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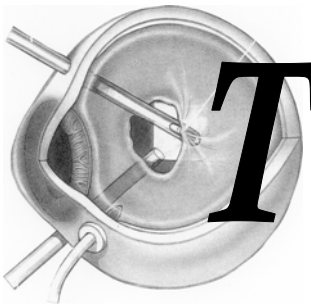

The Light Pipe

The newsletter of Georgia Retina, P.C.

Is it Classic or Occult And Why Should I Care Anyway?

There are several factors that are taken into consideration by a retinal specialist when evaluating a patient with macular degeneration. Of course the most important distinction is the presence or absence of choroidal neovascularization. This is the basic difference between the exudative and non-exudative (wet and dry)forms of age-related macular degeneration. After that question is answered the equation becomes a little more complicated. Although we can usually detect the presence of neovascularization clinically, the distinction between classic and occult choroidal neovascularization is made angiographically.

With the advent of new and innovative technologies such as photodynamic therapy, transpupillary thermotherapy, and intravitreal anti-VEGF agents, the distinction between occult and classic lesions is critical, and has to be explained to patients. The task of conveying these subtle differences among neovascular lesions to elderly patients can be quite challenging. It is sometimes hard enough for a group of retina specialists to agree on subtle angiographic findings, let alone to explain to Mrs. Jones why she does not qualify for Medicare's criteria for "on-label" PDT, because her lesion is occult.

The interpretation of an angiogram in many cases of macular degeneration is complex because lesions are frequently a combination of classic and occult. Other factors such as the presence of blood, pigment or opaque subretinal fluid further complicate the interpre-

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New Pharmacologic Therapies for CNV

The treatment of CNV associated with ARMD has been focused on reduction of severe visual loss, but has never been expected to produce visual *improvement*. According to the Macular Photocoagulation Study, the goal of thermal photocoagulation was to reduce the percentage of patients sustaining 6 or more lines of vision loss. Surgical removal of neovascular membranes uses a mechanical, physical approach to address a biological problem. Photodynamic therapy with Visudyne can preserve retinal tissue but only occasionally results in visual improvement. TTT with the 810 nanometer diode laser may stabilize some patients, but also rarely results in visual improvement. In the long run, none of these are likely to be as successful as drug therapy. We are beginning to move into an era where biochemical factors leading to the growth of these abnormal vessels will be addressed with medical therapy, and improvement in vision may be a more reasonable expectation for many patients.

VEGF (vascular endothelial growth factor) is an important stimulator of CNV. Recently, two new pharmacologic agents have been developed as VEGF inhibitors: **Eye 001** (an anti-VEGF aptamer) and **rhuFab** (a humanized anti-VEGF antibody fragment). Both are injected intravitreally. Eye001 is injected every 6 weeks, and rhuFab every 4 weeks. Phase II study results show that with

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Artifical Retinal Prosthesis

When patients present with end stage retinal degenerative conditions such as retinitis pigmentosa or macular degeneration, often their only recourse is the low vision clinic. Ongoing research into an artificial retina could open up a new range of options for these patients.

Most current concepts for a visual prosthesis are based on electrical stimulation of the nervous system at different locations along the visual pathways. Rudimentary vision may eventually be provided by electrical stimulation of the retina or the optic nerve in blindness caused by outer retinal degeneration, such as retinitis pigmentosa or age-related macular degeneration. More severe retinal damage or loss of the eye would require a cortical prosthesis.

Optobionics Corporation is developing a self-contained prosthesis termed the ASR for Artificial Silicone Retina. The device measures 2 mm in diameter and contains 3500 solar cells which act as photoreceptors. The device is or must be placed in the subretinal space. The ASR derives all of its power from light entering the eye. One concern with this style of microchip would be the threshold of light required to

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Update on Central Retinal Vein Occlusion

This venous obstructive disease of the retina is the second most common retinal vascular disorder, after diabetic retinopathy. It typically affects patients over 50 years of age. Central retinal vein occlusions are generally divided into ischemic and non-ischemic variations. Vein occlusions are associated with diabetes mellitus, hypertension, and cardiovascular disease. Chronic open-angle glaucoma is also relatively common among these patients.

Patients with CRVO show dilated tortuous retinal veins and retinal hemorrhages in four quadrants. The optic nerve may be swollen, and there is intraretinal hemorrhage and macular edema. In non-ischemic CRVO, there tends to be small dot and blot hemorrhages, mild venous engorgement, and mild to moderate macular edema. Relatively few cotton wool spots are present. There is rarely a significant APD. Anterior segment neovascularization is quite rare, unless this converts to an ischemic CRVO. Many of the clinical findings resolve over six to twelve months. Shunt vessels can appear later, as can pigmentary changes or persistent CME.

In ischemic CRVO, vision is usually worse than 20/200, with an afferent pupillary defect. Massive lipid exudation can occur, and exudative retinal detachment may even develop.

Anterior segment neovascularization may develop in over 50% of patients with truly ischemic CRVO, and can occur as early as two months after the onset. Neovascular glaucoma can develop within 90 days. Retinal neovascularization is less common but may be seen. Over time, the edema and hemorrhages will slowly resolve in most patients. The optic nerve will often show pallor and shunt vessels later. In CRVO, it is also important for a patient to have medical evaluation to look for risk factors such as blood dyscrasias, clotting abnormalities, and auto-immune disorders.

The differential diagnosis includes ocular ischemic syndrome associated with carotid artery occlusive disease. In that case, the hemorrhages tend to be more peripheral, with milder edema and less vascular engorgement. Hyperviscosity syndromes may produce a bilateral hemorrhagic retinopathy. Obviously, medical and laboratory evaluation are very important in any patient with bilateral disease.

Pathologic studies of eyes with CRVO usually reveal a thrombus at or just posterior to the lamina cribrosa in the central retinal vein. Atrophy of the inner retinal layers due to inner retinal ischemia is also a common pathologic finding.

The course of CRVO is disappointing. Even in mild, non-ischemic CRVO, up to half of the patients deteriorate to 20/200 or worse vision in the long run. Also, approximately 1/3 of non-ischemic cases convert to retinal ischemia. Patients with ischemic CRVO tend to have worse than 20/200 vision 90% of the time. There is also a small but finite risk of retinal venous occlusion in the fellow eye over time.

Treatment of CRVO has been quite disappointing. If neovascular complications develop, panretinal laser photocoagulation has been proven to be very effective at reducing the NV, if applied in a timely fashion. The neovascularization can be reversed, and neovascular glaucoma can actually resolve. The macular edema associated with CRVO can be reduced with grid photocoagulation; however, vision rarely improves with this treatment.
Grid photocoagulation is therefore rarely used in this disease.

Laser-induced chorioretinal anastomosis has been proposed by McAllister et al, with variable success. This is rarely used because of the high complication rate.

Fluorescein angiography can be somewhat helpful in CRVO patients, particularly in estimating the degree of non-perfusion. Several studies have demonstrated a strong correlation between the degree of angiographic non-perfusion and the likelihood of future neovascular complications.

The Central Retinal Vein Occlusion Study supported by the National Eye Institute was completed in 1994, with a total of 725 patients. Several guidelines for management of CRVO patients have arisen from this study.

The CRVO study did indicate a strong benefit of PRP laser in reducing neovascularization and the risk of neovascular glaucoma, after anterior segment neovascularization had developed. Interestingly, there did not appear to be a prophylactic benefit of PRP prior to the development of NV, even in patients with severe capillary non-perfusion. Grid photocoagulation did not prove effective at improving visual acuity. The major prognostic factors for neovascularization included poor visual acuity and significant retinal hemorrhage.

All eyes with CRVO require a careful initial examination, including best visual acuity, undilated slit lamp examination including gonioscopy, in addition to IOP measurement and fundus exam. This exam should be repeated at monthly intervals for the first six months. PRP laser should be instituted promptly whenever neovascularization is identified.

Because of the dismal prognosis for patients with poor visual acuity related to a CRVO, other means of treatment are being

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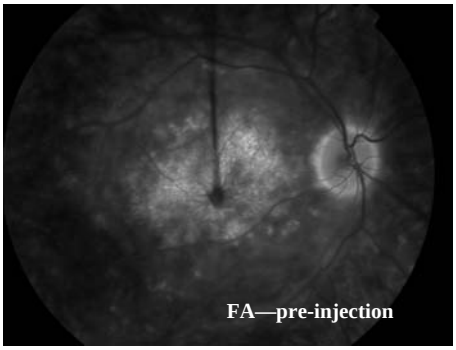
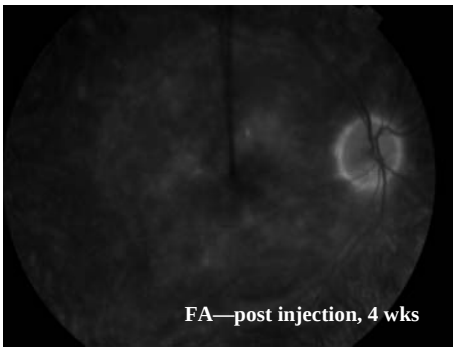

FA—pre-injection

Case Report:

Intravitreal Steroid Injections for Diabetic Macular Edema

P.H. is a 70 year old man with a 10 year history of diabetes and hypertension. Visual acuity in 1999 was 20/40 –1 in his right eye. Because clinically significant macular edema was present, a focal laser treatment was performed in 1999. In April 2001, despite maintaining 20/40 +1 vision, overt CSME persisted. Grid laser treatment was performed on April 27, 2001. At that time, the patient was advised that if the macular edema persisted and the vision dropped, vitreous surgery would be considered. In October 2001, the visual acuity had slipped to 20/50 –2, and was 20/80 level February 2002. The macula had a very cystic appearance. Fluorescein Angiography demonstsrated CME and mild ischemic maculopathy, as well as an excellent pattern of grid laser photocoagulation encircling the macula. No additional laser treatment was offered. The patient's visual acuity in March 2002 was 20/100 –1. The patient was unhappy with his vision, and was presented with the options of observation, vitreous surgery, or intravitreal steroid (Kenalog) injection. He chose the last, which was administered. One day later his visual acuity improved to 20/80 –1, and two weeks later it was 20/70 –1 with improvement of near vision as well. One month later the vision improved to 20/60 –2. At the most recent follow up visit, he had achieved a near vision of 20/30 –2 equivalent at 16". A follow up visit is planned in 4 weeks. If his visual acuity slips from this level, a supplemental intravitreal Kenalog injection may be administered.


FA—post injection, 4 wks

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Eye001 for subfoveal CNV, visual acuity stabilized or improved in 87.5% of patients, and 26% had a greater than 3 line improvement in visual acuity. When combined with PDT, 90% were stable or improved, and 60% had an improvement in acuity greater than or equal to 3 lines. With rhuFab monotherapy, 92% were stable or improved at 3 months, and 32% had an improvement in acuity of 3 lines or greater. 44% had a 2 line improvement. A study of Eye001 is enrolling patients in a phase III study, and enrollment in the rhuFab phase III trial is about to begin. A third substance also in phase III trials is **anecortave acetate**, an angiostatic steroid, whose main effect is to induce plasminogen activator inhibitor mRNA, which inhibits the breakdown of existing blood vessel walls, to slow the growth of new vessels. This is administered as a sub-Tenon's injection every 6 months. Data from phase II shows 92% stable or improved at 3 months, with 18% gaining 2 lines or more. This may also be helpful in combination with PDT, and it decreased the frequency of Visudyne re-treatments. It is still speculative what role these agents may have in combination, since they work by different mechanisms.

We at Georgia Retina are a study center for Genentech's phase III multicenter randomized controlled trial of rhuFab. This is a double-masked sham-injection controlled study. Patients must have visual acuity of 20/40 to 20/320. Patients must be willing to be randomized to the active drug group or the sham injection group. Those in the sham group will have a syringe with no needle pressed against the sclera to simulate an injection. We welcome your participation in this exciting study, and would be happy to evaluate any patients who you believe may be eligible. Please call our study coordinator, Ms. Misty Annis, at 404-299-5209, if you would like information about specific entrance criteria. We believe these treatments offer an exciting new avenue of treatment for a devastating disease, where a significant proportion of affected patients can expect an improvement in vision over baseline.

Retinal Pearls Symposiums
Now in the planning stages
Watch your mailbox for more details!

(Continued from page 2)

attempted. Very recently, Opremcak et al have published a pilot study of radial optic neurotomy for central retinal vein occlusion in the journal RETINA. The paper describes 11 patients who had an incision created with a 20-gauge microvitreoretinal blade through a pars plana approach at the nasal edge of the optic nerve. Cadaver studies showed that this type of incision would cut through the scleral ring at the cribiform plate, without creating an externalized incision. The rationale behind this is to eliminate a bottleneck configuration at the level of the cribiform plate, where the optic nerve narrows from 3 mm to 1.5 mm.

Opremcak has subsequently presented the results of a total of 30 patients at two retina meetings. Over 80% of the patients who underwent this procedure had dramatic improvement in their vision. Both perfused and non-perfused central retinal vein patients benefited. He postulates that incising the scleral ring relieves a "compartment syndrome."

Other related papers have been presented and several lines of surgical instruments are being marketed for this procedure. We look forward to further research in this area.

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tation. However, there are some relatively straightforward rules that will make understanding a formal interpretation of your patients' angiograms a little easier.

The presence of abnormal choroidal fluorescence, time to appearance of the abnormality, the presence or absence of significant leakage or pooling, and the position of the leak relative to the fovea are all important aspects of the interpretation. There are other subtleties to consider, such as fading fluorescence, staining from scar tissue and serous retinal pigment epithelial detachments (PEDs) or RPE tears. Putting these complicating issues aside, choroidal neovascularization will have components of one or a combination of the following patterns.

Classic choroidal neovascularization (CNV) is defined as abnormal choroidal hyperfluorescence that is first seen in the early frames of the angiogram usually within 30 seconds. The CNV leaks fluorescein through the mid and late frames (one to ten minutes) and fluorescein may pool in the subretinal space in the late frames. Classic lesions are usually "well-delineated", meaning that the borders are regular and sharply defined. Not all well-delineated lesions are classic, however. The terms are not interchangeable.

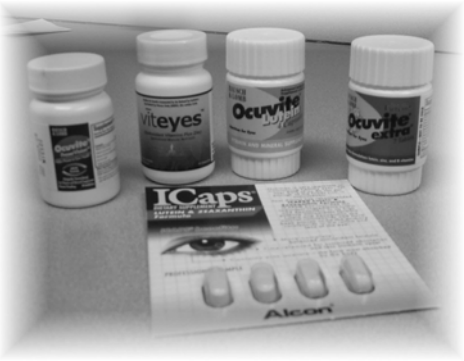
Occult CNV includes two fluorescein patterns. One is a "**fibrovascular pigment epithelial detachment"**or fibrovascular PED. Fibrovascular PEDs appear clinically as irregular elevations of the retinal pigment epithelium. Angiographically, abnormal choroidal fluorescence is noted between one and two minutes after injection, and staining or leakage persists in the late frames. Fibrovascular PEDs may also have defined borders and may be considered well-delineated. The second pattern is "**late leakage of undetermined source"**. This consists of areas of leakage in the late frames of the angiogram that are not evident in the early or middle phases. These lesions tend to cause low grade leakage and subretinal fluid that may stay stable for extended periods of time. Late leakage is generally poorly-delineated.

Most cases of CNV, particularly in age related macular degeneration, will not be purely classic or occult. In these cases we must make an estimate of the percent of the total lesion that is classic. For example, a lesion may be purely classic (100%), purely occult, primarily classic (>50%), or "minimally" classic (<50%). This determination has become extremely important in deciding which cases are eligible for on-label photodynamic therapy, because of criteria adopted by Medicare and most insurance carriers. (Medicare only allows lesions >50% classic to be covered,)

Another extremely important characteristic is the position of the lesion relative to the center of the fovea. By definition, a subfoveal lesion must have a component that sits directly under the foveal center. A juxtafoveal lesion has a portion of the lesion sitting from (1-199 microns) from the foveal center and an extrafoveal lesion sits (200-2500 microns) from the center of the fovea. (Patients are only eligible for PDT if a lesion is subfoveal rather than juxtafoveal.)

A good portion of our day is spent explaining some of these terms to elderly patients with macular degeneration, so they or their family may understand the rationale for recommending one treatment over another. Some patients want all the details and are capable of understanding why photocoagulation of a juxtafoveal lesion may leave a scotoma. Other patients don't want to hear the details and prefer to have treatment decisions made for them. The next time you see a patient with choroidal neovascularization or read a referral letter containing an interpretation of one of your patient's angiograms, it may be helpful to keep these definitions in mind.

Exercise Caution in Handing Out Those Vitamins



As you know, the AREDS trial has shown reduction in the rate of progression of age-related macular degeneration in selected groups of patients taking antioxidants and zinc compared to placebo. It is important to keep in mind that there is an increased incidence of lung cancer among patients who are smokers, when treated with beta carotene. For these patients, it is advisable to recommend either the individual vitamin components (vitamin C, vitamin E, and zinc) or a multivitamin supplement plus a zinc supplement. From a medicolegal standpoint, this issue should be taken very seriously, since the recommendations have been widely published and it is incumbent upon all of us to inquire as to a patient's smoking history before recommending these vitamins. While everyone thinks of vitamins as being relatively benign, this potential side effect is quite serious.

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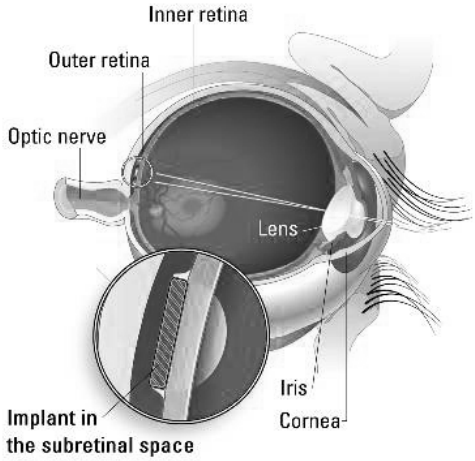
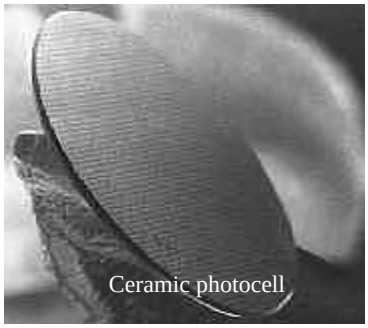
stimulate the solar cells. Accordingly, other subretinal devices are in development that require external power to amplify the incoming signal.



The Artificial Retina Component Chip (ARCC) is placed on the retinal surface. It measures 0.02 mm in thickness and 2 mm in diameter. Light is allowed to pass through the chip and strike the photoreceptors in back of the chip. However, the incoming light is not enough to power the chip. An external device is required to acquire, process and transfer the image via a trans-scleral cable into the device. At this stage, the device can provide a 10 by 10 pixel image which would be enough to see a single letter on a page. Eventually, more photoreceptors could be placed to make a 250 by 250 pixel array which would enable people to read.


Ceramic photocell

At the Japanese Institute of Physical and Chemical Research, an artificial retina was designed in 1997 which combined artificial elements with living nerve cells from newts. The early research allowed the development of a photochemical device which combines artificial photoreceptors with human neural cells.

The Space Vacuum Epitaxy Center in Houston is developing ceramic photocells as part of an artificial retinal prosthesis. Artificial retinas are constructed of 100,000 microscopic ceramic detectors attached to a polymer film, which disintegrates after implantation. Plans are to implant four arrays, totaling 400,000 detectors per eye. If successful, two additional arrays would be implanted. Human trials are expected to begin in 2002. With such a high density of photoreceptors, excellent resolution could be achieved.

Only a few of these devices have advanced beyond the concept stage. The Doheny Retina Institute is the site of an FDA approved trial of an epiretinal prosthesis. Two devices have been implanted in humans. Results show that the device, when coupled with external electronics, can allow perception of light. Each electrode can be controlled and patients can perceive individual electrodes.

Optobionics Corporation has implanted their subretinal device in six patients. An artificial retinal prosthesis is still many years away from practical application. Nevertheless, the concept offers hope to those we have not been able to help regain vision.

With research ongoing on many fronts, breakthroughs are likely.


Note chip above year 2000 on penny

"Your Most Valuable Asset is Your Staff"

Every few years we have made it a habit to survey not only doctors in the community, but also our own staff. We have found that this can provide us a better grasp of issues from their perspective. Most of us are proud of our relationships with the people who work for us, and most of us hope that we make our staff comfortable enough that they would come to us when they have issues. Even upon direct questioning, however, staff members may not reveal their true feelings. There will always be a certain intimidation factor, however unintended, when the employee is speaking to the employer. In an anonymous survey, staff are much more likely to be honest and open. In fact, we are sometimes surprised at how blunt their responses are. The process itself of surveying the staff can also improve *esprit de corps* because the staff feel that they have an opportunity to provide feedback. For this same reason we have a suggestion box in the waiting room of each of our offices, to field patient suggestions. This suggestion box also allows the (hopefully rare) dissatisfied patient to vent his feelings and concerns. Similarly, the staff members can use a staff survey to articulate their thoughts and concerns. We feel that an anonymous survey is much more conducive to eliciting useful information than a survey that identifies respondents. We think it is a good idea to distribute to the employees a brief synopsis of the survey results, highlighting information that can be used to make positive changes in the office.

Therefore, if you ask the questions, you have to be prepared to address whatever issues the survey may reveal. On a recent survey, we were pleased to find that across the board, our employees feel that Georgia Retina is a great place to work. While this was gratifying, the staff also asked for more specific training opportunities, which we are now in the process of developing.

Georgia Retina is committed to providing your patients with the best possible care. We always welcome your comments or concerns. Please feel free to call our practice administrator, Barbara Wright at 404-299-5209

We participate in the following insurance plans :

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