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FREE RADICALS, ANTIOXIDANTS AND EYE DISEASES.

NOT AS INCURABLE AS WE ONCE THOUGHT.

Our ability to see is made possible in part by the fact that our eyes allow light to pass through with relative ease. This makes the eye the most susceptible organ to oxidative damage caused by light, toxins (smoke), atmospheric oxygen, and abrasion. In the United States, age-related macular degeneration is the leading cause of blindness for persons over 60 years of age. Cataracts are still the leading cause of visual impairments in the U.S., resulting in the highest portion of the Medicare budget, consuming $3.2 billion annually. Both of these diseases have been shown to be a direct result of accumulated oxidative damage. Unfortunately, except for the replacement of opaque lenses, there is no treatment for either of these conditions. We hope to show here that through diet and the generous use of certain antioxidants you can help your patients greatly reduce and possibly reverse the oxidative damage that leads to Age-related Macular degeneration (ARMD) and cataracts.

Macular Degeneration

The macula is the central portion of the retina responsible for acute and detailed vision. In the central portion of the macula, called the *fovea centralis*, the innermost layers of the retina are displaced to one side allowing light to pass unimpeded to this portion of the retina. This allows for increased visual acuity, but also increases the possibility of light induced damage to this area of the retina. Macular degeneration is characterized by a gradual loss in central acuity and the presence of drusen (bumps) in the macula. This is commonly called the "dry" form, and constitutes about 90% of the cases of macular degeneration. The other 10%, called "wet" form, is characterized by rapid loss of central acuity, neovascularization, and vessel leakage. "Wet" ARMD is treatable with laser therapy, while "dry" ARMD is considered untreatable.

As ultraviolet and blue light pass through the retina to the photoreceptors (rods and cones) and the pigmented epithelial (PE) cells, reactive oxygen species are generated. The conversion of this light energy into a nerve impulse by the photoreceptors generates more free radicals. Typically, these free radicals are reactive oxygen species such as hydrogen peroxide, superoxide and hydroxyl radicals. These reactive molecules are quick to grab electrons from surrounding molecules to add to their unpaired electrons. This is fine when the surrounding molecules are one of the many antioxidants in the eye, which are able to quench free radicals without themselves becoming free radicals. If instead the electron is taken from one of the lipids in the photoreceptor membranes (stacks of memranous discs that are rich in polyunsaturated fatty acids), lipid peroxidation cascades through the photoreceptor outer segments. These may be subsequently quenched by vitamin E or other lipid soluble antioxidants, or they will continue to damage the integrity and fluidity of these membranes.

When photoreceptor membranes become damaged, the outer portion is sloughed off into the PE cells, and new discs are regenerated. PE cells are equipped to phagocytize, digest and recycle these compounds under normal conditions. However, when these molecules have been modified by oxidation of their unsaturated bonds, they are not easily digested by the lysosomal enzymes. The result is a build-up of undigested molecules in the PE cells called lipofuscin granules. When a sufficient amount of lipofuscin has accumulated, the PE cells deposit these granules resulting in a bump between the pigmented epithelial cells and choriod. This bump is called drusen (German: "bumps"). This physical and metabolic

Edited By:
Thomas G. Guilliams Ph.D.

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separation of the PE cells and the photoreceptors from their blood supply in the choroid results in damage to the photoreceptors and eventually macular degeneration (See Figure 1 and 2).

A case-control study was performed to determine the risk factors associated with ARMD. They found these risk factors, reported with their odd ratio: arterial hypertension (OR=1.28), coronary disease (OR=1.31), hyperopia (OR=1.33), and lens opacities or previous cataract surgery (OR=1.55) (3). Those individuals who are aphakic (have had their lens removed) were 4.6 times more likely to have ARMD (4).

Cataract

A cataract is a lens that limits the transmission of light to the retina because it has become opaque. The incidence of cataracts in persons 65-75 years range from 21% in white men to nearly 40% in black women (2). Overall, this effects nearly 10 million Americans, resulting in 600,000 lens replacement surgeries per year in the United States. A number of factors contribute to the development of cataracts, these include congenital defects, trauma, age, and metabolic or toxic agents. By far the two most common factors would be age (often called senile cataracts) and disorders of carbohydrate metabolism (especially diabetes).

Proteins in the lens are unusually long lived and are thus subject to extensive and accumulated oxidative damage. The damaged proteins accumulate, aggregate, and precipitate; causing the lens to loose its transparency. Of critical importance is the decrease in the Na^+/K^+ ATPase, resulting in the inability to maintain steady concentrations of Na^+, K^+, and Ca^{++} within the lens. The decreased activity of this enzyme is thought to be associated with oxidative damage to the sulfhydryl portions of the molecule, usually protected by the interaction of several antioxidants, especially glutathione (GSH), ascorbate, superoxide dismutase (SOD), and catalase. Like the processes leading to ARMD, senile cataracts are the result of years of damage and accumulated oxidation. Several reviews are available that discuss the relationship between cataracts and oxidative damage (5,6,7,8).

Diabetes and the Eye

The deficiency of proper glucose metabolism in the diabetic patient leads to two ocular conditions: diabetic retinopathies, and diabetic cataracts. Diabetes is the leading cause of acquired blindness in the U.S., retinopathies account for most of these. Diabetic retinopathies are associated with microaneurisms behind the retina causing edema and are prone to leakage (called background or non-proliferative type) or by new blood vessel formation (neovascularization) on the surface of the retina (called proliferative type). Laser photocoagulation is often used to destroy and delay neovascularization, which, if untreated, can result in the loss of vision for nearly 10% of IDDM patients.

Diabetic cataracts, and to some extent retinopathies, seem to have a direct relationship with the enzyme aldose reductase (9). Hyperglycemia stimulates the conversion of glucose to sorbitol in the lens via aldose reductase. Sorbitol cannot be transported through the lens membrane and is therefore accumulated in the lens tissue. This creates a hypertonic condition, causing water to flow into the lens tissue to maintain osmotic equilibrium. Membrane permeability is thus altered, resulting in the loss of several important molecules including glutathione, magnesium, and potassium. The use of aldose reductase inhibitors to reduce the sorbitol concentration within the eye has shown positive results for diabetic cataracts (10) as well as retinopathies (11).

Antioxidants- The key to prevention.

As we have outlined already, the cumulative effects of oxidative damage are the primary cause of macular degeneration and cataract formation. It would seem quite logical then, that antioxidants would play a direct role in preventing and possibly reversing the formation of these conditions. This hypothesis has been confirmed by several recent scientific studies and is now becoming more widely understood and accepted by those who have patients with an increased risk for such conditions (1, 12).

Ascorbate

Ascorbate accumulates in ocular tissues several times higher than in plasma, and furthermore is at a higher concentrations than other water soluble antioxidants in the ocular tissue. Ascorbate levels, as we shall see, are critical to the overall antioxidant protection of the eye. It has been shown that, in cells isolated from the retinal pigmented epithelium, the amount of radiation delivered by a visible laser was directly proportional to the amount of ascorbic acid oxidized to dehydro-L-ascorbic acid (DHA) (13). This implies that ascorbate is one of the first antioxidants used to quench light-induced free radicals. This would be expected since ascorbic acid is very effective at quenching hydrogen peroxide radicals, one of the major secondary free radicals formed during the quenching of superoxide by SOD (superoxide is formed directly from light energy). Ascorbate is also able to protect alpha tocopherol (Vitamin E) from oxidation within the rod outer segments (14), a function that is enhanced by both glutathione and lipoic

Free Radicals, Antioxidants, and Macular Degeneration

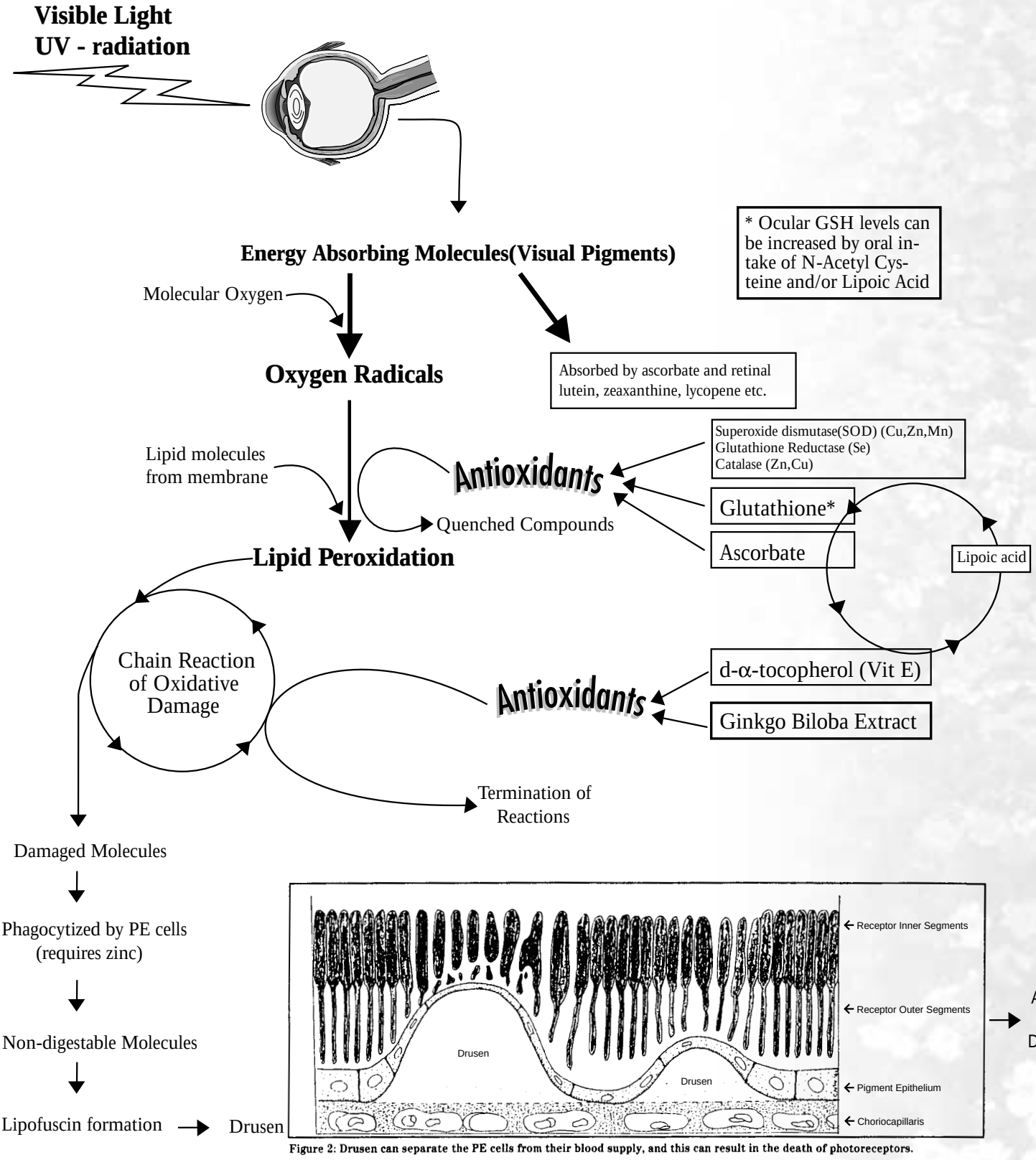

Figure 1

Adapted from van der Hagen et. al. J. Am Opt Assoc 1993; 64:871-78.

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acid. The interrelationship between ascorbic acid and glutathione is an interesting and important one in the regeneration of ocular antioxidants and retarding disease potential (15).

While one would expect that the levels of vitamin C would be quite adequate in the diet of most Americans, this would be a false assumption. In 1998, researchers at Arizona State University found that 30% of the 494 middle class individuals studied were vitamin C depleted upon examination of routine blood test (16). In fact, vitamin C deficiency has been listed among causative factors for aging macular degeneration (17). Diabetics and smokers (two groups with increased risk of oxidative ocular diseases) have been shown to have reduced levels of vitamin C. Typical supplemental levels of vitamin C range from 500 mg per day all the way to bowel tolerance (5-10g per day for some). One to two grams per day of vitamin C (as ascorbic acid) should provide more than adequate levels of this water-soluble antioxidant in the ocular tissues. Patients should keep in mind the addition of various flavonoids with vitamin C supplementation, as these are integral to the function of vitamin C (see flavonoid section).

Vitamin E

The antioxidant role of vitamin E is straightforward. As the body's major lipid-soluble membrane-bound free radical quenching molecule, vitamin E is vital to the prevention of lipid peroxidation. The average level of vitamin E (alpha tocopherol) was lower in individuals with macular degeneration than in age and risk matched controls (18). In placebo-controlled studies, oral vitamin E was able to increase the glutathione levels in the aqueous humor and lenses of humans, rabbits and rats (19). Supplemention of 400IU vitamin E (as natural D-alpha tocopherol) is commonly recommended to all individuals to help with the 'normal' oxidative load. An additional 400IU (total of 800IU) per day would be suggested for those individuals who are currently fighting or are at high risk for cardiac condition, cancers, and oxidative eye diseases.

Glutathione

The role of glutathione in the antioxidant protection of the eye cannot be overestimated. A tripeptide made from glycine, cysteine, and glutamic acid, glutathione is the most prevalent cellular thiol and accounts for more than 90% of the sulfur in many cells. Ocular concentrations of glutathione are very high when compared with most other tissues and decreased levels of glutathione are associated with both age related macular degeneration and cataract, and in diabetic patients with similar conditions.

Glutathione is critical in maintaining the reduced state of sulhydryl-containing proteins in the lens. As mentioned earlier, the accumulation of sorbitol in the lens will allow glutathione to "leak out" of lens tissues, making them more susceptible to oxidative damage. In a recent study, older patients with diabetes had a significantly reduced level of total glutathione (GSHt), while all older patients without diabetes had a lower level of the reduced form of glutathione (GSH) (20). This would suggest that increasing the levels of GSH is important in all elderly patients, while in the case of diabetics an increase in GSHt is also important. Glutathione deficiency (serum and aqueous humor) was also noted in individuals with glaucoma, although the administration of lipoic acid was able to increase glutathione levels in these patients (21).

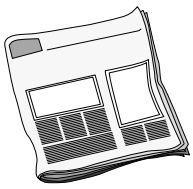
Unfortunately, serum levels of glutathione are affected little by oral administration of glutathione (22). The oral administration of N-acetyl cysteine, on the other hand, has been shown to significantly increase levels of glutathione in serum, intracellularly (23,24), as well as in cultured lens cells (25). Lipoic Acid (21), vitamin E (19), and ascorbic acid (15) levels all have positive effects on the GSHt and/or GSH, confirming the integral link glutathione plays in the antioxidant cascade that prevents ocular damage.

Lipoic Acid

Formerly known as thioctic acid, alpha-lipoic acid is considered one of the most versatile antioxidants. Having a lipid-soluble portion, a water-soluble portion and two thiol groups allows lipoic acid to recharge vitamin E, ascorbic acid (14) and glutathione (21). In experimentally induced cataract formation in rats, glutathione, ascorbate, and vitamin E were depleted to 45, 62, and 23% of controls respectively; but were maintained at 84-97% of control levels when lipoic acid was administered to the animals (26). Lipoic acid has also been shown to inhibit the activity of aldose reductase in hyperglycaemic conditions (27), indicating another way it may prevent cataract formation. Administration of lipoic acid improved visual function of glaucoma patients in as little as 2 months at 150 mg per day (28). The therapeutic use of lipoic acid is growing for many different conditions, age-related and oxidative eye diseases are clearly conditions where lipoic acid would be indicated.

Ginkgo

Extracts of *Ginkgo Biloba* L. (GBE), standardized to 24% ginkgo flavonoglycosides and 6% terpene lactones, have been used for many years to increase blood flow to the brain, as well as other conditions, with excellent results. While its use in retinal protection is less popular in comparison, the biochemistry and clinical data make GBE one of the best choices for such an application. In 1986



NEWS PERSPECTIVES

COULD TAURINE HELP WITH THOSE DIFFICULT CHOLESTEROL PATIENTS?

Last year we reviewed cholesterol management using natural ingredients (1). Here we present some recent findings that may add to your regimen with those patients whose cholesterol levels have been difficult to manage. Two different groups, one in Japan and one in Korea, have been studying the effects of oral taurine dosing on the levels of various lipids in animals, and have obtained some rather promising results.

Four groups of male rats were divided into feeding groups: cholesterol free (CF), high cholesterol (HC), high cholesterol and high taurine (HCHT), or high taurine (HT) for 5 weeks. They found that rats on the HCHT diet had 32% lower total cholesterol, 37% lower LDL, and 43% lower triglycerides in their serum than rats on the HC diet. There was also a significant reduction of all these between the HT and the CF diets as well. Taurine supplementation to the HCD reduced liver cholesterol by 50% and liver triglycerides by 30%; a result that was also seen in taurine supplemented CF fed rats (43% reduction in liver triglycerides) (2).

The Japanese group repeated similar experiments in mice and published the results early this year (3). They fed mice a high fat, high cholesterol diet and some of these were also given taurine. Taurine treatment lowered serum LDL and VLDL cholesterol by 44% and elevated HDL cholesterol by 25%. Liver cholesterol levels were also reduced by 19%. Aortic lipid accumulation, an index of atherosclerosis, was reduced by 20% with taurine. They speculate that one mechanism for this action is taurine's effect on 7-alpha hydroxylase. This enzyme is involved in the conversion of cholesterol to bile in the liver and taurine doubled the activity of this enzyme.

The Pediatrics Department of the Koshigaya Municipal Hospital in Japan published their results using taurine as adjunct therapy for fatty livers in children with simple obesity. Regardless of their ability to reduce the obesity, these authors conclude that oral taurine treatment was an effective treatment for these children (4). The use of taurine for fatty acid metabolism in heart tissue is common for many alternative medicine practitioners. The safe use of large doses of taurine (2g/day or more) has been used safely for improving cardiac conditions and ocular condition (see main article, this issue). It may now be possible to add an ingredient to our panel of natural products that benefit healthy cholesterol levels.

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research was conducted that showed that the eye tissue was among only a few tissues that had a high affinity to labeled GBE (29). In the same year, a second group performed a small (10 patient) clinical trial using GBE on patients with ARMD. Even with a small sample size, they were able to realize a significant difference in visual acuity and visual field between those patients on GBE and those on placebo (30). Ginkgo extracts were shown to protect retinas from the damage induced by xenobiotics such as chloroquine (31), proteolytic enzymes (32), induced retinal detachment (33), direct addition of oxidizing agents (34), enhanced illumination of the retina (35), ischemic/reperfusion studies in diabetic rat retinas (36), as well as induced diabetic retinopathy (37). Since this covers virtually every route of oxidative and metabolic damage the retina is likely to face, GBE is absolutely essential to the therapy of any individual with ongoing or potential retinal damage.

Carotenoids and Related Compounds

There are nearly 600 naturally occurring carotenoids, 10 of which are frequently found in human serum, and two of which are found in high concentrations in the macula lutea: lutein and zeaxanthin (38). It is believed that they serve two primary roles; to absorb excess photon energy, and to quench free-radicals before they damage the lipid membranes. Studies have shown that increased dietary intake of carotenoids, especially lutein and

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zeaxanthin, increase macular pigment (39) and lower the risk of age-related macular degeneration (40). Dark green leafy vegetables like spinach and collard greens are excellent dietary sources for these molecules. Furthermore, supplemental lutein (30 mg/day for 140 days) was able to reduce the amount of blue light transmitted to the photoreceptors and the pigmented epithelial cells, the ARMD sensitive tissues, by 30 to 40% (41). Lycopene, another carotenoid that is quite abundant in tomatoes, is the most abundant carotenoid in the serum. Low serum levels of lycopene have been shown to increase the risk of ARMD (18). We are just beginning to see the many uses of this particular pigment/antioxidant and more research will continue to come forth on its use in ARMD, as well as in other conditions.

Zinc and other metals:

The antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase, and catalase are vital to the quenching of free radicals in the lens and retina. Each of these enzymes requires divalent cations (coenzymes) in order to function. SOD requires zinc, copper, and manganese; catalase requires zinc and copper, and glutathione peroxidase requires selenium. Studies on monkeys with oxidative stressed retinas shows a 60% reduction in the activity of catalase and glutathione peroxidase as well as a 4-fold reduction in zinc concentration compared with normal controls (42).

Studies done more than 10 years ago showed that oral zinc therapy was able to significantly reduce visual loss, when compared to placebo (43). The apparent benefit of supplemental zinc has a mechanism in addition to acting as a coenzyme to both SOD and catalase. The set of RPE lysosomal enzymes responsible for digesting the sloughed-off portion of the photoreceptors, in particular alpha-mannosidase, beta-galactosidase, N-acetyl-beta glucosaminidase, and N-acetyl beta galactosaminidase, have significantly reduced activity upon aging (44). This will increase the likelihood of lipofuscin build-up and eventually drusen and ARMD. Alpha-mannosidase, a critical enzyme for the degradation of rod outer segments, derived from older individuals can be stimulated 2-fold by the addition of zinc (45). These data would suggest that while copper, selenium, and manganese are important to maintain proper antioxidant protection; zinc has both a history and biochemistry that suggest it should be used therapeutically for ARMD and cataracts.

Flavonoids and the eye:

Flavonoids are the class of compounds first discovered by Szent-Gyorgyi in the mid 1930's and designated by him as "vitamin P". These compounds, and the larger designation polyphenols, are responsible for most of the pigments of fruits and berries. These compounds also have many important health benefits when taken orally, among them, antioxidant and aldose reductase inhibition. For more than 20 years, the aldose reductase inhibition of flavonoids like quercetin, quercetrin, and myricitrin has been studied (46), and used effectively to slow the progression of cataracts (47,48). Quercetin, and its glycosides quercetrin and guaijaverin, have been shown to inhibit human lens aldose reductase in vitro (49). Furthermore, the well-known interaction between flavonoids and vitamin C (remember ascorbate's pivotal role in ocular antioxidation) make flavonoids a certain addition to any natural therapeutic approach for macular degeneration and cataracts.

Any discussion of plant compounds used for the eye is incomplete without the mention of anthocyanosides, especially those derived from bilberry (*Vaccinium myrtillus* L.). Originally used to improve night vision, extracts of bilberry are being used in France and Germany for vascular conditions, retinopathies, and night vision. As would be expected of anthocyanosides, research has shown them to have a positive influence on the permeability and tendency to hemorrhage of retinal vessels, especially in patients with diabetic retinopathy (50).

Taurine

Taurine is an amino acid, synthesized by the body from methionine and cysteine. It has for years been used as a supplemental ingredient for health concerns, primarily cardiovascular, where its interaction with calcium-dependent pathways help it relax the heart muscle during diastole. Retinal concentrations of taurine are quite high and it is required for the proper development of the retinal tissues in both man and animals. Taurine has been shown to directly stimulate the proliferation of human retinal pigmented epithelial cells (RPE) (51), protect rod outer segments from damage due to light exposure, regulate calcium influx, and regulate signal transduction in the retina (52). Taurine was among vitamin E, C, and lipoic acid in its ability to protect lens tissue from protein leakage (cataract model) during exposure to gamma irradiation (53). The use of taurine for macular degeneration and cataract protection is a welcome addition to the natural products already discussed because its mechanism is quite different from the antioxidants, enzymes, flavonoids or metals.

Conclusion: Diet vs Supplemention

The question always arrives. How then shall we supply these natural substances: by the diet alone, or through supplementation? The answer is essentially: both; but of course is not that simple. Even a diet very rich in a

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variety of fresh fruits and vegetables would fall short of the recommended intakes that would be suggested for individuals suffering from or at risk for oxidative eye diseases. However, the facts show that only 9% of Americans daily consume the two fruits and three vegetables recommended by the NCI (54). The elderly, the population most effected by these conditions, are very reluctant to change dietary habits and are more likely to benefit from supplementation of the ingredients listed above. These recommendations are coming from even the most reluctant and hesitant sources (55). In fact, a study of 17,000 male physicians over 5 years showed that those physicians who took a multivitamin (not specifically designed for the eye) were 27% less likely to develop cataracts (56). Studies are continuing with many of the ingredients listed here in long-term, double-blinded, placebo controlled clinical trials.

Practitioners should try to get patients to consume as many green leafy vegetables as possible, things such as spinach and collard greens. They should increase the intake of fruits and yellow vegetables. The more natural pigments, the better. Avoid rancid and trans-fatty acids, these will always lead to increased lipid peroxidation, decrease antioxidant concentrations, and tax an already loaded lipid enzymatic machinery. Older patients should supplement their diet with a broad multivitamin and mineral product that gives them adequate levels of all the B vitamins, magnesium, and the trace minerals. Patients with active oxidative damage should take immediate measures to increase the intake of as many of the ingredients listed in this article as possible, as well as reduce exposure to direct sunlight with the use of sunglasses that block UV-light. It should be noted that there is no other treatment available, and these processes can be slowed, stopped and possibly reversed with diet and supplemental ingredients.

Again, we see that within the natural world there are a number of compounds that have profound effects on conditions that are listed as essentially incurable. And once again the established medical paradigm reveals their view of these conditions and their treatment is still rather short-sighted.

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IN MY OPINION

To standardize or not to standardize, that is our question. In a world trapped between the exactitude of pharmaceutical science and the legitimate artistry of natural healing lies the entity known as standardized extracts. Few things have brought such contention between herbalists and M.D.s using botanicals than the use of standardized extracts. The former sees a drug in guise, the latter a botanical form that is finally suitable to be dispensed properly. The views reach their climax as one proclaims "standardize nothing!" and the other "standardize everything!" Such is the paradox of botanical medicine as we reach the end of this millenium. If we may, let us propose a third view of standardized extracts.

When we think of standardized extracts, we should not assume that because it is standardized it is necessarily better, or for that matter, more potent than other extracts. Standardized merely means that at least one constituent present in the extract will remain constant from batch to batch. For instance, St. John's wort extract is often standardized so that every batch has 0.3% hypericin (weight/weight of total extract), measured by HPLC. In this case, a 0.3% hypericin standardized extract was consistently used for most of the recent clinical trials with depression. Researchers are fairly certain that there are several active (antidepressive) components within St. John's wort, some even question whether hypericin has any antidepressive activity at all. We must be careful to make the proper conclusion from the data that is reported. If hypericin is "inactive", could an extract standardized to hypericin be active? The answer is yes, as long as the active components are extracted and concentrated with the standardizing component. When this is the case, standardizing is a mark of the strength of the active components. If this is not the case, one could increase the marker component, and actually reduce the therapeutic effectiveness of the product. Essentially, we must stick with the data.

The overwhelming push right now is to standardize all botanicals. This is unnecessary and will skew an already confused data collection system. When standardized extracts have had a track record of clinical effectiveness, they should be used. However, if the data of effective use for a botanical is an extract, powdered extract, tea, or just the plant itself; this is how it should be dosed. This is where the data lies. Standardizing plants with no rationale, except that it makes certain people feel better about dosing, is irresponsible. This will lead to inferior products that will be less effective than their unstandardized counterparts, and will cause some to turn away from trying the "real" stuff. Standardization of botanicals is a phenomenal tool which can be used to increase the health of patients using consistent delivery of natural constituents, let us be sure that a marketing tidal wave doesn't deluge the system to trivialize the effectiveness of those extracts with confirmed data.

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