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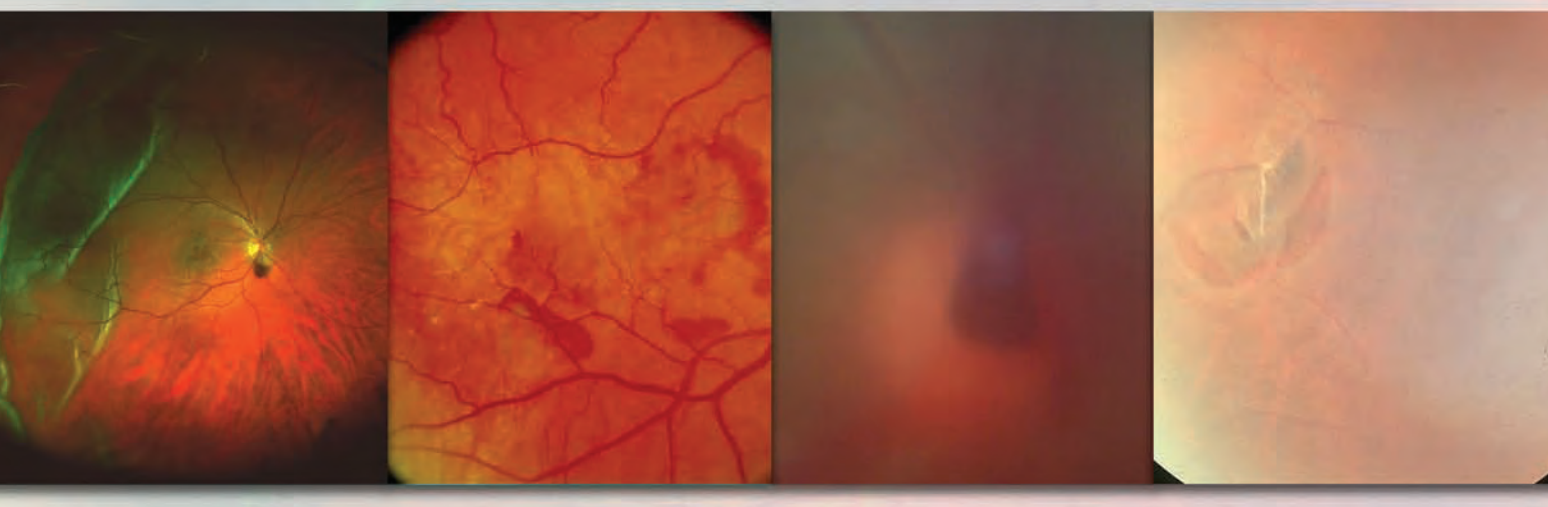
FIFTH ANNUAL GUIDE TO

Retinal Disease



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Hematological Disorders and the Retina

Sherrol A. Reynolds, O.D., F.A.A.O. and Julie Rodman, O.D., F.A.A.O

MILLIONS OF AMERICANS suffer from hematological disorders, which can cause significant ocular complications in our patients. In fact, ocular manifestations can be the presenting signs or symptoms in up to 90% of patients depending on the underlying hematological disorder.[1] Here we discuss the retinal findings of anemic retinopathy, sickle cell retinopathy, leukemic retinopathy, and lymphoma, as well as treatment options currently available.

Anemic Retinopathy

The anemias occur when the level of healthy red blood cells (RBCs) or hemoglobin (an iron binding, oxygen-carrying protein within the red blood cells) is too low. Anemia can be due to nutritional problems such as an iron deficiency, vitamin deficiency or folate deficiency. Iron deficiency is the most common type of anemia. A deficiency of vitamin B_{12} is known as pernicious anemia. Other causes of anemia include blood loss, inadequate production of red blood cells (aplasic anemia) or increased destruction of red blood cells (hemolytic anemia) that may present lifelong health problems.

Retinopathy in patients with anemia is well documented. Common findings include hemorrhages that can present at all levels of the retina and choroid, Roth's spots, exudates, cotton wool spots, retinal edema and venous tortuosity *(Figure 1)*. Roth's spots or white centered hemorrhages are typically associated with bacterial endocarditis, however the association is not exclusive, since they occur in diverse conditions including anemia. The white center could represent focal ischemia, inflammatory infiltrates, infectious organisms, fibrin and platelets, or an accumulation of neoplastic cells.[2] The exact pathophysiology of anemic retinopathy is not completely understood. However, it seems to be related to retinal hypoxia, venous stasis, angiospasm and increased capillary permeability.[3]

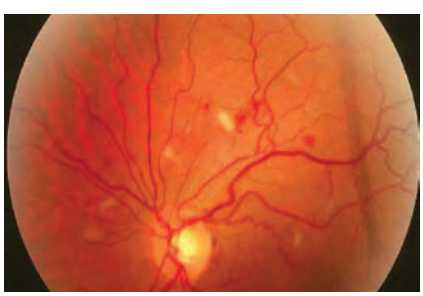


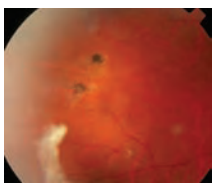
Figure 1. Retinopathy in a patient with severe anemia. Note the retinal hemorrhages, cotton wool spots and venous tortuosity.

Anemic retinopathy is most likely to occur in patients with severe anemia or when thrombocytopenia, a disorder of low platelets, is coexistant.[4] The ocular changes found in anemic retinopathy are nonspecific and may closely resemble diabetic or hypertensive retinopathy.[5] Anemic retinopathy may also be a secondary manifestation of other systemic diseases such as cancer, infection or autoimmune disorders. Therefore, in addition to ordering a complete blood count (CBC w/differential), other appropriate medical testing may be necessary. In regards to the management, anemic retinopathy is reversible with correction of the anemia.

Sickle Cell Retinopathy

The sickle cell hemoglobinopathies are an inherited group of disorders that are due to a structurally abnormal beta hemoglobin chain subunit. The result is formation of crescent-like, or sickle shaped, red blood cells in response to decreased oxygen concentration or other physiological stresses. Sickle cell disease is one of the most prevalent genetic disorders in the United States and it predominately affects individuals of African descent and Mediterranean ancestry. Approximately 10% to 14 % of North American blacks are affected with one of the four known variants of sickle cell.[6,7]

The four common variants include sickle cell anemia (SS), sickle-hemoglobin C disease (SC), sickle beta- thalassemia and sickle cell trait (AS). Individuals with sickle cell trait inherit one normal hemoglobin and one sickle hemoglobin-S, resulting in the AS genotype. The sickle cell trait is the most common of the sickle hemoglobinopathies, and it affects approximately 8% to 10% of the black population (AS).[8] To confirm the disease, the patient may require a hemoglobin electrophoresis or DNA analysis.



Proliferative sickle cell retinopathy.

The ocular complications of sickle cell disease are caused by microvascular occlusion secondary to the sickling of red blood cells. Retinal hypoxia, ischemia, infarction, neovascularization, and fibrovascularization may result from the microvascular occlusion.[9] The retinopathy can be divided into non-proliferative and prolifertive changes *(Table 1)*. Although neovascularization may be seen at the optic disc and the macula, proliferative sickle retinopathy is primarily a peripheral retinal disease that can lead to severe vision loss. Proliferative retinopathy is more characteristic of patients with SC and SB thalassemia disease than the more severe systemic form of sickle cell anemia.[10]

Additional retinal complications of sickle cell disease include sickling maculopathy, central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), epiretinal membrane, ischemic optic neuropathy, develop-

Table I

Non-Proliferative Retinopathy	Stages of Proliferative Retinopathy
• Black sunbursts *patches of RPE hyperplasia • Salmon patch hemorrhages *intra-retinal hemorrhages • Venous tortuosity of the peripheral vessels • Angioid streak • Dark with-out pressure • Iridescent spots	**Stage 1.** Peripheral arteriolar occlusion **Stage 2.** Peripheral arteriovenous anastomoses **Stage 3.** Neovascular and fibrous proliferations-sea fan formation **Stage 4.** Vitreous hemorrhage **Stage 5.** Retinal detachment

ment of optociliary shunt vessels, and choioretinal infarctions.[11] The presence of a retinal artery occlusion in black patients under the age of 40 should raise the consideration of underlying sickle hemaglobinopathies. Although rare, retinopathy can occur in patients with sickle cell trait in the absence and presence of concomitant systemic disease, such as diabetes or hypertension.[12]

Patients with non-proliferative retinopathy should be followed periodically according to the level of involvement. For proliferative retinopathy, the aim is to prevent ischemic complications, particularly vitreous hemorrhages and retinal detachments. Treatment options include the use of diathermy, cryotherapy, and laser photocoagulation.[13] Recent studies have investigated the role of pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) in the progression of neovascularization. Siqueira and associates demonstrated retinal neovascularization regression with intravitreal Avastin (bevacizumab, Genentech) injection.[14] Additional studies are necessary however, to demonstrate the reliability of anti-VEGF use in the management of proliferative sickle cell retinopathy.

Leukemic Retinopathy

Leukemia is defined as a neoplastic blood disorder characterized by the overproduction of abnormal white blood cells. Leukemia can be divided into two types; myelogenous and lymphocytic. Leukemia is further divided into acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML) or chronic lymphocytic leukemia (CLL). Approximately 50% or more of all leukemias manifest some form of ocular involvement.[15,16]

The ocular complications of leukemia may be due to a direct involvement by leukemic infiltrates or secondary to concomitant anemia or thrombocytopaenia.[17] Leukemic retinopathy is a common manifestation of leukemia and is found in both the acute and chronic forms. Features of leukemic retinopathy include multiple preretinal and intraretinal hemorrhages that are most commonly found in the posterior pole. Other features include Roth's spots, cotton wool spots, exudates, retinal venous tortuosity, perivascular sheathing, and neovascularization. Roth's spot hemorrhages may represent small areas of retinal leukemic infiltration or platelet-fibrin deposits. Retinal lesions such as peripheral neovasularization or sea fans neovascularization (reminiscent of sickle cell retinopathy) may develop in patients with chronic leukemia and are thought to occur as a result of peripheral nonperfusion and ischemia from the hyperviscosity.[15] Serous retinal detachments and various other retinal anomalies have been reported, as well as pallor and swelling of the optic nerve, which indicate optic nerve infiltration.[15]

In pathological studies, the choroid is the most commonly affected ocular structure. Choroidal masses lead to a disruption of the retinal pigment epithelium which result from decreased blood flow to the choriocapillaris.[16] In some cases a serous or exudative retinal detachment may ensue.

Leukemic retinopathy usually is not treated directly. Systemic treatment involves the use of chemotherapy, immunotherapy, and radiotherapy. Intraocular leukemic infiltrate is best treated with chemotherapy that is appropriate for the type and stage of leukemia. External-beam radiation may be applied to lesions of the optic nerve or orbit. The presence of leukemic infiltration is usually a poor prognostic indicator.[18]

Lymphoma Associated Retinopathy

Lymphomas are a diverse group of cancers of the lymphatic system that comprise 3% to 4% of cancers diagnosed annually.[19] Hodgkin's disease is the most common form of lymphoma; all other lymphomas are termed non-Hodgkin's lymphomas. Hodgkin's lymphoma follows a more predictable pattern of growth, and its spread is more limited than non-Hodgkin's lymphomas. The characteristic pathologic abnormality is a polycellular infiltrate made up of giant (Reed-Sternberg) cells that are fibrotic and necrotic in nature. Orbital involvement is a rare complication of Hodgkin's disease, whereas non-Hodgkin's is the most common type of ocular lymphoma.

Ocular abnormalities associated with lymphoma have been divided anatomically into a vitreoretinal and uveal form. The vitreoretinal form is associated with primary central nervous system non-Hodgkin's lymphoma (PCNSL) and is typically a large B-cell tumor. In contrast, the uveal form is associated with systemic non-Hodgkin's lymphoma. Involvement of the uveal tract presents as a non-resolving uveitis, diffuse choroidal infitiltration, or exudative retinal detachment. The characteristic retinal finding is a low-lying, yellow-to-white mass deep to the sensory retina. They may even appear as single, multiple, confluent, or discrete punctate lesions that may involve all layers of the retina.[20] Retinal phlebitis and the presence of cotton wool spots have been reported as initial clinical findings in Hodgkin's disease.

Treatment options for lymphoma include observation, involved-field radiation, subtotal lymphoid radiation, chemotherapy with or without radiation, and bone marrow transplant. Newer biologic therapies are also being investigated for the treatment of lymphoma.

Conclusion

Hematological disorders affect millions of Americans and represent a major public health concern due to the potential for significant morbidity and mortality. The retinal findings associated with the various hematological disorders necessitate an immediate comprehensive medical evaluation. The optometric physician may play a crucial role in the diagnosis and management of these disorders. ■

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What's New in Clinical Trials for Treatment of Dry AMD

By Thomas J. Stokkermans, O.D., Ph.D., F.A.A.O.

AGE RELATED MACULAR degeneration (AMD) is the leading cause of vision loss among older Americans, with over ten million suffering from the disorder and nearly two million suffering with wet AMD.[1] Over the past several years, we have seen major breakthroughs in the treatment of wet AMD. Because up to 90% of cases of severe vision loss are caused by choroidal neovascularization (CNV), this is indeed great news.[2,3]

Understanding the causes of dry AMD and learning how to treat it at an earlier stage are the next big challenges facing clinicians and researchers. The clinical director of the National Eye Institute (NEI), Frederick L. Ferris III, recently emphasized this fact by stating that, "The blood vessels of wet AMD are like weeds in a garden. You have a choice: You can either be picking the weeds or making a healthy garden so weeds can't grow."

We are gradually starting to understand what causes an "unhealthy garden." It is thought that oxidative stress first causes injury of the retinal pigment epithelial (RPE) and possibly the choriocapillaris. This injury results in a chronic inflammatory response within Bruch's membrane and the choroid, which is followed by the formation of an abnormal extracellular matrix (ECM). This, in turn, causes altered diffusion of nutrients to the retina and RPE, which may cause further damage. The abnormal ECM itself may also lead to geographic atrophy (GA) and/or to CNV.

These processes may not happen in a sequential fashion. It is also expected that an individual's environment and genetic makeup alter susceptibility to AMD.[4]

Several clinical trials for dry AMD are testing whether the processes described above can be slowed down, stopped or reversed. These trials include the Age Related Eye Disease 2 Study (AREDS 2) and trials testing an intra-ocular implant that delivers ciliary neurotrophic factor (CNTF); a capsule containing fenretinide; an eyedrop containing OT-551; an intravitreal injection of POT-4; a subcutaneous injection of glatiramer acetate; a juxtascleral injection of anecortave acetate; selective RPE laser treatment, RPE transplantation and Rheopheresis. New genetics data has also recently shown an important role of toll-like receptor TLR3 in the susceptibility to dry AMD with important implications for both current and future treatments of dry and wet AMD.

AREDS 2

To put AREDS 2 in the correct perspective, you must go back to the original AREDS. AREDS tested the concept that inhibition of oxidative damage to the RPE can reduce the risk of AMD. In this study, patients received 15mg beta-carotene, 500mg vitamin C, 400 international units of vitamin E, 80mg of zinc and 2mg of cupric oxide *(Figure 1)*.[5] And indeed, results from this landmark study published in 2001 showed that for patients with moderate dry AMD and patients with severe AMD in one eye, the chance of severe vision loss could be reduced by 19%.

Finally, eye care practitioners had something to offer to patients with dry AMD. As a result, offering antioxidant supplements to AMD patients has now become commonplace in the eye care practice.

However, several issues remained. One was that these supplements only had a moderate impact (19% reduction) on prevention of severe vision loss. Second, the supplements were not shown to prevent development of milder forms of AMD. Third, the intake of high levels of beta-carotene has been shown to increase the risk of lung cancer in smokers.[6] Supplements that replace beta-carotene with lutein (e.g. Preservision Lutein, Bausch & Lomb) have subsequently been made available to patients. And fourth, AREDS itself revealed that other dietary components

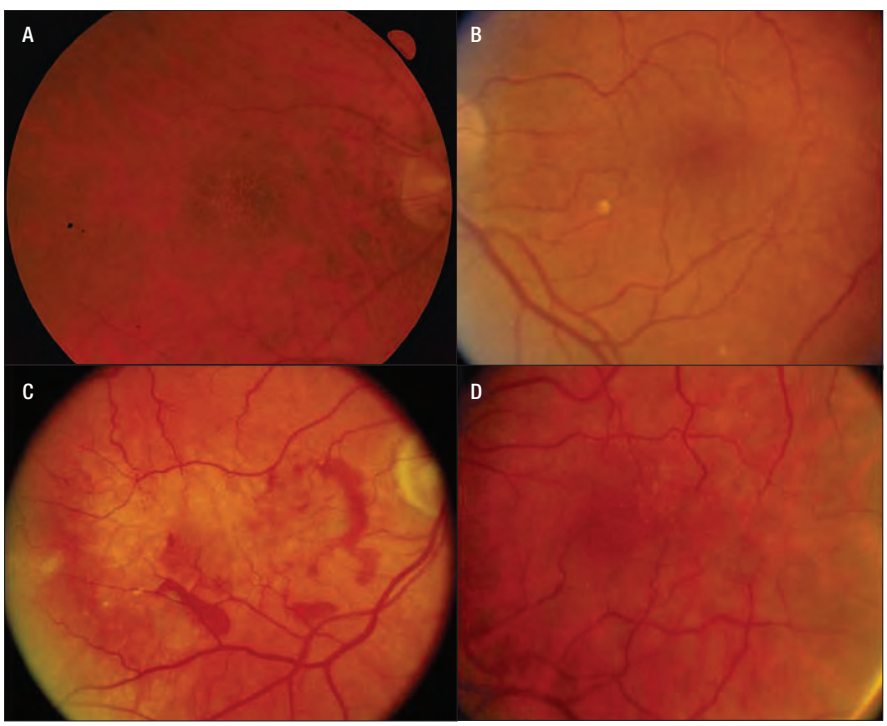

Figure 1A-D. Fundus photos exemplifying different levels of AMD in the AREDS. 1A. AREDS Category 2 AMD showing a fundus with more than 15 small drusen. (COURTESY OF NEI) 1B. Category 3 AMD showing a fundus with one large druse that is over 125 micron. 1C and 1D. Category 4 AMD OD and OS fundus, showing CNV in OD and any level dry AMD OS. The AREDS showed that for categories 3 and 4 AMD, antioxidants reduced the risk of severe vision loss by 19%.[5]

might play an even larger role in preventing AMD than anti-oxidants.

Specifically, AREDS showed that increased **dietary** intake of the macular xanthophylls lutein and zeaxanthin, omega-3 long-chain polyunsaturated fatty acid (LCPUFA) and fish decreased the likelihood of having CNV. AREDS also revealed that dietary intake of macular xanthophylls decreased GA and large or extensive intermediate drusen, while **dietary** intake of the antioxidants vitamins A, C, and E did not seem to impact the **overall** risk of AMD.[7,8]

Two other studies similarly revealed that both dietary intake and supplementation of antioxidants did not significantly impact the prevention of early AMD, while the intake of omega-3 LCPUFA and fish did have a significant impact.[9,10]

Finally the Lutein Antioxidants Supplement Trial (LAST) showed vision improvement in AMD patients.[11] Both prevention of early AMD and vision improvement had not been shown in the AREDS. While lutein and zeaxanthin may protect the macula from oxidative damage, omega-3 LCPUFAs have been shown to yield anti-inflammatory activity, indicating that inflammation may play just as much of a role in the pathogenesis of AMD.[12]

Inflammatory cells have been shown to be present in the retinas of patients with AMD, and genetic markers associated with AMD are part of the complement system.[13] Blood levels of C-reactive protein have also been shown to be high in patients with AMD.[14] AREDS also looked at non steroidal anti-inflammatory drug (NSAID) use and determined that it reduced the risk of developing central geographic atrophy.[15]

AREDS 2 may answer whether supplementation with omega-3 LCPUFA and macular xanthophylls is a more effective and safer means of preventing both dry and wet AMD. AREDS 2 is a multi-center, randomized trial designed to assess the effects of oral supplementation of the macular xanthophylls lutein and zeaxanthin and/or the omega-3 LCPUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on the progression to advanced AMD. An additional goal of the study is to test AREDS nutritional supplements with reduced zinc or no beta-carotene. AREDS 2 is a 5-year, double-blind study that has enrolled nearly 40,000 patients age 50 to 85 at nearly 100 centers nationwide since 2006.

Ciliary Neurotrophic Factor

Ciliary neurotrophic factor (CNTF) is a human gene that is part of the Interleukin-6 family of cytokines.[16] The protein encoded by this gene is a polypeptide hormone and nerve growth factor that promotes neurotransmitter synthesis and neurite outgrowth in the nervous system. CNTF enhances survival of neurons and oligodendrocytes, and may reduce inflammatory tissue destruction. For this reason, it has been postulated to be an important factor in neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and AMD. CNTF was found to be effective in retarding vision loss from photoreceptor cell death in 13 animal models of outer retinal degeneration.

The first possible medical application of CNTF was discovered in a human study in 2001. This study, testing the usefulness of CNTF for the treatment of ALS, revealed that CNTF produced significant weight loss in the study subjects without significantly affecting the course of ALS.[17] It was later established that CNTF could reduce food intake without causing hunger or stress, acting through a non-leptin pathway.[18]

In 2003, Regeneron tested a modified and more potent version of CNTF—Axokine—as a drug for obesity. In this trial, two-thirds of patients developed antibodies against Axokine. Since this could potentially interfere with the neuroprotective effect of endogenous CNTF, the drug was not commercialized.

However, since the vitreous is immunologically inert, CNTF can be applied locally to the macula without the concern of systemic side-effects. NEI-sponsored phase I and phase II clinical trials have been completed, which test the safety and efficacy of intraocular implants that deliver CNTF to the macula in patients with AMD.[19-21] In these trials, human RPE cells that have been given the ability to make CNTF were placed in an encapsulated cell technology ([ECT], see *figures 2 and 3*) intraocular implant called NT-501 (Neurotech Pharmaceuticals) and tested in patients for six months. At the end of the study period, the implants contained viable cells that still produced CNTF at what is considered therapeutic levels.

While this study was done in patients with retinitis pigmentosa, it is encouraging that three out of seven tested eyes had a two-to three-line improvement in visual acuity. Since then, two phase II clinical trials have been initiated that test the NT-501 implant in patients with atrophic AMD. One trial sponsored by Neurotech Pharmaceuticals was started in January 2007 at eight clinic sites across the United States. Another trial sponsored by the NEI at the National Institute of Health in Bethesda, Md., started enrollment in January of 2006. Both studies have followed patients over an 18-month period, remove the device after 12 months, include a high dose, low dose and sham group, have as primary outcome measure best corrected visual acuity, and include a combined total of 84 patients. Results should be forthcoming in the near future.

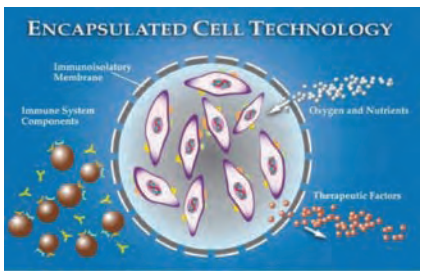

Figure 2. Encapsulated cell technology (ECT) shown to keep genetically modified RPE cells viable and producing CNTF for over 6 months.
COURTESY: NEUROTECH PHARMACEUTICALS

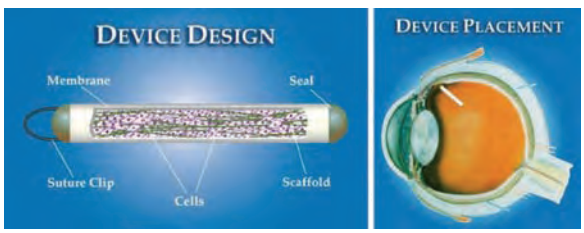

Figure 3. Neurotech Pharmaceuticals' NT-501 implant puts genetically engineered cells into an eye that produce ciliary neurotrophic factor (CNTF) for over 6 months.
COURTESY: NEUROTECH PHARMACEUTICALS

Fenretinide

Fenretinide (Sirion Therapeutics) is a retinoic acid derivative that is thought to

reduce the accumulation of lipofuscin in the retina. Lipofuscine is a major component of the abnormal extracellular matrix, which mainly accumulates in the form of drusen associated with AMD. Fenretinide binds to retinol (vitamin A), which keeps it from entering the outer retina. Retinol is a precursor to rhodopsin. The breakdown of rhodopsin may produce toxic byproducts, such as lipofuscin. Thus, less available retinol may lead to less toxic byproducts and reduce the risk of dry AMD. Fenretinide is taken as a once-a-day capsule. Sirion Therapeutics has sponsored a Phase II clinical trial that enrolled 225 patients over a two-year period. Three equal groups of patients receive either 100 mg of fenretinide, 300 mg of fenretinide, or a placebo.[22] Preliminary results are expected in late 2008.

OT-551

Othera Pharmaceuticals, Inc. has developed a drug called OT-551 that the company describes as a small molecule with primarily anti-oxidant, but also anti-inflammatory and anti-angiogenic properties. The drug is applied as an eye drop that penetrates to the retina and choroid. Two trials that test OT-551 for chronic treatment of dry AMD are ongoing. The first is a NEI-sponsored pilot study of 10 patients that was initiated in 2006 and tests the effect of 0.45% OT-551 drops taken three times a day over a period of three years. Primary outcomes measured are VA, with area of GA as a secondary measure.[23]

A second, 18-site Phase II study sponsored by Othera Pharmaceuticals which plans to enroll 198 participants with bilateral geographic atrophy was started in 2007. This study is expected to be completed in 2010, and intends to characterize the effect of 0.45% and 0.3% concentration of OT-551 eye drops given three times a day on the progression of geographic atrophy area over a two-year period.[24]

POT-4

Potentia Pharmaceuticals' first product, POT-4, is a complement component C3 inhibitor that is formulated to be dosed less frequently than currently approved intravitreal injections for AMD. POT-4 falls in the category of treatments that act on inflammation associated with AMD. In 2007, Potentia initiated a one year, Phase I trial of POT-4 at six clinical sites in 15 patients with subfoveal CNV. The company also intends to conduct clinical trials in patients with geographic atrophy.[25]

Glatiramer Acetate

Glatiramer Acetate (Copaxone®, Teva Pharmaceutical Industries) is an immunomodulatory substance that has been shown to reduce cognitive decline, eliminate plaque formation, and induce neuron survival and neurogenesis in a mouse model for Alzheimer's disease (AD). It has been tested extensively in humans with multiple sclerosis (MS), ALS and Crohn's disease, and is approved for use in patients with relapsing-remitting MS.

AD and AMD are both strongly correlated with age and demonstrate accumulation of extracellular matrix—amyloid plaques in AD and drusen in AMD. Additionally, inflammatory mediators and activated microglia are present in amyloid deposits, as well as in drusen.

Copaxone® is applied as a subcutaneous injection. Two double blind, randomized clinical trials at the New York Eye & Ear Infirmary and the Kaplan Medical Center, Rehovot, Israel, have been initiated in 2006 and 2007 respectively, and are enrolling up to 60 patients combined. The primary outcome tested in these trials is the reduction in the total area of drusen.[26,27] Results have not been published yet.

Selective RPE Laser Treatment

For the past 20 years, reports on treatment of drusen with laser have provided mixed results. While studies such as the Choroidal Neovascularization Prevention Trial (CNVPT), the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) and the Drusen Laser Study clearly showed that drusen resolve after laser treatment, the overall visual benefit and the absence of side effects still have to be determined in a convincing manner.[28]

A clinical trial at the University of Regensburg, Germany from 2004 to 2006, aimed to enroll 60 patients with drusen, GA and other macular diseases for treatment with short pulses of laser that specifically destroy the RPE, while not damaging surrounding tissues, such as photoreceptors. In theory, this treatment removes sick RPE and replaces it with new RPE, creating a healthier RPE layer and improving retinal function. No results are yet available for this study.

RPE Transplantation

Instead of interfering with the disease process, another potential treatment replaces damaged and unhealthy RPE with healthy tissue. In a 10-patient (four had AMD) study published this past July, human neural retinal progenitor cell layers and RPE were transplanted into eyes with vision of 20/200 or worse. All four patients with AMD experienced improved visual acuity, even though none improved to better than 20/200. There was no graft rejection during a follow-up time of up to six years despite the lack of a perfect match in all cases.[29]

Anecortave Acetate

Anecortave acetate (Retaane, Alcon) is applied as a posterior juxtascleral depot injection and was initially developed to treat active CNV. The Anecortave Acetate Risk-Reduction Trial (AART) was initiated to test whether the risk for CNV can be reduced in patients with dry AMD.[30] This Alcon-sponsored phase III clinical trial tested 15mg, 30mg or sham injections of the angiostatic steroid every six months for 48 months. In the study, 2,546 patients had dry AMD in one eye and CNV in the other eye.

In July of 2008, Alcon revealed that it would not continue development of Anecortave acetate for dry AMD because clinical trial results showed no reduction in the progression from dry to wet AMD and no change in the time it took for the development of sight threatening CNV.

Rheopheresis®

Developed by OccuLogix, Rheopheresis® is the name for double filtration plasmapheresis that uses plasma filtration filters specifically designed for patients with dry AMD. The filtration process removes large proteins, fats and other substances from the blood. This, in theory, improves blood flow to the macula and enhances diffusion of nutrients to the retina and RPE. In 2002, interim data published on the first 43 patients (28 test, 15 placebo) enrolled in the Multicenter Investigation of Rheopheresis® for AMD Study (MIRA-1) revealed a significant beneficial

effect in treated patients with mild and moderate dry AMD. MIRA-1 patients received eight treatments over 10 weeks.

The results showed that 13% of treated versus 0% percent of placebo-control eyes had three lines or more of improvement in best-corrected visual acuity (BCVA) at 12 months. Also, only 4% of treated versus 18% of placebo-control eyes had three lines or more loss of BCVA. This result was significant and even more pronounced in the subgroup of patients with baseline BCVA worse than 20/40.[31] More definitive conclusions may be made once results from the full 180 patients that the study aims to enroll are available.[32] As of now, this data has not been published.

Occulogix has also sponsored the Safety and Effectiveness Investigation for Dry, Non-Exudative Age Related Macular Degeneration Using Rheopheresis Study (RHEO-AMD), which is of a design similar to MIRA-1 y and aims to enroll 325 patients at 39 clinic sites. However, this study was reported to have been halted "due to the financial position" of Occulogix.[33] However, the Occulogix Web site shows that the company is still operating.

Toll-like Receptor 3

Toll-like receptor 3 (TLR3) plays a role in innate immunity and host defense, and alerts the immune system to viral infection. TLR3 may cause destruction of RPE cells when activated. In a large study, patients with less active variants of TLR3 had a reduced risk of developing GA, but no difference in the risk of CNV. The same study also showed that mouse and human RPE cells were more likely to die in tissue culture when TLR3 is activated. These results have two important implications for AMD treatments. First, TLR3 inhibitors may be used in the future to stop the formation of GA. Second, these results serve as a caution for current experimental treatments of CNV with short-interfering-RNA (siRNA), because TLR3 is activated by the presence of viral RNA, it may also be activated by siRNA causing GA while trying to protect against CNV.[34]

Summary

It was not that long ago that patients with subfoveal CNV were treated with thermal laser that resulted in immediate loss of vision and questionable functional benefit. We now have effective treatments for CNV that give hope to many patients. However, vision loss from GA still cannot be treated and dry AMD cannot be halted at an early stage or before it develops.

Current clinical trials for dry AMD test treatments that affect all the different stages proposed. AREDS 2 and OT-551 target the oxidative stress that leads to injury of the RPE and possibly the choriocapillaris. AREDS 2, CNTF, OT-551, POT-4, glatiramer acetate and TLR3 inhibitors home in on the subsequent chronic inflammatory response within Bruch's membrane and the choroid. Fenretinide and glatiramer acetate affect the formation of an abnormal extracellular matrix that follows, while Rheopheresis attempts to then reverse the altered diffusion of nutrients to the retina and RPE. The final stage of further damage to the RPE (GA) is attempted to be remedied in the selective RPE laser treatment and RPE transplantation trials.

At least some of these trials are expected to produce applicable results in the coming two to three years. It is important for the primary eye care provider to follow developments closely as these outcomes will significantly affect what is done in the optometric office. ■

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Posterior Vitreous Detachment: A Common Process with Potential for Ocular Morbidity

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Goal Statement
Posterior vitreous detachment (PVD) is a frequent consequence of aging. Understanding the anatomical makeup and biochemical properties of the vitreous are critical in the diagnosis of PVD as well as associated vitreoretinal conditions.

Faculty/Editorial Board
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Disclosure Statement
Dr. Shechtman is on the speakers' bureau of VSP, MSS and Alcon.

POSTERIOR VITREOUS DETACHMENT (PVD) is a frequent consequence of aging. With age, the vitreous degenerates, leading to a PVD. A posterior vitreous detachment is described as a separation of the posterior cortex of the vitreous from the internal limiting membrane of the retina. Vitreopapillary separation is the most common location. *(Figure 1)*

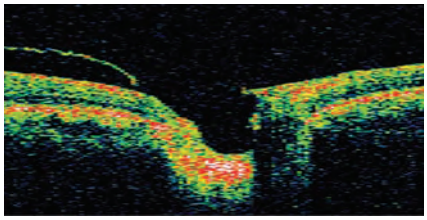

Figure 1.

This is described as an annular ring, known as a Weiss' ring, attached to the posterior hyaloid and located anterior to the optic nerve. *(Figure 2)* This process is readily observed in the elderly population, affecting 65% of patients over the age of 65.[1,2] Even though a PVD is usually detected in an older female both genders may be affected and it is believed that the process starts much earlier.[3] Conditions, such as myopia, trauma, inherited vitreoretinal disease, surgery, and inflammation may accelerate the process.[4] Floaters are the most common symptoms, described as "cobwebs, flies or hair-like-structures." Flashes, or photopsias, may also be associated with an acute PVD. Flashes do not always specify the presence of a retinal break or retinal detachment. Flashes indicate traction upon the retina, resulting in stimulating of the photoreceptors.

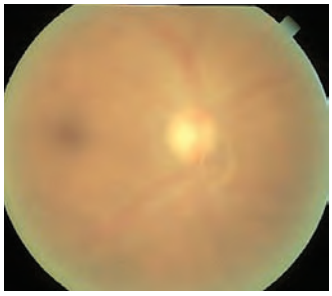

Figure 2. COURTESY OF DR. J. SOWKA

Although we have recognized the vitreous as an important ocular structure for more than a century,[5] we are only recently beginning to understand its pathogenic role in various vitreoretinal diseases. PVD is typically described as a benign process; however, the location of firm vitreoretinal adhesions plays a critical role in various pathological vitreoretinal conditions.

There are a number of firm posterior vitreoretinal attachments, which include areas along retinal vessels, the vitreous base, macula and optic nerve. Depending on the site of firm vitreoretinal attachment, an incomplete PVD may lead to the development of a vitreous hemorrhage, retinal break (RB), rhegmatogenous retinal detachment (RRD), or vitreomacular traction syndrome (VMT). Understanding the anatomical makeup and biochemical properties of the vitreous are critical in the diagnosis of PVD as well as associated vitreoretinal conditions.

Vitreous Anatomy & Biochemistry

The vitreous is considered to be a transparent gel, primarily composed of water. A small but vital component of the vitreous consists

of collagen and hyaluronic acid, which contributes to the "gel-like" consistency of the vitreous.[6,7] Collagen is a structural protein, which is connected to hyaluronic acid.[1] As we age, there is alteration between the hyaluronic-collagen complex, causing vitreous liquefaction and shrinkage. In addition, with age, the internal limiting membrane becomes thickened, causing a decrease in vitreoretinal adhesion throughout the fundus.[7] This weakening further facilitates the migration of the liquid vitreous into the subhyaloid space. The vitreous volume displacement causes a forward collapsing of the vitreous and a complete separation of the vitreous cortex from the retina, a PVD. This entire process commonly runs a complete and benign course with no further complications.

During the PVD process, if vitreous liquefaction surpasses the extent of weakening of vitreoretinal adherence, tractional forces will ensue upon areas of firm attachments.[7] Depending on the site of the firm vitreoretinal attachment, a number of pathological events can occur during the PVD process, invariably attributing to retinal disturbances, such as a vitreous hemorrhage, VMT or retinal break which potentially can lead to a RRD.[4,7,8] *(Table 1)*

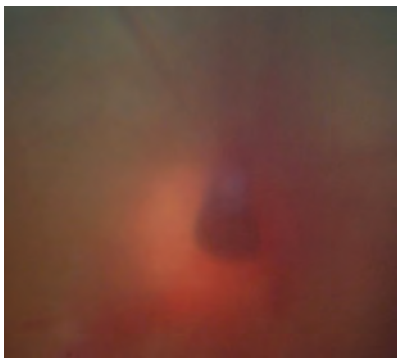

Figure 3.

What Happens in the Vitreous?

Vitreous Hemorrhage (VH)

A VH is characterized by the presence of blood posterior to the crystalline lens and anterior to the internal limiting membrane. *(Figure 3)* Since the vitreous is an avascular structure, blood found within the vitreous must come from the superficial retinal vasculature. The main causes of a vitreous hemorrhage include superficial retinal neovascularization, trauma and a PVD (with or without associated retinal breaks). A firm vitreoretinal attachment is maintained along the retinal vessels. During the PVD process sufficient traction along a vessel can lead to a vessel tear, resulting in a vitreous hemorrhage.

Table 1. Complications Associated with PVD

VR traction site	Retinal condition
Retinal vasculature	Retinal hemorrhage or VH Avulse retinal vessel
Macula	VMT
Periphery	Retinal breaks Retinal detachment

A VH can present as a large dense diffusely disperse hemorrhage within the vitreous cavity or a localized hemorrhage without characteristic borders or as a single streak of blood. Vitreous hemorrhages tend to clot quickly while resolving slowly. Patients may present with a history of multiple floaters or smoky vision, typically described as a "red" haze. Decrease in visual acuity is dependent upon the density and location of the VH. Since the VH is situated in a gel within a cavity, it will shift with head movements. Thus, patients may experience intermittent visual obstruction with head movement.

PVD without retinal breaks, account for less than 10% of VH cases.[9,10] Although PVD may be associated with a VH in the absence of a retinal break, the presence of a vitreous hemorrhages is considered a risk factor for the presence of a coexisting retinal break.[11] Vitreous hemorrhages are indicative of vitreoretinal traction and potential impending retinal break. Since many VHs settle inferiorly due to gravity, location of VH does not aid in detecting the possible site of an accompany RB. In the presence of a VH, it is imperative to scrutinize the retina for any evidence of retinal breaks. In cases of dense VH, ultrasonography (B-scan) may aid in ascertaining the presence of retinal detachment, retinal tear, or any other associated etiologies. In the absence of a retinal break, VH should be followed until complete resolution has occurred.

What Happens in the Periphery?

Retinal Break (RB)

Retinal breaks commonly result from the vitreous pulling on the retina, causing a full-thickness retinal defect. This is common following the evolution of a partial PVD with associated continuous localized traction onto the retina. Up to 15% of all patients who present with acute symptomatic PVD have at least one retinal break.[9,10,12] Since the strongest vitreoretinal attachment is at the vitreous base, most retinal breaks are located between the equator and the ora.[12,13] There is a downward gravitational force exerted on the remaining attached vitreous base, causing a greater prevalence for superior retinal breaks. Vitreoretinal traction induced by a PVD increases the risk for a RRD. Ominous accompany signs include symptomatic breaks, as well as the presence of vitreoretinal traction, a vitreal or preretinal hemorrhage, pigmented vitreal cells (Schaffer's sign) and a large retinal cuff of fluid. It is not uncommon for patients to present with an asymptomatic retinal break, which is only discovered during a routine eye exam.

The most common types of retinal breaks include atrophic retinal holes, operculated retinal holes and flap tears. Pathogenesis of each is associated with distinct mechanisms, contributing to variable propensity towards the progression to a RRD. Since atrophic retinal holes are not typically associated with vitreoretinal traction, this entity will not be discussed in this article. A retinal break provides a passage for the vitreous into the retina, thus the potential for a RRD. Management depends on the type of RB, associated findings, and risk factors *(Table 2)*. For example, myopia (>6.00D) and aphakia are considered risk factors for retinal breaks to progress to RRD.[14,15]

Table 2. Predisposing Risk Factors

- High myope
- History of previous RD
- Trauma
- Cataract surgery

Categorizing the type of retinal break, in addition to identifying associated signs and symptoms, is imperative. Not all retinal breaks progress to a RRD. Proper management relies on determining which RB may progress to RRD: in other words, which retinal breaks would benefit from prophylactic treatment.

Operculated Retinal Hole

An operculated retinal hole represents a round, red full thickness retinal defect with an associated avulsed piece of retinal tissue in the vitreous cortex. Operculated retinal holes are thought to be a sudden occurrence rather than a progressive change and most often occur at the same time as a PVD and or associated with retinal tufts.[16] Due to their close association with PVD, operculated retinal holes are found more commonly in older people.[16] Operculated retinal holes are a result of increased focal vitreoretinal adhesion in the periphery, pulling a plug of retinal tissue onto the cortex of the vitreous. This avulsed retinal tissue (operculum) is often found directly overlying the retinal break, but can be found elsewhere depending on the direction of the force of the vitreous traction at the time of the separation. The operculum is noted to be smaller than its associated retinal break due to degeneration that has occurred over time from vascular insufficiency previously supplied by the underlying retinal layers. An operculum can be distinguished from a vitreous floater due to its disc-shaped appearance as compared to the spherical appearance of a vitreous floater.[16] Operculated retinal holes may be symptomatic in the initial stages, but symptoms subside once the traction is released and the operculum is finally formed. Since they are not associated with continuous vitreoretinal traction, most are followed on an annual basis.

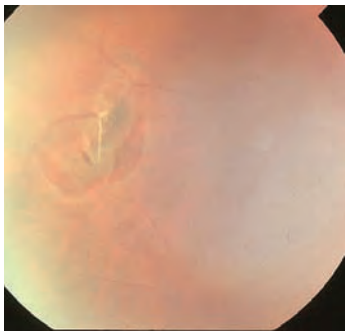

Figure 4.

Retinal Flap Tear (Horseshoe tear)

A retinal flap tear, also known as a horseshoe tear, commonly occurs is association with an incomplete PVD. During the PVD process, traction at this site may lead to the development of a flap tear. The cardinal feature of a retinal flap tear is a "U" or "Horseshoe" shape, representing an incomplete full thickness retinal tear associated with partial vitreoretinal adherence. As the vitreous is displaced forward, the flap assumes a triangular shape, with the apex oriented towards the posterior pole and the attached base parallel with the peripheral retina. *(Figure 4)*

Horseshoe tears are the leading cause of rhegmatogenous retinal detachments (RRD). Even an asymptomatic horseshoe tear can result in RRD; making the timely diagnosis of this condition extremely important. Symptomatic retinal flap tears are prophylactically treated, creating retinal scars (chorioretinal adhesions) in order to seal down the detached retina.

Management of Retinal Breaks

The decision to refer for a treatment is anecdotal, depending on variable factors, such as the type of retinal break, risk factors, and accompanying symptoms and signs.[17] Various studies have confirmed that symptoms are the single most likely predictor that a retinal break will progress to a RRD.[18,19] A retinal consult is typically considered for acute symptomatic retinal breaks. An acute symptomatic PVD can co-exist with a longstanding retinal break. Clinical trials have not aided in determining whether these retinal breaks would benefit from prophylactic treatment.[18] The presence of a retinal or vitreal hemorrhage, along with Schaeffer's sign can further help determine the acute nature of a retinal break.

Retinal break with accompanying subclinical retinal detachment (associated fluid cuff <2.00DD) should also be referred for a retinal consult. While fluid cuff surrounding a retinal break is an inauspicious sign, retinal pigment epithelial changes are considered a sign of chronicity and decrease the likelihood that the retinal break will progress to a RRD.

Most retinal holes only require a yearly dilated fundus exam. Asymptomatic retinal holes are routinely monitored. On the other hand, a symptomatic oper-

culated hole with persistent vitreoretinal traction may benefit from a retinal consult, although most have not been reported to progress to a RRD.[10]

Retinal flap tears carry the highest risk for progression but there is some controversy as to whether a non-symptomatic retinal flap tear should be treated.[18] Only 5% of asymptomatic retinal breaks progress to RRD.[20,21] At the site of a retinal flap tear, the retina is incompletely pulled away and vitreoretinal traction exerts tractional forces upon the edge of the tear. Since retinal tears have a predisposition to evolve to a RRD, one may consider that all flap tears, at the very least, deserve a retinal consult. This is especially true in the presence of other risk factors such as aphakia, myopia, or history of RD in the fellow eye.

What Happens in the Macula?

Vitreomacular Tractional Syndrome (VMT)

Vitreomacular traction is described an incomplete posterior vitreous detachment with continuous adherence as the macula.[22-24] *(Figure 5)* This continuous vitreomacular adherence induces tractional forces upon the macula. VMT is commonly described as a taut posterior hyaloid in a "dumbbell" configuration. The clinical picture is variable with symptoms ranging from mild blurred vision and metamorphopsia to severe decrease in visual acuity and accompanying photopsias. The typical patient is older with no history of cataract surgery. The nature of the vitreomacular attachment has been associated with a number of maculopathies, including cystoid macular edema, macular hole formation and epiretinal membranes.[24-26] The dynamic nature of the traction, strength of remaining attachment and extent of vitreoretinal separation may all contribute to the distinct type of associated maculopathy.[27] The clinical course is unpredictable with a few cases remaining stable for years or associated with spontaneous posterior vitreous detachment. A spontaneous PVD is typically associated with alleviation of both the associated symptoms and maculopathies, but the occurrence is low.[28] The classic course is one of progression associated with further deterioration. Thus, in many cases, pars plana vitrectomy is a necessity.[28]

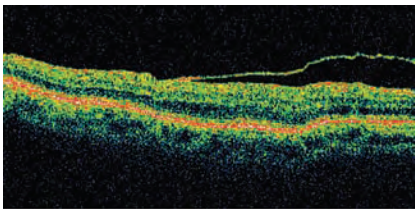

Figure 5.

Conclusion

Many PVD result in a complete detachment from the retina without any further complication. Yet, depending on the site of firm vitreoretinal attachment, the PVD process may lead to the development of vitreoretinal traction resulting in a vitreous hemorrhage, retinal break, which may be associated with a retinal detachment, or vitreomacular traction syndrome (VMT). The vitreoretinal conditions reaffirm the importance of further evaluation of every patient presenting with an acute PVD. A dilated fundus exam should be performed in all patients who present with signs and/or symptoms of a PVD. Scleral depression should also be considered, in order to rule out the presences of a retinal break or retinal detachment. The vitreous should be carefully scrutinized for the presences of hemorrhages or pigment.

In the absence of any complications, patients should be followed-up on a one–two week basis (depending on risk factors and associated signs or symptoms), until complete detachment of the posterior vitreous is noted. This commonly occurs within six weeks and is typically associated with resolution of photopsias. Any changes or progression in signs or symptoms, warrants prompt re-examination. Accompany risk factors, signs and symptoms, in addition to a complete clinical evaluation can aid in the appropriate management of a patient presenting with a PVD. ■

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Questions

1. Which of the following is not a common complaint of a patient with an acute PVD?
a. diplopia
b. flashes
c. floaters
d. patient may be asymptomatic and have no complaints

2. Common peripheral pathological conditions associated with onset of acute PVD include all the following except
a. retinal detachment
b. retinal flap tears
c. operculated holes
d. subchoroidal neovascular membrane

3. Which of the following is not a complication of an incomplete posterior vitreous detachment?
a. vitreomacular traction syndrome
b. macular degeneration
c. vitreous hemorrhage
d. retinal detachment

4. Most retinal breaks are located in the:
a. superior retina
b. inferior retina
c. nasal retina
d. temporal retina

5. An incomplete PVD associated with continuous adherence to the macula is known as:
a. vitreomacular traction syndrome
b. a macular hole
c. juxta foveal retinal telangiectasia
d. neovascularization

6. What is the main component of the vitreous?
a. water
b. hyaluronic acid
c. collagen
d. glial tissue

7. What is the strongest vitreoretinal attachment?
a. along the retinal vessel
b. ora serrata
c. optic nerve
d. macula

8. A _____ is the characteristic pattern of the PVD located in front of the optic nerve.
a. idiopathic
b. Weiss' ring
c. tractional detachment
d. disciform

9. All of the following are main causes of vitreal hemorrhages except:
a. superficial retinal neovascularization
b. non-exudative macular degeneration
c. trauma
d. complicated PVD

10. Where is the apex of a flap tear orientated towards?
a. anterior retina
b. temporal arcade
c. posterior pole
d. ora serrata

Examination Answer Sheet

Valid for credit through November 30, 2009

Posterior Vitreous Detachment: A Common Process with Potential for Ocular Morbidity

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit. There is a $30 fee to take this course

Mail to: Optometric CE, PO Box 488, Canal Street Station, New York, NY 10013
COPE approved for 1 hour of CE Credit. Cope ID 23658-PS.

There is an eight-to-ten week processing time for this exam.

1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
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9. Ⓐ Ⓑ Ⓒ Ⓓ
10. Ⓐ Ⓑ Ⓒ Ⓓ

11. The goal statement was achieved:
○ Very Well ○ Adequately ○ Poorly

12. The information presented was:
○ Very Useful ○ Useful ○ Not Very Useful

13. The difficulty of the course was:
○ Complex ○ Appropriate ○ Basic

14. Your knowledge of the subject was increased:
○ Greatly ○ Somewhat ○ Hardly

15. The quality of the course was:
○ Excellent ○ Fair ○ Poor

How long did it take to complete this course?

Comments on this course:

Topics you would like in the future CE articles:

Please retain a copy for your records. Please print clearly.

You must choose and complete one of the following three identifier types:

① SS # ___ - ___ - ___

Last 4 digits of your SS # and date of birth

② ___ - ___

State Code and License #: (Example: NY12345678)

③ ___

First Name ___

Last Name ___

E-Mail ___

The following is your: ☐ Home Address ☐ Business Address

Business Name ___

Address ___

City ___ State ___

ZIP ___

Telephone # ___ - ___ - ___

Fax # ___ - ___ - ___

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 105928

RO-UAB-11085

How to Successfully Incorporate Retinal Technology into Your Practice

By Jeffry Gerson, O.D.

IT WAS NOT LONG AGO that high technology for retinal imaging in the optometric office consisted of a non-mydriatic Polaroid camera. Although these cameras do a fine job of photodocumenting the posterior pole, they do not capture the peripheral retina, produce images that can be manipulated, or capture any sense of a cross-sectional view of either the optic nerve or macula. Older technologies do a fine job of monitoring for incremental change over time, but they cannot compare to the technologies mentioned in this article.

When it comes to retinal imaging, today's technologies make the possibilities endless. Digital images are capable of being zoomed, enhanced and changed in other ways for both the central pole and the peripheral retina. Retinal cross-sectional images can detect changes so small that it is hard to fathom. It is now possible to take measurements of the macula to proactively determine risk for macular degeneration. If patients develop AMD, we can now monitor for the earliest stages of CNVM and allow for more effective treatment. Scanning laser systems can monitor for macular edema without the need for introduction of fluorescein into the body. Beyond the macula, the optic nerve and nerve fiber layer can be closely monitored for subtle changes that may be the first signs of glaucoma.

Not only are all of these things possible, they are practical. This article reviews how these technologies work and where they fit into our current practices. Additionally, it will help us envision our practices of the future, if these technologies are not already in place. We will also discuss the importance of good clinical skills and judgment, as none of the instruments mentioned will replace the need for well-trained, experienced clinicians.

Practice setting and environment are key factors in determining the need for new retinal technology. For this reason, three esteemed colleagues from three different practice environments have contributed their perspectives to this article. What makes sense for one O.D. or practice may not pertain to another. With the views of these three forward-thinking and cutting-edge doctors, we can see first-hand how to incorporate technology into our practices and ultimately benefit our patients. From "low tech" nutritional supplements to "high tech" instruments, this article will discuss how to successfully incorporate technology into your particular practice setting.

Utilizing Retinal Technology for Prevention/Detection of Macular Disease

By Pamela A. Lowe, O.D., F.A.A.O.

As primary eye care practitioners, our first and foremost goal is the preservation of our patient's precious sense of sight. To this end, our profession has the great privilege of being on the front line for educating the public on conditions that can rob them of a lifetime of healthy vision. The three most common ocular diseases we find ourselves addressing are cataracts, glaucoma and macular degeneration. Of these three conditions, the one that can be most visually debilitating and aggressive is age-related macular degeneration (AMD).

Fortunately for optometry, some of our newest retinal technologies have provided us enhanced diagnostic capabilities for detecting AMD earlier, and even more importantly, provided essential information to use as a tool for AMD prevention. I have incorporated two of these technologies into my full-scope, primary eye care practice, and have found them to be invaluable in educating my patients on what this sight threatening condition is and how to reduce their patients risk for long-term vision loss.

The technology we have utilized for educating and identifying risk factors for AMD is the QuantifEYE unit (ZeaVision, LLC). QuantifEYE is a quick, easy test that measures macular pigment optical density (MPOD) by flicker photometry. Studies have shown that a low amount of macular pigment can put patients at a higher risk for vision loss from AMD. Other risk factors include ultraviolet exposure, smoking, obesity and, as previously mentioned, family history, gender and race. Since Caucasian females are at greater risk, we recommend this testing routinely for all Caucasian females 21 and over and, of course, any other patients with two or more risk factors. I say to my patients that they cannot change their gender, ethnicity or family history, but, if they know they have a lower MPOD score, this is a risk factor they can do something about. Diets consisting of foods rich in antioxidants and/or consumption of nutritional supplements have been shown to be beneficial in reducing the severity of AMD.

The QuantifEYE has been available since August 2006, takes up little space and is very technician and patient friendly. From start to finish, the procedure takes approximately three to five minutes. The test need only be performed on one eye; the patient is patched and given a small hand-held device with a button in the center. After being comfortably seated and positioned in the eye-piece, the QuantifEYE unit presents a target, which is a solid blue/gray circle of light, and the patient is asked to click the button when they see the target start to flicker. The target will become solid once again and the patient will continue to click the button each time they see a flicker.

At the end of the testing, the MPOD is measured in a percentage score. Those patients with a score of over 45% are considered to have a high macular pigment level and a lower risk for AMD. Those patients with a score of 25%–45% are considered mid-range, so other risk factors are taken into account to determine level of risk. Those patients below 25% macular pigment are considered at greater risk for AMD, so vitamin supplementation should seriously be considered.

In our office, we have found the QuantifEYE an invaluable tool that not only identifies patients that can benefit from vitamin supplementation but, as importantly, tracks those patients on high dose supplements to see if indeed it is improving their level of macular pigment, thus reducing their risk for AMD.

Because the QuantifEYE unit is identifying MPOD, which is only a risk factor

for AMD, there is no medical code available at this time; insurance does not pay for additional testing related to prevention. My office charges a small usage fee per test of $25; this is extremely affordable for most patients and we have over a 95% acceptance rate.

Testing and tracking a patient's macular pigment is a great tool in AMD prevention, but we have also utilized another technology to better manage those patients with known, visible macular changes. It has been well documented that patients with clinical signs of dry AMD can at any time convert to the more aggressive wet AMD. In fact, 80% of advanced AMD cases are due to choroidal neovascularization (CNV). Rightly so, we monitor these at-risk patients regularly in our offices and give them home Amsler grids for self-monitoring. Development of CNV can happen very quickly with lesions growing 20 microns per day.[1] Unfortunately, as clinicians, we are not diagnosing these lesions soon enough. Most practices pick up CNV conversion 5.5 months after progression when the lesions are about 3,300 microns.[2] We know with the great breakthrough with the anti-VEGF treatments, the earlier we pick up conversion from dry to wet leads to better therapeutic outcomes. We have found the Foresee Preferential Hyperacuity Perimeter (Foresee PHP, Notal Vision) an invaluable tool in tracking early growth of CNV.

The Foresee PHP became available in late 2006 but is the second generation unit of the original Preview PHP technology introduced in 2004. The Foresee PHP utilizes hyperacuity perimetry, which is based on Vernier acuity. Because Vernier acuity localizes an object relative to other objects in space, it is 10 times more sensitive than resolution or Snellen acuity.[3] We know the Amsler grid has basic flaws when it comes to completion, fixation and crowding. Cortical completion is found with the Amsler grid because our brain learns to "fill in" a full line if small gaps of the grid pattern are developing. Fixation is not truly forced on the Amsler grid since the test is subjective and so there is no feedback for the patient if fixation is off. Crowding is found due to inhibition of neighboring peripheral lines that reduces detection of distortions. The Foresee PHP eliminates the inherit flaws of the Amsler grid and utilizes an "automated perimetry" test of the central 14 degrees of fixation testing over 500 points three to five times each.

The testing is very interactive; the patient holds a stylus in hand and touches the screen after the stimulus (a dot deviation signal or hyperacuity pattern) is presented in a mere 160 millisecond flash. When patients are "flashed" the stimulus (a line with a "bump" in part of it), they simply hit the screen where they perceived the "bump" or broken line to be. As in peripheral automated perimetry (like the Humphrey) the Foresee PHP has fixation control and controlled stimuli, which make the results much more accurate and reliable than traditional Amsler grid testing. The instrument is also technician- and patient-friendly with a test time of approximately 20 minutes from start to finish for both eyes. Repeat testing is recommended every three months. Surprisingly, patients do not complain about the frequency of testing since the test is so much more interactive and enjoyable than peripheral perimetry. Just like peripheral automated perimetry, the test results are compared to a normative base and progression from prior tests is readily identified. The results of the test are easy to interpret and clinical recommendations are given along with test results making it very "doctor friendly." The Foresee PHP is the only FDA-cleared device to monitor conversion of dry AMD patients to wet AMD patients.

The Foresee PHP test helps determine if treatment for wet AMD is needed, so it can be billed with a visual field code. The current visual field codes are 92082, which is for automated screening, and 92083, which is for automated threshold.

Optometrists who see adult patients in a primary-care setting need to educate them on the growing prevelance of AMD and measures they can take for prevention. To implement ZeaVision's QuantifEYE, unit there is no large capital outlay. The Foresee PHP has a moderate cost that pays for itself within the first year of ownership. Any optometrist who sees adults should strongly consider both technologies.

Dr. Lowe is currently Director/President of Professional Eye Care Center, Inc., a private, full-scope primary eye care practice in Chicago. She is a member of the American Optometric Association, the American Public Health Association and a fellow of the American Academy of Optometry.

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Nutrition and the Eye

By Jeffry Gerson, O.D.

Essentially, retinal imaging tries to diagnose pathology. Although this is of extreme importance in order to afford our patients the opportunity to receive the newest and most effective treatments, it may not be the most important step in saving or maintaining vision. Preventing the need for treatment in the first place is arguably just as important.[1]

One way to potentially prevent several different ocular pathologies from ever occurring or progressing, in particular age related macular degeneration, is alteration of modifiable risk factors in our patients.[2] We, as clinicians, can help influence our patients in reducing these risk factors, which are mainly lifestyle choices. Of these modifiable risk factors (besides smoking which is potentially more difficult to influence) nutrition is a familiar area for most optometrists. While we are aware of the importance of nutrition in prevention of AMD, we may not realize its role in other pathologies, including cataracts.[3,4]

Many large scale studies, such as the AREDS, and smaller scale studies, such as LAST, point to the importance of proper nutrition when considering AMD.[5] These studies show that nutrition can be used as prevention or treatment.

To discuss nutrition in the context of using technology, you can reference several parts of this article to see how macular pigment optical density (MPOD) measuring instruments utilizing heterochromic flicker photometry can help detect one potential risk factor for AMD. The macular pigment is composed of carotenoids, which we take in from our diet. A low MPOD has been postulated to predict higher risk of development of AMD.[6] Therefore, intake of these elements is important, whether it be through a healthy diet including plenty of fruits and vegetables, or supplementation with products that have meaningful amounts of these and other important elements. We are also finding out that these same elements that seem to

influence MPOD and potential development or progression of AMD also have further value in their affects on vision.

Not only can we use supplementation as prevention, but we also can use it in order to improve vision and retinal function, as has been reported in multiple recent studies.[7,8] This allows us to talk to patients about potential improvement and not just maintenance and prevention. From a practical perspective, it may be easier to discuss the possibility of improved visual acuity and contrast than just the risk of progression.

Another important piece of the nutritional puzzle appears to be Omega 3 fatty acids. Numerous recent reports discuss the benefits of adequate intake of this essential nutrient.[9] The specific type of fat seems to be important, and this is why Omega-3 fatty acids seem to be beneficial, and other fats appear to be detrimental. We have also learned how Omega 3 can be important to other parts of the body.

Regardless of the exact element to be supplemented, it is important to discuss nutrition with our patients. From a practical perspective, it is easy to ask about diet and current supplementation and smoking status. It is also easy to then educate a patient why these things are pertinent to an eye exam and move forward with recommendations. These recommendations may include alterations to diet, use of multivitamin type products, or eye specific products, such as Ocuvite Adult 50+ (Bausch and Lomb) or ICAPS (Alcon). The more we have these discussions with our patients, the more likely we are to have a more positive impact.

Dr. Gerson practices at WestGlen Eyecare & Omni Eye Center of Kansas City.

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New Technologies in My Office

By William Jones, O.D., F.A.A.O.

As a practicing optometrist for more than 30 years, today's new technology allows me to greatly enhance detection and diagnosis of disease states in my patients. This is extremely important in delivering the quality of eye care and systemic body care that I require in my office. I have a private practice and the bulk of my patients have eye diseases. These new technologies offer many distinct advantages including tests that are easy and quick to perform—something that was not possible just 10 years ago.

One such new technology, the wrist sphygmomanometer, offers an efficient and simple way to obtain my patients' blood pressure and heart rate. It is a little faster than doing arm sphygmomanometer because the patient doesn't have to manipulate their clothing to expose their arm. I use this new technology on all my patients, and it is surprising to find patients that are unaware that they have elevated blood pressure or are in denial of the condition.

Figure 1. A migraine visual field defect is seen on this Kinetic Fields Test of a 42-year-old female patient.

Another new technology is the Kinetic Field Test (KFT, Rush Instruments). It is a continuous moving bar visual field test that tests the central 15 degrees with a bar pattern that moves in random directions. When the bars move across an abnormality, the encountered boundaries of the anomaly are perceived as a distortion in the moving bars pattern. The computer has a touch screen, so the patient can draw the distortion being perceived. It is a very sensitive test due to the fact that the continuous moving bars do not allow for cortical adaptation or completion. The degree of specificity of the test is low by its nature. The test is very fast, and it can be completed in about 30 seconds for both eyes (the test is done on a monocular basis). A positive finding alerts the examiner that further testing is required to rule out a possible disease state in the visual system.

This technology is very good at detecting disease states on the retina. In my practice, it has detected diabetic retinopathy, age-related macular degeneration (AMD), macular holes, epiretinal membranes (ERM) and vitreo-retinal traction. It has also detected severe inferior superficial punctate keratitis (SPK), dense cataracts, the edge a posterior capsulotomy, significant floaters, congenital RPE hamartoma and a quadranopic field defect due to past closed head trauma. It is the only instrument I know of that can detect residual migraine visual field defects, which I have seen in five patients. The test is fast and any technician can easily operate it.

The Preferential Hyperacuity Perimeter, commercially known as the Foresee PHP (Notal Vision), is an additional new instrument I purchased. I have used the PHP to detect CNV on suspected patients who currently have intermediate AMD, and this technology has successfully allowed me to detect the conversion of dry AMD to wet AMD. I would recommend it for the screening or early detection of CNV in patients who are in the intermediate dry AMD stage.

Another new technology I incorporated in my practice is the Panoramic 200C (P200C, Optos), the newest optical device in "ultra-wide field" fundus imaging. The P200C has a new mirror system that allows for essentially a

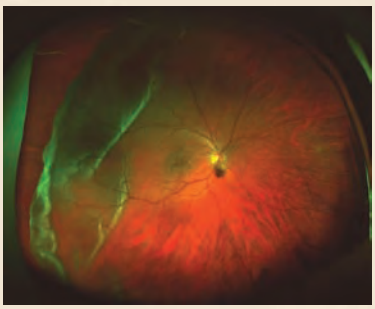

Figure 2. Giant retinal tear with detachment on the P200C.

distortion free image. The resolution of the P200C is 20 microns in the 200-degree Optomap "Standard Wellness" image, 14 microns in the Optomap plus Advanced Clinical mode, and 11 microns in the ResMax Advanced Clinical mode. The resolution is so good that, in my opinion, no other imaging instrument is required in the practice. It has advanced optical features that allow for eye-steered fundus imagery that often gets to the pars plana/ora serrata or very close to it. I recently treated a 19-year-old female patient with suspected pars planitis. With this new technology, I was able to image the "snow balls" in the vitreous that were over or just posterior to the inferior ora serrata. In my diabetic patients, I have been able to detect tiny dot hemorrhages in the posterior pole, which may have been microaneurysms (no FA was done) and tiny hemorrhages in the periphery. The P200C is great for seeing large lesions of the fundus (large tumors, large retinal detachments, numerous lattice lesions, etc.) that you can only see partially with binocular indirect ophthalmoscopy or a slit lamp with a precorneal fundus lens.

The new patient fixation system in the P200C permits a much easier capture of the fundus, especially in "eye steering" mode. Another advance is the small size of the instrument, which is two-thirds the size of the P200. Imagery with the P200C can be performed with or without dilation of the pupil. There is a great advantage to having the patient's image up on the monitor when you enter the exam room because, if there is an intraocular problem, the exam can be streamlined to the condition at hand.

Another new technology in my practice, the Stratus OCT (ocular coherence tomography, Carl Zeiss Meditec, Inc.), is a scanning light instrument that

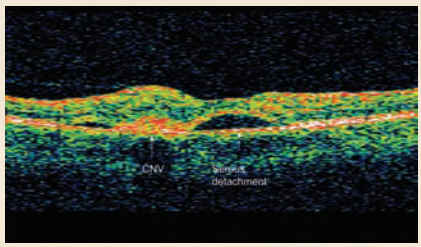

Figure 3. Stratus OCT image of choroidal neovascular membrane of the patient plotted with the PHP.

produces a cross-sectional view of intraocular structures. The scans are able to determine retinal thickness with the cross-sectional views and average the cross sections into thickness readings. This instrument is able to see details of the retina that one cannot see with regular ophthalmoscopy. It can see neovascularization in AMD, central serous chorioretinopathy, retinal cystoid spaces, vitreous posterior cortex retinal and disc attachments that may lead to traction damage and macular holes not visible with ophthalmoscopy. Optic nerve head and juxtapapillary retinal nerve fiber layer (RNFL) thickness evaluation for glaucoma and evaluation of other optic nerve head disease conditions is excellent with this technology. Determining large physiologic optic disc with large cups and the existence of glaucoma, due to RNFL loss, is very easy to obtain. I have also used the RNFL function to determine peripapillary retinal edema in papilledema and other vascular disease states of the optic nerve head. It is also useful in detecting the presence of intrapapillary drusen by determining disc elevation and imaging the drusen themselves.

The Stratus is a time domain OCT, which takes time to scan through a section of tissue. It requires some skill to obtain good scans, and eye movements can affect the results of the scan. The new Spectral or Fourier domain OCTs take instant captures of a block of tissue, so these require less skill level and training to use. Additionally, eye movements usually have little impact on the results of the scan. Any clinician interested in obtaining fine detail information of the retina and optic nerve head will find OCT technology indispensable.

Dr. Jones is in private practice in Albuquerque, N.M.

Old School Clinical Skills and Cutting-Edge Retinal Technologies Improve Patient Outcomes

By Joseph J. Pizzimenti, O.D., F.A.A.O.

As an attending optometrist in an academic health center, I have had the unique opportunity to integrate several retinal technologies into clinical practice. There are numerous features that make new technology attractive and useful to a practice. They are listed in Table 1.

Table 1. Features/Advantages of New Retinal Technology

- Mydriatic, non-mydriatic, and wide field photography capabilities.
- No film.
- Telemedicine-ready.
- High resolution images.
- Better documentation of conditions.
- Can be used as patient education tools.
- Can be marketed to attract patients.(i.e., "our practice offers 'state of the art' technology.")
- May help diagnose disease earlier.

Several factors must be considered when evaluating new retinal technology. See Table 2.

Table 2. Factors to Consider

- Patient base.
  - Current patient base: Can your current patient base support retinal technology? If you see mostly healthy children and young adults, perhaps not.
  - Future patient base: What would you like your patient base to look like? Would you like to see more retina patients? If so, you can purchase a new device and market it to current and potential patients.
- Staff.
  - New technology requires staff acceptance and education.
- Network Connectivity: Is the device EMR-friendly?
- Cost: How soon will it pay for itself?
- Space considerations.
- Future upgrades.
  - Cost of upgrades.
  - Will upgrades use the same "platform?"
- Support and training: Will the company be there when you need them?

Here is a brief synopsis of our instrumentation here at The Eye Care Institute.

Scanning Lasers

Retinal thickness measurements and qualitative studies with scanning lasers enable the identification and tracking of structural changes due to various causes, including age-related macular degeneration (AMD), vitreomacular traction syndrome, epiretinal membranes, macular holes, and various "edematous" retinopathies.

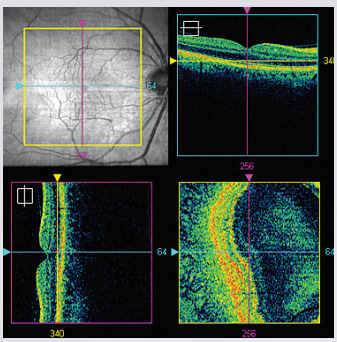

Figure 1. Cross-sectional posterior segment imaging from Cirrus OCT.

For the past seven years, Optical Coherence Tomography (OCT) has been my "go-to" instrument for cross-sectional posterior segment imaging and quantitative analysis. I currently use the Cirrus OCT (Carl Zeiss Meditec, Inc.). The Cirrus uses a spectrometer as a detector in conjunction with a stationary reference mirror. The lack of moving parts facilitates exceptional image acquisition speed.[1] *(Figure 1)*

This spectral domain technology produces high-resolution 2-D and 3-D images that help me to distinguish between subtle pathological changes and normal anatomic variations. OCT has enhanced my ability to diagnose and manage myriad retinal conditions and has revolutionized my evaluation of the vitreoretinal interface.

The HRT-3 Retina Module (Heidelberg Engineering) uses confocal scanning laser ophthalmoscopy technology to evaluate the entire retina. The HRT Edema Index is a relative indicator of fluid accumulation based on changes in light reflectance. Index values over 2.0 are highly suspicious. The HRT-3 uses TruTrack™ technology to check and align the images, remove images with questionable quality, and combine the sets into one 3-D composite, providing Reflectance and Thickness maps.[2]

The RTA-5 (Talia/Marco) offers the ability to quantitatively document anatomical changes in retinal and subretinal tissues by measuring thickness variations and topographic changes of the chorioretinal interface. Data acquired by the RTA-5 is presented as color-coded 2-D and 3-D thickness and topography maps, deviation probability maps (from a normative database), numerical values, interactive 3D cut sections, and digital fundus images.[3]

Fundus Photography

The Nidek 3Dx Stereo Fundus Camera and 3Dx/F Fluorescent Stereo Fundus Camera are available for stereoscopic macular imaging. The 3Dx has the capability for stereo color photography and fluorescein angiography.[4]

For general fundus photography, we have a Canon Digital Retinal Camera. The camera provides high-resolution color, red free, and fluorescein angiography imaging. It has user-friendly control software to achieve excellent detail, contrast, color, and archiving.

Functional Macular Testing With Foresee PHP

For the past several years, I have implemented Foresee Preferential Hyperacuity Perimetry (PHP) (Notal Vision/Sightpath) to monitor patients with dry AMD. This instrument is designed to detect early conversion to the wet form of the disease.[5] Like glaucoma, AMD is a condition best monitored by both structural and functional testing.

Macular Pigment Optical Density

Thanks to my QuantifEYE system (ZeaVision), I can now measure the amount of macular pigment on my patients. The QuantifEYE uses Heterochromatic Flicker Photometry (HFP) to quantify macular pigment. HFP uses flickering blue and green light targets to yield a measurement reported in density units as Macular Pigment Optical Density (MPOD). Lower MPOD can be associated with increased risk for AMD.

Putting it into Practice

Table 3 lists the appropriate CPT codes for the instruments that I use.

Table 3. Codes

■ Fundus Photo	92250
■ PHP	92082
■ Scanning Lasers	92135
■ MPOD	S9986 (Screening—not covered by Medicare)

"Old School" Skills

With all these great "toys" available to me, it would be easy to get carried away with the hi-tech gear. But of course, excellent patient care is not just about having the latest technology. Here are some thoughts on "low-tech" optometry.

Until the invention of direct ophthalmoscope by von Helmoltz in 1851, the living retina was not visible.[6] Simply put, I love the direct ophthalmoscope. It is quick and easy, with good examiner control and 25X magnification. I use it with the red-free filter to detect microaneurysms, small hemorrhages and vitreous opacities.

A skilled clinician is adept at performing and interpreting the results of fundus biomicroscopy. The use of a contact or non-contact fundus lens in conjunction with the slit lamp is a powerful way to evaluate the central, mid-peripheral and peripheral retina, as well as the optic disc.

Of course, no posterior segment examination is complete without binocular indirect ophthalmoscopy through a maximally-dilated pupil. Scleral indentation is a specialized skill that enables viewing of the peripheral retina in profile, yielding useful information about retinal breaks and other clinical entities.

Conclusions

No scanning laser or other futuristic technology can replace the clinical examination and diagnostic skills of an excellent optometrist. An integration of "old school" clinical skills with new retinal technologies may enable the clinician to detect disease earlier, leading to more timely treatment and improved visual outcomes.

It's not about the technology—it's about our patients' visual health and quality of life. ■

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