Cross-Talk for Health Care Providers

_Nutrition and Behavior as it Applies to Systemic and Ocular Disease_®2009

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After several years in the practice of health care and watching an increase in immune-complex disorders, inflammatory disorders and degenerative diseases, I believe it is time for the health care community to initiate cross-talk. One recent study reports a healthy lifestyle combining not smoking, a healthy weight, a healthful diet including moderate alcohol consumption, and daily exercise reduced ischemic strokes by approximately half in both men and women. *(Circulation. Published online August 11, 2008)* The transfer of this critical information to all health care providers is important to the long-term health of all. This represents the essence of the Cross-Talk.

Most specialties and sub-specialties are publishing discoveries within their own journals without communicating those findings to other disciplines in spite of the fact that the results may have direct impact on the management of a different body system. As an example, how many health care practitioners who treat herpes zoster have read:

_JAMA 1985 Mar 8;253(10):1427-30._

**Herpes zoster. The treatment and prevention of neuralgia with adenosine monophosphate.**

_Sklar SH, Blue WT, Alexander EJ, Bodian CA._

Thirty-two adults were enrolled in a randomized, placebo-controlled double-blind trial of intramuscular injections of gel-sustained adenosine monophosphate (AMP) given three times a week for up to four weeks for acute herpes zoster. Adenosine monophosphate moderately reduced the pain soon after the start of treatment, decreased desquamation time, and promoted faster healing of the skin than placebo treatment. Adenosine monophosphate treatment reduced virus shedding and cleared the virus faster than in placebo-treated subjects. At the end of the initial four-week treatment period, 88% of AMP-treated patients were pain free, as opposed to only 43% in the placebo group. After four weeks, all patients who had not recovered from pain started receiving AMP treatment without breaking the code. All these patients recovered from pain within three weeks after initiation of treatment. No recurrence of pain or lesions was experienced from three to 18 months after the end of treatment. Adenosine monophosphate, a natural cellular metabolite, showed no side effects or toxicity during and after the treatment. As a victim of shingles, I would have probably benefited from this information.

The eye provides an excellent model to illustrate the impact of one discipline on another. Cardiologists are well aware of the potential of some nutritional supplements in the management of vascular disorders. Vascular alteration to the eye results in a number of disorders including glaucoma. Why then would an eye care professional not want to realize the ongoing thought process in cardiology. Dermatology realizes that CoQ10 levels reflect the likelihood for the progression of malignant melanoma, one of the more dreaded ocular conditions. A simple PubMed search of CoQ10 and the eye reveals 88 pages of refereed citings, 20 citings per page, the overwhelming majority from journals not related to the eye care professions. Health care is forgetting that basic to all disease is the concept of “cells gone wild.” Alteration of mitochondrial function will create the
springboard for a number of disorders. Excesses in excitotoxicity precipitate progressive neurodegenerative disorders, one of which is glaucoma. Management of those disorders with standard pharmaceutical agents may lay the groundwork for the genesis of even more disorders. A listen to pharmaceutical promotion caveats reveals the “cure” is often more offensive than the “disorder.” Have you ever thought of the adds for sleeping disorders and the side effects when one of the most common sleeping disorders is Sleep Apnea. What is the potential for side effects with medicating a person with Sleep Apnea. You certainly would not want to give a person with Sleep Apnea a topical Beta Blocker dosed at bedtime. Would it not be judicious to recommend that the patient check for Sleep Apnea prior to taking the medication? Where is the Cross-Talk between the pulmonologists and psychiatrists? In our society, little attention is paid to prevention or minimizing risks, and suggestions of methods of prevention become the fodder for ridicule. Cross-Talk is the answer and this exercise will take you through the application of multiple discipline research “eureka moments” to eye care, specifically the comprehensive management of glaucoma.

Of particular interest is the behavior of our society in the creation of nutritional deficiencies. Poverty, drug side effects, drug abuse, alcoholism, gastric bypass (bariatric surgery), fad diets, and just ignorance may be opening a door to the genesis of an entirely new set of nutritionally-based diseases and disorders. A question that we all must ask in relation to the work-up of any ocular disease patient must include nutritionally-related issues. (Glaucoma Today 2007;5:33) The decreased survival of AREDS participants with AMD and cataract suggests that these conditions may reflect systemic rather than only local processes. (Arch Ophthalmol 2004;122:716) Vitamin A deficiency at the least may become an issue associated with fat mal-absorption associated with bariatric surgery (Br J Ophthalmal 2004;88:583) which will then impact directly on the genesis of dysfunctional tear syndrome. Vitamin B12 and folate deficiency is also related to malabsorption and is well known to create ocular side effects with a strong relationship to hyperhomocysteinemia which represents a major cardiovascular threat. (Am J Med 2005;118:1154, Haematologica 2006;911506, Semin Ophthalmol 2002;1729, Am J Clin Nutr 2005;82:442) In spite of a purportedly healthy diet in the US 10%-14% of Americans have a vitamin C deficiency, (Am J Public Health 2004;94:870) up to 15% of adults over 60 years have laboratory evidence of B12 deficiency (Am J Med 2005;118:1154) Treatment of the majority patients with these readily obtainable nutrients involves basic diet good sense or supplementation as well as exercise and general modification of behavior including cessation of smoking and minimizing the use of alcohol. It continues to amaze that patients believe in the magic bullet. A recent study points out that despite eating a diet rich in omega-3 fatty acids, Alaskan Eskimo are developing subclinical atherosclerosis at an early age, likely due in large part to heavy smoking. (The GOCADAN study. Stroke 2008; DOI:10.1161) The thrust of the message in this discussion is that synergism is key rather than an isolated monotherapy approach in the management of most chronic, neurodegenerative, and inflammatory disorders. Modulation (balance) is the critical watchword in the approach to the management of health in most individuals while minimizing risk. One of the most effective methods of managing excitotoxicity is sub-lingual nitroglycerin, however the collateral damage outweighs the benefits. Radical behavior or unbalanced therapy can and will create far more harm than good. Exercise potentiates effects and combinant therapies represent the theme of recent “eurekas.” Regular exercise and consuming long-chain n-3 fatty acids (FAs) from fish or fish oil can independently improve cardiovascular and metabolic health, but combining these lifestyle modifications may be more effective than either treatment alone. (Am J Clin Nutr 2007;85:1267) There is no
magic pill, but rather a mental set and lifestyle that set the tone for maximizing health. While we should expect everyone to modulate their behavior to maximize their health it just will not happen so we must arm ourselves to become “personal health advisors” to our patients. A recent review study corroborates this stating that healthy lifestyle habits include not smoking, maintenance of optimal BMI, moderate alcohol consumption, and daily exercise. In men and women, maintenance of healthy lifestyle habits is associated with an 80% reduction in the risk for stroke. (Circulation. Published online August 11, 2008)

Another critical issue regarding supplementation is that the health care provider is often unaware of the patient’s use of non-pharmaceutical products. Vitamin E and Gingko biloba may not be reported in patients using blood thinners. Pro times will definitely be affected. In a survey conducted in 1999, about 49% of adult Americans were estimated to have used herbal products during the previous year. It has been documented that as many as 31% of the patients who use herbal supplements do so in conjunction with prescribed drugs and about 70% of these patients do not regularly report the use of these products to their health care providers. (Journal of Clinical Pharmacy & Therapeutics 2002;27;391) Another enlightening report speaks to the use of “complementary medicine use in cancer survivors. It is reported that prayer and spiritual practice were the most prevalent methods, reported by 61.4% of survivors. This was followed by relaxation (44.3%), faith and spiritual healing (42.4%), nutritional supplements and vitamins (40.1%), meditation (15%), religious counseling (11.3%), massage (11.2%), and support groups (9.7%). Hypnosis was least likely to be used (0.4%), and biofeedback therapy (1.0%) and acupuncture/acupressure (1.2%) were used only slightly more often. (Cancer. 2008;113:1048)

Additionally, there is strong support in the medical literature regarding diet and nutritional modification in the management of glaucoma. Much of the supporting documentation comes from literature considered outside the realm of eye-care, in the areas of vascular and neurological literature. The manipulation of this aspect of therapy may be particularly applicable to NTG with the thought that the cause is actually reported to be vaso-regulative with neurodegenerative issues. A number of studies support a look outside the paradigm. (Expert Opin Emerging Drugs 2007;12:195)

One critical issue to address is the validity of claims that evolve from scientific studies. This discussion is intended to be scientifically-based to provide the reader with an understanding of the potential of behavioral issues as they relate to the genesis of ocular and systemic disorders. With that in mind be cognizant of the fact that numerous claims by a plethora of studies have yet to be substantiated. The difficulty in developing incontrovertible evidence stems from the difficulty involved in human trials. Extrapolation of some of the concepts to clinical application is possible, but guarded optimism is the watchword until clinical trials support results. Any analysis of published reports must be tempered by the structure of the study. Peter McDonnell in a recent editorial in Ophthalmology Times February 15, 2006, coincidently one of the major violators of the dissemination of “paid for studies”, discusses “Are you skeptical of the latest peer-reviewed results?” Dr. McDonnell cites an article by Ioannidis regarding the fact that he reviewed 49 “important” research articles published in top medical journals between 1990 and 2003 and further cited 1000 times. Over 33% of these articles were found to be wrong. According to Ioannidis over “50% of peer-reviewed biomedical science is crap.” (JAMA 2005;294:218, PLoS Med. 2005 Aug;2(8):e124, J
Critical review of new ideas prior to translation of the information to the general health care delivery team is critical in the evolution of any educational model. Increased fraud in publication of trials also seems to be on the increase with printed retractions occurring far after the potential impact of the results (J Clin Epidemiol. 2008;61:464) as well as an excess of apparently significant clinical findings. (Clin Trials. 2007;4:245) One Canadian study provided an interesting commentary on industry-sponsored research on prostaglandin medications. They found that industry-funded studies were significantly more likely (19/27 studies = 70%) to have abstract conclusions that did not match the actual reported main outcomes of the study than were nonindustry-funded investigations (2/12 = 17%, \( P = .002 \)). Conclusions of the abstracts in industry-funded studies were supportive of the company's drug 89% of the time. (Program and abstracts of the Association for Research in Vision and Ophthalmology 2008 Annual Meeting; April 27-May 1, 2008; Fort Lauderdale, Florida. Abstract 1219)

**Diet That Supports Anti-Inflammation, Neuroprotection and Overall Ocular Health**

The eyes are truly the window to both the soul and functioning of the body. All aspects of health are ultimately reflected in the health of the eye but the direct cause-effect relationship is evasive because of the cumulative effect of one's actions. Diet and diets both affect the health of the eyes. An abusive diet, drug interactions, and toxicities create health issues within the cardiovascular, endocrine and neurological systems that reflect in ocular function. Likewise radical diets and bariatric surgery rob the body of essential nutrients to promote proper function. This discussion will but touch the high points of diet, behavioral modification and supplementation but will speak to the importance of a coordinated effort in preventing and managing systemic and thus ocular disorders.

Excessive weight and obesity in concert with an inappropriate diet loom as a constant threat to both systemic and ocular health. (Surv Ophthalmol. 2007; 52;180, Harefuah. 2005;144:805, Clin Interv Aging. 2006;1:11) Morbidity and mortality are both affected by diet with a prudent approach being to maintain your weight at a reasonable level while coincidentally consuming health-sustaining nutrients. There are studies linking obesity to macular degeneration. (Arg Bras Oftalmol. 2005;68:229) In one report overall and abdominal obesity increased the risk for progression to advanced AMD, and more physical activity tended to decrease risk. (Arch Ophthalmal. 2003;121: 785, Br J Ophthalmal. 2005;89: 964) Ironically there is also increased risk should the patient be too thin. (Arch Ophthalmal 2001;119:1259) Another recent report suggests that in Latinos cardiovascular risk factors may play a role in advanced AMD. (Am J Ophthalmal. 2008;145:308) This should be of no surprise since Richer's original work demonstrated that cardiovascular risk factors including serum Fe levels contributed to the progression of AMD. (Am J Ther. 2002 ;9:25) The other risk factors often associated with heart disease such as smoking and altered blood composition are also modifiable in our patient base. (Ophthalmology 2005;112:533, Am J Ophthalmal. 2007;143:473, Arch Ophthalmal. 2007;125:55, Arch Ophthalmal. 1998;116:583, Postepy Hig Med Dose 2007;61:28) Reports also attest to the fact that obesity is actually related to a decrease in macular pigment levels that may be attributable to competition with adipose tissue. (Am J Clin Nutr. 2006;84:1107, Nutr Rev. 2005;63:9, IOVS 2004;45:3840, IOVS 2002;43:47) Serum levels of lutein and zeaxanthin are the true measures of efficacy and both levels are measured lower with obesity and diabetes. (Am J Clin Nutr. 2006;84:1107) All of these studies still do not absolutely indicate the need for diet control...
from a scientific standpoint, but all studies point to the necessity for cessation of smoking in minimizing the risk for AMD. (Med J Aust. 2006;184:455)

From the standpoint of cataract development there has been much discussion regarding diet. While very specific, studies showed a link of metabolic syndrome with the genesis of cataracts. (Medicina (Kaunas). 2006;42:115, Eur J Ophthalmol. 2007;17:605) It appears that there is a link between oxidative stress and cataract formation with smoking again being implicated. (Expert Opin Investig Drugs. 2004;12:691) In general it also appears that obesity is a positive marker for the increased likelihood of cataract formation while a bit unpredictable based on the type of cataract. (Eur J Ophthalmol. 2007;17:29, Arch Ophthalmol. 2005;123:1108, Am J Clin Nutr. 1999;69:237) With a higher Body Mass Index (BMI), abdominal obesity, and diabetes patients develop a higher incidence of cortical and posterior sub-capsular cataracts. (Ophthalmology 1998;105:1244, Am J Clin Nutr. 2003;78:400)

The link to diabetes and obesity (most specifically the metabolic syndrome) is incontrovertible. (J Gen Intern Med. 2006;21:84, Diabetes Care 2002 25:1790, Prim Care Diabetes. 2008;2: 65, Med J Aust. 2007;186:461) Metabolic syndrome denotes a common cluster of naturally connected risk factors including obesity, elevated blood pressure, insulin resistance, dyslipidemia, proinflammatory state and prothrombotic state. This scenario has the potential to lead to multiple retinal vascular flow issues within the eye. (Arg Bras Oftalmol. 2008;71:62) The link to diabetic retinopathy is more circumspect but studies have linked retinal microvasculopathy to metabolic syndrome. (Diabetes Care 2002 25:1790, IOVS 2006;47:2341) Inhibition of inflammatory mediators is likewise implicated in minimizing diabetes risks (Exp Diabetes Res. 2007;2007:95103) and can be achieved by dietary modification. A diet designed to address the metabolic syndrome seems to be the direction to go to minimize the risk of diabetic retinopathy. Additionally one must address other situations that may increase oxidative stress and decrease oxygenated blood supply to the eye such as smoking and sleep apnea.

There also exists an association of weight issues to glaucoma. There is certainly a suggestion that there is an association of insulin resistance and the metabolic syndrome to increased intraocular pressure. (Diabetes Metab Res Rev. 2005;21:434) Body Mass Index appears to have an association with elevated intraocular pressure. (Jpn J Ophthalmo. 2003; 47:191, Int J Epidemiol. 2000;29:661, Clin Experiment Ophthalm. 2002;30:237, Am J Ophthalmo. 2008;146:69) Certainly initial reaction to this fact among clinicians would be to point to neck size and positive pressure as a related factor with sleep apnea falling into the picture. (Sleep Med Rev. 2007;11:269, Can J. Ophthalmo. 2007;42:238) The relationship of cerebrospinal fluid pressure elevation, Idiopathic Intracranial Hypertension, serum cortisol, and sleep apnea also create an interesting scenario for elevated intraocular pressure. (Am J Ophthalmo. 2007;143:635) While further analysis from a scientific standpoint is critical, it does appear, quite logically, that obesity has a link to glaucoma if from no other standpoint than physical restriction of flow.

Cordain contends that our Western diet has evolved in a disparate manner from our basic biological needs. (J Clin Nutr 2005;81:341) We still have cave-man genes (genotype) requiring the Paleolithic diet that are not being properly nourished by our current diet. This aberrant diet then creates an oxidative stress that impacts on the inflammatory reaction as well as the immune system. Oxidative stress in glaucoma leads to alterations in Retinal Ganglion Cells that precipitate damage. Without proper

Additionally a recent study offers the following recommendations for an anti-inflammatory diet to improve the overall health and most specifically the cardiovascular system which has strong implications in both NTG and neurodegenerative diseases. C-reactive protein levels are a very good indicator of the presence of systemic inflammation. Any disease with elevated C-reactive proteins will potentially benefit from an anti-inflammatory diet.

**This anti-inflammatory diet should be considered for the primary and secondary prevention of coronary artery disease and diabetes.** *(J Am Coll Cardiol. 2008;51:249)*

- The glycemic index of a food is defined as the incremental increase in the area under the postprandial glucose curve after ingestion of 50 g of a specific amount of food vs that associated with 50 g of oral glucose. Ideal carbohydrates with a low glycemic index include **green leafy vegetables such as broccoli and spinach and fruits such as grapefruits and cherries.** Select high-fiber carbohydrates with low glycemic index, including vegetables, fruits, **whole grains, legumes, and nuts.**
- Excess intake of processed carbohydrates leads to a vicious cycle of transient spikes in blood glucose levels, increased insulin production, and reactive hypoglycemia. **Avoid highly processed foods and beverages, particularly those containing sugar, high-fructose corn syrup, white flour, or trans fats.**
- **Berries, dark chocolate, red wine, tea, and pomegranates** reduce postprandial oxidant stress and inflammation. Cacao beans contain a subclass of flavonoids which have been reported to augment eNOS and thereby NO. This improves endothelium-dependent vaso relaxation. *(J Nutr 2000;130:2105S)* One study showed that one square of dark chocolate was 6.3 g and represented only 30 kcal per day but previous studies have shown that 100 g of dark chocolate lowers BP by 12/8 mm Hg but with the risk of increased caloric intake. *(JAMA. 2007;298:49)*
- **Coffee** contains antioxidants and can improve insulin sensitivity. Consumption of **black tea** reduces platelet activation and plasma levels of C-reactive protein. However, previous research has not demonstrated a consistent reduction in the risk for stroke associated with coffee or tea consumption. One study suggests that higher levels of coffee and tea consumption can reduce the risk for cerebral infarction among male smokers but not rates of intracranial hemorrhage. *(Stroke*
Characteristics of the Metabolic Syndrome
1. Abdominal obesity
2. Atherogenic dyslipidemia
3. Elevated Blood Pressure
4. High insulin levels-over 10
   a. Raises fats into cells
   b. Promotes fat storage
   c. Stimulates arterial smooth muscle cells
   d. Promotes production of bad types of eicosanoid (EC) -intracellular hormones
   e. Series one ECs are good and may be inhibited by too much flaxseed
   f. Series two ECs are bad-glucagon is a strong inhibitor of EC 2 pathway
5. Promotes retention of fluids by kidneys
   Glucagon is the anti-insulin and is increased by high proteins low carbohydrates
6. High levels of inflammatory mediators as measured by C-Reactive Protein levels

Six Benefits of Dark Chocolate High in Cocoa Bean Concentration AARP April 2008
1. Lower blood pressure by vasodilation
2. Reduce risk of diabetes by reducing blood sugar and insulin
3. Activates enzymes that eliminate cancer-causing carcinogens and mutagens
4. Reduces risk of blood clots and strokes by inhibiting clumping of platelets
5. Keeps cholesterol levels stable or may improve
6. Enhances cognitive function by increasing blood flow to brain

Bitter is Better and Red Wine is Fine

- When paired with a high-glycemic-index meal, cinnamon slows gastric emptying and reduces postprandial glucose excursion.
- Nuts also slow gastric emptying and can reduce the impact of high-glycemic-index carbohydrates by as much as half. Nuts also reduce postprandial oxidative protein damage, and consumption of nuts at least 5 times weekly can reduced the risks for coronary artery disease and diabetes by 20% to 50%. Eat approximately 1 handful of nuts daily (using a closed fist), consumed with vegetables, grains, berries, or other fruits.
- Vinegar can reduce postprandial glycemia and promotes satiety. Eat salad daily, consisting of leafy greens with dressing of vinegar and virgin olive oil.
- Lean protein reduces postprandial glucose excursion and improves satiety. Such protein includes egg whites, game meat, skinless poultry breast meat, and whey protein or other nonfat dairy protein. At all 3 meals, consume lean protein.
- Drinking 0.5 to 1 alcoholic drink per day for women and 1 to 2 alcoholic drinks per day for men can reduce cardiovascular risk, and 1 to 2 drinks before a meal can reduce postprandial glucose and insulin levels. However, higher levels of drinking can impair glucose metabolism.
- Exercise acutely lowers glucose and triglyceride levels in a dose-dependent fashion. Perform physical activity for at least 30 minutes or more daily, of at least moderate intensity.
- Maintain normal weight and avoid overweight or obesity. Waist circumference should be less than one half of height in inches.
It has been demonstrated that a low glycemic index diet is beneficial for both weight loss and lipid profiles. ([Cochrane Database Syst Rev. Published online July 18, 2007](Cochrane Database Syst Rev. Published online July 18, 2007)) Additionally women in the highest quintile of consumption of a high-fat, low-fiber diet had an increase in the relative risk of developing colon cancer of 1.46 compared with those in the lowest quintile. However, consumption of a high-fiber and healthy protein diet was associated with a trend toward reduced rates of colon cancer. Diet did not significantly affect the risk for rectal cancer. ([JAMA. 2007;298:754](JAMA. 2007;298:754))

In a perfect world where we all ate the Paleolithic diet, exercised, maintained the proper weight and did not consume any substances with potential toxicity supplementation would be totally unnecessary. However, the world is less than perfect and even the most well-meaning are faced with less than optimal lifestyles therefore there must be some attention paid to reminders and supplementation. It is also critical that with any of these considerations, potential toxicities and interactions must be addressed.

**Part Two: Are there benefits to Nutritional Supplementation?**

Possible positive actions of behavior modification, proper nutrition and exercise in minimizing the risk for the development or progression of ganglion cell and nerve fiber damage in glaucoma and other ocular disease conditions include:

- **Stabilizing ocular collagen and protecting ocular tissue against the neurotoxicity of glutamate.**
- **Increasing ocular antioxidant defenses and scavenging harmful free radical molecules.**
- **Increasing the ocular level of glutathione to improve outflow and minimize antioxidant activity.**
- **Preventing inappropriate release and actions of nitric oxide (NO) and vasoconstrictors from vascular endothelium.**
- **Stabilizing and improving ocular blood flow**
- **Minimizing inflammation and modulating the immune system.**
- **Protecting the mitochondria before the process of apoptosis is unstoppable.**

The primary activity of non-pharmaceutical and traditional medical systems is in modulating the immune system, providing neuroprotection and improving cardiovascular function through action on the mitochondria, the bioenergy center of the cells. That being said, no supplement is of value without a proper diet and exercise to enhance the effect. Studies keep piling up substantiating the importance of a good workout on a regular basis. The latest study points to the fact that increased fitness is associated with 50% to 70% reductions in all-cause mortality. ([Circulation 2008;10:1161](Circulation 2008;10:1161)) Another new report states that adoption of 4 healthy lifestyle habits including exercise, eating a diet high in fruits and vegetables, maintaining a healthy weight, and not smoking, in middle age is associated with a 40% reduction in all-cause mortality and 35% reduction in CVD events within 4 years. ([Am J Med. 2007;120:598](Am J Med. 2007;120:598)) To carry this a bit further another report suggests that adherence to a prudent diet of vegetables, whole grains, fruit, legumes, fish, and poultry is associated with lower rates of mortality from cardiovascular disease, other causes, and total mortality in female nurses. To contrast adherence to a Western dietary pattern with high intake of red and processed meats, sweets and desserts, and french fries is associated with higher rates of cardiovascular disease, cancer, and all-cause mortality. ([Circulation. Published online June 23, 2008](Circulation. Published online June 23, 2008)) More than 60% of the US population is overweight according to the latest National Health and
Constituents of a Diet that Support Healthy Systemic and Ocular Function—Vitamins A Through E

Vitamin A

Vitamin A is a generic term referring to related compounds. It is available in a preformed variation called retinol found in many animal products. Preformed retinol can be toxic at levels above 10,000 IU. The other form is natural beta carotene (carotenoid), which is from fruits and vegetables and is used to form its own vitamin A.

Carotenoids comprise a class of natural fat-soluble pigments, which are found in numerous fruits and vegetables and are attributed with the characteristic of minimizing photo-oxidative damage to tissue. Retinol is an alcohol and retinal is an aldehyde, both referred to as preformed vitamin A. Retinol, retinal, and retinoic acid are retinoids. Beta-carotene and other carotenoids that can be converted by the body into retinol are provitamin A variations. Not all carotenoids synthesized by plants are provitamin A carotenoids.

Retinol reaches the eye through the circulatory system accumulating in the retinal pigment epithelium in the form of a retinyl ester. The esters may isomerizes to form 11-cis-retinol which can be oxidized to form 11-cis-retinal and transferred to the photoreceptor matrix of the rod where it binds with opsin to form rhodopsin. Absorption of light catalyzes the 11-cis-retinal to all-trans retinal triggering a cascade leading to the electrical signal that is sent through the retinal nerve fibers.

Additionally vitamin A is responsible for the normal functioning of the immune system (Preventive Nutrition: The Comprehensive Guide for Health Professionals. 2nd ed. Totowa: Humana Press Inc; 2001:329) especially in the skin and mucosal cells. (Proceedings of the Nutrition Society. 1999; volume 58: pages 289) The initial protective system from infection in the body is the mucosal system. Likewise the differentiation of white blood cells is dependant on vitamin A and retinoic acid. (Nutr Rev. 1998;56:S38) Stem cells are also dependent on retinoids for differentiation into red blood cells. (Nutr Rev. 1997;55:102) Absence of vitamin A from the diet significantly impacts on tear quality and is responsible for the genesis of Bitot’s spots associated with severe dry eye. Vitamin A deficiency among children continues to be a leading cause of preventable blindness. (FASEB J. 1996;10:1040) Vitamin A deficiency is considered by some to be a nutritionally acquired immunodeficiency disease (Proc Nutr Soc. 1997;56(1B):459)

One study reports no strong associations between antioxidant consumption and the risk of primary open-angle glaucoma. (Am J Epidemiol. 2003;158:337) Another report suggests that higher intakes of protein, vitamin A, niacin, thiamin, and riboflavin (i.e. vitamin B-complex) are associated with reduced prevalence of nuclear cataract (Ophthalmology 2000;107:450-6). Intervention trials with large doses of beta-carotene found an adverse effect on the incidence of lung cancer in smokers and workers exposed to asbestos. (Mol Aspects Med. 2005;26:459) The results of the Beta-Carotene And Retinol Efficacy Trial (CARET) suggest that high-dose supplementation of vitamin A

Uses of large dosages of Vitamin A are not without risk and should be approached cautiously. Utilization in the management of retinitis pigmentosa showed that with common forms of retinitis pigmentosa that supplementation with 4,500 mcg (15,000 IU)/day of preformed vitamin A (retinol) significantly slowed the loss of retinal function over a period of 4-6 years. *(Arch Ophthalmol. 1993;111:761)* In contrast, supplementation with 400 IU/day of vitamin E increased the loss of retinal function by a small but significant amount, suggesting that patients with common forms of retinitis pigmentosa may benefit from long-term vitamin A supplementation but should avoid vitamin E supplementation at levels higher than those found in a typical multivitamin. *(Am J Clin Nutr. 1999;69:656)* Both vitamin A serum levels and a fasting lipid profile should be obtained prior to initiation of therapy.

Hypervitaminosis A is caused by over-consumption of preformed vitamin A, not carotenoids. Preformed vitamin A is rapidly absorbed and slowly cleared from the body. Therefore, toxicity from preformed vitamin A may result acutely from high-dose exposure over a short period of time or chronically from a much lower intake. *(Nutrition in Health and Disease. 9th ed. Baltimore: Williams & Wilkins; 1999:305)* Hypervitaminosis A is characterized by dry skin, loss of appetite, headache, cerebral and optic disc edema, and bone and joint pain. In January 2001, the Food and Nutrition Board (FNB) of the Institute of Medicine set the tolerable upper level of vitamin A intake for adults at 3,000 mcg (10,000 IU)/day of preformed vitamin A for persons over age 19 but lower dosages are recommended for children. *(Food and Nutrition Board, Institute of Medicine.: National Academy Press; 2001:65)* Results of some studies indicate that vitamin A intake is not associated with detrimental effects on bone mineral density (BMD) or create an increased risk for fracture *(Osteoporos Int. 2004;15:872, J Clin Epidemiol. 1990;43:693, J Bone Miner Res. 2001;16(2):2306)* while other studies report the opposite. *(N Engl J Med. 2003;348:287, J Bone Miner Res. 2002;17:1349)*

A safe recommendation would be that combined multivitamin supplements should provide no more than 2,500 IU of vitamin A or 5,000 IU of vitamin A, of which at least 50% comes from beta-carotene.

**Take Home Message:**
Vitamin A is critical to many ocular and bodily functions but consumption of the variations in types of the supplement may be hazardous and must be carefully controlled. If you choose to prescribe Vitamin A gain some sense of the current levels of your patient and consider obtaining basic labs on patients prior to use. **Excellent Natural Sources:**
Beta carotene is less easily absorbed than retinol and must be converted. The most recent standard for vitamin A is retinol activity equivalents (RAE) which represent vitamin A activity as retinol. Two mcg of beta carotene in oil can be converted to 1 mcg of retinol at an RAE ratio of 2:1 but 12 mcg of beta carotene from food is required to give 1 mcg of retinol or a 12:1 RAE ratio. *(Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington D.C.: National Academy Press; 2001:65)* Based on the old standard, one IU equals 0.3 mcg of retinol. Retinyl palmitate is a precursor and storage form of retinol. Retinol typically is available through animal meats and products.
Carotenoids is usually identified as available from fruits and vegetables. Great sources for retinol based on RAE are cod liver oil, fortified breakfast cereals, eggs, butter, milk, and for carotenoids are sweet potatoes, pumpkin, carrots, cantaloupe, mango, spinach, broccoli, kale, collards,

Lycopene
Lycopene is a carotenoid in the same family as beta-carotene. Lycopene is given a tomato, and several other fruits, their deep red color. Lycopene is one of the major carotenoids in the diet of North Americans and accounts for close to 50% of the carotenoid distribution found in blood. One study provides the experimental evidence for protective effects of dietary tomatoes rich in carotenoids on oxidative stress in the retinal pigment epithelium. (Br J Nutr 2006;96:643) Lutein and lycopene, two prevalent carotenoids in the human diet have become increasingly popular ingredients in dietary supplements. A large body of human and animal research suggests that oral forms of these carotenoids may provide benefits in the areas of eye, prostate, skin and cardiovascular health. The evidence of safety is strong at intakes up to 20mg/d for lutein, and 75 mg/d for lycopene. (Regul Toxicol Pharmacol 2006;45:289) One study suggests that Lycopene protects against experimental cataract development by virtue of its antioxidant properties, and it may be useful for prophylaxis or therapy against cataracts. (Nutrition 2003;19:794)

Take Home Message:
Lycopenes may be effective antioxidants in the modulation of both ocular and systemic disease, but current evidence points to the fact that consumption of processed tomato products is the most efficient way to provide the body with potentially effective doses of Lycopene.

Excellent Natural Sources:
Foods that are commonly consumed which contain lycopene are tomato products, watermelon, pink grapefruit, apricots, papaya, and guava. Cooking and processing of tomato products makes lycopene more readily available to the body, indicating that there may be an added health benefit to eating processed tomato foods like tomato soup, pasta sauce and vegetable juices. In humans, the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes. (Am J Clin Nutr 1997; 66:116) Ohio State University researchers found that standard daily servings of tomato sauce, tomato soup, and V8 vegetable juice were each effective interventions to significantly increase blood concentrations of lycopene. Lycopene levels increased among study participants by 192% (pasta sauce), 122% (soup) and 92% (vegetable juice) respectively, and plateaued at a new baseline after only 14 days of consumption. The results of one study support the hypothesis that lycopene cis-isomers are highly bioavailable and suggest that special tomato varieties such as tangerine tomatoes can be utilized to increase both the intake and bioavailability of health-beneficial carotenoids. (J Agric Food Chem 2007;55:1597) No strong evidence suggests that supplementation of Lycopene is as effective as the consumption of processed tomato products in achieving effective serum levels of the antioxidant.

Vitamin B1-Thiamin
Vitamin B2-Riboflavin
Vitamin B3-Niacin
**Vitamin B5-Pantothenic Acid**

**Biotin**

Biotin is a water-soluble required in the body but only synthesized by bacteria, molds, algae, yeasts and some plants. It is attached to 5 enzymes-carboxylases. These carboxylases function in metabolic reactions including:

**Vitamin B6**

Vitamin B6 is a water-soluble vitamin discovered in 1930 during nutrition studies on rats. It must be obtained from the diet or from supplements because humans cannot synthesize Vitamin B6. It is critical in the function of many enzymes and the genesis of hemoglobin as well as interacting with gene expression influencing platelet aggregation. Vitamin B6 is critical in maintenance of the thymus and thus the integrity of the immune system. Magnesium is a cofactor necessary in the proper absorption of vitamin B6. More than 100 enzymatic functions depend on the adequate presence of vitamin B6. The Linus Pauling Institute recommends that all adults consume at least 2.0 mg of vitamin B6 daily.

An added note is that coincidental supplementation with folic acid reduces the risk of hyperhomocystenemia and thus cardiovascular disease in prone individuals. *(J Nutr. 2000;130:3090)* Most individuals employ two different pathways to metabolize homocysteine. One converts homocysteine back to methionine and is dependent on folic acid and vitamin B12. The other pathway converts excess homocysteine to the amino acid cysteine, which the kidneys flush from the body. This metabolism requires three B vitamin-dependent enzymes, made up of B6, B12 and folate. It has been suggested that the B vitamin, choline and it's metabolite, betaine, are also players in this sophisticated metabolic process. *(Am J Clin Nutr 1991;53:1275, JAMA 1995;274:1049, JAMA 1998;279:359, Circulation 1998;98:204, Circulation 1998;97:437, Circulation 1995;92:2825, Nutrition 2006;22:1146, J Nutr 1994;124:1927)* One study reports reduced oscillatory potentials suggesting microvascular damage to the retina through homocysteine. Decreased photoreceptor function as well as ganglion cell loss as indicated by pathological flash VEPs may reflect a cytotoxic impact of homocysteine on neurons of the visual pathway. *(Graefes Arch Clin Exp Ophthalmol. 2005;243:49)*

The phosphate ester derivative pyridoxal 5-phosphate (PLP) is the principal coenzyme form of vitamin B6 and has the most importance in human metabolism. *(Present Knowledge in Nutrition. Vol. I. Washington, D.C.: International Life Sciences Institute; 2006:269, Handbook of Vitamins. New York: Marcel Decker Inc; 1991:341)* Vitamin B6 deficiency has been associated with impaired immune function, especially in the elderly, because production of immune system white blood cells called lymphocytes, and an anti-inflammatory protein called interleukin-2 (IL-2) are dependent on vitamin B6 intake.

In the brain, the synthesis of the neurotransmitter, serotonin, from the amino acid, tryptophan, is catalyzed by a PLP-dependent enzyme. Other neurotransmitters, such as dopamine, norepinephrine and gamma-aminobutyric acid (GABA), are also synthesized using PLP-dependent enzymes. *(Modern Nutrition in Health and Disease. 9th ed. Baltimore: Williams & Wilkins; 1999:413)*

Gyrate atrophy of the retina and choroid is a rare autosomal recessive inherited disease,
characterized by progressive chorioretinal atrophy that results in progressive deterioration of peripheral and night vision and leading to blindness and is related to hyperornithemia. The exact mechanism of chorioretinal atrophy in hyper-ornithinemia is not known and a small percentage of the affected people respond to Vitamin B6 supplementation. *(J Med Case Reports. 2007;1:27)*

It is also recognized that Vitamin B6 is an important co-factor in stimulating the neurotransmitters associated with the blink response and the tear production as well as being a major co-factor in both Omega-6 and Omega-3 fatty acid metabolism. As such, B6 plays a role in maintenance of a healthy tear system.

Vitamin B6 also affects steroid hormones by binding to receptors and inhibiting inappropriate signaling of steroid hormones. There are suggestions that B6 deficiency may be implicated in breast cancer and prostate cancer. *(Mutat Res 2001;475:7)*

Recent studies suggest that women who take birth control pills are almost always deficient in vitamin B6. *(Am J Clin Nutr 2008;87:1446)*

**Take Home Message:**

**Excellent Natural Sources:**

Baked potato with skin, bananas, salmon, chicken with no skin, spinach, avocado, turkey without skin

**Folic Acid**

Folic acid and folate are terms used interchangeably for this water-soluble B complex vitamin but folic acid is the more stable form that occurs only rarely in foods or in the body. Folate is the form usually found in foods and the human body. *(National Academy Press; 1998:193)*

Folate coenzymes mediate the transfer of one-carbon units in a number of reactions critical to the metabolism of nucleic acids and amino acids and play a vital role in DNA metabolism through two different pathways. Those pathways are 1) The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes. 2) A folate coenzyme is required for the synthesis of methionine, and methionine is required for the synthesis of S-adenosylmethionine (SAM). *(J Nutr. 1999;129:779)*

The synthesis of methionine from homocysteine requires the folate coenzyme as well as a vitamin B12-dependent enzyme.

Folate deficiency can result in decreased synthesis of methionine and a buildup of homocysteine. Folic Acid is related to homocysteine levels and elevated homocysteine levels and decreased folic acid levels are related to a number of conditions including dementia. Deficiencies may triple the risk of dementia in the elderly. *(February 5 2008 Early Release Online Article issue of the Journal of Neurology, Neurosurgery, and Psychiatry)*

homocysteine levels greater than 14 micromoles/liter had nearly twice the risk of developing Alzheimer's disease.

The most well-recognized complication of folate deficiency is neural tube defects-anencephaly or spina bifida-in pregnancy. Randomized trials demonstrated 60% to 100% reductions in neural tube defects when women consumed folic acid supplements in the periconceptional period. In 1998 there was even FDA legislation mandating folate fortification of all enriched grain products. Unfortunately, compliance is less than ideal resulting in a continuation of a preventable disorder. (Am J Clin Nutr. 2000;71:1308S)

Observational studies have found that relatively low folate intake and high alcohol intake are associated with increased incidence of colorectal cancer. (Ann Epidemiol. 2001;11:65, Int J Cancer. 2002;97:864) While dietary folate may be protective against colorectal cancer, high doses may actually accelerate tumor growth in cancer patients with colorectal adenoma. (JAMA. 2007;297:2351) Obviously more research must be performed in this area with better controls for collateral factors. One study reported that women consuming at least one alcoholic drink per day, with folic acid intake of at least 600 mcg daily had about half the risk of breast cancer compared with women who consumed less that 300 mcg of folic acid daily. (JAMA. 1999;281:1632)

Folate deficiency is related to dietary insufficiency which may be also associated with malabsorption issues. Drug interactions may also contribute to deficiencies. NSAIDs in therapeutic dosages may interfere with folate metabolism. Long term use of anticonvulsants, phenytoin, phenobarbital, and primidone inhibits absorption. (Epilepsy Res. 2001;47:27) Anti-cholesterol agents may also decrease absorption of folate. (PDR for Nutritional Supplements. Montvale: Medical Economics Company, Inc; 2001) Methotrexate is a folic acid antagonist which simulates folate deficiency and there is a report of presumed methotrexate induced optic neuropathy reversed with folate supplementation. (J Neuroophthalmol. 2005;25:109) Trimethoprim, pyrimetamine, triamterene and sulfasalazine may likewise affect absorption.

The Linus Pauling Institute recommends that adults take a 400 mcg supplement of folic acid daily. A supplement regimen of 400 mcg of folic acid, 2 mg of vitamin B6, and 6 mcg of vitamin B12 has been advocated by the American Heart Association if an initial trial of a folate-rich diet is not successful in adequately lowering homocysteine levels. (Circulation 1999;99:178) Maximum dosages should not exceed 1 mg/day and all folic acid should be consumed with B12 and B6 to maximize effect and minimize toxicity.

Recently the Food and Nutrition Board of the Institute of Medicine set the new dietary recommendation for folate, introducing a new unit, the Dietary Folate Equivalent (DFE). Implementation of the DFE reflects the higher bioavailability of synthetic folic acid found in supplements and fortified foods compared to that of naturally occurring food folates. (Nutr Rev. 1998;56(10):294) For example: 1 microgram (mcg) of food folate provides 1 mcg of DFE, while 1 mcg of folic acid taken with meals or as fortified food provides 1.7 mcg of DFE and 1 mcg of folic acid (supplement) taken on an empty stomach provides 2 mcg of DFE.

Take Home Message:
Excellent Natural Sources:
Natural sources of folate include green leafy vegetables (spinach, asparagus), citrus fruit juices, legumes, fortified cereals and grain products.
Vitamin B-12
Vitamin B12 is water-soluble and has the most complex chemical structure of all the vitamins. Vitamin B12 contains a metal ion, cobalt and as such cobalamin is the term used to refer to compounds having vitamin B12 activity. (Brody T. Nutritional Biochemistry. 2nd ed. San Diego: Academic Press; 1999) The form of cobalamin used in most supplements, cyanocobalamin, is readily converted to 5-deoxyadenosyl and methylcobalamin in the body. In mammals, cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-CoA mutase. (Modern Nutrition in Health and Disease. Philadelphia: Lippincott Williams & Wilkins; 2006:487) Methylocobalamin is necessary for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of the amino acid, methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA. (Stipanuk M, ed. Biochemical and Physiological Aspects of Human Nutrition. Philadelphia: W.B. Saunders Co.; 2000:483).

Vitamin B12 deficiency is estimated to affect 10%-15% of individuals over the age of 60. Associations with vitamin B12 deficiency are: 1) an autoimmune condition known as pernicious anemia and 2) food-bound vitamin B12 malabsorption. Although both causes become more common with increasing age, they are separate conditions. (Ann Rev Nutr 1999;19:357) Absorption of vitamin B12 from food requires normal function of the stomach, pancreas, and small intestine. Malabsorption may be associated with issues such as alcoholism and even bariatric surgery. While most address the necessity of avoidance of oral treatment of pernicious, high-dose oral therapy is considered to be as effective as intramuscular injection. (Blood 1998;92:1191, JAMA 1991;265:94, JAMA 1991;265:96, Lancet 1998;352:1721)

Although vitamin B12 deficiency is known to damage the myelin sheath covering cranial, spinal, and peripheral nerves, the biochemical processes leading to neurological damage in B12 deficiency are not well understood. Individuals with Alzheimer's disease often have low blood levels of vitamin B12. One study found lower vitamin B12 levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia, though blood levels of vitamin B12 did not differ. (Am J Clin Nutr 2000;71:643S) Vitamin B12 has demonstrated value in improving retinal function in POAG. Vitamin B12 exerts protective action on glutamate-induced neurotoxicity at the site of the retinal neurons. The signs of nitric oxide neurotoxicity are similar to the nerve impairment and symptoms of a vitamin B12 deficiency that include retinal degeneration and visual loss. (Oftalmol Zh 1965;20(6):461-2) (Klin Oczna 1974;44(11):1183-7) (Neurology 1995;45(1):11-6) (Medicine 1991;70(4):229-45) (Blood 1996;88(5):1857-64) (Eur J Pharmacol 1995;281(3):335-40) There are many neurological manifestations of vitamin B(12) deficiency. Optic neuropathy is a rare, but important, manifestation of vitamin B(12) deficiency that should be suspected in patients with risk factors for malnutrition. Vitamin B(12) optic neuropathy is a reversible, treatable cause of vision loss and may be a harbinger for other manifestations of the disease. (Eur J Intern Med 2005;16:447)

Because vitamin B12 mal-absorption and vitamin B12 deficiency are more common in older adults, some respected nutritionists recommend that adults older than 50 years
take 100 to 400 mcg/day of supplemental vitamin B12, an amount provided by a number of vitamin B-complex supplements.

**Take Home Message:**

**Excellent Natural Sources:**
Clams, mussels, crab, salmon, rockfish are excellent sources of B12 with beef, chicken, turkey, egg and milk products providing a source as well.

**Hyperhomocysteinemia as a Systemic and Ocular Risk Factor**

Hyperhomocysteinemia, Normal Tension Glaucoma, Blood Flow Anomalies and Optic Neuropathy

Recent studies point to the fact that there is a newly recognized risk factor implicated in systemic vascular disease. This risk factor is homocysteine, an amino acid and a basic unit of protein. (Clin Invest Med. 2007;30:21, Transplantation. 2008 Apr 27;85(8):1146, Arch Med Res. 2007 May;38(4):411, Clin Chem Lab Med. 2006;44:1324, Clin Lab Med. 2006;26:591) Homocysteine is formed during the metabolism of methionine, an essential amino acid derived from the diet. Mild hyperhomocysteinemia occurs in approximately 5 to 7% of the population who remain asymptomatic until the third or fourth decade when premature coronary artery disease and arterial and venous thrombosis may develop. In the elderly population, hyperhomocysteinemia may be as high as 30 to 40%. A landmark study in 1992 of over 14,000 male physicians found that those with the highest levels of homocysteine had more that three times the risk for heart disease. (JAMA 1992;268;877) It has been estimated that hyperhomocysteinemia may be responsible for up to 10% of coronary artery disease (CAD). One study concludes that hyperhomocysteinemia is an independent risk factor for Coronary Artery Disease (CAD) in young patients (below 45 years old)--especially in men--and vitamin B12 deficiency is a preventable cause of hyperhomocysteinemia. (BMC Cardiovasc Disord. 2006;6:38) Hyperhomocysteinemia, known to be an important risk factor in endothelial dysfunction, seems to be an important determinant in erectile dysfunction (ED). In one study data suggests that slightly elevated Homocysteine levels are significantly related with arterial and probably endothelial dysfunction in patients with ED. (Metabolism. 2006 ;55:1564)

Compared with healthy women, those with rheumatoid arthritis are deficient in vitamin B6 and have elevated levels of homocysteine. This may contribute to the increased risk of cardiovascular events seen with RA. A decrease in RBC folate levels was noted but not plasma levels in RA patients. (J Am Diet Assoc 2008;108:443) There is also the link of hyperhomocysteinemia to an increase for the risk of hip fracture. (J Clin Endocrinol Metab 2008;93:2206)

Elevations in homocysteine levels typically are caused by genetic defects in the enzymes involved in homocysteine metabolism or by nutritional defects in vitamin cofactors. Homocystinuria and severe hyperhomocysteinemia are caused by rare inborn errors of metabolism resulting in marked elevations while vitamin deficiencies can raise levels exceeding 100 mmol/L. Homocystinuria is rare and creates an entirely different clinical picture than hyperhomocysteinemia and is characterized by mental retardation, skeletal deformities and bilateral lens subluxation.
It is estimated that vitamin deficiency contributes to about 67% of cases of hyperhomocysteinemia. While there is not definitive evidence whether hyperhomocysteinemia is the cause of complications or if hyperhomocysteinemia is a marker for critical vitamin levels involved in metabolism, current knowledge supports the link to increased vascular risk. Several therapeutic drugs including methotrexate, theophylline, cyclosporine and anticonvulsants also may precipitate hyperhomocysteinemia.

Typically foods rich in Vitamin B12 (Cobalamin), B6 (Pyridoxine) and Folate (Folic Acid) work to keep homocysteine at relatively safe levels. Conversely, low levels of these vitamins correlate to elevated homocysteine levels or hyperhomocysteinemia. Folate seems to be the most effective of the group of three to create a lowering of the homocysteine levels, but synergism with the B vitamin group is critical.

Research in the area of hyperhomocysteinemia suggests that a minimum of 400 mcg of folate in women of childbearing age helps prevent neural tube defects such as spinal bifida and anencephaly in newborns. There is a corollary in vascular disease suggesting that 400 mcg of folate per day is likewise necessary to decrease the levels of homocysteine.

**Naturally Occurring Folate**

Folate occurs naturally in legumes, leafy green vegetables, liver, some fruits, enriched breakfast cereals, whole grain products, and enriched grain foods. Retention of folate during preparation of foods is critical with freshly prepared foods. Canned foods do not contain similar beneficial levels. The following guidelines should be used in the preparation of foods rich in folate to get the maximum nutritional effect:

1. Avoid cutting foods into small pieces
2. Cook al dente
3. Cook with a minimal amount of water
4. Eat foods raw when possible

**Hyperhomocysteinemia and Systemic Disease**

Elevated homocysteine has been detected in 30% with coronary vascular disease, 42% of patients with cerebrovascular disease and 28% with peripheral vascular disease. *(Neth J Med 1994;45:34, N Engl J Med. 1991;324:1149)* Homocysteine has been found to be up to 40 times more predictive than cholesterol in assessing cardiovascular disease risk. *(Homocysteine:The New Cholesterol, Keats Publishing, New Canaan, CT, 1996)* Damage to blood vessels associated with hyperhomocysteinemia includes injury to arterial endothelial cells and promotion of smooth muscle growth which result in plaque. Hyperhomocysteinemia also disrupts normal blood clotting increasing the risk of thrombi. The strongest links between hyperhomocysteinemia and systemic disease involve the association to vascular occlusive events but other relationships are being discovered. Reports link elevated homocysteine levels to all of the following systemic conditions: *(Am J Clin Nutr 2001;74: pp. 130-6)*

1. Increased cardiovascular morbidity and mortality
   a. 15-30% of patients with premature vascular disease *(JAMA 1992; 268: 877)*
   b. 25% of non-diabetic patients under age 55 with heart attacks or stroke have hyperhomocysteinemia versus 5% of those without
2. Increased risk of cancer deaths (JAMA 1992; 268:877)

Homocysteine levels should be evaluated in patients with premature ateriovascular disease and a strong family history of:
1. Myocardial infarction
2. Peripheral vascular disease
3. Stroke
4. Recurrent pulmonary embolism
5. Venous thrombosis
6. Renal failure
7. Cardiac or renal transplant

**Hyperhomocysteinemia and Ocular Disease**

As you can imagine, any ocular disease with a relationship to the vascular system could be implicated in hyperhomocysteinemia. Reports link elevated homocysteine levels to all of the following ocular conditions:
1. Primary Open Angle Glaucoma (J Neural Transm. 2007;114:445)
2. Pseudoexfoliation and pseudoexfoliative glaucoma (J Neural Transm. 2007;114:571) and risk of thromboembolic events in these patients. (Saudi Med J. 2006;27:833)

**Testing for Hyperhomocysteinemia**
After an over-night fast plasma homocysteine levels are measured on a morning specimen collected in a lavender (EDTA) tube. Testing should be done immediately as the blood cells continue to release homocysteine. Enzyme immunoassay is rapid and results in excellent analysis. A methione load challenge may be administered as well in patients suspected of hyperhomocysteinemia but with normal fasting levels.

Optimal levels are considered <10mmol/L but normals usually are considered in the 5 to 15 mmol/L range. Levels tend to increase with age.

Results of a large population-based study have suggested that inflammatory markers are the major determinants of Hcy and vitamin B(6) concentrations. (Clin Chem Lab Med 2007;45:1728)

**Recommendations**

As a primary eye care practitioner you should be aware of the systemic and ocular health risks of hyperhomocysteinemia. Be aware of the benefits of supplementation and behavioral modification to reduce the health risks associated with the condition. If you as a clinician shy away from recommending vitamin supplements for macular degeneration or are hesitant about recommending lifestyle changes, the work on hyperhomocysteinemia should change your opinion about folate, vitamin B12 and vitamin B6 supplementation. Likewise vitamins E and C are known to work synergistically to facilitate the **FOLATE ANTI-HOMOCYSTEINE COCKTAIL**. If you do nothing else but recommend 400 to 1000 mcg of folic acid per day, 10 to 50 mg of vitamin B6, and 50-300 mcg of vitamin B12 per day, and have patients modify their diets, you may impact soundly on ocular and systemic morbidity and mortality in your patients. You should also be aware of the ocular and systemic associations to hyperhomocysteinemia and order blood work on patients with those presentations. In one study folic acid and **N-acetylcysteine** lowered plasma homocysteine levels and improved endothelial function. (Acta Cardiol. 2007;62:579)

It has also been suggested that should folic acid, B12 and B6 not lower homocysteine levels, that 1500 mg of betaine or 2000 mg of choline per day may be of benefit. In a subset of patients, vitamin B2 (riboflavin) was also beneficial in lowering the homocysteine levels.

Along with vitamin supplementation, persons with elevated homocysteine levels should adopt a heart healthy diet and lifestyle including low saturated fat diets, diets low in methionine (meats and eggs), and exercise. Smoking and excessive alcohol consumption may likewise impact negatively on both hyperhomocysteinemia and cardiovascular risk.

**Vitamin C**

Linus Pauling brought Vitamin C to the forefront of healthcare by advocating mega-doses of Vitamin C to fight colds and minimize the risk of cancer. Even recently studies continue to corroborate his presumptions. The new information relates that the group most prone to enjoy the benefits of Vitamin C for the common cold are those individuals under heavy short-term physical stress. (Cochrane Database Syst Rev. Published online July 18, 2007) Vitamin C is a water-soluble antioxidant working in concert with Vitamin E. Vitamin C must be obtained from the diet with absence creating the disease, scurvy.
Early symptoms of scurvy include fatigue resulting from lowered levels of carnitine and norepinephrine. (*J Emerg Med. 2001;21:235*)

Vitamin C (Ascorbic Acid) is required for collagen synthesis, the synthesis of norepinephrine, carnitine and the conversion of cholesterol to bile acids. The overwhelming fame of Vitamin C is associated with its role as an antioxidant for the protection of molecules from damage by free radicals and reactive oxygen species (ROS) created during metabolism and toxin exposure such as smoking creating oxidative stress.

IOP can be reduced by increasing concentrations of absorbate in the aqueous humor. This can be done by supplementing with vitamin C (0.5 gm/kg body weight). The IOP-lowering actions of vitamin C occur by improving collagen formation, increasing blood osmolarity, improving aqueous outflow, inhibiting lipid peroxidation and raising glutathione levels. (*Free Radic Biol Med 1996;21:97, Eye Ear Nose Throat Monthly 1968;46:1502, Oftalmol Zh OG 1989;8:114, Can J Physiol Pharmacol 1997;97:1149, Circulation 1998;97:2222*) Vitamin C is known as a very active antioxidant that also creates an increase in IgA and IgM.

There is the suggestion that vitamin supplementation suppresses leukocyte adhesion and thus endothelial dysfunction, associated with increase in iris blood flow perfusion in diabetes. The antioxidant vitamin C may be a therapeutic agent for preventing diabetic retinopathy. (*Microvasc Res 2007;74:32*) Diabetes mellitus is associated with increased oxidative stress. One study suggests that supplementation with antioxidant vitamins C and E probably plays an important role in improving the constitution of the ocular surface. (*Med Sci Monit 2004;10:CR213*) Plasma vitamin C levels are inversely associated with the risk for type 2 diabetes. There is an inverse association between fruit and vegetable intake and the risk for type 2 diabetes, with a greater effect for fruit intake. (*Arch Intern Med. 2008;168:1493*) Regarding Vitamin C as a part of an anti-ARM formula, It has been shown that blue light could induce DNA damage to RPE cells but vitamin C could protect the RPE cells from the blue light-induced DNA damage. (*Shi Yan Sheng Wu Xue Bao 2003;36:397*) Regarding anterior segment, the addition of ascorbic acid to the irrigation solution significantly reduced the amount of endothelial cell loss during phacoemulsification by approximately 70%. (*Invest Ophthalmol Vis Sci 2003;44:1866*) Likewise a significantly reduced mean level of ascorbic acid was observed in the aqueous humor of patients with exfoliation syndrome in one study. In view of the fact that ascorbic acid is a major protective factor against free radical action, a role for free radical action is suggested as a possible factor in the genesis of exfoliation syndrome. (*Am J Ophthalmol 2002;134:879*)

The utilization of Vitamin C for the prevention of cataract has long been in the literature. While studies continue to be controversial one study showed the risk for cataract is 60% lower among persons who use multivitamins or any supplement containing vitamin C or E for more than 10 years. However the use of vitamins for shorter duration is not associated with reduced risk for cataract (*Arch Ophthalmol* 2000;118:1556-63). Another study demonstrated that Vitamin C reduced the risk of cortical cataracts in women aged 60 years or less and carotenoids reduce the risk of posterior subcapsular cataract in women who have never smoked (*Am J Clin Nutr* 2002;75:540-9). Research by the Nutrition and Vision Project (NVP), a cooperative effort of Harvard and Tufts University scientists, has found that women who consume higher-than-recommended doses of
Vitamin C may lower their risk for more than one type of cataract (Harv Womens Health Watch 2002;9:1).

Vitamin C enhances PGE1 and thus assists in the regulation of T cell function. Vitamin C increases killer T cell activity and B cell function. It also increases glutathione levels. It is known to protect against viruses by strengthening connective tissue and neutralizing toxins released by phagocytes. Daily supplementation of vitamin C is recommended at 500 to 1000 mg with consideration for the increased risk for kidney stones.

Potential harms of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (beta-carotene), heart failure in people with vascular disease or diabetes (vitamin E) and hospitalization for genitourinary conditions (zinc). (Eye 2008 Apr 18 Epub)

**Take Home Message:**
Vitamin C is critical in all metabolic activities of the human body. Deficiencies will create a diseased state.

**Excellent Natural Sources:**
The best source of natural vitamin C is citrus fruits.

**Vitamin D**
Vitamin D is a fat-soluble vitamin (in actual fact a steroid hormone) essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling. (Am J Clin Nutr. 2004;79(3):362) Vitamin D₃ (cholecalciferol) can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation. It can also be obtained from the diet, but is fat soluble. Sufficient vitamin D prevents rickets in children and osteomalacia in adults and, together with calcium, vitamin D helps protect older adults from osteoporosis. A quantitative meta-analysis recently concluded that at a mean daily dose of vitamin D of 528 IU there was a significant decrease in death (7% to 8%) for those using vitamin D supplement. (Arch Intern Med. 2007;167:1709)

It has been estimated that 50% to 60% of people do not have satisfactory vitamin-D status, likely related urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, and decreases in the cutaneous production of vitamin D with age. One prospective cohort study demonstrates for the first time that low 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin-D levels are associated with increased risk in all-cause and cardiovascular mortality compared with patients with higher serum vitamin-D levels. (Arch Intern Med 2008; 168:1340, Arch Intern Med. 2007;167:1159, N Engl J Med. 2007;357:266) Another recent study found that 40.7% of patients with chronic migraine were deficient in 25-hydroxyvitamin D. The study also showed that the longer individuals had chronic migraine, the more likely they were to be vitamin D deficient. (American Headache Society 50th Annual Scientific Meeting: Abstract S33. Presented June 28, 2008)

Vitamin D deficiency is widespread among patients being treated for osteoporosis, and such deficiency should be treated aggressively. (American Association of Clinical
Recent reports have increased the awareness of a much broader role for vitamin D. Vitamin D is involved in differentiation of tissues during development and in proper functioning of the immune system. Over 900 different genes are now known to be able to bind the vitamin D receptor, through which vitamin D mediates its effects. The majority of effects of vitamin D in the body are related to the activity of 1,25(OH)\textsubscript{2}D including 50 specific genes. 1,25(OH)\textsubscript{2}D also inhibits proliferation and stimulates differentiation of cells as well as having activity as an immune system modulator. It is even suggested that 1,25(OH)\textsubscript{2}D may enhance innate immunity and protect against many autoimmune disorders. (Annu Rev Nutr. 2003;23:117, Cell Mol Biol. 2003;49:277) Evidence also continues to accumulate suggesting a beneficial role for vitamin D in protecting against autoimmune diseases, including multiple sclerosis and type I diabetes, as well as some forms of cancer, particularly colorectal and breast. (Am J Clin Nutr 2007;85:649, J Nutr 2007;137:447, Am J Clin Nutr 2005;82:281, Neurosci Biobehav Rev 2006;30:696, Am J Clin Nutr 2007;85:931) Most biological effects of Vitamin D are mediated through a nuclear transcription factor VDR. (J Cell Biochem. 2003;88:296, Mol Endocrinol. 2003;17:777, Nutr Rev. 2003;61:227) A recent review The review, currently appearing in the FASEB Journal online and in print in April 2008, concludes that there is ample biological evidence to suggest an important role for vitamin D in brain development and function, and that supplementation for groups chronically low in vitamin D is warranted. Since Calcium is so linked to neurodegeneration, one may hypothesize a link between Vitamin D, the immune system and the negative actions of the calcium ion.

Hypovitaminosis D, especially at levels less than 30 ng/mL, is associated with an increased risk for Myocardial Infarct in men. Vitamin D is likely to exert its effect on the risk for cardiovascular disease via vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure. (J Clin Invest. 2002;110:229) The rate of cardiovascular disease–related deaths is greater at higher latitudes, lower at higher altitudes, and higher in the winter months — all associations related to vitamin D deficiency. The vitamin D axis affects vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure, all of which affect cardiovascular disease and MI risk, but evidence linking hypovitaminosis D and MI is sparse. Current recommendations for vitamin D are 200 to 600 IU per day, which may be inadequate to prevent cardiovascular disease. (Arch Intern Med. 2008;168:1174) Another recent study demonstrated that use of calcitriol in patients with stage III or IV Chronic Kidney Disease with hyperparathyroidism is associated with reduced risk for mortality and long-term dialysis and that the use of calcitriol in patients with stage III or IV CKD with hyperparathyroidism is associated with increased risk for hypercalcemia. CKD affects more than 10% of the US population with disturbances in vitamin D and mineral metabolism. (J Am Soc Nephrol. Published online May 7, 2008)

but the issue is still very controversial. Indeed, vitamin D3 (cholecalciferol) is now known to be greater than three times more potent than vitamin D2. (J Clin Endocrinol Metab. 2004;89:5387, Am J Clin Nutr. 2006;84:694) In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should also be consumed. In general adults should take a supplement that supplies 400IU of vitamin D3 daily and should have 10-15 minutes of sun exposure at least three times a week as close to noon as possible. Should sunlight exposure be unattainable, 800IU of D3 is advised. Toxicity-hypercalcemia-can lead to bone loss, kidney stones, and calcification of the heart and kidneys. Because the consequences of hypervitaminosis D and ensuing hypercalcemia are severe, the Food and Nutrition Board established a very conservative upper limit of 2,000 IU/day (50 mcg/day) for children and adults (National Academies Press; 1999:250) while other reports suggest 10,000IU. (Am J Clin Nutr. 1999;69:842, Am J Clin Nutr. 2006;84:18)

A recent study, while equating low vitamin D levels to an increased risk of mortality, concludes that they would not advise people to take supplements without knowing their vitamin-D levels and that the most sensible advice for those wanting to ensure their levels remain optimal is to spend 10 to 15 minutes per day in the sun and to eat vitamin-D-fortified foods, such as milk and oily fish. (Arch Intern Med. 2008;168:1629)

Take Home Message:
Vitamin D is critical in the maintenance of the immune system and appears to be critical in the development and health of the cardiovascular system and neurological development. Sunlight exposure is critical for Vitamin D levels and excessive consumption of Vitamin D may create hypercalcemia. Vitamin D3 is the most effective supplement form.

Excellent Natural Sources:
Vitamin D is present in only a few foods (e.g. fatty fish), and is also added to fortified milk, but our supply typically comes mostly from exposure to ultraviolet rays (UV) in sunlight. UV from the sun converts a biochemical in the skin to vitamin D, which is then metabolized to calcitriol, its active form and an important hormone. Formation of vitamin D by UV can be 6 times more efficient in light skin than dark skin, which is an important cause of the known widespread vitamin D deficiency among African Americans living in northern latitudes.

Vitamin E
Alpha-tocopherol is the only form of Vitamin E in the human body and is the form recommended for supplementation. Vitamin E is the body’s primary fat-soluble antioxidant and it must be obtained from food or supplements. As an antioxidant Alpha-tocopherol neutralizes free radicals then must be transformed back to Alpha-tocopherol with the assistance of other antioxidants such as Vitamin C. Vitamin E travels through the body in low density lipoproteins which protect them from from oxidation. Vitamin E is known to affect the expression and activity of immune and inflammatory cells, to enhance vasodilation and to inhibit the activity of the cell signaling molecule protein kinase C (PKC). Modulating the PKC pathway may be relevant in glaucoma as PKC inhibitors relax the trabecular meshwork and affect matrix metalloproteinase and PGF2 alpha. It has been shown that retinal vascular dysfunction due to hyperglycemia was prevented by vitamin E. (Am J Physiol 1995;269:239, Diabetes Res Clin Pract
It has also been reported that vitamin E as d-alpha tocopheryl acetate in 300 to 600 mg/day dosages improved blood flow and reduced visual field change in glaucomatous eyes. (Eur J Ophthalmol 2007;17:528)


In the framework of diabetes, the studies are likewise inconsistent and contradictory. (Am J Clin Nutr. 1993;57:650, Am J Clin Nutr. 1994;59:1291, Diabetes Care. 1993;16:1433, J Am Coll Nutr. 1996;15:458) One study does however state that oral vitamin E treatment appears to be effective in normalizing retinal hemodynamic abnormalities and improving renal function in type 1 diabetic patients of short disease duration without inducing a significant change in glycemic control. This suggests that vitamin E supplementation may provide an additional benefit in reducing the risks for developing diabetic retinopathy or nephropathy. (Diabetes Care. 1999;22:124)

Data from the NHANES 1999-2000 indicate that mean dietary intake of alpha-tocopherol is 6.3 mg/day and 7.8 mg/day for women and men, respectively. (Am J Epidemiol. 1999;150:290, Ann N Y Acad Sci. 2004;1031:387) These intakes are well below the current intake recommendations of 15 mg/day. It is estimated that more than 90% of Americans do not meet daily dietary recommendations for vitamin E. (J Am Diet Assoc. 2004;104(6):567)

Alpha-tocopherol has been shown to enhance the immune system. Additionally, it works synergistically with Omega 3 FFAs to protect cells from TNF-a induced apoptosis. Supplementation with Vitamin E has also been shown to increase B cell activity in the aging patient. (JAMA. 2004;292:828, Proc Nutr Soc. 1999;58:697) Vitamin E also works synergistically with Vitamin C to reduce inflammatory prostaglandins and increase T cells, IL-2 and tumor necrosis factor (TNF).

In a prospective observational data from a large cohort of female health professionals, higher dietary intakes of lutein/zeaxanthin and vitamin E from food and supplements were associated with significantly decreased risks of cataract. (Arch Ophthalmol 2008;126:102) Of interest, a recent study points to the fact that results demonstrated that there was no significant difference between the 600 mg vitamin E and placebo groups in the incidence of cataract when vitamin E was the only intervention. (Ophthalmology. 2008;115:822) In the realm of ARMD, one study showed evidence that antioxidant (beta-carotene, vitamin C, and vitamin E) and zinc supplementation slowed down the progression to advanced AMD and visual acuity loss in people with signs of the disease, but no evidence that vitamin E or beta-carotene prevented AMD. (Eye. 2008;22:751, Cochrane Database Syst Rev. 2008;(1):CD000253, BMJ. 2007;335:755)
Health is not a single item but rather a cornucopia of actions and these two contradictory studies point to that.

Upper levels for safety of consumption of vitamin E are established by the Food and Nutrition Board of the Institute of Medicine to minimize hemorrhage for alpha-tocopherol supplements are 1,000 mg/day of alpha-tocopherol in any form (equivalent to 1,500 IU/day of RRR-alpha-tocopherol or 1,100 IU/day of all-rac-alpha-tocopherol). One meta-analysis reported that to reduce the risk of any disease that 2000 IU/day were necessary to reduce the risk by 6%. (Ann Intern Med. 2005;142:37) Other studies found no evidence of the decrease of the risk of death with vitamin E supplementation. (J Gen Intern Med. 2004;19:380, Arch Intern Med. 2004;164:1552, Lancet. 2003;361:2017, JAMA. 2007;297:842)

Drug interactions must be taken into account realizing that hemorrhage at excessive dosages is a potential issue. Any pharmaceutical agents, foods or supplements such as gingko biloba should raise the caution of interaction.

Scientists at the Linus Pauling Institute in Oregon feel there exists credible evidence that taking a supplement of 200 IU (134 mg) of natural source d-alpha-tocopherol (RRR-alpha-tocopherol) daily with a meal may help protect adults from chronic diseases, such as heart disease, stroke, neurodegenerative diseases, and some types of cancer. The amount of alpha-tocopherol required for such beneficial effects appears to be much greater than that which could be achieved through diet alone. ((lpi.oregonstate.edu)

**Take Home Message:**
While evidence is controversial, alpha-tocopherol appears to be of importance and benefit to the overall well being, especially when considering the importance as an antioxidant. Antioxidative activity is critical in almost all situations. It also appears that the RDA is not acquired from the western (Paleolithic diet) and as such should be supplemented with caution toward potential interactions.

**Excellent Natural Sources:**
Natural sources of alpha-tocopherol include olive oil, sunflower oil, nuts, whole grains, green leafy vegetables but usually provide less than the RDA of 15 mg/day of RRR-alpha-tocopherol. (National Academy Press; 2000:186) Supplements made from entirely natural sources contain only RRR-alpha-tocopherol (also labeled d-alpha-tocopherol). RRR-alpha-tocopherol is the isomer preferred for use by the body, making it the most bioavailable form of alpha-tocopherol. Synthetic alpha-tocopherol is less bioavailable and only half as potent. The formulas for conversion to the RRR form are:
- **RRR-alpha-tocopherol (natural or d-alpha-tocopherol):**
  - IU x 0.67 = mg RRR-alpha-tocopherol
- **all-rac-alpha-tocopherol (synthetic or dl-alpha-tocopherol):**
  - IU x 0.45 = mg RRR-alpha-tocopherol.

**Lutein/Zeaxanthin**

The yellow color of the macula lutea is due to the presence of the carotenoid pigments lutein and zeaxanthin. In contrast to human blood and tissues, no other major
carotenoids including Beta-carotene or lycopene are found in this tissue. (Dev Ophthalmol. 2005;38:70) The associations between MP density and serum lutein, serum zeaxanthin, and adipose lutein concentrations are stronger in men than in women. (Am J Clin Nutr. 2002;76:595)

A number of studies intended to examine trends in a population suggest a link between lutein and decreased risk of eye disease:

- In 1994, a National Eye Institute (NEI)-supported study indicated that consumption of foods rich in carotenoids -- particularly green, leafy vegetables such as collard greens, kale, and spinach -- was associated with a reduced risk of developing macular degeneration. (JAMA 1994;272:1413)

- In 1999, data from the Nurses Health Study showed a reduced likelihood of cataract surgery with increasing intakes of lutein and another carotenoid -- zeaxanthin. (Am J Clin Nutr 1999;70:509)

- In 1999, the Health Professionals Follow-up Study found a trend toward a lower risk of cataract extraction with higher intakes of lutein and zeaxanthin. (Am J Clin Nutr 1999;70:517)

- In 1999, a follow-up to an NEI-supported population-based study -- called the Beaver Dam Study -- concluded that people with diets higher in lutein and zeaxanthin had a lower risk of developing cataract. (Am J Clin Nutr 1999;69:272)

- In 2001, data from the Third National Health and Nutrition Examination Survey reported that higher intakes of lutein and zeaxanthin among people ages 40-59 may be associated with a reduced risk of advanced AMD. (Am J Epidemiol 2001;153:424)

- Conversely, in 1998, the Beaver Dam Study found no significant association between the risk of either early or advanced AMD in groups that had either the highest intakes of lutein and zeaxanthin or the lowest intakes of lutein and zeaxanthin. The study researchers caution that generally, the consumption of lutein and zeaxanthin in this population may have been too low to have had an impact on the risk of AMD. (Arch Ophthalmol 1996;114:991, Am J Epidemiol 1998;148:204)

- In the 2004 LAST (Lutein Antioxidant Supplement Trial) study, 90 AMD patients were supplemented daily with an OcuPower supplement capsule containing 10 mg of crystalline FloraGLO lutein, 10 mg lutein plus a mixed antioxidant formula, or placebo for 12 months. The average American ingests one to two mg of lutein daily. Patients ingesting the lutein supplement experienced significant improvements in several objective measurements of visual function including glare recovery, contrast sensitivity, and visual acuity vs. placebo. Patients also experienced a 50% increase in macular pigment density relative to those on placebo. (Optometry. 2004;75:21)
Another study evaluated a total of 1802 women from ages 50 to 79. These women were described as having dietary and serum levels of lutein and zeaxanthin either above the 78th (high) or below the 28th (low) percentile. The prevalence of nuclear cataract was 23% lower in the high-diet group compared with the low-diet group. Furthermore, those in the highest quintile were 32% less likely to have a nuclear cataract compared with the lowest quintile. (Arch Ophthalmol. 2008;126:354)

Higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen. (Arch Ophthalmol 2007;125:1225, Ophthalmology 2008;115:334) In nonadvanced AMD eyes, a selective dysfunction in the central retina (0 degrees -5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees -20 degrees) retinal areas. (Ophthalmology 2008;115:324) It has been shown that the synergistic action of zeaxanthin and vitamin E or C found in one study demonstrates the importance of the antioxidant interaction in efficient protection of cell membranes against oxidative damage induced by photosensitized reactions. (Free Radic Biol Med 2004;36:1094)

One report suggests that lutein and zeaxanthin (the only carotenoids found in the lens) may retard aging of the lens (Arch Ophthalmol 2002;120:1732-7). Another reports that observations indicate dietary modulation of diabetic retinopathy risk may be possible by increasing intakes of lutein and lycopene-rich foods. (Br J Nutr. 2008 Jun 13:1-8. [Epub ahead of print])

While Lutein and Zeaxanthin are readily available in dark leafy green vegetables, patients with concerns about blood clotting must avoid these because of the Vitamin K-clotting factor-in these vegetables. Lutein and Zeaxanthin may be supplemented without fear of interference with blood thinners.

**Take Home Message:**
**Excellent Natural Sources:**

**Glutathione**
Glutathione is the most abundant antioxidant in the body and is the primary free radical fighter. It is the regenerator of immune cells. It is produced in every cell with the help of selenium, magnesium and vitamin C. Glutathione production decreases with age. The pathway for collagen remodeling and apoptosis induction in glaucoma seems to be exogenously influenced by water-soluble antioxidants, for example, glutathione. The pathway for elastin remodelling and apoptosis induction seems to be influenced by endogenous lipid-soluble antioxidants, for example, vitamin E. (Br J Nutr 2004;91:809) L-glutathione in daily doses of 200 to 500 mg has been shown to alleviate allergic reactions. Adequate levels of glutathione can be achieved with a 75 to 150 mg/day supplement.

**Take Home Message:**
Maintenance of effective glutathione levels is best achieved by assuring intake of the critical components for the production and regeneration of glutathione, the primary antioxidant available for the human body.
**Magnesium**

Magnesium seems to have a beneficial effect on the visual field in glaucoma patients with both increased and normal IOP--possibly by alleviating vasospasm at 300 mg/day. Magnesium also works to activate enzymatic systems. *(Ophthalmologica 1995;209(1):11-3) (Surv Ophthalmol 1995;209(1):83-4)* Magnesium does not directly influence immune function but rather is critical in 300 enzymatic functions in the body. Magnesium deficiency causes an increase in pro-inflammatory cytokines and an excess production of free radicals.

Magnesium depletion is commonly associated with both insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetes mellitus. Between 25% and 38% of diabetics have been found to have decreased serum levels of magnesium (hypomagnesemia) perhaps associated with urinary issues. *(Arch Intern Med. 1996;156:1143)* It is suggested but not proven that magnesium supplementation may be beneficial in patients with diabetes. *(Diabetes Care. 2003;26:1147, Diabet Med. 2006;23:1050, J Am Coll Nutr. 2004;23:506S)*

From a neurological standpoint, persons with recurrent migraines have lower magnesium levels. *(Clin Neurosci. 1998;5(1):24) Supplementation to alleviate the headaches has produced conflicting results and the levels of supplementation result in side effects. *(Headache. 2003;43:601, Cephalalgia. 1996;16:436)*

Magnesium absorption is impaired by a low protein diet, a high fiber diet, and excesses in zinc consumption, GI disorders, bariatric surgery renal disorders, chronic alcoholism, increasing age. *(Am J Clin Nutr. 1973;26:510)* Magnesium can interact with digoxin, anti-malarials, some drugs to treat osteoporosis, tranquilizers, oral anticoagulants and some antibiotics. In seriously ill patients, the primary care physician should be consulted.
Consumption of magnesium in the US is considered lower than the RDA. Recommended daily dosage is 420 mg/day for men over 30 and 320 mg/day for women over 30 years of age. The recommended supplement is 100 mg/day assuming some dietary consumption of magnesium. The tolerable upper level of intake (UL), which is 350 mg/day set by the Food and Nutrition Board.

Take Home Message:
Excellent Natural Sources:
Natural sources of magnesium are cereals, brown rice, nuts, beans, spinach, chard, okra and bananas.

Zinc

Zinc is an essential trace element for the proper functioning of a number of human systems. Zinc is critical for 100 different enzymes relevant to their catalytic role. (National Academy Press; 2001:442) Zinc is also critical in the structure of proteins and cell membranes. Cell membranes are susceptible to oxidative damage with loss of zinc. (J Nutr. 2000;130:1432S) Zinc also has a role in gene expression acting in the role of transcription factors as well as having responsibilities in cell signaling. Zinc also plays a role in apoptosis. (J Nutr. 2000;130(5S Suppl):1459S)

Zinc served the role as the entry point for eye care into the realization of the importance of nutrition in ocular health. Use in the management of macular degeneration has resulted in mixed reports. (Arch Ophthalmol. 1988;106:192, Am J Epidemiol. 1998;148:204, Ophthalmology. 1999;106:761, Ann Epidemiol. 2001;11:328, Invest Ophthalmol Vis Sci. 1996;37:1225, Arch Ophthalmol. 2001;119:1417, Cochrane Database Syst Rev. 2002;1:CD000254, Cochrane Database Syst Rev. 2006;2:CD000254) The element is, however, a part of the AREDS recommendation. When speaking to commercially available vitamin supplements it should be noted that zinc at 80 mg/day resulted in increased genitourinary hospital admissions in the AREDS study. (J Urol. 2001;177:639) It has also been found that based on the evidence it is suggest that zinc plays a role in sub-RPE deposit formation in the aging human eye and possibly also in the development and/or progression of AMD. (Exp Eye Res 2007;84:772)

Large quantities of zinc interfere with copper bioavailability by inducing intestinal synthesis of metallothionein, which traps copper. (Modern Nutrition in Health and Disease. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2006:271-285) This action may then lead to cupric anemia. Zinc consumption must be accompanied by copper supplementation. Iron supplementation and calcium combined with phytic acid (limes) may also decrease the availability of zinc. (Br J Nutr. 2001;85:S181) Zinc is required for the enzyme that converts retinol (vitamin A) to retinal. Zinc deficiency is associated with decreased release of vitamin A from the liver, which may contribute to symptoms of night blindness that are seen with zinc deficiency. (J Nutr. 2000;130:1344S, Am J Clin Nutr. 1998;68:435S) High doses of zinc also impact negatively in the absorption of magnesium. (J Am Coll Nutr. 1994;13:479)

Zinc is important in the immune system and has gained much press in regard to the prevention of colds and respiratory disease especially as related to children. (J Pediatr.

Zinc picolinate has been promoted as a more absorbable form of zinc, but there are few data to support this idea in humans. In order to prevent copper deficiency, the U.S. Food and Nutrition Board set the tolerable upper level of intake (UL) for adults at 40 mg/day, including dietary and supplemental zinc. ([National Academy Press; 2001:442-501]) The recommendation for zinc is to take a multivitamin supplement containing 100% of the daily values (DV) of most nutrients will generally provide 15 mg/day of zinc. Use of zinc may decrease the absorption of tetracyclines and quinolones so an interval of two hours is appropriate. ([Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, 2000:27-51])

**Take Home Message:**
Zinc is critical in a number of different interactions in the body but in excess there may be danger both systemically and in the potentiation of ARMD.

**Excellent Natural Sources:**
Natural sources of zinc include crab, oysters, beef, pork, dark meat chicken and turkey, yogurt, cheese, milk, cashews, almonds, peanuts, and beans.

**Selenium**
Selenium is a trace element that is critical to the maintenance of health but can be toxic, like zinc, at higher levels. As with zinc, selenium is important in the action of enzymes for the development of proteins and in the actions of the thyroid gland. ([Lancet. 2000;356:233]) Selenium is an effective free radical scavenger that is essential to the production of glutathione peroxidase. ([Selenium: Its molecular biology and role in human health. 2nd ed. New York: Springer; 2006:99]) Glutathione peroxidase rids the body of environmental toxins. Selenium as gluthathione peroxidase also appears to support the activity of vitamin E (a-tocopherol) in limiting the oxidation of lipids. ([J Nutr. 1991;121:258]) Selenium is important in immune function. ([Selenium: Its Molecular Biology and Role in Human Health. 2nd ed. New York: Springer; 2006:311]) Deficiency reduces the activity of T cell activity and antibody production. Selenium supplementation increases IL-2 while reducing inflammatory prostaglandins and leukotrienes. ([Biol Trace Elem Res. 1994;41:103, Biol Trace Elem Res. 1994;41:115]) A double-blind, placebo-controlled study of more than 1,300 older adults with a history of non-melanoma skin cancer found that supplementation with 200 mcg/day of selenium-enriched yeast for an average of 7.4 years was associated with a 49% decrease in prostate cancer incidence in men. ([BJU Int. 2003;91(7):608]) One study indicates that selenium supplementation increased the risk of one type of skin cancer (squamous cell carcinoma) by 25% ([J Natl Cancer Inst. 2003;95:1477]) but did not significantly decrease the risk of lung cancer. ([Cancer Epidemiol Biomarkers Prev. 2002;11:1285]) Selenium supplementation has also
been suggested for decreasing the risk of cardiovascular disease by decreasing lipid peroxidation. Strong clinical support does not, however, exist at this point. (Am J Epidemiol. 1997;145:373) In regards to diabetes one study in 1,202 men and women participating in the Nutritional Prevention of Cancer trial found that selenium supplementation (200 mcg/day; mean follow-up of 7.7 years) was linked to an increase in prevalence of type 2 diabetes. (Ann Intern Med. 2007 Aug 21;147:217) Considering HIV, a trial in 174 HIV-1-positive individuals reported that selenium supplementation (200 mcg/day of selenium-enriched yeast) for nine months was associated with increased serum selenium concentrations, increased CD4 T cell counts, and no progression of the HIV-1 viral load. (Arch Intern Med. 2007;167:148)

High dosages of selenium can be very toxic. Selenosis may occur cumulatively with small doses-hair and nail brittleness and loss. Supplements may provide selenium but selenate and selinite absorption rates are unpredictable. Selenomethionine that occurs naturally in foods, is about 90% absorbed. (National Academy Press; 2000:284) Recommended dosages are 100-200 mcg/day. Eating a varied diet and taking a daily multivitamin supplement should provide sufficient selenium for most people in the U.S. The Food and Nutrition Board (FNB) of the Institute of Medicine recently set the tolerable upper intake level (UL) for selenium at 400 mcg/day in adults based on the prevention of hair and nail brittleness and loss and early signs of chronic selenium toxicity.

Take Home Message:
Selenium is critical to the maintenance of health but sufficient amounts can be obtained through the diet and excesses are potentially toxic.

Excellent Natural Sources:
Food sources of selenium are organ meats, seafood and muscle meats. Brazil nuts and enriched grains may provide selenium if grown in appropriate soil conditions.

Iodine
Iodine is a non metal element required for the synthesis of thyroid hormones, triiodothyronine (T3) and thyroxine (T4). The thyroid retrieves iodine from the blood and incorporates it into thyroid hormones. In tissues such as the liver and brain the T3 binds to thyroid receptors in the nuclei to regulate gene expression. T4 is the most abundant thyroid hormone and can convert to T3 by selenium-containing enzymes, deiodinases. (J Clin Endocrinol Metab. 1998;83:3398) As such selenium deficiencymay exacerbate the effects of iodine deficiency. Deficiencies of vitamin A or iron may also worsen the effects of iodine deficiency. (J Nutr. 1996;126(9 Suppl):2427S) Thyroid function involves the hypothalamus and the pituitary with the thyrotropin releasing hormone (TRH) secreted by the hypothalamus stimulating the pituitary to secrete thyroid stimulating hormone (TSH). The TSH then stimulates iodine trapping by the thyroid. Adequate T4 in circulation decreases the sensitivity of the pituitary, which then limits the secretion of TSH.
Iodine deficiency results in lowered levels of T4, increasing output of TSH, which then leads to enlargement of the thyroid-goiter. *(Williams Textbook of Endocrinology. 9th ed. Philadelphia: W.B. Saunders Company; 1998:389)* The more severe cases of iodine deficiency result in hypothyroidism. Iodine deficiency is considered by the World Health Organization to be the most common cause of preventable brain damage in the world. *(Bull World Health Organ. 2005;83:518)* The thyroid not only regulates growth and development but is also necessary for myelination of the CNS. In addition to thyroid dysfunction, multiple studies have suggested that insulin resistance, elevated cortisol levels, and low estrogen and testosterone levels have all been linked in the development of dementia. Low and high thyrotropin levels were associated with an increased risk for incident Alzheimer’s disease in women but not in men. *(Arch Intern Med 2008;168:1514)*

Iodine deficiency is becoming more of an issue because of dietary recommendations to reduce salt intake but most in the U.S. are considered to be obtaining enough iodine from their diet. *(J Clin Endocrinol Metab. 1998;83:3401)* The recommended daily allowance for iodine for adults is approximately 150 mcg/day. The tolerable upper level of iodine for adults is considered 1100 mcg/day. Natural sources include iodized salt, fish, shrimp, mild and eggs. Amiodarone contains high levels of iodine, which may affect thyroid function, and high levels of dietary potassium iodide may decrease the anticoagulant effect of coumadin.

**Manganese**

Manganese is a mineral necessary in the production of enzymes and the activation of other enzymes. Manganese superoxide dismutase (MnSOD) is the primary antioxidant enzyme in mitochondria where 90% of oxygen is used by the cells. As such oxidation is a major issue in proper mitochondrial function. MnSOD catalyzes the conversion of
superoxide radicals to hydrogen peroxide which is then converted to harmless water by other enzymes. *(Handbook of nutritionally essential minerals. New York: Marcel Dekker, Inc; 1997:335)* Manganese is critical in bone development and wound healing from the standpoint of modulating collagen production. *(Exp Toxicol Pathol. 2000;5:149)*

Adequate intake for manganese is considered to be approximately 1.8 to 2.3 mg/day for adults. Drugs that may negatively affect manganese absorption include magnesium antacids and tetracycline. *(PDR for Nutritional Supplements. Montvale: Medical Economics Company, Inc; 2001)* Tolerable upper levels for adults are considered at 11 mg/day but neurotoxic potential exists to preclude advice above 2 mg/day. *(Arch Environ Health. 1989;44:175, Can J Neurol Sci. 1995;22:286)* True deficiencies in humans are rare. Rich sources of manganese include pineapple, whole grains, nuts, leafy vegetables, and teas. Foods high in phytic acid, such as beans, seeds, nuts, whole grains, and soy products, or foods high in oxalic acid, such as cabbage, spinach, and sweet potatoes, may slightly inhibit manganese absorption.

**Potassium**

Potassium is a dietary mineral that also serves as an electrolyte. Potassium acts as the principal positive ion inside cells creating an electrical differential-the membrane potential- with sodium outside the cells. Control of this membrane potential is critical for the nervous system and as a result of that critical for eye health. Potassium is also critical for a number of enzyme processes.


Food sources for potassium include bananas, potato skins, prunes, orange juice, tomato juice, artichokes, lima beans, almonds and the ever-nutritious spinach. In general recommendations for potassium hover around 4.7 grams/day especially as related to diet.
The most common adverse reactions are gastrointestinal-related issues. Hyperkalemia may occur associated with kidney disease, the use of potassium-sparing agents, ACE inhibitors, anti-coagulants, digitalis, Beta and alpha-blockers, angiotensin receptor blockers, NSAIDS, and aldosterone issues. Hypokalemia is associated with beta-adrenergic agonists, bronchodilators, decongestants, mineralcorticoids, licorice, high dosage antibiotics, and caffeine.

Sodium

DHEA
DHEA (dehydroepiandrosterone) is a hormone secreted by the adrenal glands and converted to several other hormones. The body creates DHEA from cholesterol and beta-sitosterol which creates pregnenolone. When DHEA is added to the diet there is a rise in the level of all immune cells. When DHEA levels are low, cortisol is found to be elevated. High cortisol levels increase the release of IL-6 promoting inflammation. DHEA naturally decreases with age. DHEA supplementation is to be considered seriously as it is a hormone and reports of negative side effects include acne, facial hair growth, deepening of voice, mood swings, and negative effects in the presence of cancer.

Essential Fatty Acids as Related to Health
Alpha-linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid, are considered essential fatty acids because they cannot be synthesized by humans. The long-chain omega-6 fatty acid, arachidonic acid (AA) can be synthesized from LA. The long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be synthesized from ALA, but EPA and DHA synthesis may be insufficient under certain conditions.

Typical Western diets tend to be much higher in omega-6 fatty acids than omega-3 fatty acids, which are polyunsaturated fatty acids, and proper proportions are usually offered as ratios. It is estimated that 83% of Americans are deficient in Omega 3s. The best sources of Omega 3s are cold-water fish, walnuts, dark green leafy vegetables, beans, fish oils and flaxseed oil. In contrast Omega 6 essential fatty acids are overabundant in the diet Omega 3 to Omega 6 being 1:10, with the ideal Omega 3 to Omega 6 ratio being 1:1 or 1:2 largely the result of increased consumption of vegetable oil. The disproportion set up allows for an imbalance in developmental aspects of tissues as well as fostering the proliferation of more “bad” than “good” prostaglandins in the inflammatory cascade.

Omega-6 and omega-3 polyunsaturated fatty acids are important structural components of cell membranes. The phospholipids affect cell membrane properties such as fluidity, flexibility, permeability and the activity of membrane bound enzymes. (Chem Phys Lipids. 2003;126:1) DHA is found in very high concentrations in the cell membranes of the retina, which conserves and recycles DHA even when omega-3 fatty acid intake is low (Lipids. 2001;36(9):859). Recent research indicates that DHA plays an important role in the regeneration of the visual pigment rhodopsin. (Prog Retin Eye Res. 2005;24:87)
The phospholipids within the gray matter of the brain contain high proportions of DHA and AA, suggesting importance in central nervous system function. (J Pediatr. 2003;143(4 Suppl):S1) Another study showed that eating fish oil (oily fish including mackerel, tuna, salmon, sardines and herring) at least once a week is linked to a reduced risk for neovascular age-related macular degeneration. This is being further investigated in the ongoing AREDSS2 study. (Am J Clin Nutr. 2008;88:398) Most studies point to the importance of balance of essential free fatty acids in ocular and neurological development.

Two new studies have shown that Omega-3 fatty-acid supplementation improves morbidity and mortality in symptomatic heart-failure patients, while statins failed to have any beneficial effect in the same group of patients. (Lancet 2008; DOI: 10.1016/S0140-6736(08)61241, Lancet 2008; DOI: 10.1016/S0140-6736(08)61239) One study indicates that increasing intakes of long-chain omega-3 fatty acids (EPA and DHA) can decrease the risk of cardiovascular disease by 1) preventing arrhythmias that can lead to sudden cardiac death, 2) decreasing the risk of thrombosis that can lead to MI or stroke, 3) decreasing serum triglyceride levels, 4) slowing the growth of atherosclerotic plaque, 5) improving vascular endothelial function, 6) lowering blood pressure slightly and 7) decreasing inflammation. (Arterioscler Thromb Vasc Biol. 2003;23:151) Many reports show men who eat fish at least once a week have lower mortality from CHD than men who do not eat fish. (N Engl J Med. 1985;312:1205, Int J Epidemiol. 1995;24:340, World Rev Nutr Diet. 1991;66:205) One such study followed 1822 men for 30 years and found that mortality from CHD was 38% lower in men who consumed an average of at least 35 g (1.2 oz) of fish daily than in men who did not eat fish, while mortality from MI was 67% lower. (N Engl J Med. 1997;336:1046) In the Nurses’ Health Study, following over 84,000 women for 16 years, CHD mortality was 29-34% lower in women who ate fish at least once a week compared to women who ate fish less than once a month. (JAMA. 2002;287:1815) Epidemiological studies suggest that regular fish consumption is inversely associated with the risk of sudden cardiac death. (JAMA. 1998;279:23, N Engl J Med. 2002;346:1113) Another prospective study that followed more than 45,000 men for 14 years found that the risk of sudden cardiac death was about 40-50% lower in those who consumed an average of at least 250 mg/day of dietary EPA + DHA, the equivalent of 1-2 oily fish meals weekly, than those who consumed less than 250 mg/day. (Circulation. 2005;111:157) When referencing the impact on the incidence of stroke, two large prospective studies found that increased fish and omega-3 fatty acid intakes were associated with significantly lower risks of ischemic stroke, but not hemorrhagic stroke. In a study that followed more than 79,000 women for 14 years, those who ate fish at least twice weekly had a risk of thrombotic (ischemic) stroke that was 52% lower than those who ate fish less than once monthly. (JAMA. 2001;285:304) Likewise another study that followed more than 43,000 men for 12 years, those who ate fish at least once monthly had a risk of ischemic stroke that was 43% lower than those who ate fish less than once monthly. (JAMA. 2002;288:3130) The triglyceride-lowering effects of EPA and DHA increase with dose, but clinically meaningful reductions in serum triglyceride concentrations have been demonstrated at larger doses of 2 g/day of EPA + DHA. (Circulation. 2002;106:2747) and triglycerides are especially important in patients with diabetes. (Diabetes Care. 2000;23:1407) Utilization of alpha-linoleic acid reduces the risk of non-fatal myocardial infarct.

Increasing EPA and DHA intake may be beneficial to individuals with diabetes, especially those with elevated serum triglycerides while randomized controlled trials.

Omega 3 Fatty Acids
Omega 3 fatty acids are acted on by enzymes to produce prostaglandin E3 and leukotriene B5 (LTB5) which are two eicosanoids that decrease inflammation. Omega 3s through Eicosapentaenoic acid (EPA) also produce a decrease in gene expression and the proteoglycan degrading enzymes, the gene expression of proinflammatory interleukin-1α (IL-1α), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and cyclooxygenase (COX-2). Omega 3s decrease inflammation seen in joints, in dermatitis, and in meibomitis. Omega 3s also assist the meibomian glands in the manufacture of higher quality and thinner oil secretions. Certain levels of Omega 3s modulate the metabolism of Omega 6s. Eicosapentaenoic acid (EPA-Fish Oil) impacts the arachidonic acid inflammatory cascade and the conversion of DGLA to arachidonic acid. EPA also promotes the conversion of DGLA to PGE1 which has anti-inflammatory properties. Additionally EPA blocks TNF-α, a pro-inflammatory cytokine which works to increase immune activation and cellular adhesion in the conjunctival epithelium. TNF-α also increases apoptosis in the lacrimal gland which further induces lacrimal gland antibodies. Coincidentally, Vitamin E and Docosahexanoic Acid (DHA) also protect the cells from TNF-α induced apoptosis. TNF-α, with IL-1α and IL-1β also inhibit the release of neurotransmitters interfering with nervous system transmission. Blocking TNF-α IL-1α and IL-1β does much to improve the dry eye dilemma. A number of clinical studies point to the fact that the greater the Omega 3 consumption in the diet, the lower the risk for dry eye.

Omega 3 Fatty acids have many effects including modulation of intracellular calcium ion release. (Cardiovasc Drugs Ther 1992;6:605) Omega 3 FFAs also increase the production of uncoupling proteins and thereby improve ATP independent heat production, which is most probably impaired in patients with vaso dysregulation. (J Nutr 2001;131:2636, Biochem Biophys Res Commun 1999;259:85) Omega 3 FFAs can improve vascular regulation as a result of flow-mediated vasodilation properties. (Acta Ophthalmol Scand Suppl 1998;41, Eur J Pharmacol 1992;215:325) Cacao has the
same reported properties. (Nutr Rev 2006;64:109, JAMA 2003;290:1030, J Agric Food Chem 1999;47:4821, Hypertension 2005;46:398) It should be noted that a regular diet high in n-3 polyunsaturated fat, especially from fish, suggests protection against early and late ARM in an older Australian cohort. (Arch Ophthalmol 2006;124:981) A recent meta-analysis suggests that consumption of fish and foods rich in omega-3 fatty acids may be associated with a lower risk for AMD; however, there was insufficient evidence with few prospective studies and no randomized clinical trials to support their routine consumption for the prevention of AMD. (Arch Ophthalmol. 2008;126:826)

Of importance is addressing the entire picture. One study showed that groups receiving fish oil supplementation had lower triacylglycerol levels, increased high-density lipoprotein (HDL) cholesterol levels, and improved endothelium-dependent arterial vasodilation ($P < .05$). Compared with the groups not receiving the exercise intervention, those in the exercise groups had better arterial compliance ($P < .05$). Both fish oil and exercise were independently associated with reduced body fat ($P < .05$). Fish oil supplements and regular exercise both reduce body fat and improve cardiovascular and metabolic health. Further findings indicate that increasing intake of n-3 FAs could be a useful adjunct to exercise programs aimed at improving body composition and decreasing cardiovascular disease risk. Compliance rate was also increased by taking a biphasic approach. (Am J Clin Nutr. 2007;85:1267)

Current evidence implicates oxidative damage as part of the pathophysiological changes occurring in various diseases, such as coronary heart disease, cancer, neurodegenerative disease, and also aging. The Mediterranean diet has previously been demonstrated to improve mortality rates. In a study by Knoops and colleagues of individuals between the ages of 70 and 90 years, adherence to the Mediterranean diet, moderate alcohol intake, exercise, and not smoking were each associated with a reduction in total mortality as well as mortality related to coronary heart disease, cancer, and all cardiovascular causes. The study results, which were published in the September 22, 2004, issue of JAMA, also showed that combining all 4 healthy lifestyle choices resulted in a hazard ratio of death of 0.35 compared with individuals who did not practice these behaviors. In a more recent study it was demonstrated that olive oil, a rich source of monounsaturated fatty acids, a main component of the Mediterranean diet, and virgin olive oil retains all the lipophilic components of the fruit and phenolic compounds with strong antioxidant and anti-inflammatory properties. Tree nuts, which are common to the Mediterranean diet, also have a favorable fatty acid profile and are a rich source of nutrients and other bioactive compounds, such as fiber, phytosterols, folic acid, and antioxidants, which may beneficially influence the risk for CHD, (Arch Intern Med. 2007;167:1195)

"The American Heart Association (AHA) has endorsed the use of omega-3 fatty acids for secondary prevention of cardiovascular (CV) events in people with documented coronary artery disease (CAD)," writes John H. Lee, MD "The recommendation calls for approximately 1 g/d of a mixture of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Although the AHA statement identifies oily fish as the ideal source, fish oil (in capsules or liquid form) is also an acceptable option." This recommendation is the first time that the AHA has recommended a nutritional supplement for CAD prevention, and it is supported by a large and growing body of evidence supporting the CV benefits and triglyceride-lowering effects of omega-3 oils. In a recent publication it was stated that a review of studies revealed that the term omega-3 fatty acids refers only to DHA and EPA because the evidence for a CV benefit from the plant-derived omega-3 fatty acid,
alpha-linolenic acid, is much weaker than it is for DHA and EPA. To date, the strongest evidence showing a CV benefit from omega-3 fatty acid intake derives from 3 large controlled trials in which a total of 32,000 participants were randomized to a control group or to receive omega-3 fatty acid supplements containing DHA and EPA. In these trials, the supplemented group had a 19% to 45% reduction in CV events vs the control group. Based on these results, the review authors recommend increased intake of both DHA and EPA, whether from dietary sources or fish oil supplements, especially for individuals with or at risk for CAD. In the absence of known CAD, the target DHA and EPA consumption levels are at least 250 to 500 mg/day, and these levels should increase to approximately 1 g/day for persons with heart disease.

Patients with hypertriglyceridemia should consume 3 to 4 g/day of DHA and EPA, which can lower triglyceride levels by 20% to 50%. In patients with severely elevated triglyceride levels (> 500 mg/dL), 3 to 4 g/day of DHA and EPA typically lowers triglyceride levels by 45%. When added to baseline statin therapy in patients with triglyceride levels of 200 to 499 mg/dL, this dosage lowers triglyceride levels by an additional 23% to 29%. Two meals of oily fish per week can provide 400 to 500 mg/day of DHA and EPA, but patients with hypertriglyceridemia must use fish oil supplements to reach target levels of 1 g/day of DHA and 3 to 4 g/day of EPA.

"Combination therapy with omega-3 fatty acids and a statin is a safe and effective way to improve lipid levels and cardiovascular prognosis beyond the benefits provided by statin therapy alone," the reviewers write. "Blood DHA and EPA levels could one day be used to identify patients with deficient levels and to individualize therapeutic recommendations."

Standard over-the-counter fish oil concentrate contains 120 mg of DHA and 180 mg of EPA per 1-g capsule, so 1 to 2 capsules of standard fish oil per day contain 300 to 600 mg of DHA and EPA and meet the recommendations for primary prevention; 3 to 4 capsules per day contain 900 to 1200 mg of DHA and EPA and meet the recommendations for secondary prevention; and 5 to 7 capsules twice daily contain 3000 to 4200 mg of DHA and EPA and can be used to lower triglyceride levels.

Tasteless liquid products are also available that provide 1300 mg of DHA and EPA per teaspoon (3900 mg of DHA and EPA per tablespoon). One tablespoon of standard liquid fish oil twice weekly contains approximately the same amount of omega-3 fatty acids as 6 oz of salmon consumed twice weekly (500 mg/day of DHA and EPA).

Formulations and doses of DHA and EPA:
- Both DHA and EPA are present in all oily fish, and commonly consumed fish such as salmon contain the 2 in a 2:1 ratio.
- Standard fish oil capsules such as derived from menhaden, an oily fish of the herring family, contain DHA and EPA in a 2:3 ratio.
- 1 capsule of over-the-counter fish oil is equivalent to 300 mg of EPA and DHA.
- 1 tablespoon of standard liquid fish oil taken twice weekly provides the same amount of omega-3 fatty acids as 6 oz of salmon twice weekly (500 mg/day of EPA and DHA).
- Modest consumption of 200 to 500 mg/day corresponding to 1 to 2 servings of oily fish weekly has been associated with reduced CAD death.
- For primary prevention, a dose of 1 serving per week of oily fish may be sufficient to reduce risk by 15%, whereas 5 or more servings weekly may confer a 40%
risk reduction.
• Those without CAD can benefit from 1 to 2 capsules of fish oil daily, whereas those with CAD would need 3 to 4 capsules daily for secondary prevention.
• For reduced triglyceride levels, 5 to 7 capsules twice daily (3 - 4 g/day of EPA and DHA, equivalent to 10 - 14 capsules) are needed to lower levels by 30% to 50%.
• This dose may be added to statins for additive effect.
• Omega-3 fatty acids may be taken at any time, and oils persist in cell membranes for weeks after consumption; thus, dosing interval may be as long as once weekly.
• There are no head-to-head trials of EPA with DHA with controls with Coronary Artery Disease as an endpoint; thus, neither fatty acid can be said to be more effective than the other.

The review of the studies conclude that "Omega-3 fatty acid supplements can be taken at any time, in full or divided doses, without raising concerns for interactions with any medications. Omega-3 fatty acids persist in cell membranes for weeks after consumption, and thus intermittent bolus dosing, ie, twice weekly intake of fish or fish oil, provides the same benefits as daily consumption of lower doses." (Mayo Clin Proc. 2008;83:324)

Take Home Message:

Excellent Natural Sources:

**Omega-6 Fatty Acids**

**Linoleic Acid:** Food sources of LA include vegetable oils, such as soybean, safflower and corn oil, nuts, seeds and some vegetables. Included are safflower oil, sunflower seeds, pine nuts, sunflower oil, corn oil, soybean oil, pecans, and brazil nuts. Borage seed oil, evening primrose oil and black currant seed oil are rich in gamma-linolenic acid (GLA), and are often marketed as GLA or essential fatty acid (EFA) supplements. Side effects include gastrointestinal distress and may create seizure in patients with undiagnosed temporal lobe epilepsy. (Prostaglandins Med. 1981;6:375)

**Black Currant Seed Oil**
A recent study provides strong evidence that supports other studies which have suggested the anti-inflammatory activity displayed by the anthocyanidins in black currants is related to down-regulation of endothelial adhesion molecules. (Journal of Inflammation 2005;9:9) Other studies have shown that dark colored berry anthocyanidins, and particularly black currants, are beneficial in reducing age-associated oxidative stress, improving neuronal and cognitive brain function and stabilizing VEGF. (Cornea 2003;22:97, Nutr Cancer 2001;41:145)

**Omega-3 Fatty Acids**

**Alpha-Linolenic Acid (ALA):** Flaxseeds, walnuts, and their oils are among the richest dietary sources of ALA. Included are flaxseed oil, walnuts, canola oil, and tofu. Flaxseed oil is available as an ALA supplement as well as a number of fish oils marketed as omega-3 fatty acid supplements. Since EPA and DHA content will vary in fish oil and ethyl ester preparations, it is necessary to read the label to determine the EPA and DHA content of a particular supplement. All omega-3 fatty acid supplements are absorbed
more efficiently with meals. Dividing one’s daily dose into two or three smaller doses throughout the day will decrease the risk of gastrointestinal side effects. Cod liver oil is a rich source of EPA and DHA. Side effects are characterized by gastrointestinal disorders.

**Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA):** Oily fish are the major dietary source of EPA and DHA. Included are herring, salmon, oysters, trout, tuna, and crab.

Omega 3 and 6 Free Fatty Acid absorption is enhanced by the intake of Vitamin E. Fat-soluble antioxidants, such as vitamin E serve to prevent the oxidation of polyunsaturated fatty acids. Protection from rancidity is especially important outside the body, and supplements should have this consideration. Animal studies and limited human studies suggest that the amount of vitamin E required to prevent lipid peroxidation increases with the amount of polyunsaturated fatty acids consumed. *(Int J Vitam Nutr Res. 2000;70:31)* One widely used recommendation for vitamin E intake is 0.6 mg of alpha-tocopherol per gram of dietary polyunsaturated fatty acids.

The American Heart Association recommends that people without documented CHD eat a variety of fish (preferably oily) at least twice weekly, in addition to consuming oils and foods rich in ALA. *(Circulation. 2002;106:2747)* People with documented CHD are advised to consume approximately 1 g/day of EPA + DHA preferably from oily fish, or to consider EPA + DHA supplements in consultation with a physician. Patients who need to lower serum triglycerides may take 2-4 g/day of EPA + DHA supplements under a physician’s care. Although the Institute of Medicine did not establish a tolerable upper level of intake (UL) for omega-3 fatty acids, caution was advised with the use of supplemental EPA and DHA, especially in those who are at increased risk of excessive bleeding.

**Bilberry**

Bilberry gained publicity when advocated during World War II for improving night vision in British Air Force Pilots. Bilberry contains flavonoid compounds known as anthocyanosides which are potent antioxidants, electron scavengers *(J Agric Food Chem 2005;53:8485)* and vascular stabilizers. In a report of 50 patients with age-related cataracts, a combination of bilberry and vitamin E delayed the progression of cataracts. *(Altern Med Rev 2001;6:141)* Bilberry may improve ocular microcirculation and protect the vascular endothelium thus minimizing capillary leakage and acting as an antiangiogenesis agent. Bilberry is used extensively in Europe and has demonstrated efficacy in improving night vision and managing diabetic retinopathy. *(Klin Monatsbl Augenheilkd 1981;178:386) (Arch Med Int 1985;37:29) (Fitoter 1991;42:15)* Currently the potential benefits of bilberry have come to question and its use has fallen out of favor.

One further caution regarding bilberry is that it is an unpredictable blood thinner with individualized responses. This becomes even more of an issue when used in patients on blood thinners or other supplements like vitamin E, EPA, DHA, and gingko biloba. An efficacious dosage in the safety zone should not exceed 30-40 mg/day.

**Take Home Message:**

**Excellent Natural Sources:**
Nutrition and Behavior with Mitochondrial Impact

“Mitochondria can be impaired either genetically (as in Leber's) or through acquired insults (such as nutritional or toxic factors). Either may challenge energy production in all cells of the body. While this challenge may be met through certain compensatory mechanisms (such as in the size, shape, or number of the mitochondria), there exists in neurons a threshold which, once passed, leads to catastrophic changes. This threshold may be that point at which mitochondrial derangement leads to such ATP depletion that axonal transport is compromised, and decreased mitochondrial transport results in even further ATP depletion. Neurons are singularly dependent on the axonal transport of mitochondria.” (Trans Am Ophthalmol Soc. 1998;96:881) More recent studies report that IOP elevation may directly damage mitochondria in the ONH axons by promoting reduction of COX, mitochondrial fission and cristae depletion, alterations of OPA1 and Dnm1 expression, and induction of OPA1 release. Thus, interventions to preserve mitochondria may be useful for protecting ON degeneration in glaucoma. (Invest Ophthalmol Vis Sci. 2008 May 9. [Epub ahead of print])


Bruce Ames, the undisputed leader in the field of micronutrient impact on mitochondria, posits a new theory about homeostasis during micronutrient shortage which, if confirmed, will radically change thinking about requirements for micronutrients and public health. His triage hypothesis offers that the risk of degenerative diseases associated with aging, including cancer, cognitive decline, and immune dysfunction, can be decreased by ensuring adequate intake of micronutrients (the 40 essential vitamins, minerals, amino acids, and fatty acids) earlier in life, a simple and inexpensive solution to a potentially large public health problem. The triage hypothesis predicts that insidious changes may indeed be occurring, providing a unifying rationale for diverse observations in the literature that suggest links between micronutrient availability, aging, and the diseases of aging. (Proc Natl Acad Sciences USA 2006;103:17589) "Hyperglycemia induces mitochondrial stress and apoptotic cell death in diabetic tissues soon after
disease onset and before involvement can be detected by any current clinical diagnostic method," write Matthew G. Field, from the University of Michigan in Ann Arbor. The subject of a recent study suggests that Flavoprotein Autofluorescence Measurements May Be Helpful in Diabetic Retinopathy. (Arch Ophthalmol. 2008;126:934)

Alpha-lipoic (Lipoic Acid) Acid

Alpha-lipoic acid is also referred to as thioctic acid is an antioxidant that is both fat and water-soluble. It is synthesized in small amounts and is bound to proteins which function as cofactors for mitochondrial enzyme complexes. (J Biol Chem. 2001;276:38329) There are two forms of lipoic acid which may be reduced-dihydrolipoic acid (DHLA)-and the oxidized form—lipoic acid (LA). LA appears as two possible isomers but the R-LA is endogenously synthesized within mitochondria and bound to protein. (Chem Biol. 2003;10:1293, Curr Med Chem. 2004;11:1135. Nutraceuticals in Health and Disease Prevention. New York: Marcel Dekker, Inc.; 2001:129) Alpha-lipoic acid deactivates a broad range of free radicals, crosses the blood-brain barrier and mimics other less powerful antioxidants. However these actions are short-lived and long-term antioxidant activity is better achieved by other supplements. Alpha-lipoic acid is the only antioxidant that raises levels of the important ocular antioxidant glutathione. (Proc Natl Acad Sci U S A. 2004;101:3381, Arch Biochem Biophys. 2004;423:126) It also regenerates antioxidant nutrients such as vitamins C. E, and Coenzyme Q10 that have been converted into free radicals after they quench other free radicals, all the while protecting neurons from glutamate toxicity. (Arch Biochem Biophys. 1999;363:148, FASEB J. 1999;13:977) Alpha-lipoic Acid also acts to remove the strong oxidant, iron, and has a beneficial action on ocular tissue and hydrodynamic parameters. (Curr Med Chem. 2005;12:1161, Lancet Neurol. 2004;3:431, Vestn Oftalmol 1995;111:6, Vestn Oftalmol 1991;107:19, Vestn Oftalmol 1993;109:5, J Klin Monatsbl Augenheiikd 1980;177:577-83) (In: Rokan (Ginkgo Biloba) Recent results in pharmacology and clinic. Fungeld (ed) Springer Verlager, New York, 1988) (In: Ginkgo Biloba (V:Ginkgo-1) A textbook of Natural Medicine Bastyr College Publications, Seattle, WA,. 1993)

LA has also been shown to activate the insulin signaling cascade purportedly affecting cellular glucose uptake. (Antioxid Redox Signal. 2005;7:1032, Diabetologia. 2000;43:294) As such there are thoughts, yet unsubstantiated that LA may be beneficial in the management of diabetes. (Treat Endocrinol. 2004;3:173, Biofactors. 1999;10:169) Management of diabetic neuropathy does, however, appear to benefit from 600 mg/day of IV LA (Diabet Med. 2004;21:114) but the benefits of 1200 mg/day oral are yet to be totally validated. (Free Radic Res. 1999;31:171) It does appear that oral supplementation of 80 mg/day or R-LA is beneficial in the management of cardiovascular autonomic neuropathy in diabetic patients. (Diabetes Care. 1997;20:369)

LA may be consumed in the racemic (R-LA) oral form and about 30-40% absorption can be expected. It is however better absorbed on an empty stomach than with food and R-LA is better absorbed than S-LA. The plasma levels peak rapidly and decline in an hour or less. LA is rapidly changed to DHLA within the cells and then rapidly exported. (Eur J Pharm Sci. 1996;4:167, J Clin Pharmacol. 2003;43(11):1257, Eur J Clin Pharmacol. 1996;50(6):513, Eur J Pharm Sci. 1999;8(1):57, Endocr Pract. 2002;8(1):29) It is recommended that a daily dose of 200 to 400 mg/day or racemic lipoic acid is sufficient for healthy individuals. Most LA supplements contain Racemic 50/50 mixture of R-LA and S-LA. LA supplementation has the potential to alter insulin sensitivity and as such may precipitate hypoglycemia. (Br J Clin Pharmacol. 1999;48(6):819) Note that biotin is similar in chemical structure to LA and could potentially compete. (Arch Biochem Biophys. 1999;366(1):95)

Take Home Message:
Excellent Natural Sources:
R-LA is synthesized endogenously by humans and is then bound to proteins to affect action. Good food sources of alpha-lipoic acid include spinach, broccoli, spinach, beef, yeast (particularly Brewer's yeast), and certain organ meats (such as the kidney and heart). (J Appl Nutr 1997;49:3) however efficacy of utilization is questionable because of binding issues.

Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC) is a natural molecule that is a derivative of lysine widely distributed in vertebrate and invertebrate nervous system. It is synthesized from lysine and methionine depending on several enzyme systems as well as the presence of iron, vitamin C, viamin B6, and Niacin in the form of nicotinamide adenine dinucleotide. Deficiencies are essentially non-existent. ALC is a nutrient responsible for the transport (carnitine shuttle) of long-chain fatty acids into the energy-producing centers of the cells (known as the mitochondria). In other words, carnitine helps the body convert fatty acids into energy and assists in elimination of fat build up. ALC maximizes mitochondrial function which serves as the bioenergy locus of the cell. The body produces carnitine in the liver and kidneys and stores it in the skeletal muscles, heart, brain, and sperm. ALC is known to have significant effects on neuronal activity playing a role as neuroprotective and anti-nociceptive agent, as well as neuromodulatory factor. (Neuroscience 2006;142:931) ALC is also known to have potential in inhibiting acute and delayed cell death following exposure to NMDA an excitotoxic glutamate antagonist (Ann NY Acad Sci 2005;1053:153), thus the relationship to neuroprotection. A deficiency of carnitine is known to have major deleterious effects on the CNS. (Ann NY Acad Sci 2005;1053:183) Oxidative mitochondrial decay is a major contributor to aging. (Ann NY Acad Sci 2004;1033:108)

Supplementation in animal studies reduces age-associated changes in lipid metabolism. (Journal of Lipid Research 2004;45:729) It has been reported that an appropriate combination of compounds including ALC, coenzyme Q10, and Omega 3 FFAs, which positively affect mitochondrial lipid metabolism, may improve and subsequently stabilize visual functions, and it may also improve fundus alterations in patients affected by early AMD. (Ophthalmologica 2005;219:154, Ophthalmologica 2003;217:351, Orv Hetil 2007;148:2259) L-Carnitine is capable of protecting the RPE cells from H2O2-induced oxidative damage, implying that micronutrients can have a positive effect and can play
an important role in the treatment of oxidation-induced ocular disorders. Further studies are needed to understand the mechanism of LC-induced protection to the RPE cells. (Curr Eye Res. 2007;32:575) The most exciting aspect of this compound is its ability as a secondary antioxidant to reduce or block neuronal death in Alzheimer’s disease (Expert Opin Investig Drugs 2007;16:1921) which could then lead to investigation in the management of glaucoma. When used in combination one study demonstrated that administration of a combination of vitamin E (which prevents de novo membrane oxidative damage), folate (which maintains levels of the endogenous antioxidant glutathione), and acetyl-L-carnitine (which prevents Abeta-induced mitochondrial damage and ATP depletion) provides superior protection in Alzheimer’s disease to that derived from each agent alone. (Brain Res 2005;1061:114) ALC has also been recommended in chronic pain neuropathies (e.g. diabetes, fibromyalgia) for its analgesic effect. (CNS Drugs 2007;21 Suppl 1:31, Clin Exp Rheumatol 2007;25:182) Another recent study demonstrates that administering ALC may reduce both physical and mental fatigue in elderly and improves both the cognitive status and physical functions. (Arch Gerontol Geriatr 2008;46:181)

Gastrointestinal absorption of exogenous L-Acarnitine is dependent on diet. Absorption is higher in individuals adapted to high carnitine diets. (J Nutr. 1991;121:539) Bioavailability of supplemental L-carnitine is suggested to be 14 to 18% of the total oral dosage consumed with the acetylated form, acetyl-L-carnitine reported to be increased. (Ann N Y Acad Sci. 2004;1033) Certain situations such as high fat, high protein, low carbohydrate diets and pregnancy can decrease carnitine reabsorption and increase kidney excretion. (Am J Clin Nutr. 1993;58:660)

Take Home Message:
Excellent Natural Sources:
Meats, especially red, fish and milk are excellent sources of L-Carnitine.

Ginkgo Biloba

Gingko biloba is a botanical antioxidant. Gingko has several properties which may lend well to management of glaucoma including: enhancing central and peripheral blood flow, minimizing vasospasm, inhibition of platelet activating factor, lowering serum viscosity, antioxidant activity, and inhibition of apoptosis and excitotoxicity. Oxidative stress at the level of the mitochondria may be positively affected by Gingko biloba. (Pharmacopsychiatry 2003;36:S15, Ann NY Acad Sci 2005;1056:474) Utilization of antioxidants to scavenge the free radicals created under oxidative stress has been recommended as a possible method of management of neurodegenerative issues in glaucoma. (Acta Ophthalmol Scand Suppl 1998;227:41) Gingko biloba is a potent antioxidant and has demonstrated survival of RGC in experimental glaucoma by interfering with the NMDA receptors. (J Neurotrauma 2002;19:369, Ophthalmologica 1998;212:268)

One study demonstrated that Ginkgo biloba at 120 mg/day improved visual fields in glaucoma patients with safety reports suggesting this dosage acceptable. (Ophthalmology 2003;110:359, Public Health Nutr 2000;3:495)


Take Home Message:
Excellent Natural Sources:

**Coenzyme Q10-Ubiquinone**

Coenzyme Q10 (CoQ10) is a powerful fat-soluble antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane. CoQ10 works synergistically with Vitamin E. Within the framework of mitochondrial function, Coenzyme Q10 is critical in the energy production by way of the electron transport chain. As such CoQ10 does have potential in the realm of neuroprotection. (J Biol Chem 2003;278:28220, Int Rev Neurobiol 2007;82:397) CoQ10 is concentrated in the myocardium. Its role in the heart makes sense: the heart, one of the body's most energetic organs, beats approximately 100,000 times a day and 36 million times a year, and depends on CoQ10 for "bioenergetics." In a well-controlled study, 19 patients who were expected to die from heart failure rebounded with an "extraordinary clinical improvement," with CoQ10 supplementation. (Proceedings of the National Academy of Sciences of the USA 1985;82:4240). Numerous case studies demonstrated the dramatic effect of CoQ10 in cardiovascular diseases. (Biochemical and Biophysical Research Communications 1993;182:247, Wochenschrift 1988;66:583, Clinical Investigator 1993;71S:145, Clinical Investigator 1993;71S:134) Reviews suggest a role for CoQ10 in the management of cardiovascular disease (Mitochondrion 2007;7 Suppl:S154) with the coincident effect of lowering both systolic and diastolic blood pressure. (J Hum Hypertens 2007;21:297) CoQ10 levels appear to have a direct relationship to thyroid hormone levels, with decreases in hyperthyroidism. (Biofactors 2005;25:201) There are numerous studies addressing the relationship of CoQ10 to statin-induced myopathy but the results are conflicting and any general statement regarding that issue is a bit premature. (Arch Neurol 2005;62:1709, Fundam Clin Pharmacol 2007;21 Suppl 2:35)

CoQ10 is best documented in the treatment of heart failure but there is also evidence suggesting benefit in certain types of cancer (Biochemical and Biophysical Research Communications 1993;192:241, Biochemical and Biophysical Research Communications
and may assist tamoxifen when used in combination with riboflavin and niacin in reducing recurrence and metastases of breast cancer. (Biol Pharm Bull 2007;30:367) There is also the suggestion that low levels of CoQ10 are an independent prognostic factor in the risk for melanoma progression. (J Am Acad Dermatol 2006;54:234) Neurodegenerative conditions such as amyotrophic lateral sclerosis. (Free Radic Res 2008;42:221, J Neurol Sci 2008;267:66). Friedrich’s ataxia (Mitochondrion 2007;7 Suppl:S127), Parkinson’s (Nervenarzt 2007;7:1378, J Neural Transm Suppl 2006;71:113, Neurology 2007;68:20), Oculomotor apraxia (Neurology 2007;68:295), and Huntington’s disease (Neurochem Res 2006;31:1103) may also benefit from supplementation. Because of the action of CoQ10 on mitochondrial metabolism there is the suggestion that it may be effective in the prophylaxis of migraine (effects on inhibition of excess glutamate). (Current Treat Options Neurol 2008;10:20, Headache 2008;47:73) Other neurological connections include studies A recent animal study regarding the effects of excitotoxicity in the development of retinal ganglion cell damage demonstrated that CoQ10 minimized glutamate increases affording neuroprotection to the eye. The study suggests that oxidative stress and energy failure might be implicated in the mechanism of RGC death and that CoQ10 may be of benefit in ocular neuroprotection. (Int Rev Neurobiol 2007;82:397)

There are also reports that CoQ10 supplementation could extend the lifespan of patients with acquired immune deficiency syndrome (AIDS). (Biochemical and Biophysical Research Communications 1988;153:888). There is also a relationship of CoQ10 deficiency and Cystic Fibrosis-Fat Malabsorption- (J Pediatr Gastroenterol Nutr 2006;43:646) as well as cerebellar ataxias. (Orphanet J Rare Dis 2006;1:47) There is the suggestion that any disorder related to mitochondrial dysfunction, encephalopathy, lactic acidosis, stroke-like episodes (MELAS), chronic progressive external ophthalmoplegia, and Kearns-Sayre syndrome may benefit from CoQ10 therapy. (Muscle Nerve 2007;35:235, Curr Opin Rheumaol 2006;18:636)

CoQ10 is a coenzyme for the inner mitochondrial enzyme complexes that has demonstrated prevention of lipid peroxidation and DNA damage induced by oxidative stress. (In Vivo 2005;19:1005, Biochem Biophys Res Commun 1990;169:851) Co Q10 is involved in energy production within the cell with strong antioxidant properties. (FASEB J 2001;15:1425) When combined with acetyl-L-carnitine and omega 3 FFAs, there is evidence that the combination is very effective in altering the progression of ocular disease such as AMD. Studies also suggest that acute and chronic supplementation of CoQ10 may affect acute and/or chronic responses to various types of exercise and increase time to exhaustion. (J Int Soc Sports Nutr 2008;4:5, Nutrition 2008;24:293) A recent report demonstrated that CoQ10 was effective in the management of experimental glaucoma. (Invest Ophthalmol Vis Sci 2007;48:E-Abstract 4369)

Therapeutic dosages of CoQ10 for serious diseases range from 200-400 mg. daily, while a common preventive dose ranges from 10-30 mg daily. Available data suggests that CoQ10 is relatively safe and tolerated over a range of 300 to 2,400 mg/day. (CNS Spectr 2007;12:62) CoQ10 does suffer from issues of bioavailability because of its hydrophobicity and large molecular weight. Work is continuing regarding that issue (J Med Food 2007;10:731, Mitochondrion 2007;7 Suppl:S78, Eur J Pharm Biopharm 2007; 67:361) with one study suggesting that CoQ10 absorption is enhanced with food intake. (Yakugaku Zasshi 2007;127:1251) It should also be noted that alterations of CoQ10 and
alpha tocopherol occur throughout the menstrual cycle further implicating hormonal influence in levels of all fat-bound supplements. (Am J Obstet Gynecol 2006;194:e35)

Take Home Message:
Excellent Natural Sources:

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) (MT) is a hormone that acts as an antioxidant. It is produced by the pineal gland, in the gastrointestinal tract, within the immune system and within the retina and its release is blocked by light entering the eye. (Physiol Pharmacol 2007;58 Suppl 6:115, Acta Ophthalmol 2008 May 20. [Epub ahead of print]) The relationship to the gastrointestinal tract has implications in the management of GI disorders. (J Phys Pharm 2006;57( Suppl 5): 51) It has also been shown that specific melatonin receptors have been located in the cornea, ciliary body, lens, choroid and sclera, which suggests that cells in these tissues may be targets for melatonin action. (Pharmacol Ther 2007;113:507, Exp Eye Res 2003;77:219) and that there is even a relationship to dry eye syndrome (Ocul Surf 2004;2:92) and the management of glaucoma (Exp Eye Res 2007;84:1021) but moderate and severe glaucoma does not appear to be associated with abnormal melatonin concentrations in aqueous humor. (Am J Ophthalmol 2006;142:325) Light is the major synchronizer of circadian rhythms to the 24-h solar day and this activity is related to Melatonin. (Neurosci Lett 2008. [Epub ahead of print, FASEB J 2007;21:3866) It has been reported that patients with circadian rhythm sleep disorders, including some blind patients with no light-induced suppression of melatonin, benefit from melatonin treatment. (Eye 2007;21:901) Does Melatonin assist in sleep? Studies have shown that exogenous melatonin administration possesses circadian-phase-dependent hypnotic properties, allowing for improved sleep. (Sleep 2006;29:609) Current evidence suggests that melatonin may act as a protective agent in ocular conditions such as photo-keratitis, cataract, glaucoma, retinopathy of prematurity and ischemia/reperfusion injury. (J Pineal Res 2006;40:101) Melatonin is shown to scavenge free radicals and stimulate antioxidative enzymes. (J Pineal Res 2006;41:116, Endocrine 2005;27:119) One study demonstrated that in pseudophakic patients with ARMD more Melatonin is produced during the day compared to pseudophakic subjects without ARMD. It is suggested that this be caused by the reduced visual acuity in patients with ARMD, whereby less light reaches the photoreceptors, allowing Melatonin secretion to continue during the day. Because Melatonin also acts as an antioxidant and daytime levels are higher in patients with ARMD, these results might be interpreted as a rescue factor. (Acta Ophthalmol 2008 May 20. [Epub ahead of print] In another report associated with ARMD it was demonstrated that the daily use of 3 mg melatonin seems to protect the retina and to delay macular degeneration. (Ann N Y Acad Sci 2005;1057:384) Although there are numerous reports describing the effects of UVA on cells of the skin and eye, no studies have described the anti-oxidative properties of Melatonin in relation to UVA-irradiated cells but intracellular levels may positively effect the ocular tissues in UV exposure. (Postepy Hig Med Dosw (Online). 2008 Jan 22;62:23) One report addresses the fact that that elevated intraocular pressure and large cup-to-disk ratios were independently associated with earlier melatonin timing. (J Circadian Rhythms 2005;3:13) Melatonin is reported to have a strong antiapoptotic signaling function, an effect that it exerts even during ischemia. It has been reported that Melatonin cytoprotective properties may have practical implications in the treatment of ocular diseases, like glaucoma and age-related
Another study points to the fact that in animal research Melatonin therapy could increase the survival rate of the RGCs and could rescue and restore the injured RGCs. *(J Huazhong Univ Sci Technolog Med Sci 2006;26:235)*  
There is a particular circadian rhythm within the eye and the impact on the genesis of ocular disorders is evolving. *(Prog Retin Eye Res 2008;27:137)*  
One report suggested that artificial supplementation of Melatonin and zinc should be considered as an adjunctive therapy to classic treatment of Toxoplasma retinochoroiditis especially in immunosuppressed and elderly patients if our data are confirmed in a clinical setting. This suggestion was based on animal data. *(Ophthalmologica 2007;221:421)*  
Another animal based study suggested that Melatonin effectively reduced the vascular permeability in the retina of hypoxic rats that its administration may be of potential benefit in the management of retinal edema associated with retinal hypoxia. *(J Pathol 2007;212:429)*  

Of additional interest is the fact that melatonin levels in the retina are naturally decreased with age and lenticular opacification and “normal” levels may be restored with lens replacement. *(Ophthalmic Physiol Opt 2003;23:181)*  

A relationship of melatonin to estrogen levels exists and as such there is a natural relationship to cancer. Melatonin levels in cancer patients have been correlated with tumor behavior. *(Med Hypotheses 2002;59:302, Med Sci Monitor 2002;8:CR457)*  
There is an association of estrogen-receptor-positive breast cancer with low plasma melatonin levels. *(New Eng J Med 1997;336:186)*  

Melatonin does not bind to the estrogen receptor or interfere with the binding of estradiol to its receptor as do drugs like tamoxifen *(Endocr Relat Cancer 2003;10:153)* and may actually increase the therapeutic efficacy of tamoxifen. *(Br J Cancer 1995;71:854)*  

**Take Home Message:**  
Melatonin is a hormone that is produced endogenously and acts as an antioxidant with apparent neuroprotective action. Within the ocular structures light is important in the production and utilization of Melatonin. Melatonin is critical in maintenance of health because of its importance in the normal sleep cycle.  

**Excellent Natural Sources:**  
There are some foods that contain small amounts of melatonin. Oats, sweet corn, and rice are the best sources of melatonin. However, to get the same amount of melatonin that is found in a supplement pill, you would need to eat about 20 bowls of oats. Ginger, tomatoes, bananas, and barley also contain small amounts of melatonin. Natural sources of melatonin include medicinal plants such as feverfew, St. John’s wort, and huang-qin (Scutellaria baicalensis) but establishment of purity and consistency is not guaranteed. *(Lancet 1997;350:1598, Neuroendocrinol Lett 2002;23 Suppl 1:14)*  
The building blocks for natural melatonin production in the body include sufficient amounts of vitamin B6, vitamin B3, and tryptophan, which is found in high quantities in foods such as nuts, seeds, spirulina, beans, and tofu.  

Melatonin is a hormone. Studies in humans have shown melatonin toxicity to be remarkably low with no serious negative side effects even at high doses (3 to 6.6 g) administered over a period of 35 days. *(Jama1972;221:88, J Pineal Res. 2000;29:193)*
None the less, reactions to melatonin supplementation such as sleepiness, vivid dreams, headache, abdominal pain, and nausea have been reported. *(Neuroendocrinol Lett. 2002;23:118)* The National Institutes of Health has issued warnings of the potential severe side effects of Melatonin supplementation including female infertility, decreased male sex drive, interaction with hormone replacement therapy, damage to the retina of the eye, and hypothermia. It is recommended that those who are pregnant, breast-feeding, those suffering from depression or schizophrenia, and those with autoimmune diseases such as lupus should avoid melatonin until more long-term studies are completed.

High cortisol levels are common with increased stress levels. High cortisol levels at night suppress melatonin which opens the door for immune system disorders. High cortisol levels are reflected in poor sleep patterns. 5HTP may assist sleep issues (balances the thyroid) as well as melatonin.

**5 HTP**

5 HTP is the metabolic precursor to the neurotransmitter serotonin. Tryptophane, an essential amino acid, is metabolized into 5 HTP by the body. 5 HTP is in turn, converted into the neurotransmitter serotonin. Serotonin is responsible for mood, hunger, and sleep. Antidepressant drugs approved by the FDA work by increasing the amount of serotonin available to the brain. 5 HTP, therefore may serve as a natural alternative to some prescription drugs.

Low levels of serotonin have been associated with depression, fibromyalgia, chronic pain, altered mood, insomnia, PMS, and headaches. Both tryptophane and 5 HTP are sometimes used as nutritional support for these conditions. 5 HTP is about five times more potent than tryptophane for this application.

5 HTP may aid in weight loss and improve sleep patterns for some individuals. Research suggests that good serotonin levels may reduce appetite thereby assisting in weight loss. Serotonin is converted into melatonin in the pineal gland and melatonin, in turn, regulates sleep cycles. The theory is that if 5 HTP can increase serotonin levels, it may be able to improve sleep and aid in weight loss. In the medical articles reviewed, positive results have been reported, but the authors caution that more research is needed before claims can be made.

As with all nutritional supplements or medications, individual response is a variable. It is clear that large excesses of serotonin in the peripheral circulation can cause cardiovascular disease and other adverse effects. Too much 5 HTP in the diet could potentially result in too much serotonin in the peripheral circulation.

Some sources suggest that 5 HTP can be safely used as a nutritional supplement at a dosage of up to 100 milligrams (mg) per day. Some authorities maintain that much larger dosages can be consumed without adverse effects. Some also suggest that 5 HTP, especially in larger doses, should be used with the prescription drug carbidopa. The purpose of this drug is to prevent the 5 HTP from being converted to serotonin in the peripheral circulation.
5 HTP is available without prescription and is generally considered safe and may be beneficial to many individuals. Contraindications to 5 HTP use, or conditions under which 5 HTP use should only be under the supervision of a physician, are conditions in which increased serotonin levels may be harmful:

- Cardiovascular diseases (High Blood Pressure, post-Stroke, post-Heart Attack)
- Extremely elderly persons
- Those with Parkinsons Disease, Cancer or Auto-immune diseases (Scleroderma, Rheumatoid Arthritis, Multiple Sclerosis, Lupus)
- Lung diseases
- Chronic Alcoholism
- Liver diseases (Hepatitis or Cirrhosis)
- Parasitic infection
- AIDS
- Anorexia Nervosa
- Low protein diets
- Allergies (severe)
- Myalgia (persistent pain and weakness of the muscles)
- Peripheral Neuropathy (pain weakness of the muscles)
- Rash or Flushing
- Edema
- Nausea
- Diarrhea
- Sickle Cell Anemia
- Hemophilia
- Pregnancy

Concurrent drug use: 5 HTP should not be used if taking:

- Anti-depressant drugs
- Monoamine oxidase inhibitors
- Selective Serotonin Reuptake Inhibitors (SSRI's e.g., Prozac)
- Tricyclic medications
- Weight Loss medications (i.e., Dextenfluramine)
- Anti-parkinson medications (e.g., L-dopa)
- Barbiturates and other tranquilizing drugs
- Antihistamines and cold medications
- Alcoholic beverages
- Intravenous (illegal I.V.) drugs
- Cancer chemotherapy or
- Antibiotic Medications
- Alcohol and 5 HTP should not be taken together. Allow at least six hours between use of alcohol and 5 HTP.

Warning: 5 HTP can increase the effect of some tranquilizing drugs.

**Curcumin**

The suggested daily dosage is 500 to 1000 mg. Toxicities were not experienced at levels of 3600 to 8000 mg/day for four months with the exception of nausea and diarrhea. (Adv Exp Med Biol 2007;595:471) There are, however, issues with bioavailability and methods to enhance this are under investigation. (Mol Pharm 2007;4:807)

Take Home Message:
Excellent Natural Sources:

Quercitin

Quercitin is an antioxidant flavonoid that prevents the oxidation of LDL. Oxidized LDL plays a key role in vascular damage. Quercitin is also well recognized as the anti-allergy supplement. Quercitin works synergistically with vitamin E to protect the purified rod outer segments (ROS) and retinal pigment epithelium (RPE) in the eye from free-radical-induced membrane lipoperoxidation and damage. Quercitin can modulate endothelial properties including nitric oxide production and expression of adhesion molecules. Quercitin inhibits the enzyme hyaluronidase from causing a breakdown of the collagen

Quercitin combined with stinging nettle and bromelain is a well known supplement that can positively effect allergies and as such impacts on the inflammatory cascade associated with the immune system.

Take Home Message:
Excellent Natural Sources:

**Taurine**

Taurine is an amino acid essential for retinal function and is concentrated in the RPE. Taurine functions as well as a water-soluble antioxidant. It counterbalances excessive levels of excitatory neurotransmitters and protects ocular tissue against ischemia and oxidative stress. Taurine protects the eye against neurotoxins including excessive levels of glutamate that may be responsible for the loss of ganglion cells and optic nerve damage. Another important property of taurine is its osmotic regulative effect achieved by modulating normal endothelial function. The combination of taurine and timolol maleate lowered intraocular pressure and improved ocular hemodynamics of patients with POAG. The fluid discharge efficacy almost doubled, and the Becker's coefficient was normalized in 68.6 percent of patients. (Vestn Oftalmol 1990;106(4):9-11) (Vestn Oftalmol 1978;(1):22-5) (Vision Res 1988;28(10):1071-6) (Neuroscience 1991;45(2):451-9) (J Neurochem 1990;55(2):714-7) (Adv Exp Med Biol 1996;257:507-17)

Take Home Message:

**N-acetyl cysteine**

N-acetyl cysteine is a derivative of amino acid cysteine that is ultimately converted into glutathione by endothelial cells. Cysteine is often called the rate-limiting factor in the production of glutathione, a key component in the free radical protection system of the eye. N-acetylcysteine protects the eye against the cytotoxicity of nitric oxide, minimizes oxidant injury and helps prevent the development of aberrant circulation. N-acetyl cysteine also assists in the regeneration of Vitamins E and C. (Biochem Pharmacol 1991;78:13, J Inherit Metab Dis 1989;112:120, Circulation 1988;78:202, Eur J Pharmacol 1997;321:87, J Biol Chem 1997;272:18411, Hepatology 1998;272:689) N-Acetyl-Cysteine acts as a chelating agent and as such increases the excretion of zinc and other essential minerals when taken over an extended period. It is therefore necessary to supplement zinc, copper and other trace minerals when taking N-Acetyl Cysteine. Likewise when taking N-acetyl cysteine it is also recommended that two to three times as much Vitamin C be taken at the same time. Failure to do so may result in more harm than good from taking this product because of the prolonged presence of the oxidized form of L-Cysteine. Vitamin C also helps keep the glutathione that is produced from the Cysteine in its reduced form so that it can continue acting as an antioxidant. N-Acetyl Cysteine is also believed to reduce mucous secretions in the lung.
Typical dosage recommendations are in the range of 250-1500mg of NAC daily for the majority of therapeutic benefits.

**Take Home Message:**
**Excellent Natural Sources:**
N-Acetyl Cysteine is produced in the body as a metabolite of cysteine.

**Resveratrol**

Resveratrol is a naturally occurring substance that is found in the vines, roots, seeds, skins and stalks of grapes, peanuts, mulberries, the Japanese knotweed plant and several other plants. Resveratrol, along with other polyphenols including quercetin, catechins, gallocatechins, procyanidins and prodelphidins are extracted from grape seeds and skins and found in red wine. The most powerful polyphenolic antioxidant in red wine is resveratrol which activates the sirtuin enzyme system. Resveratrol increased the lifespan in several animal models by activating sirtuin-2 an enzyme linked to the benefits of caloric restriction which then extends the lifespan. *(Nature Rev Drug Disc 2006;8:493)* A single infusion of resveratrol can elicit neuroprotective effects on cerebral ischemia-induced neuron damage through free radical scavenging and cerebral blood elevation due to nitric oxide release. *(J Agric Food Chem 2006;54:3126)* Its anti-apoptotic activity suggests that resveratrol may minimize oxidative injury in immune-perturbed states and human chronic degenerative disease. *(Eur J Clin Invest 2003;33:818)* Resveratrol inhibits the oxidation of low-density lipoprotein (LDL) cholesterol, inhibits smooth muscle cell proliferation and inhibits platelet aggregation. Resveratrol also reduces the synthesis of lipids in the liver and inhibits the production of proatherogenic eicosanoids by human platelets and neutrophils. *(Nature 2004;430:686, Int J Mol Med. 2002;9:77, Eur J Clin Nutr. 2006; 60:4, Brain Res Brain Res Rev. 2006;52:316, Nutr Clin Care. 2000; 3:76, Eur J Pharmacol. 2007;554:196, Coron Artery Dis. 1997;8:645, Cardiovascular Res. 2000; 47:549)*

Since resveratrol is known to inhibit platelet aggregation and blood clot formation, individuals with bleeding disorders or taking anti-coagulant medications should consult their physician before using resveratrol supplements.

It takes approximately 41 glasses of red wine to equal the resveratrol in one 20 mg capsule.

**Take Home Message:**
Resveratrol is currently enjoying a lot of press but clinical trials need to be performed to validate the advantages as well as developing an efficient method for delivery to the intended end organs.

**Excellent Natural Sources:**
41 glasses of red wine per day.

**Cautions Regarding Potential Overdose Toxicities and Drug Interactions Associated With Supplementation**
While Over the Counter medications and supplements are perceived by most to be totally safe, there are several cautions that must be addressed. It has already been discussed that while zinc is critical to a high percentage of enzyme functions, excesses in zinc recommended by many for ARMD may actually precipitate the formation of early ocular signs of ARMD and is associated with an increase in genitourinary tract infections. Certainly logic dictates that patients on blood thinners must exercise caution with aspirin, but a number of supplements will also create both a negation or potentiation of the effects of blood thinners. For example, Vitamin E and Gingko Biloba which have blood thinning capacities should only be recommended with caution for patients taking blood thinners. Likewise, spinach which is an excellent source for lutein should be avoided in patients on blood thinners because the coincident presence of Vitamin K enhances coagulation. The following will summarize the potential toxicities of a number of supplements while highlighting as well interactions with other supplements and prescriptive medications:

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Benefit/Potential Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercitin</td>
<td>Antioxidant flavonoid preventing oxidation of LDL. With Vit E protects rod outer segments and RPE from lipoperoxidation. Modulates nitric acid production. Inhibits hyaluronidase.</td>
</tr>
<tr>
<td>Biotin</td>
<td>Assists in cell growth and metabolism and utilization of B complex vitamins.</td>
</tr>
<tr>
<td>Taurine</td>
<td>Amino Acid that is a potent antioxidant concentrated in the eye (RPE) to protect from damage, and it facilitates elimination of toxic debris in the eye RPE. Protects against excessive levels of glutamate. Has osmotic regulatory effect.</td>
</tr>
<tr>
<td>Vit B1/Thiamine</td>
<td>Cofactor in a number of enzyme systems. Enhances circulation.</td>
</tr>
<tr>
<td>Vit B2/Riboflavin</td>
<td>Involved in recycling antioxidants. Necessary for red blood cell formation and antibody production.</td>
</tr>
<tr>
<td>Vit B5/Pantethine</td>
<td>Production of energy and some hormones.</td>
</tr>
<tr>
<td>Vit B6/Pyridoxine</td>
<td>Important in the generation of nerve conduction and minimizes cardiovascular disease in some patients. Involved in more bodily functions than any other single nutrient. May cause neurological damage above 500 mg/day.</td>
</tr>
<tr>
<td>Vit B12/ Cyanocobolamin</td>
<td>Important in the generation of healthy red blood cells. Very important in overall metabolism of the retina and body. Protects against neurotoxicity of glutamate and nitric oxide.</td>
</tr>
<tr>
<td>Iron</td>
<td>Essential for red blood formation and function. A natural oxidant that can potentiate damage above 100 mcg. High serum ferritin levels associated with increased risk of myocardial infarct.</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Important in the generation of healthy red blood cells, and minimizes</td>
</tr>
</tbody>
</table>
cardiovascular disease in some patients. Important for healthy cell division.

<table>
<thead>
<tr>
<th>Element</th>
<th>Functions and Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boron</td>
<td>Involved in calcium metabolism.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Essential component of metabolism. Important in the maintenance of regular heartbeat and transmission of nerve impulses. Critical for muscle and bone growth. May inactivate oral antibiotics.</td>
</tr>
<tr>
<td>Chromium</td>
<td>Increases HDL which increases availability of antioxidants, lowers blood lipid levels, and is also thought to be important in blood glucose control.</td>
</tr>
<tr>
<td>Iodine</td>
<td>Critical in thyroid metabolism and enzyme formation.</td>
</tr>
<tr>
<td>Manganese</td>
<td>Critical in the formation of enzymes useful in ridding the body of oxidant radicals.</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Important in the formation of detoxifying enzymes.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Critical in metabolism.</td>
</tr>
<tr>
<td>Choline</td>
<td>Important in the maintenance of the health of the brain, nervous system and liver. With inositol protects cell membranes from hardening.</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>Slows the destruction of vitamin C, a powerful antioxidant.</td>
</tr>
<tr>
<td>Flaxseed and Fish Oil</td>
<td>Modulates the Immune System. May create gastrointestinal problems, acne and prostatic hypertrophy</td>
</tr>
</tbody>
</table>

**Exercise**

Exercise reduces IOP  *(Int J Neurosci 2006;116:1207)* and is sustainable. In another study it was shown that in persons with increased IOP, regular, moderately intense aerobic exercise rather than short-lived intense exercise is more useful. *(Int J Neurosci 2006;116:351)* Another study showed that exercise changes Ocular Perfusion Pressure and produces increased tissue blood flow in the retina in the immediate postexercise period, while blood flow increases more persistently in the choroid-retina. Difference in control of blood flow in these two regions may be related to stronger autoregulatory mechanism of blood flow in the retina. Nitric oxide may play a role in the regulation of blood flow. *(Eye 2006;20:796)* It is further confirmed the ocular hypotensive effect of strenuous exercise on the IOP and demonstrates that Pulsitile Ocular Blood Flow increases significantly after exercise. *(Optom Vis Sci 2003;80:460)*

A recent study points to the fact that following a regular exercise routine through middle age can delay biological aging by up to 12 years. In this study Dr. Shephard states that "Regular exercise substantially reduces the risks of obesity, maturity onset diabetes mellitus, hypertension, myocardial infarction, some forms of stroke, several forms of cancer and osteoporosis, not only in middle age but also during the retirement years. It is also helpful in rehabilitation following such critical incidents as a myocardial infarction.
or congestive heart failure. Regular aerobic exercise may have some impact on the likelihood of becoming blind because of a reduced risk of maturity onset diabetes mellitus, and catastrophic falls are less likely if regular aerobic exercise maintains muscle power, balance and coordination." A decline of 16% per decade in aerobic power is expected in older persons, resulting in greater risk for dependency. Exercise programs reduce the rate of decline in aerobic capacity and reduce the risk for dependency in elderly subjects. *(Brit J Sports Med. Published online April 10, 2008)*

Current recommendations call for adults to participate in at least 30 minutes of accumulated moderate-intensity physical activity on 5 or more days per week. However, less than one half of Americans meet this minimal goal. Clinician visits have significant potential to reduce this trend of inactivity because 84% of Americans visit a clinician annually. The average number of clinician visits per individual is 2.1 per year, and clinicians usually spend 1.5 to 3 minutes in health education and counseling during these visits.

The 5 A's (Assess, Advise, Agree, Assist, Arrange) counseling model can help primary care clinicians deliver brief, individually tailored physical activity messages to patients. "The Centers for Disease Control and Prevention, American College of Sports Medicine, U.S. Surgeon General, and American College of Preventive Medicine recommend that adults participate in at least 30 minutes of accumulated moderate-intensity physical activity (i.e., walking fast [3 to 4 miles per hour] or the equivalent) on five or more days of the week. The following are key principles for physical activity: (1) the more activity the better, (2) accumulated time is more important than intensity, (3) activity can be accumulated in 10-minute increments, and (4) lifestyle activities (e.g., substituting walking or biking for short car rides, using a push rather than a riding lawn mower) are more likely to be sustained than structured activities (e.g., exercising at a gym)."

Specific clinical recommendations for practice are as follows:

- Adults should take part in 30 minutes or more of accumulated moderate-intensity physical activity, such as brisk walking, on at least 5 days per week (level of evidence, B, based on systematic reviews of evidence from observational studies, with strong quality, quantity, and consistency of the evidence).
- Clinicians should advise their patients to meet recommended levels of physical activity (level of evidence, C, based on randomized controlled trials varying in quality and with short duration of follow-up).
- The 5 A's model should be used to counsel patients about physical activity (level of evidence, C, based on theory, observational studies, and randomized controlled trials of counseling regarding physical activity and smoking cessation).
- Expert advice from professional associations is conflicting with regard to medical clearance before patients with risk factors begin exercise programs (level of evidence, C).

Specific components of the 5 A's Model for Helping Patients Change Physical Activity Behavior are as follows:

- Assess: The type, frequency, intensity, and duration of current physical activity should be evaluated, as well as contraindications to physical activity, the patient’s degree of readiness for change, specific benefits to the patient, and their social support system and willingness to help others. Self-efficacy (or the patients’ level of confidence that they can change their physical activity level) should also be
assessed. The authors of the review describe tools that are available for the assessment of physical activity.

- Advise: The clinician should deliver a structured, individually tailored counseling message. Although the national recommendation is for 30 minutes or more of accumulated moderate-intensity physical activity on at least 5 days per week, this amount may be modified based on specific findings from each patient's assessment, as described above.

- Agree: The clinician should lead shared decision making based on the patient's stage of change. When the patient is not ready for change (pre-contemplation stage), the clinician should ask the patient for permission to discuss physical activity in the future. When the patient is thinking about changing (contemplation stage), the next steps should be discussed. In the preparation stage, the patient intends to change soon, so the clinician should assist the patient in planning and in setting a start date. In the action/maintenance stage, the patient is already meeting goals and should be congratulated, encouraged, and asked about his or her readiness to start another healthy behavior.

- Assist: The clinician should give the patient a written prescription for physical activity; printed support materials; a pedometer, calendar, and other self-monitoring tools; and Internet-based resources.

- Arrange: This phase of the model includes scheduling a follow-up visit, using telephone or email reminders, and using Internet-based counseling. Patients who are deconditioned, injured, or have co-morbid conditions affecting physical activity, such as arthritis or back pain, should be referred to a dietitian, physical therapist, or other specialists as appropriate. (Am Fam Physician. 2008;77:1029)

Exercise is also critical in the maintenance of weight loss regardless of the method to achieve the end (Arch Intern Med. 2008;168:1550), as well as being reported to be beneficial in protecting against premenopausal breast cancer reported to work through hormone-related mechanisms by reducing lifetime exposure to estrogen and its mitogenic effects. (J Natl Cancer Inst. 2008;100:728, Br J Sports Med. Published online May 13, 2008) Laughter yoga offers another method of stress reduction as well as offering potential for increasing overall health and oxygen perfusion. (American Society of Hypertension 2008 Annual Meeting; May 14, 2008; New Orleans, LA)

One of the methods of exercise even more beneficial regarding the metabolic syndrome has been described as aerobic interval training. The aerobic interval training (AIT) is described as a 10 minute warm-up at 70% of maximal heart frequency, four 4-minute intervals at 90% of maximal heart frequency, 3-minute active recovery at 70% of maximal heart frequency between intervals, and 5 minute cool-down. The AIT group compared to the continuous moderate exercise group demonstrated: (Circulation. 2008; DOI: 10.1161)

- Increased nitric oxide availability
- Improved mitochondrial biogenesis and excitation-contraction coupling, based on 138% increase in peroxisome proliferative-activated receptor γ coactivator 1α levels \( (P < .01) \) and 50% increase in maximal rates of sarcoplasmic reticulum calcium uptake \( (P < .05) \)
- 9% improvement in endothelial function, assessed by flow-mediated dilatation with high-resolution vascular ultrasound (vs 5% in CME group; \( P < .001 \))
- Improved insulin action in skeletal muscle and fat tissue, based on increased
insulin induced receptor phosphorylation
- Reduction of fatty acid transporter protein 1 levels in fat tissue
- Reduction of protein content of fatty acid synthase in white adipose tissue
- Improved fasting blood glucose levels
- Improved insulin sensitivity and beta-cell function, based on homeostasis assessment model analysis
- 25% increase in HDL cholesterol levels

Take Home Message:
Exercise is a critical aspect of any health pursuit. In addition to the cardiovascular benefits, one must realize that the immune system circulation is controlled by muscular activity. Lymph is pumped by activity. Without the comprehensive approach including exercise, health will not be maximized.

Special Topic - Sleep Apnea

Sleep Apnea, Normal Tension Glaucoma and Optic Neuropathy
There are three basic types of SLEEP APNEA, 1. obstructive (OSA) which occurs when throat muscles relax, 2. central-stroke or tumor of brainstem, heart disease-which occurs when your brain doesn’t send proper signals to breathing muscles, and 3. complex or mixed which is a combination of both. Obstructive SLEEP APNEA occurs two to three times more often in older adults and two times more often in men compared to women. It is estimated that over 11,000,000 Americans are affected, with up to 24% of Caucasian males and 9% of Caucasian females. (N Engl J Med 1993;328:1230)
Sleep apnea appears to affect African Americans more often than whites.

The link between glaucoma and obstructive sleep apnea (OSA) is a bit controversial but certainly offers a potential link. (Thorax 1982;37:845, Eur Jophthalmol 1997;7:211, Ophthalmology 1999;106:1009, Acta Ophthalmol Scand 2000;78:638, Ophthalmojologica 2000;214:115, Ophthalmologica 2002;216:180) Patients with OSA demonstrated significant 24-hour IOP fluctuations, with the highest values at night. CPAP therapy causes an additional IOP increase, especially at night. Regular screening of visual fields and the optic disc is warranted for all patients with OSA, especially those treated with CPAP (Invest Ophthalmol Vis Sci 2008;49:934) There are enough reports to create a potential link, and the investigation of normal tension glaucoma should include OSA. (Eye 2007; Advance online publication 4, Br J Ophthalmol 2007;91:1524) The other associations with OSA of non-arteritic ischemic optic neuropathy and papilledema also implicate some alteration occurring within the architecture of the optic nerve head. (Br J Ophthalmol 2007;91:1524) The alteration may either be pure, an association with blood flow or an association with increased cerebrospinal fluid pressure (CSFP). In patients under age 50 there is also a strong link between NAION and an underlying anomalous or small disc (92%) and an increased likelihood of involvement of the fellow eye. (Am J Ophthalmol 2007;144:953) One issue of primary concern is the fact that in our typical case history form, Sleep Apnea is often not addressed and we as clinicians are usually unaware of the condition.

SLEEP APNEA is a disorder in which breathing repeatedly stops and starts during sleep, usually 10 to 60 second interruptions. Apnea is Greek for “without breath.” While seemingly innocuous and more annoying to the bed partner than the patient, SLEEP
APNEA represents a genuine threat to both systemic and ocular health because of the associated compromise of oxygen flow to end organs.

**Signs and Symptoms**

Attention to the signs and symptoms of SLEEP APNEA are important in the practice of primary eye care. While the signs and symptoms may be mixed, the more common include:

- Excessive Daytime Sleepiness and Fatigue
- Trouble Concentrating
- Memory Loss and Forgetfulness
- Loud Snoring (Obstructive) With Gasps and Typically No Report of Dreams
- Observed (Usually by Partner) Episodes of Cessation of Breathing During Sleep- Often Obstructive
- Abrupt Awakening With Dry Mouth and/or Sore Throat- Often Central Causation
- Morning Headaches
- Difficulty Staying Asleep
- Irritability
- Rapid Weight Gain
- Mood and Behavior Changes
- Anxiety and/or Depression

**Causes, Related Systemic Conditions and Risk Factors**

SLEEP APNEA is usually associated with obesity but you don’t have to be obese to be afflicted. Related conditions include:

- **Neck Circumference over 17 Inches**
- Gastro Esophageal Reflux disease (50%) GERD
- Hypertension
- Inherited Narrow Airway
- Irregular Sleep Hours
- Polycystic Ovary Syndrome
- Alcohol or Sedatives Before Bedtime
- Smoking
- Nasal Congestion
- Asthma and Chronic Bronchitis
- Family History
- Diabetes
- Hypothyroidism
- Neuromuscular Disorders
- Sleeping at a Higher Altitude Than You are Used To

**Overall Take Home Message**

Maintenance of health does not occur in a vacuum. Each medical discipline seems to have a knowledge base in refereed journals regarding the importance of nutrition to cellular thus organ health. However each of these disciplines appears to be working in that very vacuum and not coordinating activities and advice to maximize patient health.

Unfortunately, the health care team does not concentrate on advice regarding total lifestyle modification. Diet is important relating to both obesity and proper consumption
of nutrients. Likewise exercise is critical. De-stressing is very important in the overall management of disease with the American Institute of Stress saying that “90% of all health problems are related to stress.” Laughter, humor, breathing exercises, contemplation, relaxation strategies, are all issues for de-stressing that will contribute positively to the maintenance of the immune system.