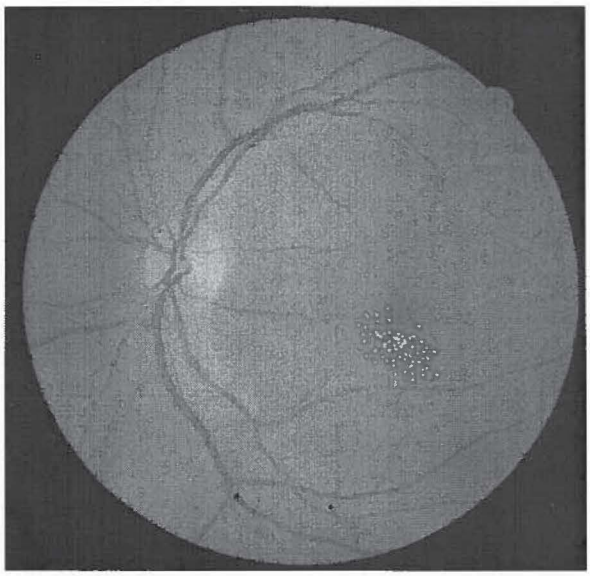
ARMD

CHANTEL S. LIGHTNER

Senior Paper / Michigan College of Optometry
Advisor Dan Wrubel O.D.



Age Related Macular Degeneration

Age-Related Macular Degeneration (ARMD) is a degenerative disease of the macula. The macula, which is the part of the retina responsible for our central vision, can be severely affected. In fact, ARMD is the number one cause of legal blindness in the United States today.[3,15] There are many risk factors for this disease process, such as a possible hereditary component, higher levels of serum cholesterol, smoking (which increases the risk of developing ARMD 2.5 times)[1,2], and cardiovascular disease (which nearly doubles the rate of visual impairment in patients with ARMD).[1,2] However, the biggest risk factor for ARMD is age. The statistic that up to 33% of the population 75 years and older have some form of ARMD[3] coupled with the prediction that the number of people aged 65 years and older will have doubled (as compared to 1990) by the year 2050, makes ARMD a frightening disease.[22,27] For this reason, much research has been done in recent years on a number of possible treatments and preventative measures. Many studies have focused on the use of antioxidants.

To someone just diagnosed with ARMD, the concept of what the disease can do to their vision can be terrifying and mysterious. And the information on antioxidant use can be confusing and vague. This paper, then is designed to help professionals involved in health care as well as patients being diagnosed with ARMD (or their family and friends) to understand what ARMD is, the process underlying the disease, and to review some of the studies concerning antioxidant treatments. In order to do this, we must start at the "beginning" with retinal anatomy.

Review of Retinal Anatomy

The retina is the neural tissue on the back of the inside of the eye. It functions to receive light information and to transmit that information, through the optic nerve, to the back of the brain where it is interpreted. The retina consists of ten layers (diagrammed below).

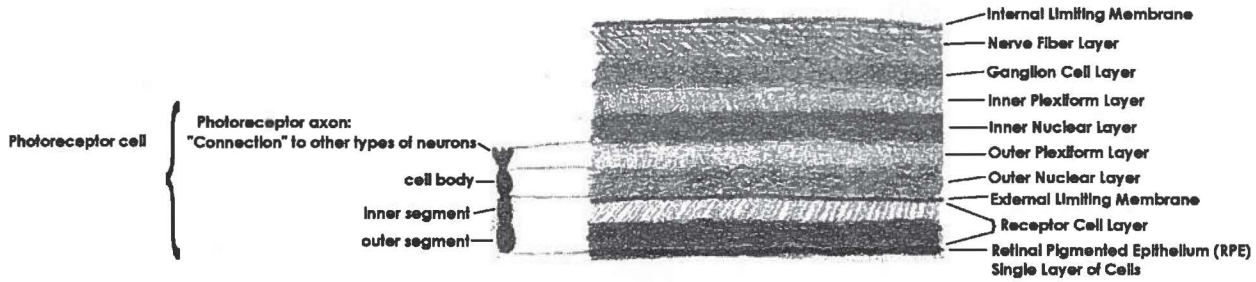


Figure 1

Each layer has a separate function and contains different types of cells. The two layers of most importance to the discussion on ARMD (age-related macular degeneration) are the photoreceptor cell layer and the retinal pigment epithelium, or RPE for short.

The photoreceptor cell layer contains the inner and outer segments of rods and cones. These photoreceptor cells absorb light energy and turn it into electrical impulses which are eventually transmitted to the back of the brain via the optic nerve. Absorption of the light energy occurs in the outer segments of rods and cones which are full of coin-like structures that are hollow on the inside and contain photopigments in their outer membranes. The photopigments absorb light energy causing a change in their overall molecular configuration. (Figure 2) This change in configuration is what sets off the chain of electrical impulses that will be sent to the brain. Visual pigments must resume their original configuration in order to again be able to absorb light energy and set off the chain of electrical impulses. Therefore, receptor cells must constantly generate new discs as eventually the photopigments in their membranes become unusable. Rods, which have approximately 1000 discs in their outer segment, form 1 to 5 new discs per hour. And, because as new discs are formed the older ones must be sloughed off, shed approximately 30 of the old discs at a time.[21] This is done in the morning or after a period of darkness. Cones, on the other hand, shed discs at night and are much slower to replace them. Cones take nine months to a year to completely replace an outer segment while rods replace an outer segment in 8 to 14 days.[21]

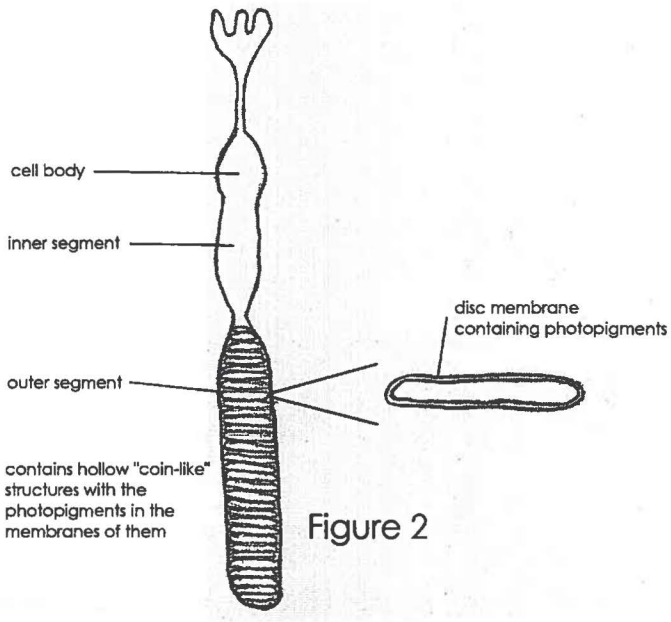
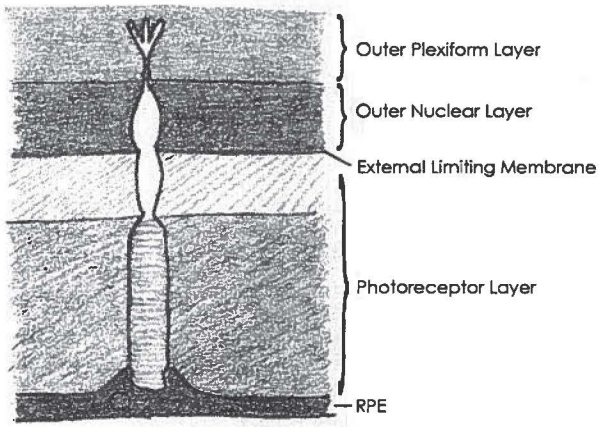


Figure 2



The RPE will engulf the end of a photoreceptor cell.

It will take this end and "digest" it by fusing it with a lysosome which contains digestive enzymes.

Figure 3

So what is done with the old discs that are sloughed off? This is where the RPE (retinal pigment epithelium) comes into play. The RPE is the most posterior layer of the retina. It is a single layer of cells with many functions, one of which is to phagocitize - or eat and destroy - the old discs. An RPE cell takes up the old discs and uses enzymes to "digest" them. (Figure 3) This is an enormous task when you consider that there are about 120 million rods and 6 million cones in the human retina and that each RPE cell must digest the discs from approximately 45 photoreceptor cells.[21]

In addition to phagocitizing shed photoreceptor outer segments, the RPE helps to maintain the sensory retina by transporting nutrients from the choroid (the vascular tissue underneath it) to the photoreceptor layer. In turn, it also transports the waste products from the photoreceptor cells back to the choroid. It does this by maintaining a barrier between the retina and the very vascular choroid through which it allows only certain molecules (nutrients and cellular waste) to pass. This barrier is called the outer blood-retinal barrier. Bruch's membrane, which is situated directly underneath the RPE and separates it and the choroid, helps to maintain this barrier. (Figure 4) The RPE's relationship to Bruch's membrane is crucial to the normal metabolic functioning of the retina because of this blood-retinal barrier it provides and because of the transport of materials to and from the choroid.

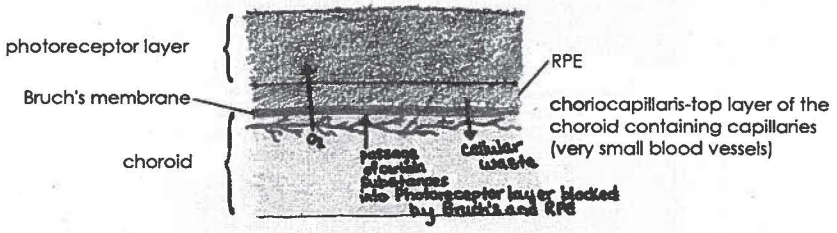


Figure 4

The choroid is the vascular tissue beneath Bruch's membrane. The layer adjacent to Bruch's membrane is called the choriocapillaris because it contains many capillaries (very small blood vessels). These capillaries have fenestrations, or openings, in their outer walls which make them "leaky". This is one of the reasons why there must be an outer

blood-retinal barrier so that the retina does not take up too much of the "leaked" material from the choriocapillaris which might disrupt the delicate interconnections between the layers.

The retina obtains nutrients from two different sources. One of which is the choroid which supplies the outer retina. The other source are the retinal vessels. These retinal vessels, unlike those in the choriocapillaris, do not leak and therefore allow only certain nutrients to pass to the retina. This is called the inner blood-retinal barrier. These vessels provide the blood supply to the inner two thirds of the retina and the choroid supplies the outer third.

One area where there are no retinal blood vessels is the macula. The macula is the portion of the retina which is responsible for central vision, the most detailed vision. It does not have the ten layers of tissue like to rest of the retina. It has only the outer portions. Because of this, the macula must receive its blood supply solely from the choroid. (Figure 5) This relationship between the macula and the choroid necessitates the crucial maintenance of the outer blood-retinal barrier and the transport of nutrients and waste through the RPE for the survival of the macular cells. If the functioning of the macular cells (mostly cones) becomes impaired or if cells are destroyed, then central vision is lost, as in Age-Related Macular Degeneration.

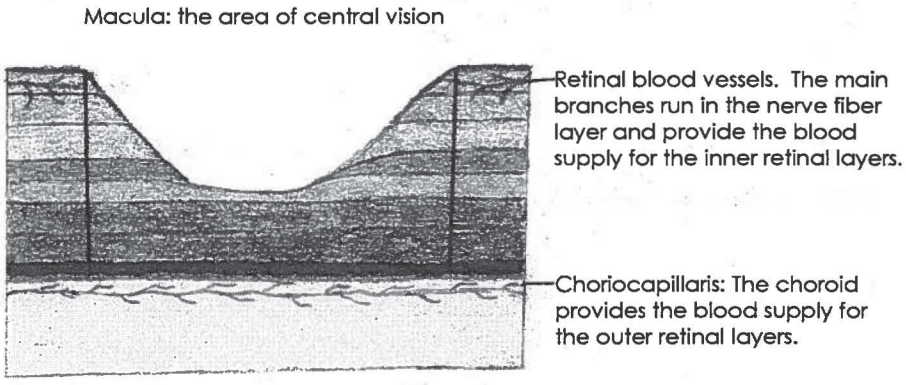


Figure 5

ARMD Changes in the Retina

What happens to the retina with ARMD is of major concern. The first sign of ARMD in the human retina is the presence of cellular deposits in Bruch's membrane called drusen. Drusen can be detected in over 70% of people over the age of 50 (but do not negatively affect all eyes).[3] This deposition of material disrupts the delicate balance between the photoreceptor cells, RPE, and choroid. (Figure 6) First it causes an alteration in the amount of oxygen that both RPE and the photoreceptor cell layers receive from the choroid. Hypoxia, or lack of oxygen perfusion to the tissue, results in cellular malfunction and death. Malfunctioning of the RPE causes additional increase of cellular deposits and lack of transport of oxygen to the photoreceptors. This is especially important in the macular area because, as you may remember from the discussion on retinal anatomy, the macula receives its nutrients (for example oxygen) only from this transport by the RPE from the choroid. Additionally, the macula is a highly metabolic tissue and, thus, requires more oxygen than the rest of the retina. It becomes a viscous cycle because as drusen disrupts Bruch's and disrupts the functioning of the RPE, the hypoxic RPE creates more cellular deposits and thus less perfusion of oxygen to the retina.

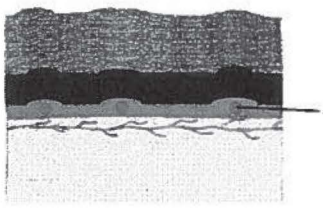
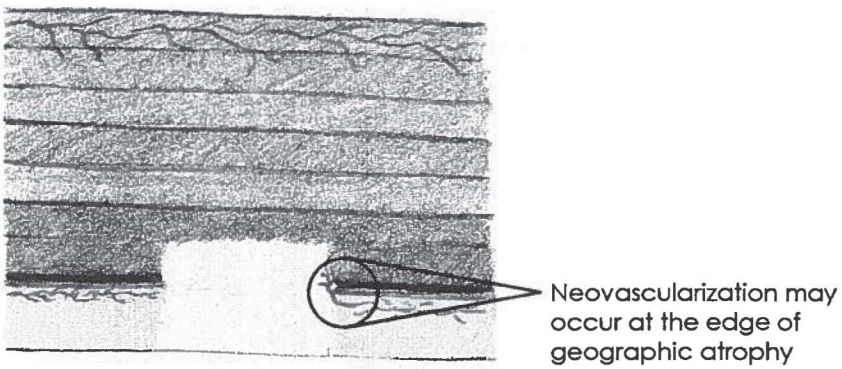


Figure 6

This mechanism of cellular deposition, tissue hypoxia, cellular malfunction, and cell death is the process that occurs in the atrophic or "dry" form of ARMD. It appears as "geographic atrophy" or wasting away of a well demarcated area of retina. First by loss of the RPE and choriocapillaris and secondarily with loss of the photoreceptors directly associated with that region.[3] (Figure 7) Although this can cause a severe decrease in vision, the prognosis



GEOGRAPHIC ATROPHY: loss of the choroid and RPE with secondary loss of the photoreceptor layer

Figure 7

for people with the dry form is fairly good. It takes an approximate loss of 80% of the photreceptor/RPE complex before a line loss of vision on the Snellen chart can be detected.[1,2] In fact 90% of people with dry ARMD will never progress to legal blindness and only 10% of people will develop the more severe "wet" form of ARMD.[3]

In some patients with the dry form of ARMD, the deposition of material in Bruch's membrane may cause the RPE to detach from it. This in turns creates additional hypoxia, additional dysfunction of the cells, and cell death. Up to 30% of people with RPE detachments, where the RPE has separated from Bruch's membrane, may develop new blood vessel growth, or what is called neovascularization.[3] (Figure 8) Neovascularization may also occur at the edge of an area of geographic atrophy. Although the atrophy generally indicates that the choriocapillaris has wasted away, and therefore can not grow new vessels, healthier retina at the edge of the area may be able to support the new growth.[3]

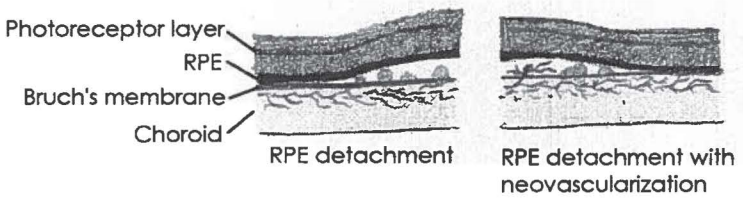


Figure 8

When neovascularization occurs, it is called exudative or "wet" ARMD because the new blood vessels are leaky. Because the outer blood-retinal barrier (RPE and Bruch's membrane complex) has been compromised, these vessels can leak fluid through the breaks beneath the RPE. This would be called a serous RPE detachment. If the RPE is compromised so that the fluid may also leak underneath the photoreceptor layer, this layer may detach creating a serous retinal detachment. Additionally, these new blood vessels may bleed possibly causing subRPE hemorrhages and subRetinal hemorrhages (Figure 9). Unfortunately, 90% of people who develop wet ARMD will become legally blind.[3] They lose dramatic amounts of vision because the fluid and blood, along with possibly detached RPE and retina will become fibrotic and form scar tissue underneath the

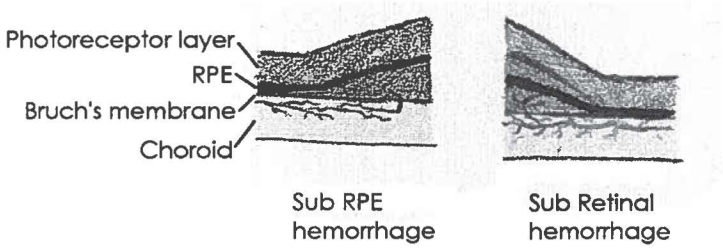


Figure 9

macula. This is termed disciform scarring and is what eventually causes the greatest loss in vision.

Discussion on the Possible Mechanisms Involved in ARMD

It should be obvious that the deposition of cellular waste causes many problems in the retina. ***So what causes this deposition?*** There are several possible mechanisms that may, together, work to create this situation.

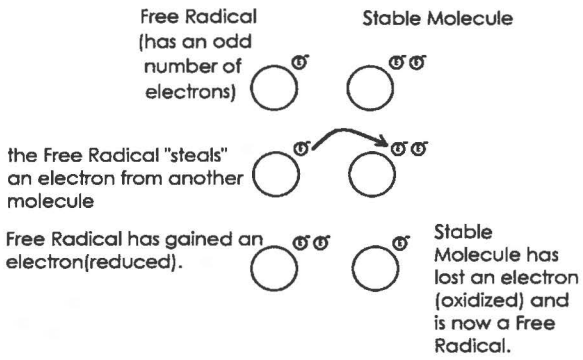


figure 10

A popular theory is that drusen accumulation may be a result of damage to photoreceptor outer segment membranes by free radicals. ***But what exactly are free radicals?*** A free radical is an unstable highly reactive molecule. In general, molecules must have pairs of electrons (which carry a negative charge). If there is an odd number of electrons then the molecule will become highly reactive and unstable. In order to stabilize, the molecule will "steal" an electron from another molecule . This is called reduction, when a molecule adds an electron (increases its negative charge). Unfortunately, this causes the second molecule to become a free radical itself (it loses an electron which decreases its negative charged, therefore it has been oxidized), and the process continues. (Figure 10) Photoreceptor cell membranes are extremely susceptible to this process because they contain polyunsaturated fats in their membranes. Polyunsaturated fats contain a number of double bonds between their "segments". Double bonds are convenient sources for electrons. Therefore, free radicals "attack" these double bonds. To complicate matters, oxygen derived free radicals are the most reactive, and because the retina requires a great deal of oxygen in order to function, it also has a large number of oxygen derived free radicals.[3, 8, 15, 22, 27]

So what causes the free radicals? Free radicals are generated by normal metabolic functioning. They are also generated by various environmental factors, such as cigarette smoke or electromagnetic radiation (light energy).[15] The visible light spectrum is from approximately 400-700 nm, with ultraviolet radiation being shorter than 400nm and infrared radiation being longer than 700nm. In the human eye, wavelengths

below 400nm are generally absorbed by other structures of the eye, namely the cornea and lens, before arriving at the retina. However 400-500nm light, or what is called blue hazard light, is able to penetrate to the retina.[22, 27] It is theorized that, because shorter wavelengths of light have a higher amount of energy per quanta (per "package" of light) that the blue light hazard wavelengths have enough light energy to stimulate a change in the configuration of photopigments with energy left over to create free radicals. These then go on to stimulate the chain of free radical formation that damages the photoreceptor cell outer segment.

When the RPE attempts to digest these altered photoreceptor outer segments, its enzymes do not recognize them and therefore do not degrade them completely. This creates cellular waste called lipofuscin (when deposited in the RPE) and drusen (when deposited in Bruch's membrane).[14, 21] The precise relationship between lipofuscin and drusen has not been established, however both are considered to be forms of cellular debris.[14]

Now that we have established a theory for the deposition of cellular waste in the RPE/Bruch's membrane complex, ***what exactly happens to create the macular changes in ARMD?***

It is possible that lipofuscin in the RPE is just cellular debris that fills up so much space in the RPE cell that it interferes with normal metabolic functioning. Another means by which RPE cellular deposition may cause problems is that it may leak molecules that are abnormal for the cell, and therefore toxic to it. This toxicity can also affect cellular function. Lastly, it has been postulated that lipofuscin, which is autofluorescent, absorbs the shorter wavelengths of light and then re-emits them at other wavelengths, causing further photodynamic damage to the RPE cell.[14] This, of course, would begin the process of free radical damage all over again.

And what about drusen, the deposited material in Bruch's membrane? How does it disrupt function? Generally, drusen first appear in the retina as hard discrete areas. This may disrupt the RPE/Bruch's/Choroid complex by physically blocking the flow of metabolites. Over time areas of drusen may become calcified and possibly cause breaks in Bruch's membrane. On the other hand, the drusen may remain unchanged or become confluent and appear "soft". This confluence of drusen may allow the in growth of choroidal neovascularization.[3] As a matter of fact, soft confluent drusen is a significant risk factor for the development of wet ARMD.

Another mechanism that may be a factor in the development of ARMD is disease of the choriocapillaris (that vascular tissue just beneath Bruch's membrane containing

numerous small blood vessels). A great deal of attention has been given to vascular problems such as atherosclerosis and hypertension and the widespread effects these conditions have on the body. The eye is, of course, no exception. With age, it has been found that there is a 50% decrease in the number of choroidal capillaries in patients with ARMD.[13] Additionally, these capillaries have been found to have a narrowing of the space in the middle of the vessel (the lumen), atrophy, and loss of cells.[3] This means a reduction in overall blood perfusion through the choroid, and therefore a reduction in nutrients, mainly oxygen, available to the RPE. This creates the hypoxia, or lack of oxygen, that has been discussed previously. This hypoxic RPE can not maintain transportation of materials to and from the photoreceptors and the choroid. The photoreceptors eventually become "starved" for oxygen themselves and lose function and degenerate. Additionally, because the RPE is now hypoxic and dysfunctional, it will not degrade the photoreceptor outer segments as well and will end up with cellular waste. The cellular waste, lipofuscin and drusen, further disrupts RPE function and the process is continued.

Lastly, there may be failure of the enzymes in the RPE that digest the photoreceptor outer segments. The enzymes that digest the outer segments are called lysosomal proteases. A lysosome is a compartment within a cell that contains enzymes, in this case enzymes that break down proteins and products of proteins called proteases. Two of the main lysosomal proteases in RPE cells are Cathespin D and alpha-Mannosidase. The concentration of both of these enzymes have been found to decrease with age.[14] Therefore, not only does the RPE have to try to digest photoreceptor membranes that have been changed oxidatively, but they may be trying to do so with less of the enzymes that do the digestion. This, of course, leads to cellular waste deposition and the process of cellular dysfunction and death is furthered. Studies have shown that primary lysosomes, the compartments that contain the enzymes, may fuse with lipofuscin deposits, suggesting that repeated attempts at digestion are occuring.[14]

Ocular Photodynamic Damage Control

There are many ways in which our bodies protect against the damage of free radical formation. Two physical barriers to ultraviolet radiation in the eye are the lens and the cornea which absorb most of the ultraviolet light before it can reach the retina. The cornea absorbs ultraviolet radiation between 100-290 nm, while the lens absorbs UV radiation between 290-320nm. And, as the lens ages and yellows, it absorbs up to

370nm.[3] This is an example of an aging change that is protective. Unfortunately, as noted before, much of the blue hazard light (between 400-500nm) is still allowed to penetrate to the retina. Therefore, it is necessary for the retina to have molecular protective mechanisms.

One type of protective mechanism utilized by the retina are chemical reactions that change free radicals to stable molecules. The chemical reactions are facilitated by the help of enzymes (proteins that accelerate the reaction). Below is a list of a few of the oxygen derived free radicals and the enzymes that help stop the free radicals from damaging the retina.

FREE RADICALS	THE OCULAR "DAMAGE" CONTROL
Superoxide Free Radical This free radical is formed by the addition of an electron to an oxygen molecule (O_2-).[22,27]	**Superoxide Dimutase** This is a cellular enzyme that helps to convert the superoxide free radical to hydrogen molecules. ($2O_2$-(two superoxides) + 2H + (two hydrogens) → H_2O_2 (hydrogen peroxide) + O_2 (oxygen)[23] • requires zinc, copper, and manganese to function properly [22,27] • found in the outer segments of photoreceptors [3]
Hydrogen Peroxide This can be formed by the addition of two superoxide free radicals (O_2- + O_2- → H_2O_2) [22,27]	**Catalase** This enzyme helps to convert hydrogen peroxide to water[23] • requires zinc and copper in order to function properly [22,27] • present in the RPE [14] **Glutathione Peroxidase** This enzyme helps the molecule glutathione donate an electron (become oxidized) in order to help convert hydrogen peroxide to water[23] • requires selenium in order to function properly [22,27] • found both in the neurosensory retina to the RPE **Glutathione Reductase** Once glutathione peroxidase is oxidized (gained an electron), it must be reduced (get rid of the extra electron before it can again be functional. Glutathione Reductase helps to reduce it. [6,23]
Hydroxyl Radical (OH-) In turn, a reactive Hydroxyl free radical can be formed by adding an electron to Hydrogen Peroxide. • these are highly reactive free radicals that will generally steal an electron from a double-bond found in polyunsaturated fats found in photoreceptor membranes. [22,27]	**Glutathione Peroxidase** Also converts lipid peroxyls (hydroxyl radicals with a lipid attached to it) to non-radical lipids [22,27]

Melanin, a pigment in the RPE, also serves protective functions against photodynamic damage. Two ways In which melanin is thought to do this is by "scavenging" the free radicals themselves or by preventing their formation by reducing the amount of light that is reflected from tissues behind the retina. By absorbing the light energy that has gone through the neurosensory retina into the RPE, melanin prevents this light energy from being reflected (off of the posterior structures, the RPE and choroid) back into the neurosensory retina. This then prevents the reflected light from generating more free radicals in the retina. It is a well known risk factor that lighter retinas, as in Caucasians versus blacks, are at a greater risk for the development of ARMD. This could possibly be because a Caucasian retina reflects approximately 5% of the incident light, whereas a darker retina reflects only 1% because they contain greater concentration of melanin.[14] We also tend to lose melanin pigment as we age, especially if deficient in zinc which is required to maintain melanin levels.[1,2]

In addition to enzymes and melanin, the retina also utilizes antioxidants to prevent the formation of free radicals before they can exert damage on the photoreceptor membranes. Currently there is much in the media about the use of antioxidants to help protect our bodies against aging changes and diseases such as cancer. So what is an antioxidant? Remember that reduction was when an electron, with its negative charge, is added to a molecule thereby making it more negative. Oxidation is the process by which a molecule has an electron taken away. This makes the molecule "less negative", or oxidized, because it has one less electron (which carries a negative charge). An antioxidant, then, would prevent oxidation from happening. If this is prevented, then the free radical formation is prevented. It has been reported that with the use of some vitamins, which are antioxidants, the deposition of drusen in the human retina decreases.

Summary of ARMD Changes in the Retina
Tissue hypoxia (lack of oxygen) and cellular deposition disrupt the delicate balance between photoreceptor cells, RPE, and choroid. This leads to cellular malfunction which in turn leads to further hypoxia and cellular deposition. Ultimately, death of retinal tissue can occur.
Two Types of ARMD:

1. Dry (non-exudative) ARMD
- May eventually have "geographic atrophy" - a wasting away of well demarcated areas of the retina. This is the most visually devastating type of dry ARMD.
- 10% of people with dry ARMD will progress to the wet form.

2. Wet (exudative) ARMD
- The most visually devastating form of ARMD
- Can have ingrowth of new blood vessels (neovascularization) that are "leaky". This may create subRPE or subRetinal detachments and/or hemorrhages.
- Fluid and blood lead to fibrotic scar tissue beneath the macula (the area of central vision) creating a substantial loss in vision.

Summary of Mechanisms Involved in ARMD
1. Free Radical Damage to Photoreceptor Outer Membrane
- Free radicals damage outer segments making them difficult to degrade by the RPE. This leads to cellular deposition both in the RPE (lipofuscin) and Bruch's membrane (drusen).

  Lipofuscin
  - Fills up space in the RPE cell which interferes with normal metabolic functioning
  - Leak material toxic to the cell
  - Autofluorescent properties allow drusen to re-emit light energy creating more free radicals

  Drusen
  - Physically block metabolites
  - Calcify and cause breaks in Bruch's membrane
  - Become confluent and allow ingrowth of vessels

2. Disease of the Choriocapillaris
Disease of the Choriocapillaris leads to less blood perfusion to the outer retinal layers. This creates a loss of oxygen which leads to the cycle of cellular deposition, malfunction, and death.
- Especially crucial for the macula (the area of central vision) which relies solely on the choriocapillaris for its blood supply.

3. Primary failure of Lysosomal Enzymes
- With age there is a decrease in the number of enzymes that digest the photoreceptor outer segments that are shed into the RPE.

Summary of Ocular Photodynamic Damage Control
1. Chemical reactions, facilitated by enzymes, that change free radicals to stable molecules
- Superoxide Dimutase - enzyme that requires zinc, copper, and manganese to function properly[22,27]
- Catalase - enzyme that requires zinc and copper
- Glutathione Peroxidase - enzyme that requires selenium
- Glutathione Reductase

2. Melanin
- Scavenges free radicals
- Reduces the amount of light reflected back into the retina (thereby reducing additional formation of free radicals).

3. Antioxidants
- Help to prevent the formation of free radicals by serving as electron donors. This protects stable molecules from being oxidized (having an electron taken away) and thereby becoming free radicals.

Review of Studies Concerning ARMD and Antioxidants

So, now that we understand the way in which the retina protects itself from free radical damage at the molecular level, ***how can we use this to help prevent or treat ARMD?*** There have been many studies done in recent years on the effects of antioxidant therapy in the treatment of ARMD. Before we review some of these studies, we first need to understand the use of vitamins and minerals and their overall effect on the aging and age-related macular degeneration processes.

First, what is a vitamin?

A vitamin is a compound that is necessary for our bodies to function properly. Vitamins are necessary to help activate enzymes so that they can facilitate chemical reactions.[11] Think of a chemical reaction as the opening of a door, and think of the enzyme as the door handle and lock. A vitamin is the key. Once they key unlocks the lock, the handle can be turned to open the door. The vitamin (the key) activates the enzyme (unlocks the lock and turns the handle) which facilitates the chemical reaction (or the opening of the door). One point to remember, there are only so many locks to be unlocked and doors to be opened. This meaning that we make only a limited number of enzymes and have only a limited number of chemical reactions. Therefore, any amount of vitamin above the amount that is needed becomes an unnecessary chemical in our bodies.[11] As a matter of fact, too much vitamin can become toxic and can have some serious consequences.

Now, what about minerals?

Minerals are metallic or nonmetallic elements that form important parts of enzymes and other proteins in the body. Selenium, for example, is a part of the enzyme glutathione peroxidase.[22, 27] Remember that glutathione helps to convert free radicals into stable molecule, thereby reducing the damage to photoreceptor membranes. As with vitamins, minerals can reach toxic levels in the body if enough is ingested. An example of this is taking too much zinc. Zinc competes for absorption in the gastrointestinal tract (stomach and intestines) with copper. If there is too much zinc present, not enough copper will be absorbed into the blood stream from the GI (gastrointestinal) tract.[11] This can cause anemia which may have severe consequences.

Because we must obtain these nutrients mainly from our diets, as our bodies do not produce enough to sustain proper functioning, we have a couple of established guidelines that we can follow. These guidelines were set in order to prevent deficiency by recommending enough of the nutrient, and to avoid toxicity by limiting the amount we

ingest daily. Most everyone has heard of the US RDA. This is the US Recommended Daily Allowance which is what we use as guidelines to determine how much of these nutrients we should have in our daily diets. The US Food and Drug administration established the US RDA in 1968. There is another set of guidelines that were established by the National Research Council (Food and Nutrition Board) that were set in 1989. These guidelines, termed RDA's or Recommended Dietary Allowances, are estimates of necessary dietary intakes of nutrients based on variables such as age, weight, height, and gender. Although based on a more complicated system of variables than the US RDA's, both RDA's and US RDA's are only estimates on how much of the nutrients should be ingested daily. Individuals vary, therefore the guidelines should be treated as such - guidelines. [11]

So what does all of this mean? It means that, although there are recommendations for daily intake of vitamins and minerals, these recommendations are only estimates, and how much of a nutrient is needed to prevent or treat a disease such as ARMD is unknown.

The following studies attempted to answer these questions; whether antioxidants helped to prevent or treat ARMD, if so which ones, and how much of each is required.

Baltimore Longitudinal Study on Aging

The Baltimore Longitudinal Study on Aging is an on going project at the National Institute on Aging. Patients who participate are part of a study on the process and effects of aging. They return every two years for a number of tests to be run, including having blood drawn and a routine physical examination. Shelia West et al at the Dana Center for Preventive Ophthalmology, at the Wilmer Ophthalmological Institute at Johns Hopkins Hospital, studied all of the 976 patients who were 40 years old or older who were scheduled to return between 1988 and 1989. At the time of their return, assessments of their macular areas (the central part of the retina responsible for central, detailed vision) were made. They compared the level of macular changes, and severity of those possible changes to previous fasting plasma levels of the following antioxidants: alpha - tocopherol (vitamin E), ascorbic acid (vitamin C), beta - carotene (the pro form of vitamin A), and retinol. Their results showed that vitamin E (alpha - tocopherol) had a significant protective effect against ARMD. Beta - carotene and ascorbic acid (vitamin C) were also each associated with a protective effect, however the effects were not statistically significant. Additionally an antioxidant index, a compilation of all of the antioxidants investigated, was suggestive of a protective effect but, again, was not statistically significant. Vitamin supplementation was also found to not have a significant

protective effect against ARMD. Men were found to have more ARMD than women, but women were more likely to have severe ARMD (geographic atrophy or neovascularization). Additionally, none of the antioxidants were found to have a significant protective effect against severe ARMD, although they all showed protective associations that were not statistically significant. The only factor shown to have a significant association with the severe forms of ARMD was age.[15, 24]

What does all of this mean? We'll begin by reviewing some of the studies techniques so that the results can better be understood.

First, fasting plasma levels are measurements of the nutrients in the plasma of blood drawn after a period of fasting (not eating). In the case of this study, plasma levels were taken approximately two to four years before retinal assessments were made. Dr. David Newsome, a well respected doctor in New Orleans that has pioneered much of the work with antioxidants and ARMD, criticizes the study for this.[20] Other studies on this subject compare retinal assessments with concurrent plasma samples. He believes that this is a more accurate way of determining how the antioxidants affect ARMD because it is more direct. However, it must be kept in mind that plasma levels are a measurement of the antioxidant level at a point in time, which may not be representative of past antioxidant use.[20] Since the objective of the study was to determine whether antioxidant use had a protective affect against the development or progression of ARMD the authors of the study feel that the drawing of plasma years before the retinal assessments are an advantage.[25]

Why was vitamin E associated with a statistically significant protective effect while vitamin C and beta - carotene were not? The participants of the Baltimore Longitudinal Study on Aging were primarily white, male, upper class residents of Baltimore and Washington D.C. Therefore, most were well nourished. Even so, approximately 12% of the study population showed a clinical deficiency in vitamin E where they did not show a deficiency in any of the other nutrients. The antioxidants were measured in "quartiles". Those with the lowest level of a nutrient were grouped together, while those with the highest levels were in another group (quartile). Because vitamin E was the only nutrient showing a clinical deficiency in some of the population, the difference between those in the lowest quartile and the highest would be greater than those in other low and high nutrient groups. This, then, may account for some of the difference between the protective effects of vitamin E versus vitamin C and beta - carotene (although bear in mind it may not account for all of the difference). Also keep in mind that vitamin C and beta - carotene were associated with protective effects, but were not statistically

significant effects. Had the population also been deficient in these nutrients, a greater effect for them might have been found.[24]

If vitamin E and the other nutrients were found to be protective, and vitamin supplements contain these nutrients, ***why wasn't vitamin supplementation found to be protective?*** First of all, the assessment of vitamin supplementation by the authors was admittedly crude. If the participant reported using any type of vitamin supplementation within the past two years, they were assessed as current supplement users. In addition, because the study was of basically well nourished people, how effective the supplementation was is hard to quantify. Someone who is deficient in a vitamin, such as vitamin E, may be taking supplements while someone whose diet is rich in vitamin E is not. This then would give a false impression of supplementation because one would expect the person not taking the vitamin supplements to be deficient in vitamin E, but who is not because their diet is rich in it. More sophisticated measurements of diet and supplementation use are needed to rule out vitamin supplements as advantageous. However, because the authors did not find a significant protective effect for them, they can not recommend vitamin supplementation use in the prevention of ARMD. [24]

Why was ARMD found to be more common in men with the severe forms greater in women? These are associations that are widely accepted in much of the literature, therefore these results are not surprising. However, one must again remember that the study was mostly comprised of white men. The results, then, may not be representative of the general population.

The age association with both the nonexudative (dry) form of ARMD and the exudative (wet) form of ARMD is also not surprising. For dry ARMD it has been found that after 4 years 23% of patients with it in one eye will develop it in the other eye.[1,2] In patients with neovascular (wet) ARMD in one eye there is a 10% chance per year of the other eye developing wet ARMD.[3] For example, the first year after developing wet ARMD, the other eye has a 10% chance of also developing wet ARMD.[3] The second year there is a 20% chance of the second eye developing wet ARMD and so on. Therefore, the association of age to the development of ARMD and the advancement of the severe forms found in this study are not surprising at all.

Below is a review of findings of The Baltimore Longitudinal Study on Aging:

1. The incidence of ARMD increases with age (this includes the severe forms of ARMD)
2. Vitamin E (alpha - tocopherol) was found to have a significant protective effect for non-severe forms of ARMD.
3. Vitamin C (ascorbic acid) and beta - carotene (pro form of vitamin A) were associated with a protective effect (for non-advanced forms) but they were not statistically significant. The same result was found for an antioxidant index containing all of the antioxidants studied.
4. Vitamin supplementation was not found to have a protective effect and therefore its use to prevent or treat ARMD can not be recommended by the authors.

Eye Disorder Case-Control Study

The Eye-Disorder Case-Control Study is a multicenter study on the effects of five different retinal disorders, one being neovascular (wet) ARMD. The study used common protocols for all five diseases and had a selection of controls (patients without evidence of any of the retinal disorders being studied) from a large pool of patients. The centers studied 421 patients with wet ARMD and compared them to 615 controls without wet ARMD between May of 1986 and December of 1990. All of the patients were between 55 and 80 years old, with only six non-white patients. Like the Baltimore Longitudinal Study on Aging, antioxidants were grouped into quartiles - low, medium, and high - and were compared on an individual basis and as an index of the all of the antioxidants studied. Those were alpha - tocopherol (vitamin E), ascorbic acid (vitamin C), beta - carotene (pro form of vitamin A), and selenium (a mineral necessary for the makeup of the enzyme glutathione peroxidase). Their results showed a significant protective association with an increasing serum index of beta - carotene (pro form of vitamin A). There was also a significant reduction in the risk of wet ARMD with increasing levels of the antioxidant index combining all of the antioxidants studied. And, although there was an association of a reduction in wet ARMD with vitamin E and C individually, these results were not statistically significant. Selenium was also found to not produce a significant reduction in the incidence of neovascular (wet) ARMD. Additionally, the studied concluded that higher serum levels of cholesterol and smoking were associated with an increased risk of ARMD.[8]

Like the Baltimore Longitudinal Study on Aging, there are a few factors that need to be considered when interpreting these results.

One factor to consider is that, like the BLSA, levels of antioxidants were measured as the level that was in blood serum. How well the amount of antioxidants in the diet are absorbed into the blood, and how well the levels of these nutrients in the blood are representative of the levels in the retina are unknown. Therefore, the association between blood levels and reduced risk of neovascular (wet) ARMD can only be taken as significant associations.

Secondly, the controls were supposed to be free of any sign of the retinal diseases being studied. However 18% of the controls for this group had large drusen, one of the early signs for ARMD and a risk factor for wet ARMD. However, the results were essentially the same when compiled without the data from this 18%.[8]

As with any case-control study there is always the possibility of bias when selecting the controls. Additionally, there is always the chance of the cases and controls being non-comparable (matched in age, gender, diet, smoking habits etc.). However, in this study cases and controls were monitored at regular intervals. If a discrepancy was detected, the clinics would change their criteria for the controls in order to attempt to correct the discrepancy and make the cases and controls more equal. An example of this was age. When it was discovered that the cases and controls did not match in age (the overall control group was younger), the clinics raised their minimum age cut-off for controls in an attempt to make the overall age of the groups more equal. Furthermore, analysis was redone using a second set of controls and, again, the results were essentially unchanged.[8]

Review of results found by The Eye Disorder Case-Control Study:

1. A statistically significant reduction in risk of neovascular (wet) ARMD was found with increasing levels of beta - carotene (the pro form of vitamin A) and the antioxidant index reflecting levels of beta - carotene, vitamin E, vitamin C, and selenium combined.
2. A reduced risk was also found with higher levels of vitamin E and C, however these were not statistically significant.
3. A significant protective effect of selenium was not found.
4. Smoking and higher levels of serum cholesterol levels were found to have an association with increased risk of ARMD.
5. As only six of the participants were non-white, the results are restricted to Caucasians only.
6. There may be unrecognized ways to explain the way in which the risk of ARMD was reduced, therefore, the authors feel the results can not be translated into nutritional recommendations.

Beaver Dam Eye Study

The objective of the Beaver Dam Eye Study was to evaluate the relationship between the use of vitamin supplements and ARMD.[4] The study utilized approximately 2000 participants from the local Beaver Dam, Wisconsin area. They found a significant association between patients who reported taking supplements of vitamin C (ascorbic acid) ten years prior to the study and the absence of early signs of ARMD. However, this relationship did not hold true when compared to more severe forms of the disease. The Beaver Dam Eye Study group also conducted a nested case-control study to investigate any association between blood serum levels of tocopherols (such as vitamin E) and carotenoids (such as beta - carotene). A nested case control study is like a "sub" study in which a smaller group is selected from the larger group to do a related study. This nested case-control study was made up of 167 cases and 167 controls selected from the larger groups. Patients with signs of late ARMD (such as soft drusen, geographic atrophy, and neovascularization) were compared with controls without these signs. Changes in the patient retinas were compared to levels of nutrients in the non-fasting blood serum samples taken concurrently. They found that the average level of carotenoids were similar between the patients with late ARMD and those without. They also found that, on the average, levels of alpha - tocopherol (vitamin E) were lower for patients with wet ARMD but not significantly lower. Additionally, patients with the lowest serum levels of

lycopene (a type of carotenoid) were twice as likely to have ARMD, while other levels of carotenoids (lutein and zeaxanthin) had no correlation to the presence or absence of ARMD.[17]

The larger studied concluded that patients who reported using vitamin C supplementation for 10 years before the study were less likely to have early signs of ARMD. It must be kept in mind that these are self reported supplementation use and are, therefore, subject to reliability of memory. Additionally, as noted in the BLSA study, comprehensive evaluations of diet are necessary to determine how effective the supplementation is for those with diets rich in nutrients versus those with deficient diets.[17]

The nested case control study was unable to confirm what had been found in the BLSA and Eye Disorder Case-Control Study.[17]

First, the BLSA found that serum levels of vitamin E were significantly associated with a protective effect for ARMD. Although the Beaver Dam Nested Case-Control study confirmed that patients with wet ARMD had lower levels of vitamin E, the results were not statistically significant (when adjusted for cholesterol levels because the serum samples were nonfasting serum samples). However, something to keep in mind is that the BLSA also concluded that no factor was associated with the severe forms of ARMD except for age. In the nested case-control study, all of the 167 cases had some form of severe ARMD (soft drusen, geographic atrophy, or neovascularization). Therefore, the results are not comparable.

Secondly, the Eye Disorder Case-Control Study concluded that higher levels of carotenoids had reduced risk of wet ARMD. The Beaver Dam Eye Study, however, concluded that low levels of lycopenes, a type of carotenoid, were associated with ARMD. A carotenoid is a yellow or orange pigmented lipid found in the body and many plants (such as green leafy vegetables, corn and sweet potatoes). There are different types of carotenoids. Lycopene is the most abundant carotenoid found in the serum. Lutein and zeaxanthin are also carotenoids and are what make up the pigment in the macular (the area of the retina responsible for central vision) area. The Beaver Dam Eye Study is unique in that it studied the carotenoids -lycopene, lutein, and zeaxanthin - separately.[17] The disagreement between the authors of this study and the Eye Disorder Case-Control Study may, therefore, only be a result of the way in which levels of carotenoids were evaluated. The Eye Disorder authors evaluated the carotenoids all together and found an association between lower levels and wet ARMD, whereas the Beaver Dam authors examined them separately and only found an association with lower levels of lycopene and ARMD.

Review of the results of The Beaver Dame Eye Study:

1. Individuals who reported prior vitamin C supplementation were less likely to have early signs of ARMD.
2. Lower serum levels of vitamin E were associated with an increased risk of neovascular ARMD, but this was not a significant association.
3. Lower serum levels of lycopene, but not other carotenoids (those that are found in the macula) were associated with an increased risk of ARMD.

Visaline Study

Visaline is a registered medication for the treatment of ARMD in Switzerland. It contains 1.5 mg of Buphenine HCL (this increases blood perfusion to the brain), 10 mg of beta - carotene (pro form of vitamin A), 10 mg alpha - tocopherol (vitamin E), and 50 mg ascorbic acid (vitamin C). The study was a six month long double blind study in which twenty patients participated. One month prior to the study patients were instructed to discontinue other forms of multivitamins and medications that would interfere with absorption of Visaline. The authors concluded that the effect of treatment between the group treated with Visaline and those treated with a placebo were not significant. Oddly, the patients in the Visaline group reported a subjective increase in vision (they thought their vision had improved even though through objective testing in the clinic it had not). This may have been a result of the increased blood perfusion to the brain, although it is uncertain. Because the study was short term and the number of participants was small, the authors concluded that more extensive study is warranted.[13]

Zinc Study

David Newsome, MD conducted a two year study in the 1980's at the LSU Eye Center. The study was done to test the effectiveness of zinc in the treatment of ARMD. It had 151 participants, half of whom received 100 mg of zinc twice daily with the other half receiving placebos. The study was conducted for two years with the patients being examined and assessed for macular changes every two years. Dr. Newsome found zinc to have a significant treatment effect. Although some of the patients in the treatment group (those patients receiving zinc twice daily) had severe macular changes and vision loss, the number of patients in the placebo group with severe vision loss was 2.5 times greater. He concludes, however, that because of the possible toxic effects of oral zinc supplementation and because of the pilot nature of his study, that the use of it as a

treatment for ARMD is not recommended. He suggests that more studies must be done to fully understand the effects of nutrients such as zinc and other antioxidants.[15]

Age-Related Eye Disease Study

Many of the studies reviewed have deferred the recommendation of vitamin supplementation until the results of the Age-Related Eye Disease study could be concluded. The objectives behind this research were three fold. One was to answer the question if an antioxidant could prevent the progression of dry ARMD in the veteran population. Second, if that positive effect could become apparent after only a short period of time. Lastly, to discover if there are any side effects to the therapy. The study was carried out at eight different Veterans Affairs Medical Centers and at the Pacific University College of Optometry. Sixty-four total participants were divided into three groups, two groups of cases and one group of controls. The first group of cases, dry ARMD Group 1, were given a placebo twice daily while the second case group, ARMD Group 2, was given an over-the-counter, multivitamin-mineral-antioxidant combination capsule (Ocuguard) on the same schedule (refer to diagram). The study was conducted as a double blind study, meaning that neither the optometrist, coordinating dietician, nor the patient knew which they were receiving - the placebo or the Ocuguard capsule.[1,2]

The criteria for participation in the study was deliberately stringent and included specific exclusion criteria for the veteran population. Additionally, because of the limited number in the veteran population, only 5 female participants were available and met the criteria. The study was conducted for 18 months with data from the participants being collected at base line, run in (a two week check on the patients to insure compliance), 6 months, one year, and eighteen months. If even one appointment was missed, the results and data from that subject were discarded. The data collected at each visit were demographic baseline data, ocular health status and photographs, nutritional data, blood laboratory data, and events of adverse effects (gastrointestinal symptoms).[1,2]

There were a few differences between the three groups. Differences between the ARMD groups and the controls were as follows:

1. There was a significantly greater amount of general systemic pathology (disease effecting the whole body) in the ARMD groups.
2. The ARMD free group of controls used less diuretic medications (medications that cause an increase in urine output, thereby leading to loss of nutrients) as well as less antidiarrheal medications.
3. The ARMD free group also had a higher level of self described activity (they reported being more physically active than the ARMD participants did).
4. The presence of vascular pathology was greater in the ARMD groups than in the group of controls. (Cardiovascular disease is a known risk factor for ARMD).
5. A greater percentage of participants with ARMD had light colored irides (the colored part of the eye) than those without ARMD (69% vs. 54%) Although this was not a statistically significant difference, lighter colored irides are thought to be associated with the presence of ARMD.[1,2]

Differences between the two ARMD groups were as follows:

1. There were 32 participants in Group 1 (the placebo group), while there was 39 participants in the Ocuguard group.
2. Although the selection of participants for the groups was random, there was a statistically significant difference in average weight between them. Group 2 (Ocuguard) was significantly heavier than group 1 (placebo). This meant that the nutritional requirements for that group were greater.
3. Phosphate beverage intake, which interferes with the absorption of zinc, was greater in ARMD group 1 (placebo). While group 2 consumed greater amounts of manganese and vitamin C. Although this may have been because they were heavier on the average and, therefore, needed a larger diet.[1,2]

Interestingly, there was no difference in the incidence of smoking between the groups, nor was there a difference in vitamin C intake between the cases and the controls.[1,2]

At the end of 18 months, seven patients had withdrawn from the study, four patients died, and one patient had to drop out of the study after suffering from an allergic reaction to the Ocuguard capsule. Although there were a few reported cases of

diarrhea along the way, possibly caused by vitamin C which produces a temporary buildup of water in the bowel, only this one patient had a severe adverse reaction to the capsule. It occurred on day 25 of the study and was possibly a result of cross reactivity to some other medication the patient was taking. It produced a rash all over the patient's body, however the patient was resistant to discontinuing the therapy because he reported seeing better.[1,2]

Results of the study were as follows:

1. Group 2 patients (receiving Ocuguard) had a stabilization of three measures of visual function that were statistically significant.
2. Group 2 also had a stabilization of all other measures of visual function tested that were not statistically significant.
3. There was a self perceived stabilization of vision in Group 2.
4. An association was found between the serum levels of vitamin E and the incidence of ARMD.[1,2]

From these results, the authors of the study made the following conclusions:

1. They concluded that the study is consistent with the theory that the ARMD disease process responds to nutrients or the lack thereof.
2. They believe that clinicians should redouble their efforts to promote healthy eating habits through the "Food Triangle". This includes recommending dark green, leafy vegetables which are rich in B Complex vitamins, carotenoids, glutathione and its precursors, and magnesium. It also includes eating less fat and correcting existing nutritional deficiencies.
3. Because vitamin E can not be obtained in adequate amounts in the diet, the authors also suggest a moderate intake of vitamin E supplements, as recommended by cardiologists.
4. They feel that vasorelaxing substances, those that relax and dilate blood vessels, such as magnesium and niacin may also be advantageous when combined with antioxidant therapy to increase blood perfusion to the retina. (German studies have demonstrated positive outcomes to these types of therapies).[1,2]
5. Lastly, the authors feel that it is "foolish" to attempt antioxidant therapy while still permitting the hazardous short wavelengths to reach the retina. They, therefore, recommend the use of ultraviolet protection, noting that the most vulnerable times for light energy to cause damage to the retina is before the third decade of life when the eye is very transparent and transmits the hazardous light readily to the retina, and after the sixth decade when the loss of protective elements begins.[1,2]

What Now?

"Ecologic Recipe for ARMD"

(From the authors of the Age Related Eye Disease Study)

- Excessive fat intake
- Sedentary lifestyles
- Smoking
- Excessive alcohol
- Reduced GI (gastrointestinal) nutrient absorption
- Accumulated lifetime exposure to UV and blue hazard radiation[1,2]

If you have been diagnosed with ARMD there are a few important things to keep in mind. First, you must always continue to visit you eyecare provider at regular intervals. Secondly, you are ultimately responsible to tell your doctor what is happening to your vision. You should have been given a home Amsler Grid to use everyday. If you do not have one, ask you doctor's office for one and how to use it. The guidelines and conclusions outlined in the Age-Related Eye Disease study are very good guidelines to live by. However, you should always consult a physician if you are planning to use vitamin supplements (such as the vitamin E supplementation recommended by the Age-Related Eye Disease Study). Lastly, there is much information on ARMD out there, and there are other forms of treatment such as laser surgery. Additionally, low vision devices may be available if your vision has decreased sufficiently and there are organizations, such as the Commission for the Blind that can help. Ask your eye care provider for any information she can provide you with.

Most importantly, be active in your health care and take care of yourself.

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