Findings from AREDS:

The Role of Nutrition, Vitamins and Supplements and Lifestyle Choices in Age-Related Macular Degeneration

The Age-Related Eye Disease Study (AREDS) is a landmark study funded by the National Institutes of Health (NIH) and National Eye Institute (NEI). The study grew from concern of the widespread use of nutritional supplements by Americans in the treatment of age-related macular degeneration (AMD) where the effectiveness and safety of those treatments were previously inadequately studied. The purpose of the study therefore was to clarify the role of vitamins and nutritional supplements as well as other lifestyle choices on the progression of AMD. Additionally, AREDS evaluated other risk factors for the development of AMD and attempted to sub-classify the disease to help physicians determine an individual's risk for disease progression. The first phase of this ongoing study began in 1992. Critical reports from the first phase of the study are summarized below.

AREDS Report Number 3: Risk Factors Associated with AMD

Advanced AMD is generally broken down into 2 subcategories: 1. dry AMD (or non-neovascular AMD) and 2. wet AMD (or neovascular AMD). In dry AMD, progressive disease results in thinning of the central retina with loss of normal retinal tissues and pigment. This characteristic pattern is identifiable on exam and is termed geographic atrophy. In wet AMD, poor circulation from progressive disease results in the growth of abnormal new vessels into the dying retinal tissue. These abnormal vessels can spontaneously break causing extensive bleeding within and under both diseased and normal retinal tissue.

In studying potential risk factors for AMD, AREDS found that increasing age and cigarette use were associated with greater risk for the presence of geographic atrophy. Cigarette smokers were 61% more likely to have geographic atrophy than non-smokers.

The presence of wet AMD was 4.2 times more likely in white study participants over non-whites. Wet AMD also occurred more commonly in those with hypertension, cataract, farsightedness, and obesity. Cigarette users again were at higher risk with a 91% greater risk of having wet AMD over non-smokers. Interestingly, both dry and wet AMD occurred less commonly in participants with a higher education (defined as having completed at least 12 years of schooling).

It is suspected that cigarette smoking promotes macular degeneration either by oxidative stress from chemicals in the smoke or by promoting atherosclerosis which in turn reduces blood flow to the retina. Several studies support the theory of oxidative damage. One such study has shown decreased luteal pigment (a protective antioxidant normally found in the macula) in the retinas of smokers. Other studies have shown decreased plasma beta carotene in smokers even when adjusted for dietary differences. It is not unlikely

that both vascular disease and oxidative damage from smoking promote macular degeneration.

AREDS theorizes that obesity may increase risk of AMD because of increased oxidative stress and that hypertension may contribute to the vascular damage promoting AMD.

Drusen are small deposits within the retina found with increasing frequency as people age. They are believed to represent accumulated outer segments of the photoreceptors which are shed on a daily basis and are less completely absorbed into the blood stream as people age. The size, number and location of drusen were found to be correlated to the rate of progression of macular degeneration in AREDS. Drusen occur in all races but in non-whites they more often tend to be small whereas whites are more likely to have intermediate and large drusen. It is theorized that increased pigmentation of the retina in non-whites may act as a free radical scavenger as well as filtering the amount of UV light reaching the outer retina thus reducing the accumulation of drusen and the risk of progressive AMD.

"Education itself is unlikely to be a direct risk factor, but rather a surrogate for other factors….smoking is inversely associated with education achievement…"

AREDS Report Number 8: A Randomized, Placebo-Controlled Clinial Trial of High-Dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss

Summary of the Study:
The ARED Study was designed as a double masked placebo controlled prospective study. Enrollment included 3,640 participants age greater than 55 years with findings of either drusen or early macular degeneration. Participants were randomly assigned to one of four treatment groups receiving only one of the following:

1. Antioxidants: Vitamin C 500 mg, Vitamin E 400 IU and Beta carotene 15 mg
2. Zinc 80 mg (as ZnO) and Copper (CuO) 2 mg
3. Antioxidants plus Zinc
4. Placebo

The treatment groups were then followed to determine the rate of progression of AMD. The follow-up period of this phase of the study was 6.3 years with 2.4% of participants being lost to follow-up.

Adverse effects reported in the study included yellow skin in patients in the antioxidant groups (a result of beta carotene) and more frequent genitourinary problems including urinary retention from benign prostatic hypertrophy (BPH) in men and stress incontinenece in women in patients randomized to Zinc groups (8.6% vs. 4.4% of placebo). Interestingly, participants in antioxidant arms reported less frequent chest pain (20.2% for 23.1% of placebo group). No statistically significant difference in mortality rates were observed among the treatment groups though zinc plus antioxidants trended toward lower mortality rate over placebo alone.

Results:

Overall, the risk of progression to advanced AMD over 5 years for the four treatment groups was:

- 28% for those assigned to placebo
- 23% for those assigned to antioxidants
- 22% for those assigned to zinc
- 20% for those assigned to both antioxidants and zinc

The overall risk of progression to advanced AMD over 5 years was therefore reduced by 25% in those participants receiving a combination of antioxidants and zinc.

The study went further to clarify which participants received the greatest benefit from supplementation. The participants were broken down into four categories based on retinal exam findings. Category 1 participants had minimal drusen. Category 2 participants had extensive small drusen or early pigment changes. Category 3 participants had extensive intermediate sized drusen, one large drusen or small, non-central geographic atrophy. Category 4 participants had advanced AMD in one eye only.

When categorizing the participants in this manner, it was shown that treatment with antioxidants plus zinc reduced the 5 year risk of progression by:

- 25% for all participants
- 37% for categories 3 & 4 combined
- 24% for participants in category 3 alone
- 48% for participants in category 4 alone

Study Conclusion:

The conclusion of this phase of the AREDS study is that supplementation is appropriate for people older than 55 with extensive intermediate size drusen, one or more large drusen, non-central geographic atrophy in 1 or both eyes or in advanced AMD with vision loss due to AMD in one eye. Importantly, it's recommended that smokers avoid beta-carotene.

Other Conclusions:

Because of confounding, the potential effects of taking a daily multivitamin could not be elicited from the study although there was a trend towards a beneficial effect.

The carotenoids lutein and zeaxanthin were not included in the study because formulation was not widely available at the time the study began. Beta carotene, another carotenoid, was included in the study at 15 mg/day. Subsequent studies have shown an increased risk of lung cancer and mortality in asbestos patients and smokers who take beta carotene.

80% of Americans over age 70 fall into the low risk categories 1 or 2. The risk of disease progression to advanced AMD over 5 years for these categories are <1% for category 1 and 1.3% for category 2. Because of the low power of the study for these two categories, a determination of the effect of antioxidants plus zinc on the risk of progression could not

be made. Analyses seem to indicate that antioxidants and zinc do not reduce the risk of progression from category 2 to category 3 or 4 status. At this time, supplementation is recommended only to the higher risk categories.

Advanced neovascular glaucoma was not studied by AREDS and no conclusions or recommendations can therefore be drawn about supplementation in these patients.

Alternative Medicine for Macular Degeneration

Adapted from **Alternative Medicine for Glaucoma**. Given by Lisa S. Garnell, MD, FACS, Assistant Professor of Ophthalmology and Visual Sciences, Alterrt Einstein College of Medicine. Given at the Royal Hawaiian Eye Meeting, January 2005.

Introduction

- Alternative medicine is defined as those treatments and healthcare practices not taught widely in medical school, not used in hospitals and not usually reimbursed by Medicare or other insurance companies. Currently, more money is spent in the U.S. on alternative medicine than on prescription medications. Often these treatments have been poorly studied and little is known about their efficacy or side-effects. Alternative medical therapies are usually sold as food supplements and therefore fall outside of the regulation of the FDA. Because these treatments are sold without a prescription a misconception is promoted that they are somehow not pharmacologic agents and that they are without risks. This could not be farther from the truth. What follows here is some limited information about what is known about commonly used alternative medical treatments and their impact on the treatment of AMD.

Vitamins & Supplements

- Vitamin A – Vitamin A is a well studied essential nutrient that also has antioxidant properties. It has been clinically proven in the Age Related Eye Disease Study (AREDS) to reduce the rate of progression of age-related macular degeneration (the leading cause of legal blindness in the United States) in certain patients. Recommended dosing of Vitamin A is 10,000 IU per day. At doses more than 30,000 IU per day toxicity can ensue resulting in alopecia (hair loss), fatigue, headache, vertigo, increased intracranial pressure (elevated fluid pressure around the brain) and cirrhosis. Smokers should not take supplemental vitamin A because of an even greater risk of cancer.

- Vitamin B12 – The role of Vitamin B12 in the treatment of AMD is unclear. Deficiency of Vitamin B12 can result in optic nerve disease similar to glaucoma. Recommended dosing is 100 mcg/day or as part of a Vitamin B complex. No toxicity has been documented.

- Vitamin C – Vitamin C is another well studied essential nutrient and antioxidant proven in AREDS to lower the risk of progression to advanced AMD. Recommended dosing of Vitamin C is 500 mg per day.

- Vitamin E – Vitamin E also studied in AREDS has been shown to reduce the risk of progressive disease in AMD. Recommended dosing of Vitamin E is 400 IU per day. Recent studies have shown that oral supplementation may have an anti-fibrotic effect (slows scar formation). Side effects of Vitamin E include impaired blood clotting and it may be advisable to discontinue use of Vitmain E prior to any surgery. The increased bleeding tendency is more common in patients already taking anticoagulants such as Coumadin and antiplatelet medications like aspirin. Patients taking these medications should speak with their managing physician about whether it is safe to take supplemental vitamin E.

- Bilberry – Studies of bilberry use have shown no improvement of visual function of any kind. Usual dosing is 60 – 160 mg three times daily or, in leaf form, one cup three times daily. Side effects include digestive complaints (nausea, diarrhea). Bilberry is known to interact with other medications including anticoagulants such as Coumadin (warfarin) and aspirin. Overdose of bilberry can result in cachexia (generalized wasting), anemia and icterus.

- Ginkgo biloba - The leaf of the maidenhair tree is the source of ginkgo biloba. It has been used for centuries in China and Western Europe. The most common preparation (EGb761) contains 24% ginkgo-flavone glycosides and 6% terpenoids as the active ingredients. The function of these ingredients is the inhibition of PAF (platelet activation factor). The normal function of PAF is to coordinate the formation of a blood clot. However excessive PAF activity can result in bronchoconstriction, increased vascular permeability and increased glutamate excitotoxicity resulting in brain injury. The properties of ginkgolide B include antioxidant and prolongation the life of endothelial derived relaxing factor which can theoretically improve ocular blood flow and blood vessel health in patients with AMD. Ginkgo however has side effects and drug interaction similar to bilberry.

Diet

- Caffeine – There is a theoretical risk that caffeine induced vasospasm could promote progressive AMD by impairing ocular blood flow.

- Omega 3 Fatty Acids – Omega-3 fatty acids are naturally found in fish oils Human studies with supplemental omega 3 fatty acids have demonstrated decreased risk of progressive AMD as well as improved visual field and contrast sensitivity testing results. Further testing to establish efficacy, correct dosing, side effects and risk profile are needed.

- Total Caloric Intake – Several studies including AREDS have now shown an association between increased BMI (body mass index) and more advanced AMD in elderly patients. It is suspected that this is due to increased oxidative stress from excessive caloric intake.

Lifestyle

- Relaxation Techniques – It has been postulated that increased cortisol release from chronic physical or emotional stressors may deleteriously affect autonomic function (important in autoregulation of ocular blood flow). Studies linking stress to macular degeneration however are inadequate and no study has demonstrated an effect of relaxation techniques or biofeedback on AMD progression

- Smoking – It is widely believed by ophthalmologists that cigarette smoking - with its known roles in atherosclerosis, heart disease, stroke and hypertension - exacerbates macular degeneration. AREDS as well as numerous other studies have shown conclusive associations between the frequency, severity and rate of progression of AMD. Stopping use of cigarettes is the single most effective step that someone can take to help reduce their risk of developing macular degeneration. For those who have macular degeneration, smoking cessation is critical in reducing their risk of progressive vision loss.

Concluding Remarks

- The role of alternative medicine in the management of diseases such as macular degeneration is slowly being elucidated. There is however a significant amount that is not understood. Always discuss with your physicians the alternative therapies that you're using especially in context of your prescription medications and diseases.

- Antioxidant vitamin supplements, ginkgo, and omega-3 fatty acids may be of benefit in the treatment of macular degeneration provided overdosing and systemic drug interactions can be avoided. Smokers should avoid vitamin A. Smoking cessation is ideal. Stop vitamin E two weeks prior to surgery. Do not take bilberry or ginkgo if also using anticoagulants.