high-speed digital indocyanine green angiography (HSICG) to identify a feeder vessel which can then be treated in an extra-foveal location to close the choroidal neovascular membranes. Because it is infrared, it provides excellent detail of feeder vessels and some subpigment epithelial membranes that are obscured on fluorescein studies. It allows 12 frames per second and does an excellent job of identifying feeder vessels. The feeder vessels are gone in a couple of seconds and require a great deal of time to look for on HSICG. The feeder vessels are rarely seen on still-frame fluorescein or standard ICG. It is unclear how many feeder vessels you would need to treat in one patient. Although feeder vessel therapy has been discussed for many years and is performed in relatively few centers, the data to date is convincing for those who have explored the technique.

What are the new areas of interest in anti-angiogenesis therapy?

Anti-angiogenesis therapy may hold the greatest promise for treatment of subfoveal nets due to age-related macular degeneration. Anti-angiogenesis may

involve the administration of multiple drugs or perhaps in conjunction with other therapies.

With multiple possible targets for anti-angiogenesis, many drugs are coming onto the scene. These include vascular endothelial growth factor inhibitors, protein kinase-C inhibitors, matrix metalloproteinase inhibitors, Alpha-V-Beta integran antagonists, and steroids/steroid analogs. There are several ongoing trials evaluating the potential for such novel treatments.

What evidence supports the use of vitrectomy for diabetic macular edema?

Dr. Brooks W. McCuen, II, indicated that vitrectomy for recent, severe, diabetic vitreous hemorrhage was appropriate for vitreous hemorrhages obscuring the disc and macula, vitreous hemorrhages that persisted for at least one month and less than five months, and when visual acuity was 5/200 or light perception. His rationale was that this would reduce traction to reduce retinal distortion and detachment and inhibit new proliferations, shorten the period of traction on the retina, and remove membranes and posterior cortical vitreous to the extent technically feasible. Results have indicated that in Type I diabetics, early vitrectomy is more likely to produce 20/40 vision or better than late vitrectomy. There were no differences in modest vision or loss of all vision between early and late groups. In Type II diabetics, there was no benefit of early vitrectomy in the likelihood of achieving 20/40 or better vision and slightly higher incidence of NLP in the early group.

Dr. Hilel Lewis published an article in the American Journal of Ophthalmology, Vol. 131, No. 1, January 2001, pgs., 123-125, that indicated the vitrectomy should be considered where a shallow macular detachment is found. The article stated that the available evidence and the scientific rationale are both very suggestive. It appears that evidence exists that the vitreous plays a role in the development or exacerbation of macular edema in diabetic patients and that removing it is beneficial.

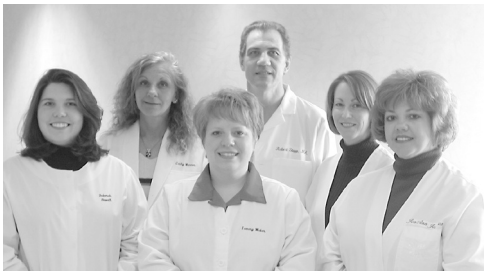
What is the status on implantation of miniaturized telescope?

To date, 26 patients have been completed in Europe and 15 in the United States. The FDA has not allowed an expanded number to be done in the U.S. until the initial results have been evaluated. We hope to become part of the study if the FDA allows it to expand to other centers. For updates, check their website at www.visioncare.co.il.

What services and equipment are available for patients who have poor vision, secondary to age-related macular degeneration?

The clinical staff has gathered extensive information regarding low vision services, social work services, and equipment available for low vision aid assistance. They are well versed in discussing this information with our patients, and updated lists of available equipment and types of services that are best suited for each patient's condition are provided to them.

Our administrative staff is very attuned to the needs of our patients and they give each individual a great deal of personal care regarding their own special circumstances. Issues addressed are timely appointments, insurance concerns, and follow-up with the results for patients of special testing in and out of the office.



Clinical Staff (L to R), Deborah Howell, Cathy Werner, Tammy Weber, Robert Stepp, Tina Borders, JonAnn Johnston.

Administrative Staff (L to R), Cathy Edens, Peggy Dennis, Cynthia Cranmer, Beverly Goatley.

Cathy Edens, Editor of Update

Cathy was been with the Retina Vitreous Resource Center since 1985. She has become an integral part of the administrative staff and has been instrumental in our preparation for obtaining an FDA IND number concerning our research efforts. She frequently assists in the development of our grant and scientific article submissions, maintains and coordinates continuing medical education, obtains CME certification for instructional courses, and has been responsible for the preparation and editing of our Update issues.

Cathy also transcribes our patient records and provides timely communication between our office and the referring doctors on each patient's clinical evaluation and test results.

update
RETINA VITREOUS RESOURCE CENTER

Dedicated to professionalism in the field of ophthalmology. Articles appearing in Update may be reprinted with proper credit given. Norman D. Radtke, M.D., P.S.C., Three Audubon Plaza Drive, 240 Audubon Medical Plaza, Louisville, Kentucky 40217. 502 636-2823.