NUTRI NEWS

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Recent health and nutrition information from Douglas Laboratories *July/August 2003*

Zeaxanthin and Lutein – the Macular Pigments and a Review of Their Role in Eye Health

Dennis L. Gierhart, Ph.D.

INTRODUCTION TO EYE ANATOMY AND EYE PATHOLOGIES

As seen in Figures 1 and 2 (see page 3), the eye is a complex structure with exquisite structures to harvest, control, focus, and react to light to produce vision. The cornea and flexible, clear lens work to focus light on the retina and create a clear picture.

Light travels through the cornea and lens, and the liquid humors to the inner retinal layer where it passes through a nerve layer called the ganglions and Henle fiber layer to the photoreceptors and to a lesser extent the Retinal Pigmented Epithelium (RPE).

With time, the aging eye accumulates more photooxidative damage from its interaction with light. These events lead to two prevalent eye diseases: cataracts and age-related macular degeneration (AMD).

CATARACTS

Age-related cataract is the leading cause of blindness worldwide and the most costly item of the Medicare budget in the U.S. The prevalence and risk of cataracts increases significantly with age, from 5-10% of people under the age of 65 to 30-40% of people 75-85 years old. Women may have a slightly higher risk of cataracts than men. Other risk factors for cataracts include smoking, exposure to sunlight, diabetes, inflammation, and poor nutrition.

Cataracts develop when lens proteins are damaged, which causes them to become cloudy or opaque. Oxidative stress, principally from ultraviolet light is thought to play a crucial role in the development of age-related cataracts. The two most common types of age-related cataracts are called "nuclear" and "cortical" cataracts, according to their location.

In current practice, cataracts are allowed to develop until a patient's vision is severely impaired, at which time

Inside this issue

Clinical Protocols and Practice

"Nutritional approach enhances response to Statins in Severe Hypercholesterolemic Patient" presented by Robert H. Lerman, M.D., Ph.D. is a case study involving a 39-year old male patient on a low-fat, low-cholesterol diet and exercising daily experiencing difficulty controlling cholesterol via statin drug use. After reviewing labwork, the patient was started on a low-glycemic-index diet supplemented with flaxseed oil, evening primrose oil, chromium picolinate and later with fish oils. Within a month, blood lipids showed significant improvement, but did not normalize. Statin drugs were reinstated resulting in marked improvement in blood lipids, suggesting that correction of nutrition and fatty-acid abnormalities may assist greatly in resistant patients.

You may view this article in its entirety on the Douglas Laboratories website: www.douglaslabs.com.

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the cloudy lens is removed and an artificial lens is implanted. Cataract extractions are the most common surgical procedure performed in the U.S., at considerable expense for the public health care system (some estimates are up to 10 percent of the Medicare budget!) The National Eye Institute (NEI) estimates that there are greater than 1.7 million surgeries for cataract each year in the U.S. Epidemiologists have calculated that if the progression of cataracts could be delayed by ten years, the number of cataract extraction surgeries per year would be reduced by 45 percent.

AMD

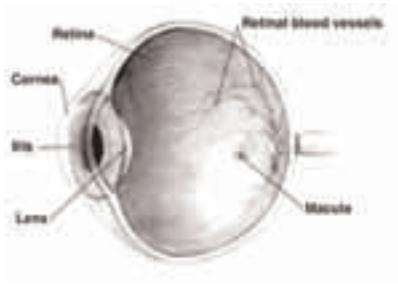
The second serious vision problem is age-related macular degeneration (AMD). AMD is the leading cause of acquired blindness and vision impairment among elderly Americans. It is estimated that up to 17 million elderly have at least early signs of this disease called, Age Related Maculopathy (ARM). These patients have early symptoms noticeable only by an eye exam. The NEI estimates that nearly 1.7 million elderly Americans have the more advanced stages of AMD and a new case is diagnosed every 3 minutes (up to 500,000 new diagnoses/yr) The prevalence increases with age affecting one in six Americans aged 55-64 rising to one in three in Americans over 75. Of the 1.7 million currently afflicted the most prevalent form is called Dry AMD accounting for nearly 85% of the cases.

Patients who are affected have gradual loss of central vision due to the death of photoreceptor cells (rods and cones) and their close associates; retinal pigmented epithelium (RPE) cells. Photoreceptors, the cells in the retina that actually "see" light, are essential for vision. RPE cells are like the nursemaids for photoreceptor cells

and are necessary for photoreceptor survival and functioning. Death of either of these cell types leads to death of the other. The cell death occurs in the macula. This is unfortunate because the macula contains the highest concentration of cone-type photoreceptors which are responsible for providing color and fine detail in the center of the visual field. Therefore, patients with AMD gradually lose their central vision, and with it the ability to drive, read, and see faces of loved ones. As bad as this may seem, it is a gradual process and is compatible with reasonable functioning for many years.

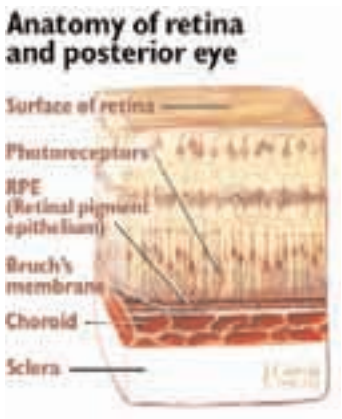
However, there is another aspect of AMD that is even more devastating. As the photoreceptor and RPE cells slowly degenerate, there is a tendency for blood vessels to grow from normal location in the choroid into an abnormal location beneath the retina.

Figure 1 - Diagram of the Human Eye



Source: http://www.nei.nih.gov/health/maculardegen/armd_facts.htm

Figure 2 - Diagram of the Human Eye



Source: http://www.wilmer.jhu.edu/mdp/retina.html

This abnormal new blood vessel growth is called choroidal neovascularization (CNV) or Wet AMD. This abnormal blood vessels leak and bleed, resulting in sudden and severe loss of central vision. Depending on the location, laser treatment can sometimes be given to destroy the blood vessels. New drugs are currently under development for the wet form.

When retinal cells are lost they are not replaced and central vision loss can be profound. Recently the NEI released a report of an intervention trial with dietary antioxidants that show promise for delaying the progression of late stage AMD (AREDS - Report #8, 2001). Two promising antioxidants, zeaxanthin and lutein, were not far enough along in development to be included in this NEI Trial. This review will explain why these two promising antioxidants are ready for major clinical intervention trials.

HISTORICAL PERSPECTIVE AND MAJOR DEVELOPMENTS

The macula lutea or literally "yellow spot" was first described in the eye in 1782 and speculation on its nature and purpose were rampant until 1945 when G. Wald and collaborators at Harvard tentatively identified it as lutein. Wald's more famous work (Nobel prize-winning) was elucidation of the chemistry behind the visual cycle of Vitamin A aldehyde (retinal) and rhodopsin (the visual pigment). Retinal was known to be produced from related plant pigments, or carotenoids, particularly beta-carotene. In this same time period the photoprotective role of carotenoids were being elucidated in bacteria and to a lesser degree in green plants. These series of events led to the first experimental supplementation trials in the late 1940s thru 1960s with supplements like sunflower extract (helenium or adaptinol). These early experiments

showed some effects with dark adaptation, night vision, threshold sensitivity, retinitis pigmentosa, various luminous and chromatic sensitivities, and visual acuity.

The modern era in this field accelerated in 1985 when a group in Miami (Bone & Landrum) determined that the macular pigment was composed of both lutein and the related carotenoid zeaxanthin. Two major events in 1994 were prominent in accelerating this field: the legislative passage of DSHEA (Dietary Supplement Health & Education Act) and publication of a seminal epidemiology study from Harvard linking high dietary consumption of lutein/zeaxanthin rich vegetables with reduced risk for wet age-related macular degeneration (AMD)

CHEMISTRY/BIOCHEMISTRY

Carotenoids are a family of 700 compounds found in fruits, vegetables and green plants and provide much of the color to the human diet (particularly yellows, oranges, and reds.) These colors reveal themselves in all their glory in the autumn when the green chlorophyll degrades revealing the beautiful colors of autumn leaf foliage.

Of these 700 colorful compounds only about 20 have been detected in human plasma and tissues. For this review we can divide the carotenoids found in humans into vitamin A precursors, like beta-carotene and the non-vitamin A precursors that have hydroxyl groups attached on the end-ring structure like the macular pigments, lutein and zeaxanthin (also called xanthophylls). See Table 1.

The unique structures of carotenoids (40 carbon long molecules along with centrally located conjugated double bonds) are responsible for their color spectra and their ideal performance as antioxidants that can quench free radical reactions. Lutein and zeaxanthin are remarkably similar in structure. While lutein and zeaxanthin have the same number of double bonds, zeaxanthin has 11 conjugated double bonds while lutein's eleventh double bond (10 conjugated) forms a more chemically reactive allylic hydroxyl end group. Conjugated double bonds are particularly effective at quenching singlet oxygen that produces Reactive Oxygen Species (ROS). A three dimensional view of zeaxanthin shows it to be a straight molecule that is able to easily transverse a biological cell membrane because of its hydrophilic end groups and lipophilic hydrocarbon chain. Lutein has a much more bent structure and one less conjugated double bond making it a poorer membrane antioxidant. Lutein is more prevalent in nature because of this bent structure. Lutein plays a prominent role in green leafs (and thus more prominent in our diet) because the bent structure makes it the perfect chemical molecule to fit into the three dimensional view of the photoreaction center of a chloroplast.

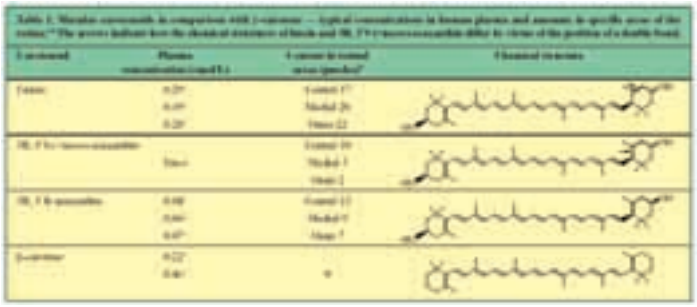
Lutein sitting in this structure is perfectly designed for its role in harvesting and transferring energy from light and supporting the chloroplast's generation of energy to support the plant cell.

Because of these differences in structures, lutein is probably 10-20 times more prevalent in the average US diet than zeaxanthin. Table 2 shows the content of lutein and zeaxanthin in fruits and vegetables. From this table it becomes obvious that dark green leafy vegetables contain high levels of the two pigments but the ratios of lutein/zeaxanthin are 20:1 - 40:1. Some non-green leafy vegetables like corn, oranges and orange peppers have lower total xanthophyll contents but higher ratios of zeaxanthin to lutein.

Dietary Intake. Determining the daily intake of lutein and

zeaxanthin is problematic because food composition databases often did not analyze lutein and zeaxanthin separately and comparisons of published data are often inconsistent. (See Table 2.) Despite many health agencies recommendation of eating at least five servings of fruits and vegetables per day, there remains wide variation in consumption among various human sub-populations. Lutein intake ranges are between 0.5 to 6mg/day with an average of probably 1mg/day. Zeaxanthin intake ranges are probably between 0.1 mg/day to 2mg/day with an average of probably 0.2 - 0.5mg/day.

Table 1 - Macular Carotenoids in Comparison with B-Carotene



Source: Schalch, W. (2002) Possible contribution of lutein and zeaxanthin, carotenoids of the macula lutea, to reducing the risk for age-related macular degeneration: a review. HKJOphthalmol vol.4 no.1.

Table 2 - Amounts of Carotenoids in Selected Plants

Source: Schalch, W. (2002) Possible contribution of lutein and zeaxanthin, carotenoids of the macula lutea, to reducing the risk for age-related macular degeneration: a review. HKJOphthalmol vol.4 no.1.

Dietary Gap. There are several major epidemiological studies attempting to link dietary carotenoid consumption with risks of AMD and cataract. This dietary gap between the low and high risks individuals equilibrated to around 6mg/day of lutein and zeaxanthin. These studies do not directly show causal relationship with zeaxanthin and lutein but rather a strong relationship with fruits and vegetables high in these xanthophylls. These data suggests that there may be a dietary gap of 4-5mg/day of these xanthophylls that could influence the risks of eye disease. This level of consumption probably relates to a daily dietary consumption for prevention or reducing the risks of eventual eye disease and might be a basis for a maintenance dosage.

These analyses do not address intervention in an ongoing eye-disease state. Perhaps, hints for appropriate xanthophylls levels may be found from the 2001 Age-Related Eye Disease Study (AREDS) reports. The AREDS trial is the largest eye-disease intervention trial completed to date. The AREDS intervention trial used dietary intervention levels of 7-15 times the normal recommended daily allowance (RDAs) of established dietary antioxidants. This dietary antioxidant combination reduced risks in advanced AMD but did not show statistical relevance in intervention of cataracts. Two cautions are relevant, however. Copper was added to the formula because of concerns about the high level of zinc used and concerns about high levels of beta-carotene became apparent during these trials when two unrelated intervention trials showed a significant increased risk of lung cancer with high doses of beta-carotene in smokers.

These analyses suggest that while caution should be exercised, doses significantly greater than average daily intake should be considered for intervention in the disease process.

ABSORPTION (BIOAVAILABILITY) TRANSPORT, AND TISSUE DEPOSITION

Unlike the pre-vitamin A carotenoids, lutein and zeaxanthin are absorbed and transported like other lipids.

Briefly, lutein and zeaxanthin or their corresponding diesters are released from their food or supplement matrix. This first step may be extremely important and unfortunately continues to be ignored by many researchers. Bioavailability is affected by many factors, but the matrix it is presented in must address numerous stability issues and other factors that influence absorption. Some major issues that effect bioavailability include;

- Stability to digestive tract and storage conditions
- Binding by macromolecules like fiber and protein
- Presence or absence of fats and its ability to stimulate bile salts release and presence of pancreatic lipase
- Malnutrition factors
- Food processing to reduce particles size or mild heating to release xanthophylls from macromolecules or "cell wall trapping"
- Presence of competing carotenoids

It cannot be overstated how important bioavailability is to carotenoid nutrition. There are several reports of bioavailability of xanthophylls from both food matrixes and supplements of less than 5%. This means a consumer may believe they are ingesting 10 mg of lutein or zeaxanthin and actually only absorb 0.5 mg. For this reason it is important that you buy carotenoids for the eye from reputable companies.

The xanthophylls, upon release from the food/supplement matrix, are transferred to lipid micelles that contain other lipids and bile salts. The micelle is taken up by the intestinal mucosal cells and diffuses through cell membranes and is released to the other side of enterocytes. Esters of the xanthophylls are hydrolyzed by gut lipases and possibly at the intestinal lining. Because xanthophyll esters are hydrolyzed upon entering the intestine, nutritionists consider them equal on the actual mole/wt. basis. The free xanthophylls are transferred into chylomicrons and transported to the lymph system and with action of lipoprotein lipase are eventually taken up by the liver and are either stored or transferred to VLDL and then LDL and HDL particles. Xanthophylls are widely distributed among the lipoproteins and on the surface of these complexes where they may play an important role in protecting the lipoproteins from oxidation and subsequent atherosclerotic lesions.

Tissue Distribution. While the liver packages xanthophylls for blood transport, it is also a major deposition organ. The other major "sink for xanthophylls" is adipose (fat) tissue. Both tissues may "compete" with the eye for the xanthophylls. Several human surveys have demonstrated an inverse relationship between Body Mass Index (BMI) and lowered macular levels of pigment

Several animal studies and at least one human volunteer study have shown lutein to be deposited in adipose tissue greater than zeaxanthin, and there is a greater "retinal capture efficiency" for zeaxanthin over lutein (4:1). The xanthophylls also deposit broadly in many other organs but are particularly high in adrenal, kidney, breast, prostate, and eye.

Eye Tissues. The highest concentration of xanthophylls in the entire human body are in the macula region of the retina, in fact so high that they give this tissue its name macula lutea or yellow spot. These two xanthophylls are also found in the lens and Uveal bodies including ciliary body, iris, and, most importantly, the retinal pigment epithelium (RPE) and choroid. The levels in the macula

are at 500-1,000 times greater in concentrations than any other tissue in the body. This very dramatic and compelling fact first grabbed scientists' attention and provides an intriguing hint that nature has a purpose for macular pigments in eye health. There is a 10-15 fold difference in human sub-populations in the natural concentrations of the macular pigment in the inner retinal layer (0.05 - 1.0 pmole/mm2). In the lens, the xanthophylls are about 10 times higher in the epithelial/cortical layer than the nuclear layer (44 vs. 4 ng/g lens wet weight). This represents orders of magnitude less than the retinal tissues.

Within the retina, a significant portion of the xanthophylls reside in the Henle's Fiber, a layer of axons in the inner retinal layer where xanthophylls can filter light prior to light striking photoreceptors (rods and cones) and the very important RPE cells. This location would suggest a strong role for the xanthophylls filtering damaging light (particularly the most damaging blue part of the spectrum). The xanthophylls are also found in the Rod Outer Segments suggesting a very strong membrane ordering and antioxidant role. Finally, the xanthophylls are found in the RPE cells where they may have multiple functions (see insert on eye anatomy).

The distribution of macular pigment is another strong biological hint that there is a role for xanthophylls in retinal health. As can be seen in Table 1 the macular pigment is highest in the exact center of the macula where dietary zeaxanthin and a related isomer, meso-zeaxanthin, dominate. In the peripheral retina, lutein dominates by 2-3 fold. The central sparing evident in AMD is the current theory that suggests that high macular pigment protects the portion of the macula with the highest exposure to photooxidative insult. Very high metabolic rates found in the fovea require extra antioxidant protection. AMD pathology often starts at the edges of the macula where macular pigment concentrations start to decrease. Analyses of cadaver eyes have shown this direct link by analyzing macular pigment concentrations at distances from the center of the macula between AMD eyes and normal control matched eyes. In these experiments, there is a significant drop in pigment concentration at the edges of the fovea in AMD eyes.

To summarize, the eye concentrates just three xanthophylls, dietary zeaxanthin, non-dietary meso-zeaxanthin and lutein in the macula (and other ocular tissues.) While there are 16-20 carotenoids in the blood serum, only two are selected for deposition and hyper-concentration in the eye. This highly selective process is the most specific distribution in the entire field of carotenoid biochemistry.

Non-Dietary or Meso-Zeaxanthin. This isomer is not found in the human diet or blood serum and is currently believed to be biotransformed from lutein. Levels of this isomer also have a specific spatial distribution. Why does this biotransformation take place only in the eye and nowhere else in nature?

There are currently three theories to explain this rare phenomenon:

a) Biological artifact

b) Reaction product of photooxidation

c) A highly specific ocular-tissue specific enzyme based reaction to transform the more prevalent xanthophyll, lutein, into a compromise structure closer to the structure of dietary zeaxanthin.

This specific biotransformation converts the bent structure of lutein by migration of a double bond. Thus, meso-zeaxanthin has a three-dimensional structure closer to the non-bent or straight structure, dietary zeaxanthin. The meso-zeaxanthin would again have 11 instead of 10 conjugated double bonds making its antioxidant strength closer to dietary zeaxanthin. This would mean the eye specifically works to create a compromise structure from the more abundant lutein (lutein is 5-10 times more abundant than dietary zeaxanthin in the blood and 10-20 times more prevalent in the diet.). This selective uptake of zeaxanthin over lutein has also recently been shown in the human brain. In this neural tissue, zeaxanthin and lutein occur in approximately equal ratios once again. This effect has also been seen in primates and the animal model, Japanese quail.

This selective deposition of high concentration of strong antioxidant in the center of the macula has also been demonstrated for vitamin E and selenium ("other important dietary antioxidants"). This high concentration of several antioxidant systems in the fovea or center of the macula, along with the presence of the rare xanthophyll, meso-zeaxanthin, have led some scientists to wonder whether it would be possible with dietary zeaxanthin supplementation to extend the deposition of this more powerful antioxidant to a broader or wide area, thus protecting the edges of the macula where atrophy or pathology often starts. This was not feasible until zeaxanthin became available as an individual ingredient in 2002.

EPIDEMIOLOGICAL STUDIES LINKING DIETARY OR SERUM LEVELS AND RISK OF AMD OR CATARACTS.

Before discussing these results, the reader should know of three inherent problems in this area. In dietary studies, the subjects are attempting to recall broad dietary histories on questionnaires, and then dietary intakes are calculated from inconsistent food composition tables. Can you recall how much of what fruits and vegetables you ate last year? Early studies focused on beta-carotene and not the xanthophylls, and the separate analyses of foods and serum for lutein and zeaxanthin has only recently been initiated. In addition, blood serum analyses are a measurement of a transient and highly variable analyate. Xanthophylls can rise several fold in the serum and then drop to baseline in one day. This is analogous to trying to interpret a film from one still shot taken from a movie.

To summarize, the relationship between serum levels of the xanthophylls and AMD and cataract appear to be inconsistent and researchers are now hoping that Macular Pigment Optical Density (MPOD) measurement may be a better way of assessing tissue history of xanthophyll long-term intake.

At first glance, dietary intake based epidemiological studies also appear to be inconsistent, however, when studies are segregated by studies that had quintiles of sub-populations with very low consumption of xanthophyll containing foods are compared versus quintiles of people eating very high consumption of these same foods, a strong consistent pattern emerges. In populations consuming foods containing approximately 6 mg xanthophylls/day (lots of fruits and vegetables, particularly dark green leafy, the risk reductions are very strong.

These very consistent studies showed lower risk for prevalence of nuclear cataracts, cataract extractions, lens opacity and AMD, particularly wet AMD. Unfortunately while these were strong and compelling studies, all of them only show

(Continued on Page 10)

ADVANCEMENTS IN ANTI-AGING MEDICINE

By Dr. Robert Goldman and Dr. Ronald Klatz

Welcome to the Ageless Society

In 1993, we convened a meeting of a group of a dozen physicians that, nearly a decade later, has profoundly changed the course of preventive medicine. Recognizing that scientific research was quickly making important discoveries towards identifying the mechanisms of deterioration and vulnerability to age-related diseases, we introduced a new definition of aging. In this new perspective, the frailties and physical and mental failures associated with normal aging are caused by physiological dysfunctions that, in many cases, can be altered by appropriate medical interventions. As a result of this meeting, an innovative model for healthcare was proposed that focused on the application of advanced scientific and medical technologies for the early detection, prevention, treatment, and reversal of age-related dysfunction, disorders, and diseases. "Anti-aging medicine" was born.

Since then, anti-aging medicine has achieved international recognition and is now practiced by thousands of physicians in private medical offices as well as some of the most prestigious teaching hospitals around the world. Many medical schools now include anti-aging in their curriculums and health practitioners attend continuing medical education sponsored by the A4M. Anti-aging medicine is now being embraced as a viable solution to alleviate the mounting social, economic, and medical woes associated with the aging of nearly every nation on the planet.

When we rang in this new millennium, we also shattered previous records for life expectancy. Since 1950, average life expectancy worldwide has increased by twenty years, and now stands at 66 years. By 2050, the UN projects steady increase in life expectancies for all countries: worldwide, life expectancy will stand at 76 years.[1] Eventually, lifespans of 120 years may be the norm, and the oldest and healthiest of us may not start feeling past our prime until age 100. We will all be citizens of The Ageless Society. Through this regular column in *NutriNews*, we hope to provide insight on this fast-growing clinical specialty, so you may subsequently empower your patients to enhance and extend their lives and achieve maximum peak performance.

The following are but a few of the recent and most notable nutritional advancements in anti-aging medicine:

Coenzyme Q10 Slows Progression of Parkinson's – Results of a recent study presented at the annual meeting of the American Neurological Association suggest that coenzyme Q10 could slow down the progression of Parkinson's disease. Lead researcher Professor Clifford Shults of the Univ. of California in San Diego and his colleagues enrolled 80 Parkinson's patients, all of whom had early-stage Parkinson's, and did not yet need levodopa. The patients were randomly assigned to a treatment with 300 - 1200 mg/d of CoQ10, or an inactive placebo. After eight months of treatment patients who had received the highest dose of CoQ10 were fairing significantly better than those given the placebo and exhibited a 44% reduction in disease progression, compared with the placebo group. Even patients treated with the lowest CoQ10 dose were more able at carrying out simple daily activities and demonstrated better mental functioning and mood. The findings suggest that Q10 slows the progression of the neurodegenerative disease; although Shults stresses that his research is not conclusive proof as the study group was relatively small. He also believes that it would be "premature" to recommend the supplement to people with the disease.

SOURCE/REFERENCE: Archives of Neurology 2002; 59:1541-1550

Vitamins C and E Protect Arteries – Taking vitamin C or vitamin E could help to keep your arteries healthy, say researchers from Johns Hopkins University in Baltimore. Dr. Han-Yao Huang and colleagues got participants to follow one of four daily regimens in order to determine what effects the antioxidant vitamins C and E have on lipid oxidation, a process thought to play a key role in the development of the arterial disease atherosclerosis. Participants took either 500 mg of vitamin C alone; 400 I.U. of vitamin E alone; both vitamins together; or an inactive placebo for 2-months. Results showed that both vitamin C and E lowered urine levels of a by-product of lipid oxidation, however taking both vitamins at once was no more beneficial than taking either vitamin alone. The researchers also note that the daily dose of vitamin C used in the study is easily achievable by eating vitamin C-rich foods, however it would be "virtually impossible" to consume the dosage of vitamin E through food alone.

SOURCE/REFERENCE: American Journal of Clinical Nutrition 2002; 76:549-555

Dietary Supplements Restore Rats Youth – Researchers at the Univ. of Berkeley found that rats given acetyl-L-carnitine and alpha-lipoic acid performed better on memory tests and had higher energy levels. Tests also revealed that their mitochondria (energy-producing cell organelles) worked more efficiently. The effect of the supplements on the rats was so dramatic that many researchers were surprised by the results. An increasing body of evidence is indicating that the deterioration of mitochondria plays an important role in aging, thus these researchers believe that they can rejuvenate cells by preventing this deterioration caused by free radicals.

SOURCE/REFERENCE: Reported by www.eurekalert.org on the 18th February 2002

Dr. Robert Goldman and Dr. Ronald Klatz are the physician co-founders of the anti-aging medical movement and of the American Academy of Anti-Aging Medicine (A4M; Chicago, IL USA; www.worldhealth.net), a non-profit medical organization dedicated to the advancement of technology to detect, prevent, and treat aging related disease and to promote research into methods to retard and optimize the human aging process. A4M is also dedicated to educating physicians, scientists, and members of the public on anti-aging issues.

1 "World population prospects: The 2000 revision—highlights," (ESA/P/WP.165), Population Division, Department of Economic and Social Affairs, United Nations, 28 February 2001.

a direct link with the fruits and vegetables (not distinctively the xanthophylls) and reduced risks of eye disease.

The ability to influence the concentration of the xanthophylls in the target eye tissues is an important piece of evidence that the target organ is responsive to modification. There are now numerous studies showing the desired dose response. Macular Pigment Optical Density can be measured indirectly and non-invasively by at least six different techniques. A discussion of measurement techniques is beyond the scope of this review and has been subject to some criticism on reproducibility. No non-invasive technique is currently available to measure lens pigment content in-vivo. The MPOD human volunteer supplementation trials can be summarized as follows:

- Both foods and supplements containing lutein and zeaxanthin are capable of raising retinal levels of the xanthophylls in most, but not all volunteers. The reason for non-responsive volunteers is not yet delineated (measurement artifact or truly physiologically non-responsive)
- The retinal response is very slow relative to blood serum response (months versus days) but appears to remain stable for months upon cessation of supplementation. This suggests that an intervention dosage may be significantly higher than a preventative or maintenance dosage.
- There appears to be a relationship between peak serum levels and ability to increase MPOD suggesting high dietary intake may raise retinal levels faster and more effectively.
- There are factors other than peak blood serum levels that appear to affect the ability to increase MPOD. These include many of the risk factors for AMD but may also include genetics, obesity, and other serum or retinal transport/binding proteins for the xanthophylls.
- There has been only one small trial to date directly comparing lutein's and zeaxanthin's ability to influence MPOD in humans where bioavailability was directly controlled (Garnett, et. al. 2002). In this trial, blood serum responses were equal but more individuals retinally responded to zeaxanthin.

We can conclude that for most people the retina does accumulate xanthophylls upon supplementation. While the human lens contains the xanthophylls, there is little else known about the responsiveness of human lens. The first report of dietary manipulation of lens xanthophylls content in an animal model was reported this year.

EXPERIMENTAL EVIDENCE IN ANIMALS

The first experiments in animals were completed in 1980 when a group depleted a primate's (macaque monkey) diet of xanthophylls for three years. Upon examination of the excised retinas, many AMD-like pathologies were seen including lipofuscin accumulation, abnormal cones and RPE abnormalities.

The Japanese quail were studied in the latter part of that decade by Fite et. al. and was picked up in the mid-1990s by Dr. K. Dorey and colleagues at Schepens/Harvard Medical School. The quail contain a cone-rich retina, forms drusen, and show other symptoms similar to those of AMD in humans. In addition, they accumulate the macular pigments selectively from their diet. The Schepens' team carried out extensive light damage and aging studies by manipulating the diet of the

birds such that their retina contained little, normal, or high levels of zeaxanthin. These series of studies for the first time directly demonstrated experimentally that retinal zeaxanthin dramatically, and in a dose related manner, protects rods and cones from light damage. In addition to these conclusions, the Schepen's team also demonstrated that beta-carotene did not show positive effects in this animal model of light damage.

- The protection was mediated by reduced apoptosis of both types of photoreceptors and slowed both the rate and total amount of cell death.
- Showed positive or protective effects in the aged quail like basal membrane thickening
- Prevented the migration of destructive glial cells into the retina
- Demonstrated that adipose and liver tissue compete with retina for serum xanthophylls and that the "retinal capture" efficiency for zeaxanthin over lutein is about 4:1
- The quail lens xanthophylls content can be increased by up to five fold by dietary manipulation.

In 2002, a number of the researchers involved with first primate studies repeated the light damage experiments using a blue laser in monkeys. This group supplemented directly with lutein or zeaxanthin for six months. The researchers concluded that zeaxanthin was more photoprotective than lutein by gross size and number of lesions and that the greater spread of lesions in the lutein-fed monkeys suggested a free-radical mechanism. While primate research is probably the most appropriate animal model for studying xanthophylls and eye health, it is very expensive and time consuming. We can expect more results to come in from experiments with Japanese quail.

Small clinical intervention trials have been initiated with lutein supplements. In 2002, Richer, et al. described the results of a prospective, 12-month, placebo controlled, double-blind, crossover trial with lutein supplementation in 90 male veterans with atrophic AMD. With lutein supplements of 10 mg/day there were significant concurrent improvements in visual function including glare recovery, contrast sensitivity, and distant/near visual acuity. Video documentation of patients' symptoms pre and post treatment were consistent with objective data. The addition of other antioxidants provided an added improvement with contrast sensitivity. This study confirmed again that AMD is a nutrition-responsive group of multi-component pathologies.

In 2001, an Italian group presented the effects of a lutein/zeaxanthin supplement at 18 months in a three-year, single-blind, placebo-controlled, randomized, parallel group study of 50 early stage AMD patients. At 18 months, the study was showing marginal but measurable improvement in visual acuity and drusen progression.

Most recently, in 2002, a Spanish group investigated lutein in 17 cataract patients in a double-blind supplementation trial with lutein ± alpha tocopherol. These 15 mg doses three times per week for two years showed significant improvements in visual acuity and glare sensitivity in people with age-related cataracts.

These small intervention trials are showing promising results in an early stage of the disease with visual functions important to the patient and their view of symptoms. The reports are consistent with individual reports and accounts from patients. The definitive result for the FDA is likely to be statistical relevance in a functional end-point (visual acuity, three lines of improvement). The ophthalmology

community will wait for definitive improvements in visual acuity coupled with significant improvements in fundus photograph grading and other acceptable gross pathology improvements including area of atrophy and lack of neo-vascularization.

ADDITIONAL EVIDENCE FOR A PROTECTIVE EFFECT OF THE MACULAR PIGMENTS IN EYE DISEASES

While there are several major clinical intervention trials in early stages of execution, the critical, convincing evidence for the ophthalmology community is not yet in. In the absence of this clinical evidence, a critical systematic evaluation of other evidence is warranted. For this review, the Mares-Perlman 2002 modification of Hill's classic guideline for linking causal relationships between environmental factors and disease state will be used. In addition, a short summary of interesting ancillary evidence will also be listed.

1. Biological Plausibility. Evidence that a valid, scientific theory for ocular protection is consistent with and backed up by evidence from animal or cell culture experiment is very important. Good correlation between experimental theories and actual observations in cell culture, animal models, or humans greatly enhances the validity of a concept. There are currently two leading theories of how lutein and zeaxanthin may protect the eye, the UV-blue light filtering, and the antioxidant mechanisms. Neither mechanism is mutually exclusive nor the only possible mechanism.

a. Antioxidants. Both lutein and zeaxanthin are capable of quenching free-radical reactions that create Reactive Oxygen Species (ROS) that then react with cell membranes and macromolecules to create pathogenesis leading to many human degenerative conditions. In the eye tissues, these oxidative processes can be further enhanced due to the presence of light (which accelerates photooxidation), extremely high metabolic rates (retina) and by the highly poly-unsaturated lipids found in the retina and other neural tissues. Both singlet oxygen and peroxyl radicals are likely generated in eye tissues and quenched by the xanthophylls. Light-driven photooxidation likely generates excited triplet state species that also causes severe oxidative damage. It is firmly established that plants use lutein to dissipate excessive photon and heat energy from the reaction center. However, under very stressful or high light exposure conditions, plants use the "zeaxanthin cycle" or even zeaxanthin directly to protect the plant cell. As stated earlier, zeaxanthin is a better antioxidant and is more directly embedded in a manner to protect cell membranes than lutein. Xanthophylls are particularly effective at lower oxygen tensions (concentrations) like the interior of a cell membrane or the center of lens tissue. The tocopherols are more effective at higher oxygen tensions, and, thus, it is highly likely the two lipophilic antioxidants are synergistic and complement ascorbates and the metal containing enzyme-based antioxidant enzymes that are active in ocular tissues for protection against oxidative damage.

b. UV and Blue Light Filtering. The xanthophylls are also excellent light filters and absorb that part of the UV and blue spectrum thought to be most damaging to the eye. In the lens, the xanthophylls absorb the U.V. light thought to be a principal oxidative stress that results in cross-linking of the component crystallins that in turn reduces the clearness of the lens. The lens xanthophylls would also reduce the amount of blue light reaching the retina. The absorption of blue light in the lens and from reflection in the retina would reduce light-scatter and

chromatic aberrations. This would suggest a more direct role in reducing visual effects like glare and starburst effects seen in early stages of these diseases. This blue light filtering may directly reduce the photooxidation in the susceptible axons (Henle fiber) and likely reduces photooxidative damage directly in the photoreceptors and posterior RPE cells that support and maintain the photoreceptors. Besides antioxidant and UV-near blue light filtering protective mechanisms there are other plausible mechanisms possible. Because eye diseases have multi-factorial causes, it is reasonable that xanthophylls may intervene in other possible routes to pathogenesis. These are listed below:

c..Xanthophylls and Other Plausible Biological Mechanism for Preventing Eye Disease

i. Reduced Drusen Accumulation. The progression of drusen, a lipid rich compound observable in eye exams, is a major AMD biomarker.

ii. Inflammation. Inflammatory responses have been implicated in AMD pathology possibly through ROS production. Carotenoids have been inversely related in epidemiological studies to the inflammation biomarker, c-reactive protein.

iii. Cell to Cell Communications. Xanthophylls can modify communications between cells through modification of gap-junction proteins. Zeaxanthin is, perhaps, the only natural molecule that could directly link the inside of a cell to the outside of a cell membrane. Could they modify communications between RPE cells and photoreceptors?

iv. Gene Expression. Xanthophylls can modify gene expression and have been postulated to be an internal "Red-ox indicator."

v. Apoptosis (programmed cell death). Zeaxanthin has been directly shown in animal models to directly slow and/or prevent apoptosis of photoreceptors presumable by interfering upstream from the genes and cell signals responsible.

vi. Lysosomal Stability. By stabilizing lysosomal membranes, xanthophylls may allow natural clean-up processes to proceed.

vii. Membrane Ordering. The membranes in ocular tissues consist of highly polyunsaturated lipids. While xanthophylls clearly provide antioxidant support, these membranes would be highly fluid.

3. Consistency of Protective Effect in relationships across human population and among various studies.

About the Author

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4. Temporality. The evidence for the protective effect of the xanthophylls is strengthened when the development of the eye diseases are measured before, during, and late in the disease state. Such evidence rules out the possibility that diet, serum, or eye levels are a consequence of the disease and not an antecedent or preventative effect. This data is provided by prospective epidemiological and clinical intervention data.

5. Strength of Relationship Between Xanthophyll Intake and Risks for Eye Disease. Strong relationships are indicated by large odds rations or relative risks and consistent findings lower the likelihood of the observations being artifacts.

6. Specificity of the Relationship of Xanthophylls to Eye Disease. This evidence, gathered from large prospective studies, rules out that the relationship is some other non-causal effect like other lifestyle, environmental or other dietary effects. This is difficult data to generate.

SAFETY AND RISK/BENEFIT RATIOS.

While the benefits of dietary consumption of lutein and zeaxanthin are becoming increasingly evident, what is known about their safety profile? Both compounds have been in the U.S. diet for a long time, and Average Daily Intakes (ADI) look to be between 1 and 6 mg/day.

Lutein supplements have been on the U.S. market since 1995-96 without reports of adverse effects. Recently, several companies have completed GRAS self-affirmation processes for lutein and lutein-esters to extend the uses into food fortification.

A review of the safety of zeaxanthin shows that there is an adequate technical basis for safety assessment. Acute studies show an LD50 greater than 8,000 mg/kg. Sub-chronic (90 days) show no toxicity at 1,000 mg/kg/day. These studies in five species of animals showed a NOAEL (no adverse effect level) for a 60 kg human of 1,200 mg/day.

These same safety criteria were also established for maternal, fetal, or teratotoxicity. Mutagenicity testing in multiple batteries of microbial tests was also negative. The extensive safety review shows no adverse effects.

Currently, there are promising benefits possible from increased consumption of lutein and zeaxanthin. The safety margin for consumption is excellent. The safety (risk) benefit is strongly in favor of increased usage.

SUMMARY

There are well-supported, biologically plausible mechanisms to support a role of the xanthophylls in eye protection with good recent support from two animal models. The consistency of epidemiological data of high-dietary intake of xanthophyll rich fruits and vegetables, reducing the risks of AMD and cataracts is good, but from these studies, it cannot conclusively be proven that it is the xanthophylls in the fruits and vegetables. The association of lowered MPOD and risks of increased AMD and cataracts is very compelling, but does not substitute for a major controlled double-blind intervention trial, which is still needed. The most compelling facts from the author's perspective below:

- The major human eye tissues use the same two xanthophylls to the exclusion of all others that the plant world uses to harvest light and protect against excess levels.
- The macula selectively concentrates these two xanthophylls up to 1,000 times higher concentration in

the macula than anywhere else in the body.

- The macula selectively places zeaxanthin in the center of the macula where the greatest protection is needed and which is last to degenerate and converts the more abundant lutein into a structure similar to dietary zeaxanthin.
- The lens also accumulates zeaxanthin and lutein even though it is one of the most metabolically inactive tissues in the body.
- A biologically plausible theory for protection has been elucidated and is backed up by direct experimental evidence in an animal model.
- The concentration of xanthophylls in the target organ (retina) can be increased by dietary manipulation.
- The evidence from epidemiological studies is relatively consistent in that high dietary intake of xanthophylls-rich fruits and vegetables reduce the risks of AMD, lens opacity, onset of cataracts and risks of cataract extraction.
- The MPOD is inversely related in most sub-population studies to major risk factors for AMD and cataracts.
- The 2001 AREDS results demonstrated that other dietary antioxidants can intervene in the late stages of AMD, significantly increasing the credibility of one of the theorized protective mechanisms.
- Early results from small human studies are consistent with a protective effect, but not yet conclusive.

A final report from patients may hint at another eye health benefit. Since the introduction of zeaxanthin supplements, customers are reporting back that within 60-90 days, people with extreme sensitivity to light are reporting decreased sensitivity. This decreased sensitivity may relate to reduced glare sensitivity. Clinical trials with zeaxanthin supplements in chronic-light-hypersensitivity are now being planned.

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Resources:

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ZeaVision – http://www.zeavision.com

American Academy of Ophthalmology – http://www.aao.org/

Association Fighting Blindness – http://www.afb.org/

American Optometric Association – http://www.aoanet.org/

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