Nutrition and Eye Diseases

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Abstract *The eye is a delicate sensory organ exposed daily to bright light and environmental toxins. Light and toxins such as chemicals and smoke generate free radicals that cause damage in eye tissues. Therefore the eye is susceptible to degenerative diseases related to oxidative stress and aging. In macular degeneration, oxidized products of metabolism gradually build up in a layer underneath the retina, eventually causing retinal detachment and blindness. In glaucoma, the intra-ocular pressure builds up due to oxidative stress, causing retinal axons entering the optic nerve to progressively die. In retinitis pigmentosa, rods die from a genetic abnormality and cones progressively die due to oxidative stress. In diabetic retinopathy, high blood sugar causes progressive damage to the retina. High levels of antioxidants such as vitamins C and E in the body are associated with a lower incidence of these diseases, and oral administration of these and other antioxidants reduces oxidative stress and the disease risk. Success is dependent on a sufficient level of supplements taken over a sufficient duration of time. There is abundant evidence that many eye diseases can be effectively slowed or prevented using supplements of antioxidants and other essential nutrients at high enough doses.*

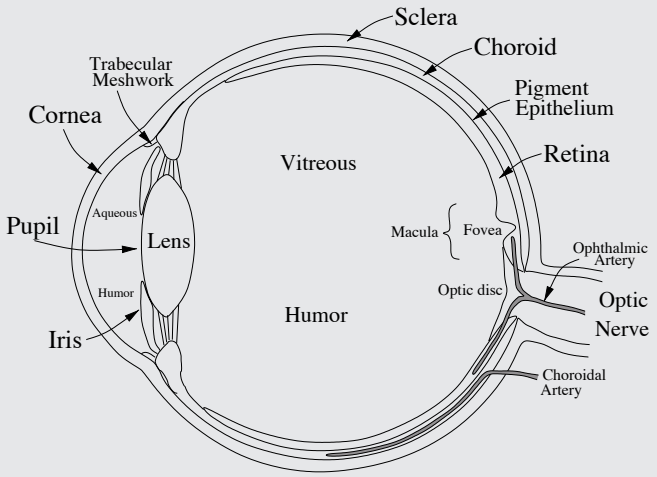
Structure and Function of the Eye

The eye is one of the most wondrous organs in the body because of its function, sight, but also because of its structure.[1] It is a sphere that maintains its shape with a higher pressure inside than outside. At the front of the eye, a clear protective coating called the cornea, nourished and lubricated by tears and a fluid inside the eye called the aqueous humour, allows our eyelids to quickly slide up and down. Behind the cornea and aqueous humour sits the iris which can open and close its pupil like a camera lens diaphragm. Just behind the iris sits the lens, which is a transparent tissue analogous to a camera lens comprising cells containing a clear crystalline protein. Behind the lens, filling most of the eye, is a gel-like transparent liquid called the vitreous humour. Near the back of the eye, attached to the inner lining of the eyeball, sits the retina. The neurons in the retina convert the light into electrical impulses, which are carried by the axons of ganglion cells across the surface of the retina to the "optic disc" where they exit the eyeball and become the optic nerve that carries visual impulses to the brain. The retina is attached to the "pigment epithelium" (RPE), a layer of cells that are continually active in the nourishment of the photoreceptors. At the back of the eye, behind the pigment epithelium sits the choroid, a plexus of blood vessels nourishing the pigment epithelium and retina. **Figure 1,** p.68.

Antioxidants

A variety of mechanisms cause damage to the biological machinery of life, and the eye is particularly susceptible because it is right at the surface of the body and is deli-

Figure 1. Structure of the eye



cate. Although oxygen is necessary to efficiently metabolize food and provide energy, it also can cause damage when an oxygen molecule binds to biochemicals in a way that damages them, called "oxidative stress." This can result in molecules with a free unbound and energized electron, known as "free radicals," which are highly reactive.[2] Free radicals can bind to any of a cell's biochemicals, damaging them. Such oxidative stress can also be caused by bacterial or viral infections, toxins, physical damage (bruises), or free radicals generated by light. The body's main defense against such oxidative stress is antioxidants such as vitamin C, vitamin E, and glutathione.[3] Vitamin C is transported into cells where it helps to maintain a reducing environment in the cytoplasm. Vitamin C in the cytoplasm and nucleus can prevent free radicals floating among the biochemicals there from damaging the intricate metabolic pathways and its DNA. It can also regenerate other antioxidants such as vitamin E and glutathione. Vitamin E sitting in the lipid bilayer of the cell's membrane can prevent oxidation of its fatty acids and proteins. Thus, antioxidants are essential to prevent mutations in a cell's DNA and to keep our cells functioning normally, so they are crucial for life and health.[2] Vitamin C is also important beyond its role as an antioxidant, for it is necessary in the synthesis of collagen, a crucial component of the body's organs and vasculature. Further, some evidence suggests that vitamin E acts as a cell signalling modulator to reduce damage in addition to its known antioxidant properties.[4,5]

Effects of Light on the Eye

The eye is the only part of the body besides the skin that is exposed to ultraviolet (UV) and blue light for long periods. Light rays that pass into the eye are damaging because the photons when absorbed can create free radicals that damage the essential proteins and DNA throughout the eye.[6] Although the cornea, lens, and retina are transparent, they all absorb a small amount of the light and thus are susceptible to damage over many years of exposure. This of course is one good reason to wear dark glasses and broad-brimmed hats outside; by reducing the high-energy light, especially UV and blue, you can greatly reduce your eyes' exposure to oxidative damage from light. Most of the UV is absorbed in the cornea and lens,[6]

but much of the blue light passes on to the retina, which has one of the highest metabolic rates of any tissue in the body. Because the retina contains a lot of polyunsaturated lipids, and has near-arterial oxygen concentration, higher than most other tissues, it has one of the highest risks of oxidative damage.[7,8] Mitochondria in the axons of retinal ganglion cells, necessary for the high metabolic rate, contain cytochromes that can absorb light and generate free radicals, damaging the cell's metabolism and ability to recover from further oxidative stress.[2,7,9] The iris helps to prevent the light damage. Its pupil, the central open area that passes light, is controlled by the brain according to the light intensity outside (and our mood), and its pigment absorbs light. The pigment, a melanin molecule similar to the pigment in skin, is a dark brown color; people with blue eyes are at greater risk of damage because the blue color represents a lack of the light-absorbing pigment.

The eye can recover and regenerate to some extent from the chemical reactions caused by light. Photoreceptor pigment, opsin, is located in flat discs located in the outer segments of the photoreceptors at the back of the retina. Each opsin molecule contains a sub-molecule, retinal, that is chemically modified (bleached) when it absorbs a photon, and must be regenerated. The bleached retinal is released by the opsin, and transported into the RPE cells, which regenerate it and transport it back to the photoreceptors. In addition, the photoreceptors slough off their oldest discs to allow them to be renewed. In a process called "phagocytosis," the old discs at the photoreceptor tip are removed and digested by the RPE.[10] New discs containing a fresh array of pigment molecules and enzymes are generated at the base of the photoreceptor's outer segment and move progressively outwards. Interestingly, whenever we go out into sunlight, virtually all of the pigment in our rod photoreceptors is bleached in a few seconds, and must be regenerated before we can see again in the dark.[1] The pigment is regenerated using vitamin A (retinyl or carotene) which we must obtain from our food. This is the normal process of vision, and the eye is normally able to keep this up over our whole lifetime, as long as we keep eating enough carrots or dark green leafy vegetables. But over years of exposure to sunlight, cells in the cornea, lens, and retina are damaged by photon absorption in other molecules besides the photoreceptor pigment. The energy in a blue or UV photon is great enough to break chemical bonds between atoms, and thus when a photon is absorbed, it can generate a free radical ready to attack any molecule nearby. After many decades spent outside in bright sunlight, the oxidative damage can build up and cause the cells to be dysfunctional or die.

Antioxidants and the Eye

Oxidative stress can overwhelm the eye's antioxidant defences, and many lines of evidence suggest that oxidative stress such as light exposure is a major factor in age-related eye diseases.[6,7] Early studies showed that aging eyes derived a prompt (within two weeks) benefit in vision from 600 mg of supplemental vitamin C. The benefit was thought to be in the retina, optic nerve, and their vasculature,[11] and was shown even for patients who did not have an acute vitamin C deficiency. The eye concentrates vitamin C by a factor of 25 over its level in the blood, which is thought to help the eye prevent damage caused by light.[12] The eye is also susceptible to other types of oxidative damage such as free radicals in the bloodstream caused by environmental toxins like smoke and pesticides. Smokers have lower vitamin C levels in the bloodstream and also in the eye, so they are at risk for eye diseases. Obesity is also a risk factor for eye disease, possibly due to increased oxidation of lipids and lower production of antioxidant compounds such as glutathione.[13] The carotenoids lutein and zeaxanthin, the principal phytochemicals in green leafy vegetables, are the primary constituent of the macular filter that removes blue light from traversing the retina. These are antioxidants and are thought to lessen oxidative stress in the macula, the central part of the retina. A diet supplemented with

lutein and zeaxanthin is associated with lower risk for eye disease.[13] Vitamin E is known to be helpful in preventing oxidative stress to photoreceptors *in vitro*[14] and can lower intra-ocular pressure. Further, vitamin E and other anti-oxidants such as glutathione have synergistic effects.[15] These lines of evidence may all be related, because vitamin C can regenerate vitamin E and other anti-oxidants to their reducing form. Recent evidence suggests that natural antioxidants concentrated in mitochondria are essential for preventing oxidative damage.[16] New antioxidants designed with properties that target mitochondria have been found to prevent damage in RPE cells, extend the life of mice, and prevent oxidative eye damage in dogs, cats, and horses.[8,17] Thus, abundant evidence suggests that anti-oxidants are important in preventing damage from free radicals in the eye.

Retinal Detachment

In a normal eye, the retina is only weakly attached to the pigment epithelium and can be easily separated by physical damage such as a blow to the eye or inflammation. In diseased retinas such as wet age-related macular degeneration (AMD) or diabetic retinopathy (see below), the attachment is weakened so retinal detachment is more common. When this occurs, fluid may accumulate beneath the retina, progressively detaching a larger area from the pigment epithelium. Wherever the retina is detached for more than a few hours from the pigment epithelium, the photoreceptors start to degenerate, and after a few days of detachment, the photoreceptors will start to die.[18] Once such damage has occurred, the remainder of the retinal neurons do not receive normal responses and will eventually degenerate and die as well. Thus, acute retinal detachment is a medical emergency, where quick treatment is very important to preserve sight. An ophthalmologist can save the retina by pulsing a laser to cause small spots of scar tissue in the retina and pigment epithelium that holds the retina in place at the back of the eye. Although good nutrition is important in recovering from a detached retina, taking adequate amounts of antioxidants throughout our lives is crucial to prevent the build-up of oxidative stress-induced damage that can cause retinal detachment.

Macular Degeneration

Macular degeneration is a progressive disease of the retina where photoreceptors slowly die near the center of the eye.[19] Age-related macular degeneration (AMD) is the leading cause of blindness in people aged 50 years or more worldwide.[20] In the "dry" form of AMD, cellular waste deposits called "drusen" and "lipofuscin" build up between retinal photoreceptors and the choroid. How or why these deposits build up is unknown. They are thought to be waste deposits caused by oxidative damage to the retina and pigment epithelium. In the "wet" form of AMD, new blood vessels grow from the choroid at the back of the eye, pushing the retina away from the choroid, tending to cause retinal detachment. Although a large risk factor for AMD is genetic, both forms are thought to be initiated by oxidative damage, consistent with a typical onset after age 50.

The single most important environmental risk factor for developing AMD is smoking, which causes oxidative damage in many tissues of the eye.[19,20] Several toxic chemicals present in smoke are known to induce cell death in the retinal pigment epithelium.[21] Other important risk factors are exposure to bright sunlight and inflammation.[19] Cumulative exposure to light is associated with AMD in people with low antioxidant levels.[22] Conversely, a diet with a low glycemic index, high in omega-3 fatty acids and antioxidants (vitamins C,E, zinc, and lutein/zeaxanthin), is associated with the lowest risk of drusen and advanced AMD.[23-27] The protective effect is thought to be greater when the antioxidants and other beneficial nutrients are taken at a sufficient level for a decade or more. Antioxidants can prevent oxidative stress-induced damage to arteries in the retina and choroid, which helps to prevent wet AMD. This benefit is thought to come from reducing free radicals.[28] A relatively low level of vitamin E (average of 300

IU/day) produced a small reduction in the risk for AMD, but a greater effect was shown for those who also took multivitamins.[29] The levels of supplements necessary to achieve an optimal reduction in AMD are easy to get but are not contained in most multivitamin tablets.[30] The level of vitamins C and E in most eye studies has not been high by orthomolecular standards, e.g. a vitamin C level of 500 mg/day or lower and a vitamin E level of 200-400 IU/day typically used in studies is considered low to minimal, and higher levels of these non-toxic antioxidants are very likely beneficial in the long term.

Night Blindness

A variety of problems with the eye can cause difficulty seeing at night. A reduction of contrast sensitivity from cataracts can cause low vision at night because glare from bright lights can obscure low-contrast details. Night-blindness from a lack of vitamin A to regenerate the rhodopsin pigment in the rod photoreceptors can be prevented with an adequate intake of vitamin A or carotene. Deterioration at the back of the eye generates waste products from oxidation of fatty acids (lipofuscin and drusen) that can cause night blindness symptoms and AMD. In some cases this has been cleared by application of polyphenols that remove metal ions.[31] Many genetic diseases can cause rod photoreceptors or other retinal neurons to die or malfunction, causing night blindness. A common type of night blindness is caused by retinitis pigmentosa.

Retinitis Pigmentosa (RP)

RP is a group of night blindness diseases related to AMD in which rod photoreceptors die, usually due to a genetic abnormality.[32] In a common form of RP, the cone photoreceptors survive but then progressively die, resulting in gradual blindness. This gradual cone death is thought to originate in part from oxidative stress due to free radicals generated by light, possibly through an effect on vasculature. The stress is thought to spread through oxidative damage to lipids.[33] Compared to rods the cones are scarcer and therefore use less oxygen. After the rods die in RP, the cones still receive the same amount of oxygenation from the choroidal blood vessels, so they are subject to increased oxidative stress. Antioxidants and omega-3 fatty acids can slow or prevent this damage. Vitamin C reduces oxidative stress in photoreceptors due to bright light, but only when taken before the light exposure, implying that it directly prevents free radical formation by light.[34] In a mouse model of RP, a supplement of vitamins C, E, and other antioxidants reduced cone cell death.[35] Genetic manipulation of a RP model that increased expression of natural antioxidants in cones also prevents cone cell death.[36] Further, people with a genetic abnormality that prevents vitamin E uptake are prone to RP,5,[37] supporting the oxidative stress hypothesis. Painkiller drugs that affect mitochondrial function are thought to cause oxidative stress and this may contribute to RP and other ocular diseases.[38] Depending on which genes are affected, vitamin A, necessary for vision, can delay loss of cone function in RP to preserve sight.[32,39]

Glaucoma

Glaucoma, a leading cause of blindness worldwide, is a progressive disease of the eye in which the nerve cells that send visual signals to the brain degenerate and gradually die. By the time this is noticed, it is usually too late to preserve sight. It is usually associated with high pressure inside the eyeball, which pinches the axons of the ganglion cells where they exit the eyeball. The pressure in the eye is created by fluid pumped into the eye from the bloodstream. The fluid pressure is drained by small canals around the edge of the iris. When the trabecular meshwork covering the canals gets blocked, the intra-ocular pressure increases and the optic nerves become damaged. Normal-tension glaucoma causes a similar type of damage to the optic nerve but is not associated with high pressure in the eyeball. It is thought to be caused by unusually fragile axons in the optic nerve, or restricted blood flow in the optic nerve.

In all types of glaucoma, damage to

their axons causes the ganglion cells on the surface of the retina to progressively degenerate. Oxidative stress is thought to be a common component in the degeneration of ganglion cells in glaucoma.[7] Oxidative stress has been shown in the axons of animal models of glaucoma, and free radical scavengers can prevent retinal ganglion cell death.[40,41] The damage to the axons may be worsened when micro-circulation of blood flow within the optic nerve is disrupted.[42] The ganglion cells are thought to die at different times during the disease because they receive differing secondary insults, including oxidative stress from light.[9]

The canals that normally regulate the intraocular pressure can be blocked by debris from degenerating eye tissue, especially the neurons of the retina, the iris, and lens due to oxidative damage from light absorption. The debris is carried to the canals where it can clog them and allow the pressure to build. The trabecular meshwork is also directly affected in glaucoma from oxidative stress which damages the meshwork cells and their DNA.[40,43] This can be countered very effectively with anti-oxidants such as vitamins C and E, lutein, and glutathione.

The standard treatment for glaucoma is to lower the intraocular pressure. High levels of vitamin C (2-10 g/day or higher) are very effective at reducing intraocular pressure, through its osmotic effect, and likely other mechanisms such as reducing lipid oxidation and increasing outflow through the trabecular mesh and canals that drain the eye.[44,45] In normal-tension glaucoma, supplemental magnesium may allow the blood vessels supplying the optic nerve to relax, increasing its blood supply. Increasing the neural energy supply is currently hypothesized to increase ganglion cell survival. One way to achieve this is with anti-oxidants that scavenge free radicals generated by light and oxidative stress.[41] To preserve ganglion cells under oxidative stress, oral supplements to enhance mitochondrial function such as lipoic acid, niacinamide (vitamin B_3), and creatinine may prove useful.[42] In glaucoma, levels of vitamin C and other antioxidants such as glutathione are lower inside the eye, suggesting that they are protective against damage.[46] Although glaucoma is not considered to be a vitamin deficiency disease, vitamin E is known be an important regulator of the oxidative damage that causes glaucoma.[15] Vitamin E can delay the onset of glaucoma symptoms in retinal blood vessels.[5]

Diabetic Retinopathy

Diabetes is produced by an inability to utilize blood sugar which causes damage to tissues throughout the body. Insulin secreted by the pancreas causes cells of most tissues to take up glucose from the bloodstream. Because the retina does not respond to insulin, it is particularly susceptible to diabetes and to damage caused by high blood sugar. Several nutrients, including alpha-lipoic acid, vitamins C and E, magnesium and zinc are thought to increase uptake of blood sugar and reduce blood pressure, and are known to be helpful in preventing retinopathy.[47]

Cataract

Cataract is another leading cause of vision loss very common past age 60. During most of our life, the lens tissue can actively repair itself to keep the lens proteins intact. But with old age and damage due to oxidation from absorbing UV rays and ionizing radiation, the lens tissue cannot maintain itself in good condition,[6] and its crystalline protein becomes cloudy and absorbed water causes it to swell. Airline pilots have a higher rate of cataract, thought to be caused by their exposure to radiation from outer space.[48] Although currently there is no treatment to cure cataracts, their onset can be delayed or prevented by antioxidants in the diet. The blood level of vitamin E is lower in patients with cataracts, suggesting the use of supplements to prevent cataract occurrence.[5,49,50] A combined supplement of vitamins C, E and other antioxidants such as selenium and lipoic acid is helpful in reducing the occurrence of cataracts,[13,45,51] and this is thought to remove free radicals and enhance the activity of glutathione in the eye. Vitamin supplements are associated with reduced risk of cataracts if taken for 10 years or more.[45,52]

Need for Sufficient Doses

What are we to make of these tantalizing results and tentative conclusions? From test tube and animal studies, it is clear that to effectively neutralize free radicals the level of antioxidants must be sufficiently high. Indeed, large human studies using relatively low levels of supplemental nutrients have sometimes found little effect. For example, some randomized controlled trials (RCTs), widely considered to be the gold standard for testing the benefit of supplements, have not shown statistically significant health benefits for antioxidants. But when a benefit of supplements from an observational study on a specific at-risk group is backed up by a likely mechanism such as preventing oxidative stress, a negative result in a RCT cannot trump the positive result in the observational study.[53] The reason is that RCTs can be confounded by bias factors such as the complexities of diet and daily habits such as smoking and related physiological and disease states. For example, some participants who take supplements are at risk because they have early indications of disease. Alternately, participants who take supplements may be health-conscious individuals without indications of disease. Both of these possibilities will introduce bias in a study about the benefits of supplements, which can confound the conclusion of the study.[53]

Thus, it seems likely that the equivocal results from some RCTs testing the benefits of antioxidants for prevention of eye disease are a consequence of the relatively low doses of supplements involved. For example, the amount of vitamin C typically taken in RCTs (often 500 mg or less) would not be expected to show a large effect.[3] The effects of low supplement levels on eye diseases are likely to be confounded by differences in diet correlated with other risk factors.[54] Further, many RCTs testing the effect of antioxidants on eye diseases have collected only short-term data (less than a few months) on antioxidant intake. Because oxidative damage in the eye is age-related, antioxidants are more likely to be beneficial when taken at relatively high doses over several decades.

Orthomolecular Doses

Although the minimum RDA for nutrients prevents the symptoms of acute deficiency, taking additional amounts of nutrients (i.e., orthomolecular doses) allows the body's metabolic reactions to proceed more fully, providing a greater health benefit.[55] An individual's need for nutrients such as vitamins C and E differs depending on their unique genetics, biochemistry, diet, and level of stress and disease.[3,51,56] Vitamin C cannot be synthesized by humans, primates, and guinea pigs, but most other animal species make 10-20 g/day (relative to human body weight), and they make more when they are stressed physically or by disease. Typically vitamin C is titrated to bowel tolerance, which for a healthy individual is an oral dose of 2-10 g/day. However, when disease or oxidative stress affects the body, the gut absorbs more vitamin C according to the body's need, and then the individual's bowel tolerance can be ~ten-fold greater.[3] Vitamin E to prevent oxidative stress and disease has been shown to be safe and effective at high doses (800-3,200 IU/day) for most people.[57] For these "mega-" doses, the benefit in reducing oxidative stress is likely to be more obvious. When taken in combination, a cocktail of nutrients including antioxidants dosed according to the individual's need will likely multiply the beneficial effects.

Common Benefit

Current knowledge about the risk of oxidative stress for eye diseases suggests the use of nutrient supplements because of the extensive literature over the past 70 years showing large benefits. Yet, because the necessary random controlled trials to test the optimal combinations and levels of supplements in eye disease have not been performed, the proper rationale depends on one's outlook; should one simply heed the standard conservative advice to wait until more is known before taking supplements?[53] From the evidence, it is apparent that many eye diseases have a common root in age-related oxidative stress, and that a common set of antioxidant supplements is likely to

be helpful. What combinations and doses of supplements are optimal? The field of nutrition and age-related oxidative stress is moving quickly, and as more trials of dietary and supplemental nutrients are published, we will surely learn much more about which combination is best. However, because the efficacy and safety of vitamins and nutrients is well known,[3,55] the rationale for picking the combination of nutrients seems clear. Individuals should take generous doses of those vitamins and nutrients known to be non-toxic, and a helpful guide is the orthomolecular literature.[55] Those with special conditions or needs should consult a nutrition-aware medical professional for precautions and to determine doses. Antioxidants are known to be synergistic, and it seems likely that a combination that maximally protects against age-related cataract, for example, may also be effective in protecting against retinitis pigmentosa, macular degeneration, diabetic retinopathy, and glaucoma.

Conclusion

A combination of nutrients is most effective. A multitude of evidence shows that supplemental antioxidants and nutrients are effective at preventing eye disease, and when taken in combination is more effective than one or two taken alone. Thus, vitamins C, E, carotenoids (lutein/zeaxanthin), zinc, selenium, magnesium, omega-3 fatty acids, when taken at the proper levels in combination with a well-balanced diet containing lots of fruits and vegetables over a decade or more, can do much to prevent oxidative damage to the eye and prevent or delay the onset of typical age-related eye diseases.[24,45,47] Zinc is found in relatively high concentrations in the retina and is necessary for several enzyme systems to preserve health.[24] Selenium in the proper amount is an important antioxidant and can help to prevent macular degeneration. Supplemental magnesium can correct a very common deficiency, and helps to reduce blood pressure, maintain health of arteries, and prevent retinopathy. The carotenoids are helpful in preventing light from reaching the macular photoreceptors, and are antioxidants that help to prevent oxidation caused by light. Vitamin E is helpful in reducing oxidation of fatty acids in cell membranes, which is very important for reducing damage to the retina and its photoreceptors. Vitamin C is helpful to prevent permeability and fragility of capillaries, and to neutralize free radicals, and it helps the body to regenerate vitamin E. It is also helpful in reducing oxidation in all the tissues of the eye, and in reducing ocular pressure to prevent glaucoma. Although proper nutrition is not a panacea, when taken together in a medically supervised program, these nutrients can do much to prevent diseases of the eye (and in the rest of the body). They are most effective taken at a sufficient level starting early in life.

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