Nutrition and eye disease of the elderly

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Introduction

Humankind has long recognized that one's diet is directly linked to health and vitality. Cosman[1] in her delightful review on historical diets of medieval times remarked on the implied Doctrine of Nutritional Responsibility. "Every nutrient was believed to achieve a good or bad effect. Sequelae were observed or hidden, immediate or delayed. No food or drink was without physiological effect. Food helped or hindered health. Vigilance in eating or drinking, therefore, was every intelligent citizen's responsibility." She further cited Platina, a Venetian composer of books on hygienic cookery, who in 1475 wrote, "If a hero in time of war merits commendation for saving a life, so much more so in time of peace should a bold writer deserve public credit for a culinary regimen that enhances health and prevents death."

Today we can evaluate the importance of nutrition in health and disease on sound scientific principles using the perspectives of specific nutrient biochemical functions and interactions, pathogenesis of disease processes, and the genetic background of the patient. This paper presents a review of the role of nutrition as regards the two most common maladies of the eye in the elderly population, cataract and age-related macular degeneration (AMD). A clinically significant cataract is present in about 5% of Caucasian Americans aged 52 to 64 years and rises to 46% of those aged 75 to 85.[2] Although surgical removal of the afflicted lens accompanied by ocular lens implant is highly successful in restoring sight, the procedure is costly, accounting for 12% of the Medicare budget. AMD (also known as age-related maculopathy or ARM) affects nearly 30% of Americans over the age of 75. Because little can be done medically to arrest or reverse its effects, it has become the leading cause of vision loss among the elderly.[3]

The function of the lens is to transmit and focus light on the retina, hence it must be transparent *(Figure 1)*. The lens is an encapsulated organ without blood vessels or nerves. The anterior hemisphere is covered by a single layer of epithelial cells containing the full complement of subcellular organelles. At the lens equator the epithelial cells begin to elongate and differentiate to become fiber cells.. When fully differentiated, they possess no organelles but are filled with structural proteins known as crystallins, which are organized in a repeating lattice. The high density and repetitive spatial arrangement of the crystallins produce a medium of nearly uniform refractive index with dimensions comparable to light wavelengths.[4] Events that cause loss of order and induce abrupt fluctuations in refractive index result in increased light scattering and loss in transparency, commonly called cataract. Three basic categories of cataract can be identified.[5,6] Cortical cataracts are those opacities that originate in the outer layers of the lens. They typically display overhydration and eventual liquefaction of the lens fiber cells secondary to electrolyte imbalance. Nuclear cataract occurs when modification and aggregation of lens structural proteins creates light-scattering zones in the central region of the lens. Posterior subcapsular cataract (PSC) is described as an accumulation of abnormal epithelial cells at the posterior pole of the lens and just inside the capsule. Instead of differentiating into elongated fiber cells at the equator in the normal manner, the cells assume an irregular form and are displaced toward the posterior pole. This type of cataract probably arises as a result of damage to DNA. Many individuals will develop pure cortical, nuclear, or PSC cataracts, but mixed cataracts are quite common. It is important to

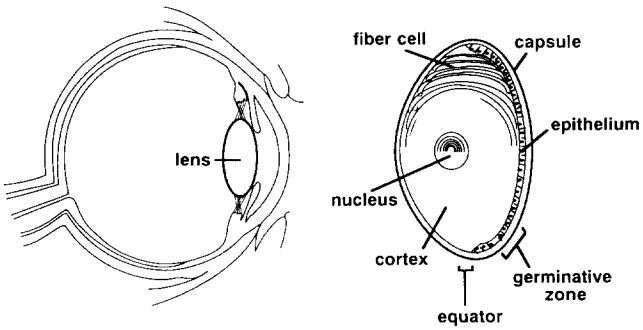

Figure 1 Cross-section of the mammalian lens showing typical organization and terminology. (Adapted with permission from Bunce, G.E. and Hess, J.L. (1988). Cataract—What is the role of nutrition in lens health? *Nutrition Today* **23**, 6–12.)

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recognize that age-related cataract in humans is a multifactorial disease that develops over decades. It is believed that oxidation is an initiating or very early event in the overall sequence that leads to age-related cataract. Oxidative damage may adversely affect lens membranes, thus driving a disturbance of electrolyte homeostasis. It may also cause modifications of proteins leading to protein aggregation and loss of enzymatic function. Mutations arising from oxidation of purine or pyrimidine bases can generate errors in differentiation of epithelial cells into fiber cells.

The function of the retina is to transform information in light to a form acceptable to the brain *(Figure 2)*. The retina is composed of highly specialized neurons called photoreceptors. Rods are nocturnal receptors with high sensitivity; thus they are crucial for night vision but contribute little to vision under well-lighted circumstances. Cones are diurnal light detectors. The light absorbing molecules, 11-*cis* retinaldehyde bound to proteins called opsins, are packaged within membrane-enclosed discs that are constantly synthesized and shed. Discarded material is phagocytized and digested by the lysosomal apparatus within the adjacent retinal pigment epithelium (RPE). AMD is a condition of degenerative changes in the RPE followed by death of associated photoreceptor rods and cones. These changes are believed to arise after failure of the RPE to perform its digestive function in an adequate manner with consequent accumulation of abnormal deposits called drusen within the extracellular space and lipofuscin within lysosomal residual bodies.[7] Although the specific pathogenesis of AMD is still unknown, chemical- and light-induced oxidative damage to the photoreceptor cells is considered to be an important determinant in the dysfunction of the RPE.

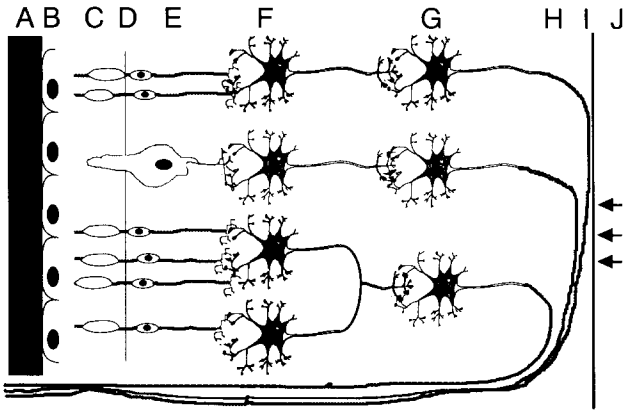

Figure 2 Structure of the vertebrate retina. (A) Choroid, with blood vessels; (B) Pigment epithelium, which produces melanin pigment to protect the outer limbs of the rods against intense illumination; (C) Rods and cones showing rhodopsin, which is present in the outer limbs of the rods (shown in black); (D) Outer limiting membrane; (E) Outer nuclear layer; (F) Inner nuclear layer of bipolar cells; (G) Nerve ganglion cells; (H) Nerve fibers, which run over the retina's surface and back into the optic nerve; (I) Inner limiting membrane; and (J) Direction of light rays. (Adapted from T. Moore (1957), *Vitamin A*, p. 269, Elsevier, Amsterdam, The Netherlands.)

Oxidant stress

Chemical reactions are a function of the electrons that surround the atomic nucleus. In covalent bonds, electrons are shared between atoms so that stable associations are formed. The direction of a chemical reaction is determined by the energy content and molar concentrations of the products and reactants. The likelihood of reaction, however, is dependent on the energy of activation, that is, the energy required for a productive collision. Redox reactions occur when electrons are exchanged between two species. Under circumstances where this exchange generates a product that has one or more unpaired electrons, a free radical will be formed. Two especially reactive free radicals are superoxide radical ($O_2^{\cdot-}$) and hydroxyl radical (·OH). Superoxide radical is the product of a one-electron reduction of molecular oxygen. Hydroxyl radical may be produced by interaction between superoxide, hydrogen peroxide, and transition metals such as iron or copper. Highly reactive free radicals can oxidize a large selection of organic molecules including lipids, proteins, carbohydrates, and nucleic acids. In some instances, the damage can be propagated in chain reactions through adjacent molecules. A further reactive metabolite of oxygen that is of special importance to the eye is singlet oxygen ($^1O_2$), which can be formed as an excited state of oxygen by the capture of light energy. The high energy electron thus produced may react with neighboring molecules before returning to its ground state. Oxidant injury to cells is dependent on the nature, concentration, and lifetime of the oxidant species; the tissue where reaction occurs; the nature and function of the organic target molecules; the potential for repair or replacement of damaged molecules; and the duration of time over which oxidant stress is applied. Living organisms are continually exposed to oxidants both from endogenous and exogenous sources. Endogenous sources of oxidants include mitochondrial respiration, enzymes such as lipoxygenase, xanthine oxidase, and the NADPH oxidase/myeloperoxidase system of phagocytes. Examples of exogenous sources of oxidants are natural dietary constituents, UV radiation, natural radioactive gases, and environmental pollutants such as car exhaust and cigarette smoke.

Phototoxicity

According to the quantum theory, a beam of light is composed of many units of radiation called photons. The energy of one photon is called a quantum of energy, and it varies according to the wavelength of the light. Light of shorter wavelength is more energetic than light of longer wavelength. Absorption of light involves the displacement of electrons within molecules. Only certain displacements are permissible; there must be correspondence between the energy value of the photon and the innate nature of the electron shell. The light energy thus acquired by the absorbing molecule will then be transformed in one of several different ways. The most common effect is release of heat. Other possibilities include molecular fragmentation, ionization, fluores-

cence, or formation of free radicals or excited molecules (as for example singlet oxygen) that may be highly reactive. Most of the visible light entering the lens is neither reflected nor absorbed but transmitted onto the retina. The high energy photons of the UV region, however, are absorbed with high efficiency and the thermal output promotes recemization of aspartic acid, deamidation, glycosylation, and partial hydrolysis; all of which can yield aggregation and destroy lens structural order with consequent loss of transparency.[6] The damage produced on any one day seems negligible, but the cumulative effects over decades in the absence of effective renewal processes leads to inevitable deterioration. Only a small fraction of the transmitted light that strikes the retina is absorbed by the visual pigments and used in the generation of vision. Current theory holds that light absorption by other molecules in the retina and RPE leads to thermal and photochemical damage and is an important component in the development of AMD. The seminal paper in this area was the study by Noell et al.[8] in which albino rats exposed to low levels of constant fluorescent light for extended periods of time developed retinal degeneration and this work has been confirmed and extended by many others. It must be admitted, however, that although the existence of an interrelationship between light exposure and aging of the retina and RPE is well established experimentally, direct evidence of chronic phototoxicity as a possible etiological factor in clinical AMD has not yet been brought forward.

Osmotic stress and glycosylation

The recognition that consumption of diets rich in lactose or galactose (>35% sugar by weight) caused lens opacities in rats has provided a highly valuable model for cataract research. Blood glucose and galactose enter the lens by passive diffusion. When the uptake exceeds the capacity of the usual metabolic pathways, the excess is converted to the respective sugar alcohols by the enzyme aldose reductase. This end product accumulates because it is not metabolized further and because it has a rate of outward diffusion that is slower than the rate of sugar entry. An osmotic disequilibrium is thus created that leads to swelling, increased membrane cation leakiness, increased vulnerability to oxidation, and cation imbalance. Rupture of fiber cells leaves vacuoles, clefts, and nonuniform areas of refraction.[9] Two clinical conditions associated with sugar cataract are galactosemia and diabetes. In the absence of these diseases, voluntary intakes of galactose and glucose or their precursors by humans are not likely to lead to lens osmotic injury. Diabetics under the age of 60, however, have a cataract prevalence that is three to four times that of the normal population.[10] Retinopathy is also a complication of diabetes. Of the approximately 11 million people in the US with diabetes, 40% have some degree of retinopathy, and it is second only to AMD as a cause of permanent blindness.[11] Diabetic retinopathy has a complex progression beginning with thickening of the capillary basement membrane and formation of micro-aneurysms culminating in neovascularization, vitreous hemorrhage, and retinal detachment. The time frame may be 5 to 30 years after diagnosis. Although the detailed metabolic pathway that leads to diabetic retinopathy is not known, hyperglycemia per se is considered to be the root cause of the problem. Osmotic stress arising from the activity of aldose reductase may play a role in pathogenesis, but vasoproliferative factors and platelet abnormalities are also suspected to be of great importance.

Nonenzymatic glycosylation may also be a pathogenetic factor in cataract and diabetic retinopathy.[12] Reducing sugars can react with lysine or arginine to form a Schiff base that in turn can rearrange to give an Amadori product. Glycosylated enzymes can show significant loss of function dependent on the specific conformational consequences of adduct formation. Short-lived proteins will then undergo digestion and replacement. With long-lived proteins, such as lens crystallins, further reactions and arrangements can occur, yielding irreversible products that have been termed Advanced Glycosylation End-products or AGEs. Van Boekel and Hoenders[13] have examined clear human lenses of different ages (4 to 81 years) and lenses showing senile or diabetic cataract. They found an increase in glycosylation in α-crystallin as a result of aging alone and a two-fold higher increase in age-matched lenses from diabetics. Ascorbic acid could also contribute to such a process in that it is an aldose and is present in high concentration in the lens. Nagaraj et al.[14] have described an ascorbate oxidation product, xylosone, crosslinked to human lens proteins, principally α-crystallins. A high correlation was noted between the presence of these pentosidines and lens pigmentation in cataractous lenses. Nucleic acids are another potential target for nonenzymatic glycosylation. Auto-oxidation of aldoses can also produce both free radicals and enediol products that are even more likely to generate Amadori products.[15]

Defenses against oxidant stress and phototoxicity

The primary mechanisms for defense against oxidant stress can be separated into two categories, antioxidant enzymes and antioxidant compounds. The enzyme superoxide dismutase (SOD) converts the superoxide anion into hydrogen peroxide (H_2O_2). In turn, H_2O_2 can be reduced to water by glutathione peroxidase using glutathione (GSH) as the reductant or electron donor. The GSH supply is renewed by drawing reducing equivalents from glucose through the hexose monophosphate shunt and glutathione reductase. Alternatively, H_2O_2 can be converted to water by the heme protein catalase. Antioxidant compounds react nonenzymatically to intercept oxidant molecules and terminate free radical chain reactions and produce harmless end products. Tocopherols (vitamin E) and carotenoids are lipid-soluble oxidant scavengers that protect biomembranes. Ascorbic acid (vitamin C) and glutathione are important water-soluble antioxidants. Ascorbate also reduces the tocopheroxyl radical and thus promotes regeneration of tocopherol. Other compounds such as uric acid, taurine, and the sulfhydryl-

rich protein metallothionein display antioxidant potential and may be of physiological relevance.

Phototoxicity defense consists of three options; renewal, benign light absorption, and vascular heat dissipation. Differentiated lens fiber cells, by virtue of their metabolic inertness, transparency, and lack of vascular supply, are largely denied the benefits of these mechanisms. The retina, however, makes use of all of them. Rod and cone outer-segment components are constantly synthesized as discs and are shed in a cyclic fashion and the discarded materials are phagocytized and digested by the RPE cells. In fact, it is the decline in the effectiveness of the disposal function of the RPE that is the central and identifying characteristic of AMD. The two principal retinal pigments not involved in the visual process are melanin and xanthophylls. Melanin is located in the melanin granules found in the apical portion of the RPE and in the melanocytes of the choroid, the vascular bed that nourishes the retina. Melanin absorbs light across the visible spectrum but most efficiently in the blue and near UV region and converts the absorbed energy to heat. It may also function as a suppressor of photosensitized molecules, including singlet oxygen, as well as a quencher of free radicals. In humans, synthesis and assembly of the melanin granules begins before birth and is completed by the second postnatal year. With aging, a gradual depigmentation of the RPE occurs, exposing the RPE and outer retina to increasing light hazard. Xanthophylls are a class of carotenoids containing oxygen functions. Lutein is 3,3′-dihydroxy-α-carotene, and zeaxanthin is the dihydroxy β-carotene analogue. Xanthophylls are concentrated in the macula or central region of the retina within the inner plexiform layer and the receptor axons. These pigments are also efficient absorbers of light in the blue end of the visible spectrum and lutein is a good quencher of activated O_2 and free radicals. They are derived solely from the diet. Non-polar carotenoids such as lycopene and α- and β-carotene are present in only minor (<3%) quantities.[16] Absorption of photons by melanins and xanthophylls protects against harmful photochemical effects, and the increased burden of heat is dissipated by the highly efficient choroidal circulation. On a per gram basis, the choroid has the highest vascular flow in the body. Finally, as noted previously, the proteins of the crystalline lens quite efficiently absorb UV light (<400 nm), thus shielding the retina from phototoxic effects but at the price of its own well being.

Experimental studies

Nutrient cofactors for antioxidant enzymes

The antioxidant enzymes possess mineral cofactors. The dietary availability of the enzyme cofactors, therefore, has the potential to limit effective enzyme activity. The relationship, however, is not simple. To determine the impact of cofactor deficiency on oxidant defense, one must consider the magnitude and duration of the deficient intake, the initial enzyme concentration and turnover rate, the binding affinity of the cofactor for the enzyme, the size of the oxidant burden, and the ability of other enzymes and of antioxidant compounds to compensate for lost activity. The oxidant defense system is a coordinated one with considerable interdependence.

Mammalian cytosolic SOD requires both Cu and Zn and its mitochondrial counterpart is a Mn-dependent enzyme. Even severe Zn deficiency does not appear to affect cytosolic SOD activity, but activity of this enzyme is depressed in numerous tissues when a copper-deficient diet is fed.[17] In a study with young Cu-deficient rats from Cu-depleted dams, imposition of hyperoxia (85%) for 1 week led to an increase in lung cytosolic SOD activity despite a decrease in lung Cu, and lung damage was not markedly increased as detected by magnetic resonance imaging (MRI).[18] On the other hand, Zn-deficient young rats exposed to hyperoxia were not able to increase lung activity of cytosolic SOD and showed more severe MRI-detectable lung damage.[19] MnSOD activity is significantly lower than normal in tissues of Mn-deficient animals, but concomitant increases in CuZuSOD are seen.[20,21] MnSOD activity has also been reported to increase under circumstances of lowered activity of the CuZn enzyme.[22] Most importantly for the subject under consideration, the characteristic deficiency syndromes for these three minerals in mammals do not include either lens or retinal degeneration that seems to arise directly from a loss in SOD activity. Zinc nutrition, however, has been linked to cataract in fish and to retinal abnormalities in the rat, as will be discussed later in the context of other biochemical mechanisms.

Both the enzymatic and spontaneous dismutation of $O_2\cdot$ generate H_2O_2, which itself is a dangerous cellular oxidant. The enzymes catalase and glutathione peroxidase require Fe and Se, respectively. They collaborate in the defense against peroxides. Feeding aminotriazole, a catalase inhibitor, to rabbits raises the concentration of H_2O_2 in the lens and induces cataracts,[23] but cataract does not develop in mice with an inborn deficiency in catalase activity. Iron deficiency is one of the major nutritional deficiency states in the world. Numerous Fe-dependent tissue enzymes have been shown to be lowered under conditions of Fe deprivation, and catalase is among them. However, neither lens nor retinal pathology is characteristic of chronic or acute Fe deficiency. Glutathione peroxidases catalyze the reductive destruction of both hydrogen and lipid hydroperoxides. The pathology of selenium deficiency is clearly linked to a failure in oxidant defense, but neither the lens nor retina appear to be the most vulnerable sites of injury. Cataract has been observed in rats fed diets extremely limiting in Se, but only after long periods of depletion sometimes requiring extension into second generation animals.[24,25] In summary, the mineral-dependent antioxidant enzymes are vital to the defense against oxidant stress, but nutritional deficits of their mineral cofactors do not seem to be likely candidates as factors in the emergence of senescent disease of the lens or retina. In fact, Fe, Cu, and Se in excess may pose potential hazards. Free Fe and Cu ions may catalyze production of the hydroxyl radical by reaction with superoxide and promote conversion of lipid hydroperoxides to free radical species. Sys-

temic administration of excess Se in the form of selenite is highly cataractogenic in suckling rats and damages rat and rabbit lenses in vitro.[26]

Glutathione reductase (GR) is responsible for the restoration of reduced glutathione from oxidized glutathione (GSSG). GR is an FAD-dependent enzyme, raising the possibility that riboflavin deficiency could be a factor in eye disease. Indeed, the earliest studies of the effect of feeding diets free of "B complex" to weanling rats reported a high incidence of cataract.[27,28] Subsequent research has confirmed cataract as an outcome of riboflavin deficiency in several species but has shown the incidence to be quite variable.[29] This variability may be related to the amount of coincident oxidant challenge. Srivastava and Beutler,[30] for example, showed that only 10% of rats fed a high galactose diet had visible cataract after 18 days when dietary riboflavin was adequate, whereas 80% cataract was found when riboflavin was also withheld. Flavins are light sensitive and exposure of unbound flavins to light can generate toxic byproducts and activated oxygen species. Increased fragility of photoreceptor outer segments has been reported in rats fed 12 mg riboflavin/kg diet, a value double the recommended level.[31] Batey and Eckhert[32] examined the effect of dietary riboflavin on flavin content of rabbit lens, cornea, and retina. Purified diets containing 3, 30, or 300 mg riboflavin/kg diet were fed to adult male rabbits for 1 month. In all tissues, the primary flavin detected by high performance liquid chromatography was FAD followed by FMN and riboflavin. Only minor increases were observed in flavin values in the eye tissues even at the highest dietary content, leading the authors to conclude that ocular flavin pools were saturated at the minimal intake level. Moreover, the absence of significant changes in flavin concentrations in whole blood as a function of diet suggested that dietary flavin excesses were either not absorbed or were rapidly excreted. The previous report of retinal pathology associated with an excess of dietary riboflavin needs further investigation.

Nutrients with antioxidant potential

The provision of enzyme cofactors or cofactor precursors in excess of the amounts necessary to assure enzyme expression and saturation will not enhance enzyme effectiveness. Antioxidant nutrients, however, function as reactants and their concentrations ought to be directly related to their benefits over some range of intake. An enormous body of evidence exists that supports this contention under a variety of in vitro and in vivo circumstances. Caution is necessary, however, because antioxidants may also act as prooxidants under given circumstances.

GSH and ascorbic acid are considered to be the most important water-soluble antioxidants. GSH is present in many cells at a concentration in the order of 5 mM. It is formed by enzymic catalysis from glutamate, glycine, and cysteine, the latter being a potentially limiting amino acid. The availability of cysteine is determined by its content in food protein and also the content of methionine, which can be converted to cysteine. The synthesis of GSH can be prevented by buthionine sulfoximine (BSO). Injection of very young mice with sufficient BSO to achieve near-total depletion of lens GSH is followed within a few days by the appearance of dense nuclear cataract.[33] Creation of a dietary sulfur amino acid deficit does not appear to create a selective decline of GSH of this magnitude nor specific lesions of the visual apparatus in mammals. Restriction of sulfur amino acid content sufficient to limit growth to 25% of normal was accompanied by grossly visible cataracts in 90% of fingerling Atlantic salmon after 12 weeks.[34] Dietary supplements of methionine or cysteine above the amount necessary for optimal growth do not increase cellular levels of GSH.

Ascorbate has been shown to efficiently scavenge superoxide, hydrogen peroxide, hydroxyl radical, peroxyl radical, and singlet oxygen. Frei et al.[35] used human blood plasma as a physiological model system with which to compare the antioxidant efficiency of ascorbate with that of protein thiols, bilirubin, urate, and α-tocopherol against the peroxyl radical. In the presence of 50 mM AAPH as a source of aqueous peroxyl radicals, ascorbic acid protected against lipid peroxide formation until it was entirely consumed. The response to increasing ascorbate concentration was linear up to 1 mM. Between 1 and 5 mM ascorbate, trapping efficiency declined, probably due to increased peroxyl-catalyzed autooxidation. Ascorbate can also act to protect membranes against peroxidation by reducing the tocopheroxyl radical, thereby renewing its radical scavenging ability.[36,37] In turn, ascorbate may be regenerated by glutathione or NADH by either enzymatic or nonenzymatic reactions.[38,39]

Ascorbic acid levels in human plasma are in the range of 25–50 μM but are generally far higher within cells indicative of an active uptake process. Ascorbate concentrations of up to 1.5 mM have been found in human lens, cornea, retina, aqueous humor, and vitreous humor.[40] Blondin et al.[41] studied the effect of dietary ascorbate on lens concentration of ascorbate and lens protein damage. Guinea pigs were fed a semi-purified diet containing either 2 or 50 mg ascorbate/day for 21 weeks. Lens ascorbate concentrations at the end of this period were 3.3 times higher in the high intake group relative to the low intake group, and the difference was highly significant ($P < 0.001$). Lens homogenates were subjected to photooxidative stress for up to 4 hours in the form of UV light at an exposure intensity comparable to a "sunny summer day in Boston." Examination of the homogenate proteins by sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed more extensive formation of high molecular weight aggregates (>200 kDa) in the 2 mg ascorbate-fed group as compared with the group fed the high ascorbate supplement, a result that was interpreted by the authors as suggestive of lens protein protection by dietary ascorbate. Varma et al.[42] incubated lenses from mature Sprague-Dawley rats for up to 3 hours in 95% oxygen in media containing xanthine:xanthine oxidase as a source of hydrogen peroxide and reactive oxygen species. Lens injury was evaluated by measuring the net accumulation of rubidium or alpha-amino isobutyric acid (AIB). Ascorbate was added to the medium over a concentration range of 0–2 mM. In the absence of ascorbate, uptake of Rb or AIB was decreased by fourfold. Incubation in the presence of

0.5 mM ascorbate did not prevent damage but did improve uptake to about 50% of normal. Further increases of ascorbate up to 2 mM were without added benefit.

Another model for cataractogenesis is streptozotocin-induced diabetes. Although the primary insult in this model is the osmotic stress induced by polyol accumulation, the disturbed metabolic state within the lens makes it more vulnerable to oxidative stress as well. Linklater et al.[43] administered streptozotocin to adult rats and evaluated the effect of either 0.3 or 1.0% ascorbic acid supplements to a powdered Purina diet on visual scoring of cataract and on leakage of γ-crystallins from the lens into the aqueous or vitreous humor. Following institution of the 1% ascorbate supplement, both serum and lens concentrations of ascorbate were increased by 34 to 42% within a few days and remained significantly elevated. A 1% supplement (about 200 mg/day) in the rat corresponds approximately to 4 to 6 g ascorbate/day in the human.. Diabetes caused five-fold and 2.5-fold increases in γ-crystallin, respectively, in the vitreous and aqueous humor, respectively, when measured at 10 weeks following injection of streptozotocin. This leakage was prevented in the aqueous humor by either of the supplement levels of ascorbate and reduced from five-fold to two-fold elevation in the vitreous fluid by the 1% supplement. The higher supplement also reduced the extent of visible lens damage.

Devamanoharan et al.[44] studied the potential of ascorbate to ameliorate the selenite-induced cataract. Intraperitoneal (IP) injection of sodium selenite (0.5 μmol/rat administered at the age of 10 days) in rat pups causes the appearance of large nuclear cataract within 3 to 4 days post injection. The primary insult is thought to be the production of hydrogen peroxide and free radical species.[45] Daily IP injections of 0.3 mmol sodium ascorbate beginning on day 8 post partum reduced cataract incidence from 85–95% to 13–41% (combined results from three separate trials).

Supplementation with ascorbic acid has also been found to be effective in protecting the retina against photooxidative injury. Organisciak et al.[46] raised weanling male Sprague-Dawley rats in the dark until the age of 60 days. Twenty-four hours before and just prior to the first light exposure, one-half of the animals were injected IP with 0.5 mg ascorbate/g body wt. (about 100 to 150 mg per rat per injection). Both supplemented and unsupplemented rats were then exposed to intense green light in an intermittent schedule with total exposures of 3, 8, or 24 hours. Supplementation increased retinal ascorbate levels 36% and significantly protected against loss of rhodopsin and DNA after either 3 or 8 hours of total light exposure.

Concerns have been raised about the prooxidant properties of ascorbate. Ascorbate can react with dioxygen to generate hydrogen peroxide. In fact, this is thought to be the major source of hydrogen peroxide in the aqueous humor.[47,48] In the presence of the free transition metals iron and copper, ascorbic acid fragmentation can occur, forming labile and highly reactive enediol products.[15] Studies on the interactions of ascorbate and lens proteins have produced evidence that oxidation and glycosylation can produce protein adducts that strongly resemble naturally detected lens products.[49–52] An important question is the availability of free copper and iron in the lens and other biological sites. Frei et al.[35] argue that binding of transition metals to proteins is sufficient to make oxidant damage unlikely. Garland[53] has stated that a review of the evidence supports the proposition that metal-catalyzed oxidation reactions make a significant contribution to the events of cataract formation. Bensch et al.[49] saw no increase in browning products in 10 lenses from five mice fed a diet containing 8.3% ascorbic acid from the age of 7 weeks to the age of 1 year. On balance it would seem that protein adducts derived from products of ascorbate oxidation probably do form during normal lens aging, but that the rate of this process would not be harmfully accelerated by moderate dietary supplements of ascorbate.

Carotenoids and tocopherols are the most important lipid-soluble antioxidant nutrients. The ability of carotenoids to function in photoprotection, radical quenching, and antioxidant activity has been well documented and studies with cell or organ culture or whole animals have consistently demonstrated the benefits of these compounds, especially in the inhibition of mutagenicity, malignant transformations, tumor formation, and immunoenhancement.[54,55] Relatively fewer studies have been performed on carotenoid protection of the lens. One such study did yield evidence of a beneficial effect in vitro.[56] Rat lenses were incubated for 4 hours in a standard medium in the presence of hematoporphyrin and light, a system that generates singlet oxygen. Photodamage was assessed by the decrease in capacity for rubidium uptake. Addition of 1 mM B-carotene maintained normal function, whereas neither SOD nor catalase delivered any beneficial protection.

The possible benefit of tocopherols to the maintenance of eye health has received considerable experimental attention. In studies with isolated rat lenses, vitamin E addition to the media protected lenses to a significant degree against swelling, degeneration, and cataract caused by irradiation,[57] excess glucose[58] or galactose,[59] corticosteroids,[60] or heat.[61] Nutritional supplementation with tocopherol also decreased lens damage in rabbits, mice, or rats challenged by streptozotocin,[62] 30% galactose diet,[63] oxidant treatment,[64] or irradiation.[65] Systemic delivery of 10 mg α-tocopherol every other day for 9 months strikingly reduced the percentage of cataract in Emory mice, a strain that spontaneously develops cataract between 6 to 12 months of age.[66] In a dietary study with Emory mice, 83% of untreated controls consuming α-tocopherol–stripped liquid diet displayed cataract at 10 months of age, as opposed to only 11% of animals fed the same diet supplemented with vitamin E.[67] Katz et al.[68] conducted a thorough light and electron microscopic study of the effect of a dietary antioxidant deficiency on the retina and retinal pigment epithelium of rats. A simultaneous deficit of tocopherols and selenium resulted in a dramatic accumulation of lipofuscin-like pigment in the retinal pigment epithelium along with a reduction of over 75% in the number of phagosomes per unit RPE cell length. These changes were accompanied by a pronounced loss of photoreceptor cells from the central retina. Stone et al.[69] and Hollis et al.[70] fed rats diets deficient in vitamin E and sele-

nium for 17 weeks and added the stress of hyperbaric oxygen for the last 15 weeks. They reported abnormal electroretinograms, photoreceptor cell necrosis, and extensive damage to the apical rod outer segment disc membranes as a consequence of this treatment.

Stephens et al.[71] investigated the effect of diet on the accumulation of α-tocopherol in ocular tissue in the rat. They used microdissection to obtain samples of appropriate size and measured α-tocopherol by a gas chromatographic-mass spectrometric technique capable of detecting less than 1 pg/g tissue. They employed AIN-76 as the basal diet (50 mg vitamin E/kg diet) and prepared additional diets containing either 3000 or 0 mg vitamin E/kg diet. After 102 days, whole lenses from animals fed the basal diet contained between 1 and 2 μg vitamin E/g dry wt and lens along with cornea, vitreous, and sclera showed "only minor change" in vitamin E content as a function of these variations in intake. By contrast, rod outer segments and RPE contained approximately 160 μg tocopherol/g dry wt when the animals were fed the basal diet, compared with 500 to 800 μg/g dry wt or 15 to 20 μg/g dry wt in rats fed the vitamin E-supplemented or depleted diets. This study clearly demonstrates that the lipid-rich retinal tissue significantly reflects variations in dietary intake of vitamin E, but that the lipid-poor lens contains little endogenous tocopherol and shows little change in concentration over a wide range of intakes. The apparent benefits of dietary vitamin E in protecting the lenses of intact animals against cataract may be indirect by lowering the total body burden of oxidant challenge.

Other nutrients with specific roles in ocular health

The relationship of dietary Zn to the activity of the Zn-metalloenzyme SOD has already been addressed. Zinc has additional functions that may be of importance to ocular health. The many studies of Zn deficiency in warm-blooded animals have failed to mention cataract as an outcome, although the vast majority have been of relatively short duration that might not have allowed sufficient time for development of lens opacities. A deficit of dietary Zn has, however, been clearly linked to cataract in fish raised commercially. Practical salmonid fingerling diets generally include fish meals and phytate-containing plant meals. Increased use of calcium-rich residues after filleting (white fish meal) lowered Zn availability through formation of calcium phytate chelates with Zn. Ketola[72] observed 75 to 85% cataract in fingerling trout after 16 to 38 weeks of consumption of a white fish meal diet. A supplement of 150 ppm of zinc completely prevented this response. The reason for the special vulnerability of trout lenses to a zinc deficit is not known, but it may be related to the prevention of protein phase transitions at cold ambient temperatures.

Other studies have suggested important links between zinc and retinal health. When weanling male Sprague-Dawley rats were maintained for 7 weeks on a diet containing 0.7 μg Zn/g, they showed markedly retarded growth and characteristic dermatologic signs.[73] Electron microscopic examination of the retina revealed vesiculation and degeneration of the photoreceptor outer segments and numerous large osmiophilic inclusion bodies in the retinal pigment epithelium. Retinal tissue was normal in pair-fed and weight-paired control rats. Newsome et al.[74] performed a clinical study designed to determine if zinc supplements might be useful in slowing or halting macular degeneration in humans. Daily supplements of 200 mg zinc sulfate (80 mg zinc) were taken by 80 subjects and 71 subjects received placebo capsules. To be included in the study, individuals had to have macular degeneration as evidenced by visible drusen with varying degrees of pigmentary change and visual acuity in one eye had to be 20/80 or better. Follow-up was performed at 6-, 12-, 18-, and 24-month intervals. The authors reported that although some eyes in the zinc-treated group lost vision, this group had significantly less visual loss than the placebo group at 12 and 24 months.

It has been suggested that zinc may play an important role as an antioxidant and membrane stabilizer independent of its presence in SOD. The evidence for this argument has been reviewed by Bray and Bettger.[75] Zinc may be able to stabilize critical protein sulfhydryl groups, thus preventing undesirable disulfide formation. Another possibility is that zinc can compete with proxidant metals such as copper and iron, thus decreasing their ability to transfer electrons. Zinc in pharmacological doses is able to induce synthesis of the sulfhydryl-rich protein metallothionein, a compound that can scavenge free radicals. Zinc ions may stabilize peroxidized membranes so that they can retain function. There is, however, only minimal evidence that excessive oxidation occurs in vivo in tissues from zinc-deficient animals.

The normal functioning of the retina depends on the efficient operation of the phagolysosomal system of the retinal pigment epithelial cells that are responsible for processing the turnover of retinal discs. At least one of the hydrolytic enzymes of the lysosomal apparatus, α-mannosidase, requires zinc and may be subject to age-dependent loss. Wyszynski et al.[76] measured the activity of six acidic glycosidases and three other enzymes (LDH, citrate synthase, and acid phosphatase) in cultured human RPE cells from donors of ages ranging from 19 to 80 years. Alpha-mannosidase was unique among these enzymes in showing a statistically significant decline in both specific activity ($P < 0.02$) and V_{max} ($P < 0.009$) but not K_m as a function of donor age. Moreover, addition of either 0.5 or 5.0 mM $ZnSO_4$ to the assay medium significantly increased specific activity from both young (<30 yrs) and old (>65 yrs) donor cells. The authors cited other references in which human α-mannosidase from non-ocular tissue was activated by up to 190% by elemental zinc. Previous studies of AMD have emphasized the conclusion that oxidation of the substrates for lysosomal digestion was the cause of impaired digestion and consequent accumulation of residual materials. This work suggests that decline in activity of a zinc-dependent degradative enzyme might also contribute to a loss in digestive capability.

Caloric restriction has been shown to increase longevity and slow senescence in various experimental models. The lens appears to show some benefit from this treatment. Leveille et al.[77] fed female mice diets that delivered

either 85 or 50 kcal/wk for up to 30 months of age. The calorically restricted diet was enriched with protein, vitamins, and minerals so as to equalize intake of these nutrients between both groups. Lens senescence was evaluated by measuring the rate of disappearance of the γ-crystallins, the smallest of the water-soluble structural proteins and the richest in thiols. Caloric restriction was consistently and significantly associated with a lower rate of loss of these proteins. Taylor et al.[78] maintained Emory mice from weaning to age 12 months on an otherwise complete diet that restricted caloric intake by 21%. The incidence of cataract was 85% (n = 29) in the ad libitum-fed group at the end of the study, as compared with 41% (n = 34) in the calorically curtailed group.

The effects of food restriction on the prolongation of life span of rodents have been recently reviewed by Masoro and Yu, who have investigated this phenomenon over nearly two decades.[79] Their results indicate that the retardation of the aging processes in food restriction is due to the restriction of energy intake rather than of a specific nutrient. Beginning caloric-deficit feeding (60% of ad libitum intake) at 6 months of age was as effective as starting at 6 weeks in its effect of the extension of life span. Low caloric intakes were accompanied by less lipid peroxidation and higher hepatic cytosolic levels of antioxidant substances and antioxidant enzyme activities. Restricted-fed rodents also experienced a significant lessening of blood glucose. In a longitudinal study, the mean 24-hour plasma glucose concentrations were determined from 3 to 25 months of age. The mean value of the calorically restricted group was 15 mg glucose/dL less than that of the ad libitum-fed controls. They conclude that caloric restriction retards the primary aging processes by enabling the rodent to utilize fuel in less damaging ways and thus blunts the toxic consequences of oxygen and glucose metabolism. It remains to be proven that caloric restriction would have an anti-aging impact of similar magnitude in humans, but the probability would seem to be high that it would.

Epidemiological studies

Studies with human subjects provide information on the strength of associations between personal, medical, and environmental factors and the frequency of a disease. Such studies can be powerful and valuable means of identifying and evaluating risk factors but are difficult to compare and can often be limited by small numbers of subjects or inadequate data collection. Moreover, it is difficult to know whether or not a single blood value for a nutrient is a reliable indicator of long-term status. Calculations from dietary recall can also be misleading. Nevertheless, credibility is enhanced by cross study agreement, and results reported during the past 10 years suggest a recurring theme that risk of cataract is inversely associated with dietary intake or plasma concentrations of vitamins C and E, riboflavin, and carotene.[80–87] Three of these studies were developed as sister studies with National Eye Institute support and utilized similar, but not identical, methodology.[83,85,87] Schoenfeld et al.[88] have examined and compared the results of these three case-control studies, which were performed at widely separate sites; Boston, MA USA, New Delhi, India, and Parma, Italy and recruited 1,380, 1,990, and 1,477 subjects respectively. The subjects ranged in age from about 40 to 79 years. Cataract was characterized by slit lamp examination into categories of nuclear (N), cortical (C), posterior subcapsular (PSC), or mixed. Nutritional information was gathered by dietary recall questionnaires and food composition tables. Each study employed polychotomous logistic regression analysis for calculation of relative risk in terms of odds ratios (OR). Blood studies were performed on a subset of subjects in each study.

Even in these studies that were intended to achieve similarity, circumstances arose that introduced various important disparities. For example, the Indian study utilized a different cataract classification scheme and excluded persons with diabetes or multiple vitamin users. The Indian subjects were younger and their diet and sociocultural background differed markedly from those of the other two groups. The nutritional status of the subjects comprising the Italian study was uniformly high, making it difficult to detect nutritional variables between subjects. Factors found to be statistically significant in at least one of these three studies are noted below. In the Indian study, a high blood antioxidant index (highest levels of RBC glutathione peroxidase and glucose-6-phosphate dehydrogenase and plasma ascorbic acid and vitamin E) was associated with decreased risk of PSC and mixed (PSC + N) cataract (OR = 0.23 and 0.12, respectively). Dietary protein was highly correlated with each of the other dietary variables. As a surrogate for nutritional intake, a high intake of protein was associated with a reduced odds ratio (0.84) for PSC, N, and mixed but not C. High blood copper and, surprisingly, high blood ascorbate, were associated with a higher risk of PSC + C and PSC + N, respectively (OR = 1.56 and 1.87). In the US study, high levels of blood vitamin E (N), a high blood albumin/globulin ratio (mixed), and a high blood iron (C) were linked to reduced risks (OR = 0.44, 0.41, 0.43, respectively). In addition, high levels of glycine and aspartic acid, chosen as indicators of dietary protein, decreased cataract risk (OR = 0.33). Risk for C, N, and mixed cataract was also reduced (OR = 0.40) in the US study for those with a high dietary antioxidant index and for all types of cataract in those persons claiming to take multivitamin supplements (OR = 0.41). The Italian study reported no significant associations between cataract and diet, but, as noted above, the uniformly high nutritional status of the population sample may have prevented a real comparison.

Another case-control study appeared in late 1992.[89] This report, conducted in Finland, consisted of an initial population of 1,419 persons enrolled during the period 1966 to 1972. Serum samples were drawn at entry and kept at −20° C until 1974, when they were thawed and analyzed for α-tocopherol, B-carotene, selenium, retinol, and retinol-binding protein. The latter is an indicator of overall nutritional state. Between January 1970 and January 1985, 22 men and 25 women from the initial group were admitted to ophthalomological wards with a diagnosis of senile cataract that required extraction. Two controls matched for sex, age, and municipality were selected for

each patient from subjects who had no record of a hospital discharge for cataract by the date of admission of the patient with whom they were matched. Odds ratios were computed for the lowest third compared to the two higher thirds using a conditional logistic model. Patients with both α-tocopherol and B-carotene concentrations in the lowest third had an OR of 2.6 relative to subjects in the top two thirds. Serum concentrations of selenium, retinol, and retinol binding protein were not related to the risk of cataract.

A recent large prospective study has been completed in the USA on a subset of 50,828 women drawn from the Nurses' Health Study.[90] The subjects were between the ages of 45 and 67 years at the onset of the study. When subject recruitment was completed in 1980, a questionnaire was sent to participants to determine the frequency with which they consumed certain foods over the past year, with nine options ranging from "once or less a month" to "more than six times a day." Intake scores were calculated using food composition data tables. Nutrient intakes were adjusted for total energy intake and were standardized to 1,600 kcal/day. Subjects were assigned to quintiles based on reported intake of each specific nutrient. Persons taking supplements or not were considered as separate groups. A total of 493 participants reported having undergone cataract extraction during the years 1984 to 1986. Relative risk was calculated using both age-adjusted and multivariate models. Women in the highest fifth of total carotene intake (14,588 IU/day) had an OR of 0.73 when compared with the lowest quintile. Intake of vitamin E or riboflavin in the absence of supplements was inversely related to risk (OR = 0.73 and 0.74, respectively) in the age-adjusted analysis, but significance was lost with multivariate analysis and in subjects who used supplements. The median intake of vitamin C with supplements ranged from 70 mg/day to 705 mg/day, but the association between estimated intake and cataract extraction was weak and nonsignificant. When relative risk was calculated according to the duration of supplement consumption, however, the use of a vitamin C supplement for more than 10 years conferred a significant 45% risk reduction using the multivariate analysis. Furthermore, when an antioxidant score was calculated by summing intakes of carotene, vitamins E and C, and riboflavin, women whose score was in the highest quintile (excluding supplements) had a 40% lower risk (multivariate model). These authors also calculated age-adjusted relative risk of cataract extraction by frequency of consumption of foods rich in carotenoids. Intake of carrots, the largest source of B-carotene, was not associated with incidence of cataract extraction and only weak associations were found for other yellow vegetables such as sweet potato and winter squash. Risk was 47 to 65% lower, however, in persons who ate spinach and other greens five or more times per week compared with those who consumed such foods less than once a week. Spinach, unlike carrots, is rich in the oxycarotenoids lutein and zeaxanthin, substances that are concentrated in the retina. One should not forget that these are associations that do not prove causal linkage and may in fact be markers for unidentified food constituents.

Many fewer epidemiological studies on diet and AMD have been conducted. The major work to date is the study performed by the Eye Disease Case-Control Group and published in two papers describing risk factors[91] and antioxidant status[92] in association with AMD. The authors selected only cases with the neurovascular or "wet" form of AMD as opposed to the atrophic or "dry" form. Neovascular AMD appears to be more visually threatening in that, while it was present in fewer than 10% of the subjects with AMD in the Framingham Eye Study, 79% of eyes with AMD and visual acuities of 6/60 or worse had the neovascular form. It has been suggested that underlying systemic vascular disease may be important in the pathogenesis of neovascular AMD. The subject pool consisted of 421 patients and 615 controls. Although no association was found with a history of cardiovascular disease, a relationship did emerge between neovascular AMD and several cardiovascular risk factors. A total blood cholesterol of >6.748 mM (261 mg/dL) was associated with a highly significant increased risk (OR = 4.1) when compared with subjects with <4.888 mM (189 mg/dL). There was also a strong positive association between current cigarette smoking and risk of AMD (OR = 2.2, $P < 0.002$). Postmenopausal estrogen users exhibited a significantly reduced risk (OR = 0.3). These results suggest that the prudent diet for reduced risk of cardiovascular disease might also provide benefits with regard to neovascular AMD. With regard to AMD and antioxidant status, it was determined that persons with serum total carotenoid levels in the medium to high range (1.024 to 2.393 μmol/L, >2.394 μmol/L) had markedly reduced risks (OR = 0.5 and 0.33, respectively) relative to those in the low group (<1.024 μmol/L). When carotenoids were examined as individual species; lutein/ zeaxanthin, β-carotene, α-carotene, and cryptoxanthin, but not lycopene, each displayed highly significant associations for reduced risk of AMD. In this study, however, no significant associations were seen for serum vitamin C, vitamin E, or selenium. Serum zinc was also evaluated, but no associations with AMD were detected whether or not the subjects were using supplements containing this mineral.

Conclusions

In the development of nutritional guidelines for the adult-elderly age group, it is important to distinguish between disease conditions that have distinct preventable causes and those that are an inevitable manifestation of senescence. Both of the principal eye diseases of the elderly, cataract and macular degeneration, appear to be outcomes of the multiple processes of deterioration that accompany aging. As stated by Young, "the transition from senescence to disease is signaled by a loss of vision."[6] Thus, nutrition is one of many factors that come together to influence the rate of progression of an individual along the continuum of biological decay. The challenge is to identify those factors that either hasten or delay the rate of passage.

All the experimental evidence points toward oxidant stress as a powerful factor in the aging process. Oxidative damage to DNA has been estimated in humans in the fol-

Table 1 Nutrients of importance in the retardation of age-related and diabetic deterioration of lens and retina

Category	Function	Requirements
1. Cu, Fe, Mn, Zn, Se, Riboflavin	Cofactors for antioxidant enzymes	Assure intake of recommended daily allowance (RDA)
2. Tocopherol, ascorbate, β-carotene	Intercept and eliminate oxidants and free radicals	Assure intake of RDA plus moderate supplement
3. β-carotene, lutein, zeaxanthin	Absorb UV light	Assure daily portions of fruits and vegetables
4. Dietary fat	Minimize vascular disease risk for "wet" form of ARM	Do not exceed 25% calories as fat. Follow American Heart Association guidelines.
5. Total caloric intake	Minimize risk of Type II diabetes (non-insulin-dependent diabetes)	Do not exceed 20% overweight. Exercise and maintain caloric discipline.

lowing way. Normal humans excrete a daily total of about 100 nmoles of three compounds derived from the repair of oxidized DNA thymine residues. This quantity represents an average of about 10^3 residues per day for each of the body's 6×10^{13} cells. Extrapolation from this number allows the calculation of the total number of oxidative hits to DNA per cell per day to be about 10^4.[93] To this must be added the number of oxidant molecules that strike proteins, lipids, and carbohydrates and those that are intercepted by the antioxidant enzymes and molecules. It is little wonder that deterioration appears to be an inexorable process. Nevertheless, it is also obvious that the antioxidant defenses are sufficient to allow a life span of 70 to 100 years. Thus, measures that diminish oxidant burden or support cellular recovery should slow the process of senescence. The most basic rule would be the assurance of regular delivery of all the essential nutrients so as to provide the body with the constituents necessary for vigorous and timely maintenance, repair, and replacement. The mineral and vitamin cofactors for enzymes that directly participate in oxidant defense; copper, zinc, iron, manganese, selenium, and riboflavin; ought to be provided in adequate amounts. A calorically sufficient, balanced diet should meet this need and quantities in excess of those required for enzyme saturation will provide no extra benefit and may pose a degree of hazard. More research is required to determine whether extra zinc beyond that needed for SOD and provided by a balanced diet can confer useful antioxidant protection or slow the rate of macular degeneration. At the moment, the data supporting these claims are, in my opinion, insufficient to warrant the risks of iatrogenic effects of excess zinc.

The antioxidant chemicals; tocopherol, ascorbic acid and carotenoids; can directly intercept and harmlessly eliminate oxidants and free radicals. There is an abundance of experimental and epidemiological data to show that these substances are able to diminish but not prevent oxidant and photochemical damage to the lens and retina (and other tissues) *(Table 1)*. The amounts required to achieve these benefits are often considerably in excess of the Recommended Daily Allowance (RDA). Fortunately these three chemicals exhibit very low toxicity.[94] I take the position that daily supplements of 200 to 400 IU of α-tocopherol and 100 to 250 mg of ascorbic acid are unlikely to be injurious and are likely to confer a beneficial level of resistance against unavoidable oxidant stress in many tissues of the body including the eye. β-carotene supplements of 25 mg/day are probably also of general benefit in reducing the total oxidant burden and may have specific anticarcinogenic properties.[95] The very low concentrations of β-carotene in the lens and the retina suggest that it may not have a direct impact on the visual apparatus. The oxycarotenoids lutein and zeaxanthin, however, are important antioxidants and light absorbing pigments in the retina. Fruits and vegetables are good dietary sources of all of these substances, especially the dark-green vegetables such as spinach, peppers, and broccoli, and should be consumed frequently. A low fat diet (<25% calories as fat) would offer the familiar protection to the vascular system and thereby lessen the possible contributions of vascular disease to the neovascular or wet form of AMD.

Long-lived lens crystallins, especially α-crystallins, are vulnerable to non-enzymic glycosylation, and this process can be accelerated by diabetes.[13] Glycosylation leads to conformational changes, crosslinking, and aggregation. Moreover, sugars in excess promote osmotic swelling and increased oxidant stress. In addition to the specific perils of diabetic retinopathy, diabetes increases cataract prevalence by 3 to 4 fold in persons younger than 65 years. Obesity, defined as more than 20% overweight, is considered a major risk for non-insulin-dependent or maturity-onset diabetes and 95% of diabetics fall into this category. These facts, coupled with the proven benefits of caloric-restriction in models of rodent aging and cataract, lead to the recommendation that weight control is a prudent, safe, economical, and effective strategy for diminishing diabetic risk and its attendant effects on ocular pathology. Important non-nutritional preventive measures would include abstinence from smoking and protection of the eyes from high-energy UV radiation. This combination of appropriate choices, moderate supplementation, and caloric discipline, all practiced for decades, should produce a lifestyle that promotes vigor, longevity, and visual health.

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