

The Role of Lutein and Antioxidants in Eye Health

John R. Trevithick, PhD* and Kenneth P. Mitton, PhD**

*Professor, Biochemistry Department, Faculty of Medicine & Dentistry, University of Western Ontario

**Assistant Professor, Eye Research Institute, Oakland University

The Eye and Vision

Of all our senses, vision is most highly valued. It involves a complex set of physical, chemical and nervous processes. Defects in any of these processes will affect our ability to see the world around us. The image is formed by light passing through the air-cornea interface, where the major focusing occurs. This is followed by focusing at the eye lens and at the vitreous humor, and finally forming an image on the retina. Interaction of light with rhodopsin starts the visual transduction cascade, closing cGMP-gated calcium channels, which triggers the nerve impulse in the retina, leading to an image which the optic nerve passes on to the brain.

As we grow older, our vision can be impaired by several diseases of vision. Most common is cataract, which by age 75 affects approximately half the population. Cataract is the most common cause of blindness worldwide. In the United States, operations to replace the eye lens with a plastic intraocular lens number more than the sum of the next five most frequently performed surgical procedures, and account for the largest single line item (over \$4 billion, 12% of the total budget) in US Medicare. The major cause of blindness in western countries is age-related macular degeneration (AMD), which affects about 20% of the population age 75 and older. Unfortunately, unlike cataract, which can be treated surgically, macular degeneration is not generally viewed as susceptible to surgical intervention. However, Jorge Vasco-Posada in Medellin, Columbia, has developed a procedure that in individual cases has significantly improved vision in those with AMD. Recently several other interventions, including photodynamic therapy, laser photocoagulation and irradiation have shown limited effectiveness in treating AMD. Glaucoma, which causes progressive loss of peripheral vision, also increases in prevalence with age. Since oxidative damage appears to be involved at some stage of progression of all three of these eye diseases, prevention or at least reduction of risk of these diseases may be possible using antioxidants.

Cataract Risk Reduction and Vitamins E and C

The lens is the only organ in the body that contains our entire life history. Lens cells are laid down, like tree rings, at approximately one cell layer per day at the periphery of the lens in the lens cortex. This stress which weakens cell defences may result in damage being expressed many years later, because the damaged cells die prematurely, and form opacities in the lens. These are seen as cloudy areas, and are termed cataracts when they interfere with vision.

Packer¹ has suggested, that most cells have multiple interconvertible antioxidant defences including small molecules, vitamins E and C, lipoic acid, glutathione and cysteine, as well as enzymic antioxidant defences which include glutathione peroxidase, superoxide dismutase, and catalase. Similarly, recent studies which have implicated homocysteine elevation suggest that B vitamins B12, folate and pyridoxine (B6) may act as antioxidants in lowering homocysteine concentration². Vitamin C can regenerate tocopherol (vitamin E) from its oxidized form, the tocopheroxy radical^{3,4}. Vitamin C and glutathione also can regenerate each other.

There is evidence that antioxidants reduce

cortical cataract risk by protecting mitochondrial integrity. Damaged mitochondria release calcium: calpain activation leads to proteolysis of crystallins⁵ and the cytoskeletal protein spectrin/fodrin⁶. Loss of the rigid cytoskeletal framework can result in cell membrane blebs, which scatter light resulting in the typical milky appearance of a cortical cataract. In vitro antioxidants protect mitochondrial integrity, preventing elevation of intra cellular calcium and lens opacification. In aging humans, a study showed that vitamin C supplementation reduced cataract risk by 74%^{7,8}, while vitamin E reduced cataract risk by 56%. Vitamins E and C together also reduced risk by 72%. Taylor's group⁹ found similar risk reduction for vitamin C supplementation, which only achieved significance after 10 years of supplementation. Other antioxidants such as lycopene¹⁰ did not reduce cataract risk, although lutein and zeaxanthin¹¹ did. Taurine although an osmotically regulated amino acid, also functions as an antioxidant^{12,13}.

MACULAR DEGENERATION: Non-Visual Interactions of Light with Biomolecules

The energy of light photons depends inversely on their wavelength. Thus, photons of blue light and ultra violet light have higher energy. When these photons interact with rhodopsin, forming the image on the retina, they function appropriately for vision. Interaction with light of vitamins such as riboflavin can result in free radical formation¹⁴. Herbal remedies can also contribute reactive oxygen species: St. John's wort, commonly used for depression, contains an active component, hypericin, which¹⁵ can be activated by light, producing singlet oxygen by transferring its energy to oxygen molecules. Such transfer of energy damages retinal and lens cells in tissue culture¹⁶.

Why Blue Light Damages the Retina

Blue light can form singlet oxygen and even oxygen free radicals. Because the retina has a high content of polyunsaturated fatty acids, damage to the retina results in the formation of oxidized proteins, lipid peroxides and hydroperoxides. The oxidized proteins appear to clog the proteasomes, so that unrecycled proteins accumulate. These may be precursors of drusen, blobs of oxidized hydrophobic proteins and lipids, which characterize macular degeneration. Drusen can be hard or soft depending usually on the individual and their appearance (dry macular degeneration) characteristically is followed by growth of new blood vessels (neovascularization) termed wet macular degeneration.

Protection of Retina by Lens Sunscreen Molecules

The eye lens also contains a light-absorbing sunscreen molecule 3-hydroxykynurenine (3HK)¹⁷ formed by metabolism of tryptophan. Its accumulation with age results in the increasing yellow colour of the aging human lens, due to the absorption of higher energy blue light photons by 3HK and its glucoside^{18,19}. These molecular sunscreens also protect the retina from damage by blue light. Unfortunately no attempt has been made to duplicate the natural lens absorption of blue light. For this reason, it may be prudent after cataract surgery (1) to instruct them to wear yellow-orange sunglasses (available as fishing-sunglasses in sporting goods departments) and also (2) to assess their dietary intake of lutein and zeaxanthin.

Lutein and Zeaxanthin

To minimize the damage caused by light, the area of the retina responsible for fine vision, the (fovea) macula, specifically accumulates two carotenoids, lutein and zeaxanthin²⁰⁻²³. These molecules give the macula a yellow orange colour, because they absorb blue light, reflecting the yellow. Snodderly¹¹ and Landrum²⁴ have suggested that the role of these carotenoids is the absorption of blue light. Preliminary experiments have indicated that lutein has strong antioxidant activity. These activities are clearly complementary, since absorption of blue light would reduce the production of radicals, while antioxidant activity would actually detoxify the radicals produced by the blue light.

Although, several studies have showed that lutein and zeaxanthin supplementation increases the concentration of lutein and zeaxanthin in the eye, it still needs to be elucidated whether this will translate into lowering the risk of eye disease. Although most of the evidence for lutein and zeaxanthin benefits to eye health is derived from dietary related studies, lutein and zeaxanthin are currently available in supplement forms^{21,24,25-28}.

Vitamin E and Macular Degeneration

West²⁹ reported a risk reduction of 57% for macular degeneration in people taking vitamin E supplements. This magnitude of risk reduction is similar to the risk reduction we reported for vitamin E and cataract, suggesting that the mechanism of risk reduction may be similar for both cataract and macular degeneration.

Vitamin E and Retinopathy of Prematurity (ROP)

Premature infants treated with oxygen are at increased risk of retinal neovascularization leading to retinopathy of prematurity (ROP) and in extreme cases, blindness. As we reported previously³⁰, Hittner and Kretzer found that this was because of inadequate vitamin E, which is passed by placental transfer to the infant during the final weeks of the pregnancy^{31,32}. Meta-analysis of the available trials indicated a significant risk reduction in infants given supplemental vitamin E parenterally or orally, but such therapy was stopped because of infant deaths. Nevertheless, vitamin E is currently added at supplemental levels (corresponding to 400 I.U./day for 70 Kg. adult) to parenteral and oral infant formulas, to prevent hemolytic disease of the newborn, associated with vitamin E deficiency.

Vitamin E and Diabetic Retinopathy

Recent work by Azzi's group³³⁻³⁸ has suggested that vitamin E may play a regulatory role in cell physiology. Protein Kinase C (PKC) which increases in diabetes^{39,40} is normalized by treatment, and neovascularization is also decreased by vitamin E treatment. A clinical trial for this promising treatment is warranted⁴¹.

Vitamin E and Retinitis Pigmentosa (RP)

In retinal degeneration, loss of photoreceptors, as occurs in RP can lead to extra free radical stresses from the release of cellular debris, which oxidizes. This leads to a requirement of vitamin E for the healthy functional retina. Quite recently it has been shown that mutations of the liver alpha-tocopherol transport protein (alpha-TTP) which lead to lowered serum alpha-tocopherol levels cause Retinitis Pigmentosa and ataxia^{42,43}. Supplementation in these patients alleviates the progression of RP and the ataxia. The efficacy of

using supplementation for all the other many forms of RP is not known.

Nature and Nurture In Retinal Disease: Rod Visual Cycle and ABCR, a lesson in genetics and oxidation stress

Mutations in the photoreceptor-specific ATP-binding Cassette Transporter ABCR cause Stargardt macular dystrophy, RP and cone-rod dystrophy and is one example of mutations in a single protein leading to very different phenotypes and disease progression⁴⁴⁻⁴⁷. Recently, Sun and Nathans⁴⁸, have shown *in vitro* that all-trans-retinal itself is a potent photosensitizer that readily causes photo-dependent oxidation damage to normal ABCR protein.

Other Functional Sensitive Targets for Oxidation Damage

There are already about 40 known disease genes with numerous mutation examples that cause retinitis pigmentosa and allied disease of the retina⁴⁹. Any protein that can be damaged by mutation to its sequence or oxidation could potentially lead to loss of photoreceptors. Such genetic differences may result in varying individual requirements for lutein, zeaxanthin, or vitamin E.

GLAUCOMA: Vitamin E and Glaucoma

Although glaucoma results in loss of peripheral vision and degeneration of the peripheral retina, increased intraocular pressure (IOP), which is estimated routinely in eye examinations, is not responsible for all cases of glaucoma. In fact, a significant proportion of glaucoma cases are not associated with increased IOP.

Although mainly Russian workers have reported efficacy of vitamin E and antioxidants in treatment of glaucoma⁵⁰⁻⁵⁵ until recently few papers related to this topic had appeared in the Western literature. Cellini et al.⁵⁶ reported that a combined therapy using DHA, vitamin E and vitamin B complex showed significant improvement after 90 days of treatment in both perimetric indices (MD, SF CPSPD, pL0.05) and in the RLS frequency values (pL0.05), suggesting that such therapy should be considered for delaying the progress of damage in glaucoma. In a related area, vitamin E had beneficial effects in glaucoma filtering surgery. Both animal⁵⁷ studies

of glaucoma filtering surgery and Azzi's group showing inhibition of human Tenons capsule fibroblasts *in vitro*⁵⁸, offered hope of reducing fibrocellular scar formation associated with failure of glaucoma filtering surgery.

CONCLUDING SUMMARY

Antioxidants which can interact with each other to regenerate antioxidant activity can potentially function in reducing risk of several eye diseases,

including cataract, AMD and glaucoma. Lutein and zeaxanthin appear to absorb blue light and detoxify the free radicals produced by the light, which provides a teleonomic explanation for their specific accumulation in the retinal fovea. Individual differences in antioxidant requirements may occur depending on the genetic background of each person.

The most common carotenoids in human serum are also the most prevalent in the diet and they include, beta-carotene, lycopene, lutein, beta-cryptoxanthin and alpha-carotene. These compounds are absorbed passively and are introduced into the bloodstream with lipids in the chylomicron fraction, absorbed into the liver and excreted again in lipoprotein. Studies have shown that carrots are the major source of beta-carotene (25%) in the diet and also for alpha-carotene. Broccoli, cantaloupe and soups made with carrots and tomatoes are also major contributors. Lutein and zeaxanthin are obtained mostly from spinach, collard, mustard, turnip greens and broccoli. Lycopene is mostly obtained from tomatoes, tomato-sauces and catsup. Watermelon is a rich source of lycopene. It is important to note that high content does not translate into high bioavailability. Raw carrots are a poorer source of carotenoids than mildly cooked carrots for example. Processing and digesting sources with fats increases bioavailability. The American Cancer society recommends five servings of fruits and vegetables per day to obtain about 5 mg/day of beta-carotene and reduce cancer risk⁵⁹. Cataract risk should also be reduced by consuming vegetables such as broccoli and spinach¹⁰. It is important to note that these recommendations are based on whole foods and the fact that carotenoids in isolation may not have anticancer effects, but work in synergy with other compounds obtained from food sources.

The Whitehall-Robins Report is a Whitehall-Robins publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

Editor: Whitehall-Robins Inc.

If you have any comments about the Whitehall-Robins

Report or would like to be added to the mailing list, please write to:

The Editor: The Whitehall-Robins Report,
5975 Whittle Road, Mississauga, ON L4Z 3M6



© 2001-November. May be reproduced without permission provided source is recognized.

- References** 1. Packer L. Interactions among antioxidants in health and disease: vitamin E and its redox cycle. *Proc Soc Exp Biol Med*. 1992;200:271-6. 2. Spence JD, Howard VI, Chambless LE, Malinow MR, Pettigrew LC, Stampfer M et al. Vitamin Intervention for Stroke Prevention (VISP) trial: rationale and design. *Neuroepidemiology* 2001;20:16-25. 3. Niki E, Noguchi N, Tsuchihashi H, Gotoh N. Interaction among vitamin C, lutein, and beta-carotene. *Am J Clin Nutr*. 1995;62:1322S-6S. 4. Niki E. Interaction of ascorbate and alpha-tocopherol. *Ann N Y Acad Sci*. 1987;498:186-99. 5. Kelley MJ, David LL, Iwasaki N, Wright J, Shearer TR. alpha-Crystallin chaperone activity is reduced by calpain II *in vitro* and in senile cataract. *J Biol Chem*. 1993;268:18844-9. 6. Kilic F, Trevithick JR. Modelling cortical cataractogenesis. XXIX. Calpain proteolysis of lens fodrin in cataract. *Biochem Mol Biol Int*. 1998;45:963-78. 7. Robertson JM, Donner AP, Trevithick JR. A possible role for vitamins C and E in cataract prevention. *Am J Clin Nutr*. 1991;53:346S-51S. 8. Robertson JM, Donner AP, Trevithick JR. Vitamin E intake and risk of cataracts in humans. *Ann N Y Acad Sci*. 1989;570:372-82. 9. Jacques PF, Taylor A, Hankinson SE, Willett WC, Mahnen B, Lee Y et al. Long-term vitamin C supplement use and prevalence of early age-related lens opacities. *Am J Clin Nutr*. 1997;66:911-6. 10. Brown L, Rimm EB, Seddon JM, Giovannucci EL, Chasan-Taber L, Spiegelman D et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. *Am J Clin Nutr*. 1999;70:517-24. 11. Hammond BR, Jr., Wooten BR, Snodderly DM. Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeaxanthin. *Optom Vis Sci*. 1997;74:499-504. 12. Kilic F, Bhardwaj R, Caulfield J, Trevithick JR. Modelling cortical cataractogenesis 22: *in vitro* reduction of damage in model diabetic rat cataract by taurine due to its antioxidant activity? *Exp Eye Res*. 1999;69:291-300. 13. Mitton KP, Linklater HA, Dzialoszynski T, Sanford SE, Starkey K, Trevithick JR. Modelling cortical cataractogenesis 21: *in vitro* reduction of damage in model diabetic rat cataract by taurine due to its antioxidant activity? *Exp Eye Res*. 1999;69:291-300. 14. Varma SD, Srivastava VK, Richards RD. Photoperoxidation in lens and cataract formation: preventive role of superoxide dismutase, catalase and vitamin C. *Ophthalmic Res*. 1982;14:167-75. 15. Scheel KL, Patat S, Chignell CF, Datillo M, Wang RH, Roberts JE. Photooxidation of lens alpha-crystallin by hypericin (active ingredient in St. John's Wort). *Photochem Photobiol*. 2000;72:200-3. 16. Sgarbossa A, Angelini N, Gioffre D, Youssef T, Lenzi F, Roberts JE. The uptake, location and fluorescence of hypericin in bovine intact lens. *Curr Eye Res*. 2000;21:597-601. 17. Berry Y, Truscott RJ. The presence of a human UV filter within the lens represents an oxidative stress. *Exp Eye Res*. 2001;72:411-21. 18. Gaillard ER, Zheng L, Merriam JC, Dillon J. Age-related changes in the absorption characteristics of the primate lens. *Invest Ophthalmol Vis Sci*. 2000;41:1454-9. 19. Bova LM, Sweeney MH, Jamie JF, Truscott RJ. Major changes in human ocular UV protection with age. *Invest Ophthalmol Vis Sci*. 2001;42:200-5. 20. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of completed trials. *Ann Epidemiol*. 2000;10:125-34. 21. Sommerburg O, Keunen JE, Bird AC, Van Kuijk FJ. Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. *Br J Ophthalmol*. 1998;82:907-10. 22. Jacques PF. The potential preventive effects of vitamins for cataract and age-related macular degeneration. *Int J Vitam Nutr Res*. 1999;69:198-205. 23. Bernstein PS, Khachik F, Carvalho LS, Muir GJ, Zhao DY, Katz NB. Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. *Exp Eye Res*. 2001;72:215-23. 24. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE. A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res*. 1997;65:57-62. 25. Mares-Perlman JA. Too soon for lutein supplements. *Am J Clin Nutr*. 1999;70:431-2. 26. Mares-Perlman JA, Klein BE, Klein R, Ritter LL, Freudenheim JL, Luby MH. Nutrient supplements contribute to the dietary intake of middle- and older-aged adult residents of Beaver Dam, Wisconsin. *J Nutr*. 1993;123:176-88. 27. Lavine JB. Lutein supplementation of green vegetables. *Am J Clin Nutr*. 2000;71:147-64. 28. Dagnelie G, Zorge IS, McDonald TM. Lutein improves visual function in some patients with retinal degeneration: a pilot study via the Internet. *Optometry* 2000;71:147-64. 29. West S, Vitale S, Hallfrisch J, Munoz B, Muller D, Bressler S et al. Are antioxidants or supplements protective for age-related macular degeneration? *Arch Ophthalmol*. 1994;112:222-7. 30. Trevithick J, R., Mitton, K. P., and Robertson, J. M. Vitamin E and the Eye. Packer, L. and Fuchs J. Chapt. 61, 873-896. 1-6-1992. New York, NY, Marcel Dekker Inc. Vitamin E in Health and Disease. Packer, L. and Fuchs J. 31. Kretzer FL, Hittner HM. Retinopathy of prematurity: clinical implications of retinal development. *Arch Dis Child* 1988;63:1151-67. 32. Hittner HM, Rudolph AJ, Kretzer FL. Suppression of severe retinopathy of prematurity with vitamin E supplementation. Ultrastructural mechanism of clinical efficacy. *Ophthalmology* 1984;91:1512-23. 33. Azzi A, Breyer I, Feher M, Ricciarelli R, Stocker A, Zimmer S et al. Nonantioxidant functions of alpha-tocopherol in smooth muscle cells. *J Nutr*. 2001;131:378S-81S. 34. Azzi A, Breyer I, Feher M, Pastori M, Ricciarelli R, Spycher S et al. Specific cellular responses to alpha-tocopherol. *J Nutr*. 2000;130:1649-52. 35. Azzi A, Stocker A. Vitamin E: non-antioxidant roles. *Prog Lipid Res*. 2000;39:231-55. 36. Pastori M, Pfander H, Boscoboinik D, Azzi A. Lycopene in association with alpha-tocopherol inhibits at physiological concentrations proliferation of prostate carcinoma cells. *Biochem Biophys Res Commun*. 1998;250:582-5. 37. Ricciarelli R, Tassinato A, Clement S, Ozer NK, Boscoboinik D, Azzi A. alpha-Tocopherol specifically inactivates cellular protein kinase C alpha by changing its phosphorylation state. *Biochem J*. 1998;334 (Pt 1): 243-9. 38. Azzi A, Boscoboinik D, Fazio A, Marilley D, Maroni P, Ozer NK et al. RRR-alpha-tocopherol regulation of gene transcription in response to the cell oxidant status. *Z Ernahrungswiss*. 1998;37 Suppl 1: 21-8. 39. Bursell SE, Clermont AC, Aiello LP, Aiello LM, Schlossman DK, Feener EP et al. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type 1 diabetes. *Diabetes Care* 1999;22:1245-51. 40. Kunisaki M, Bursell SE, Umeda F, Nawata H, King GL. Prevention of diabetes-induced abnormal retinal blood flow by treatment with d-alpha-tocopherol. *Biofactors* 1998;7:55-67. 41. Bursell SE, King GL. Can protein kinase C inhibition and vitamin E prevent the development of diabetic vascular complications? *Diabetes Res Clin Pract*. 1999;45:169-82. 42. Yokota T, Uchiyama T, Kumagai J, Shiojiri T, Pang JJ, Arita M et al. Postmortem study of ataxia with retinitis pigmentosa by mutation of the alpha-tocopherol transfer protein gene. *J Neurol Neurosurg Psychiatry* 2000;68:521-5. 43. Yokota T, Shiojiri T, Gotoda T, Arai H. Retinitis pigmentosa and ataxia caused by a mutation in the gene for the alpha-tocopherol-transfer protein. *N Engl J Med*. 1996;335:1770-1. 44. Allikmets R. Simple and complex ABCR: genetic predisposition to retinal disease. *Am J Hum Genet*. 2000;67:793-9. 45. Allikmets R, Shroyer NF, Singh N, Seddon JM, Bernstein PS et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. *Science* 1997;277:1805-7. 46. Martinez-Mir A, Paloma E, Allikmets R, Ayuso C, del Rio T, Dean M et al. Retinitis pigmentosa caused by a homozygous mutation in the Stargardt disease gene ABCR. *Nat Genet*. 1998;18:11-2. 47. Cremers FP, van de Pol DJ, van Driel M, den Hollander AJ, van Haren FJ, Knoers NV et al. Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. *Hum Mol Genet*. 1998;7:355-62. 48. Sun H, Nathans J. ABCR, the ATP-binding cassette transporter responsible for Stargardt macular dystrophy, is an efficient target of all-trans-retinal-mediated photooxidative damage *in vitro*. Implications for retinal disease. *J Biol Chem*. 2001;276:11766-74. 49. Phelan JK, Bok D. A brief review of retinitis pigmentosa and the identified retinitis pigmentosa genes. *Mol Vis*. 2000;6:116-24. 50. Head KA. Natural therapies for ocular disorders, part two: cataracts and glaucoma. *Altern Med Rev*. 2001;6:141-66. 51. Filina AA. [Antioxidant therapy of primary glaucoma]. *Vestn Ophthalmol*. 1994;110:33-5. 52. Fishbein SL, Goodstein S. The pressure lowering effect of ascorbic acid. *Ann Ophthalmol*. 1972;4:487-91. 53. Hilsdorf C. [On the decrease of intraocular pressure by intravenous drop infusion of 20 per cent sodium ascorbate]. *Klin Monatsbl Augenheilkd*. 1967;150:352-8. 54. Kramorenko IS, Dobritsa TA, Imanbaeva ZA, Egorov EA. [Emoxipine in the treatment of primary glaucoma]. *Vestn Ophthalmol*. 1992;108:14-5. 55. Kuryshva NI, Vnitskaia MI, Erichy VP, Demchuk ML, Kuryshva SI. [Contribution of free-radical reactions of chamber humor to the development of primary open-angle glaucoma]. *Vestn Ophthalmol*. 1996;112:3-5. 56. Cellini M, Caramazza N, Mangiatico P, Possati GL, Caramazza R. Fatty acid use in glaucomatous optic neuropathy treatment. *Acta Ophthalmol Scand Suppl* 1998;41:2. 57. Pinilla I, Larrosa JM, Polo V, Honrubia FM. Alpha-tocopherol derivatives in an experimental model of filtering surgery. *Ophthalmic Res*. 1999;31:440-5. 58. Haas AL, Boscoboinik D, Mojon DS, Bohne M, Azzi A. Vitamin E inhibits proliferation of human Tenon's capsule fibroblasts *in vitro*. *Ophthalmic Res*. 1996;28:171-5. 59. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: A review. *J Amer Dietetic Assoc*. 1996;96:1027-1039.