The visual function and dietary intake of males of age 50 or older

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Abstract
Age-related macular degeneration (ARMD) is the leading cause of blindness among the elderly in the United States. This study is an effort to develop a cost-effective testing protocol that can be used by eye care clinicians to identify who is likely to develop ARMD so that these individuals can receive preventive care. This study is part of a nationwide, multi-center, double-masked project on the effectiveness of antioxidant vitamin/mineral supplementation to treat ARMD. Five testing procedures used to diagnose ARMD were evaluated: foveal red threshold automated perimetry, contrast sensitivity, Amsler grid, nutritional intake data analysis, and blood chemistry analysis. The results indicate that normal subjects and those with ARMD have different results when tested using these procedures. When these tests are used in combination, they provide a strong protocol for identifying individuals who are likely to develop ARMD.

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The Visual Function and Dietary Intake of Males of Age 50 or Older

By

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A thesis submitted to the faculty of the College of Optometry
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Fran Tabor received her Bachelor of Arts degree in Psychology from Washington College and her Master of Arts degree in Psychology from the University of North Carolina. Prior to attending Optometry school, Fran had a career in human resources management with large international corporations. Optometry memberships include: AOA Contact Lens Section and the American Academy of Optometry. Anticipated date of graduation in May 1995 from the Pacific University College of Optometry. Following graduation, Fran will complete a one-year residency at the Portland Veterans Administration Medical Center.
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ABSTRACT

Age-related macular degeneration (ARMD) is the leading cause of blindness among the elderly in the United States. This study is an effort to develop a cost-effective testing protocol that can be used by eye care clinicians to identify who is likely to develop ARMD so that these individuals can receive preventive care. This study is part of a nationwide, multi-center, double-masked project on the effectiveness of antioxidant vitamin/mineral supplementation to treat ARMD. Five testing procedures used to diagnose ARMD were evaluated: foveal red threshold automated perimetry, contrast sensitivity, Amsler grid, nutritional intake data analysis, and blood chemistry analysis. The results indicate that normal subjects and those with ARMD have different results when tested using these procedures. When these tests are used in combination, they provide a strong protocol for identifying individuals who are likely to develop ARMD.

KEY WORDS
age-related macular degeneration, visual function, antioxidants, vitamin/mineral supplements
INTRODUCTION

As the population of persons age 50 years and older in the United States continues to increase, the incidence of ocular disease associated with aging is also increasing. In the aging of the U.S. population, age-related cataract and age-related macular degeneration (ARMD) are the leading causes of visual impairment and blindness 1,2. Approximately 25% of people aged 65 years and older have some manifestation of ARMD including large or confluent drusen, retinal pigmentary changes, geographic atrophy, or exudative disease3. And, because the elderly are the fastest growing segment of the population, the prevalence of both these disorders is expected to increase dramatically during the next two decades. In addition, the dry form of ARMD does not have any form of treatment or cure, nor can we predict who is likely to acquire ARMD.

In order to identify who is likely to develop ARMD, it is necessary to identify the possible causes and risk factors associated with the disease. Several approaches that have been taken include:

1. Etiological studies of ARMD
2. Antioxidant protection including dietary intake and blood levels.
3. Blood chemistry
4. Functional visual testing

ETIOLOGICAL STUDIES OF ARMD

Age-related macular degeneration is a puzzling disease of unknown etiology and the predilection of the disease for the macula has never been fully explained. In 1982, Klein and Klein4 examined the prevalence of ARMD with the use of data from the first National Health and Nutrition Examination Survey (NHANES-I) ophthalmology examination. Their study examined the prevalence of ARMD in relation to five variables: age, race, sex, hypertension, and hematocrit. The results of their analysis indicated a positive
correlation of ARMD with both age and systolic hypertension. This positive association of hypertension and systolic blood pressure with ARMD in the Klein and Klein study is in accord with the results from the Framingham Eye Study\(^5\) and the case-control study of Delaney and Oates\(^6\).

Recent research has suggested that light-generated free radicals play an important role in the etiology of ARMD\(^7\)-\(^9\). In living systems, free radicals are formed from both internal and external sources. Internally, free radicals are produced in cell structures including mitochondria and plasma membranes. Externally, free radicals result from light, ionizing radiation, air pollution, organic solvents and cigarette smoking\(^10\),\(^11\). The damage to tissues from these free radical attacks has been implicated in diseases such as cancer, atherosclerosis, heart disease, and strokes and is thought to contribute to aging\(^10\)-\(^13\).

In the eye, it is believed that free radicals are formed in the retina as a result of light absorption by the photopigments and/or other materials in the outer segments of the photoreceptors, containing lipid molecules\(^14\). These lipid molecules can be easily attacked by free radicals. When the lipid molecules lose electrons, they are altered to become free radicals themselves. If the transformed lipids accumulate within the receptor outer segments, the probability of receptor injury/death increases. To reduce this from happening, sloughed portions of the outer segments are phagocytized by the retinal pigment epithelium (RPE). It is believed, however, that some of the transformed lipid molecules are not metabolized by the RPE’s digestive enzymes due to their altered structure and, as a result, accumulate as lipofuscin inside the RPE cells\(^7\).

Evidence has been presented that lipofuscin accumulation in retinal pigmentary epithelium cells is responsible for ARMD. Dorey et al.\(^15\) and others \(^16,17\) have reported that the RPE in the area of the macula exhibits the greatest amount of lipofuscin and that the annular pattern in macular degeneration is well correlated with the area of greatest lipofuscin concentration\(^18\). Most of the lipofuscin within the RPE may be derived from phagocytosis of oxidatively
damaged (and other non-degradable) lipids in the photoreceptor outer segments\textsuperscript{19}. Therefore, RPE cells phagocytosing greater quantities of outer segment lipids may accumulate more lipofuscin. This material could be deposited onto Bruch's membrane in the form of drusen and could cause the RPE to separate from its blood supply in the choroid. This reduces the ability of the RPE to provide metabolic support to the photoreceptors and could result in their death. Death of the receptors would be expected to lead to the reduction of central vision associated with ARMD. The data of Dorey et al.\textsuperscript{15} and others \textsuperscript{19-21} support this hypothesis.

ANTIOXIDANT PROTECTION

Animal research and some epidemiological research have indicated a role for certain vitamins and trace minerals with antioxidant properties in protecting against the deterioration of macular degeneration.

The role of micronutrients and exposure to light have been studied experimentally and have suggested a possible biological mechanism for the development of ARMD. Feeney and Berman\textsuperscript{22} reported that exposure to ionizing radiation, ultraviolet light, or blue light, especially blue wavelengths, can lead to free radical formation. The free radicals are associated with the overall aging process\textsuperscript{23} and to lipid peroxidation of the photoreceptor outer segment membranes that are rich in polyunsaturated fatty acids\textsuperscript{24}. Vitamins A, C, and E and the mineral selenium are known to function as antioxidants\textsuperscript{22}, inhibiting cellular damage by acting as scavengers for the superoxide radicals. It is believed, therefore, that long-term deficiencies in antioxidants in the presence of free radical formation may be related to the development of ARMD.

Young\textsuperscript{8} suggested that micronutrients with antioxidant potential and a variety of trace minerals necessary for the proper functioning of some key enzyme systems may protect against ARMD. Antioxidants such as vitamins C and E, beta-carotene, glutathione, and selenium-dependent glutathione peroxidase could prevent cellular damage by acting as singlet oxygen and free radical scavengers.
In 1988, Goldberg et al.\textsuperscript{25} analyzed the data collected from the 1971 and 1972 NHANES-I study to determine what factors were associated with ARMD. They reported that an increased frequency of consumption of fruits and vegetables rich in vitamins A and C reduced the risk of ARMD after a stratified adjustment for age. In a logistic regression analysis, adjusting for demographic and medical factors, the protective effect of vitamin C with age-related macular degeneration was no longer present. However, the frequency of consumption of fruits and vegetables rich in vitamin A remained correlated with a protective effect for ARMD even after the adjustment for demographic and medical factors.

Newsome and Rothman\textsuperscript{26} demonstrated that zinc is taken up in vitro by human epithelial cells via a temperature saturable process. They suggested that zinc is strongly related to proper chorio-retinal functioning. Since ARMD involves a breakdown of the retinal pigment epithelium, it is suggested that the intake of zinc may prevent or slow down the process of ARMD.

In 1982, Sandstead et al.\textsuperscript{23} reported that zinc is a major deficiency in the elderly. Low zinc intake was related to poor taste acuity, poor healing, and immune dysfunction. They found that the daily dietary intake of zinc of groups of elderly persons in the U.S. range from 7 to 13 mg. As a result of their findings, they recommended that a threshold for zinc deficiency be defined and that zinc bioavailability be considered in food selection.

In 1988, Newsome et al.\textsuperscript{28} administered oral zinc sulfate supplements over a 2-year period to patients with ARMD. They found that these patients suffered significantly less vision loss than the controls. They compared macular photographs before and after treatment. The results of the photographs showed that the zinc-treated patients either remained stable or had less accumulated drusen than did the controls.

Richer\textsuperscript{29} hypothesized that reduced antioxidant defense of the retina secondary to poor nutrition and smoking combined with increased life expectancy and exposure to solar radiation provides a triple assault on the aging retina. Richer presented an overview of recent animal research and recent epidemiologic studies along with
an overview of ocular free-radical biochemistry to promote a conservative prevention/treatment strategy involving the identification of at-risk patients, solar radiation protection, nutritional counseling based upon the new USDA Food Pyramid concept and vitamin/mineral supplementation if necessary for non-compliant, high-risk patients.

The Eye Disease Case-Control Study\textsuperscript{30} evaluated the risk factors associated with neovascular age-related macular degeneration. Risk factors were assessed through interviews, clinical examination, and laboratory analysis of blood samples. Decreased risk of neovascular ARMD was associated with higher levels of carotenoids in the serum samples, higher horizontal cup to disk ratios, and the use of post-menopausal exogenous estrogens in women. Increased risk of neovascular ARMD was associated with cigarette smoking, higher levels of serum cholesterol, and parity greater than zero. No support was found for sunlight exposure, serum zinc levels, or iris color. Although no association was found with a history of cardiovascular disease itself, the associations with post-menopausal exogenous estrogen use, cigarette smoking, and serum cholesterol were seen by the authors as a hypothesis linking risk factors for cardiovascular disease with neovascular ARMD. The association noted between serum carotenoid levels and neovascular ARMD supported that hypothesis that higher levels of micronutrients with antioxidant properties may decrease the risk of ARMD.

Liles et al.\textsuperscript{31} quantified the antioxidant enzymes catalase and superoxide dismutase activity in the RPE, retina, iris, and vitreous from human donors. They evaluated whether aging or macular degeneration affects RPE catalase or superoxide dismutase activities. Measurements of enzyme levels in the RPE from donors aged 50-90 years with and without ARMD were obtained. Superoxidase dismutase activity showed no significant correlations with aging or ARMD. Catalase activity was found to decrease with age and ARMD in the macular and peripheral retinal pigment epithelium.

A study by Prashar et al.\textsuperscript{32} was undertaken to assess the levels of antioxidant enzymes in red blood cells of subjects with ARMD and age-matched controls. The results indicated a significant
decrease in the activities of superoxide dismutase. A correlation was also found between age and decreased activity of antioxidant enzymes in controls but the correlation with ARMD was higher. The researchers concluded that oxidative stress as assessed by antioxidant enzymes is more pronounced in patients with ARMD. These results contradict those found by Liles et al.31 presented above.

The relationships between fasting plasma levels of retinol, ascorbic acid, alpha-tocopherol and beta-carotene and age-related macular degeneration were studied in a population of 976 participants enrolled in the Baltimore Longitudinal Study of Aging (BLSA)33. The results indicated that alpha-tocopherol was associated with a protective effect for ARMD, adjusted for age, sex, and nuclear opacity. An antioxidant index, including ascorbic acid, alpha-tocopherol, and beta-carotene was also protective for ARMD. However, they reported that the use of vitamin supplementation to prevent ARMD was not supported by the data, which showed no protective effect of vitamin use. These findings are contrary to those reported by others8,34.

West et al.33 also assessed fasting plasma, retinol, alpha-tocopherol, ascorbic acid, and beta-carotene levels. The results suggested a protective effect for ARMD of high plasma levels of alpha-tocopherol. An antioxidant index composed of plasma ascorbic acid, alpha-tocopherol, and beta-carotene, was also protective. This study also showed no protective effect of vitamin supplementation.

BLOOD CHEMISTRY

There are virtually no studies evaluating the diagnostic or predictive value of blood chemistry tests with regard to ARMD.

As discussed above, the Eye Disease Case-Control Study30 evaluated the risk factors associated with ARMD. Risk factors were assessed through interviews, clinical examination, and laboratory analysis of blood samples. The results showed that neovascular ARMD was associated with higher levels of serum cholesterol.
FUNCTIONAL VISUAL TESTING

Since it is known that visual function decreases with age-related macular degeneration, it should be possible to measure central visual function at an age in maturity prior to the onset of the disease and to predict who are the likely individuals to acquire ARMD.

Several approaches to predicting ARMD have focused on identifying or developing functional tests that are more sensitive in identifying patients with early (pre-) ARMD or that are early predictors of who are likely individuals to develop ARMD. The functional tests which have received the greatest attention with regard to ARMD include automated perimetry, contrast sensitivity, and the Amsler grid. These tests were selected since they evaluate central visual function.

AUTOMATED PERIMETRY

ARMD is associated with central vision loss. In order to quantify this vision loss, many researchers have used various types of automated perimeters.

In 1976, Greve et al. described the central and paracentral visual function in patients with drusen and in disciform macular degeneration and in the stages between these two extremes of the disease. Defects were measured using fluorescein angiography and function was measured using central single stimulus static perimetry at a mesopic and photopic level of adaptation. The study showed that differential static perimetry is a better indicator of the severity of the disease than fluorescein angiography. They study also demonstrated that differential static perimetry indicated severe paracentral defects when visual acuity was still good.

Threshold static perimetry was performed by Hart and Burde using test object patterns that covered contiguous areas of the central visual field. Computer imagery was used to display a three-dimensional surface that was interpolated between the sensitivity values at each of the test object locations. The examinations covered the area out to and including 10 degrees of eccentricity from the point of fixation, corresponding to the same
area of the visual field covered by the Amsler grid. It was found that in a variety of macular diseases, including those caused by vascular, as well as primary degenerative disorders, central scotomas were characterized by relative sparing of visual sensitivity at the point of fixation. The pattern produced instead was one of a ring-shaped depression within the central 10 degrees of the visual field. This phenomenon was present in 20% of cases with central scotomas resulting from macular disease, but was not found in any eye of patients suffering from central scotomas as a result of optic nerve disease. It was suggested by these authors that preservation of foveal sensitivity may be a marker for macular disease, as distinct from central visual field loss arising from optic nerve disease.

Cone adaptation was measured in patients with ARMD and age-related matched controls. A red stimulus was used to selectively bias responses toward cone function and adaptation was measured 5, 10, 20, and 40 degrees, with threshold difference reducing to 0.5 log units at 40 degrees. The data suggested that cone adaptation is significantly affected in ARMD patients, with raised cone thresholds occurring for areas well into the peripheral retina. The authors' data suggest that age-related "maculopathy" may not be confined to the macular area, and that early signs of the degeneration may be present in the peripheral retina even when central acuity is normal.

In a related study, reaction times to red lights of the same size and chromaticity as traffic signals were studied in normal elderly, pre-ARMD elderly, and ARMD elderly patients. The targets were projected under photopic and mesopic conditions with both central and fixation at 5 degrees eccentricity. The data showed greatly prolonged reaction time in the ARMD group compared to the normals. The pre-ARMD patients had results between the other two groups. The results indicate that functional changes are present before a definitive ARMD diagnosis can be made by conventional means.

Peripheral retinal function in age-related macular degeneration was studied by Sunness et al. These researchers employed static perimetric measures of absolute thresholds at loci spanning the horizontal meridian of the retina to determine retinal function at
specific locations. Absolute thresholds were measured on the Tubinger perimeter for 2 degrees, red (656nm), and blue-green (550nm) stimuli at 19 visual-field positions spanning the entire horizontal meridian. Absolute thresholds were measured using a method of ascending limits. The results showed sensitivity loss in the central 20 degrees, but normal thresholds peripheral to this. The authors suggested that retinal function abnormalities in ARMD are confined to the central retina and the small age-related peripheral changes found do not correlate with the degree of ARMD. They also noted that there was no significant correlation of the magnitude of the loss with the degree of drusen present or with visual acuity.

Automated perimetry was used in a study that evaluated foveal sensitivity as a predictor of macular degeneration. This study was a prospective study of subjects who had participated in the earlier ARMD study of Sunness et al. The results of this study demonstrated that foveal dark-adapted sensitivity to a 1.8 degree red target was an excellent predictor of the subsequent development of advanced ARMD in eyes with drusen.

Atchinson et al. studied the effects of early macular pigmentary and drusen changes on central visual fields in elderly patients with normal visual acuities. Visual field measurements were obtained using the Humphrey Field Analyzer's 24-2 and 10-2 full-threshold programs. No significant differences were found between the two patient groups, one with and one without macular changes. The results found in this study conflict with those from previous studies in which functional losses were found in subjects with pre-ARMD.

Swann and Lovie-Kitchin investigated the nature of central visual field loss in ARMD and pre-ARMD patients and compared them with age-matched normal subjects. Central visual fields were examined using the Friedmann Visual Field Analyzer, Mark II, the Bausch and Lomb Autoplot Tangent Screen and Amsler charts. The central visual field defects in ARMD were found to be predominantly paracentral with a relative sparing of foveal sensitivity. The pre-ARMD subjects showed no significant visual field defects.
Tolentino et al.\textsuperscript{44} evaluated visual field deficits in early age-related macular degeneration. Their purpose was to determine whether deficits of form recognition as well as light sensitivity were related to RPE atrophy and/or drusen. Their findings indicated that the number of visual field defects by each test performed was significantly correlated with the areas of atrophy, but not with the area of drusen. There was also no significant tendency for a patient with a regional preponderance of drusen to have more impairment in the corresponding visual field. The authors suggested that deficits of form recognition and sensitivity in patients with early ARMD can be attributed to alteration of photoreceptor function associated with RPE atrophy, but not with drusen.

It is well established that ARMD is associated with central visual field loss. Some studies attempting to quantify the visual field loss have been able to show a direct correspondence between the observable macular changes and the quantified field loss as measured by an automated perimeter. Other studies have not.

\textbf{CONTRAST SENSITIVITY}

Gratings and other spatially periodic visual stimuli of variable contrast have been demonstrated to be powerful tools in the study of the normal physiology of the visual system, but may also be equally powerful in the study of abnormal physiology\textsuperscript{45}. Wolkstein et al.\textsuperscript{46} studied contrast sensitivity findings in patients with retinitis pigmentosa, central serous retinopathy, glaucoma, and macular degeneration. Four patients with macular degeneration were tested. All four showed a high frequency deficit. However, there was a poor correlation between Snellen scores and the cut-off frequencies. In fact, three of the four subjects had cut-off frequencies better than predicted by the Snellen score. In normal subjects with 20/20 acuity or with reduced vision due to refractive error, the grating cut-off frequency was in agreement with the Snellen score. This study suggested a dissociation between the grating cut-off score and the Snellen acuity for patients with macular degeneration. The study concluded that contrast sensitivity measurements demonstrated central visual deficits not apparent with Snellen testing.
Owsley et al. demonstrated that sensitivity for stationary gratings of low spatial frequency remained the same throughout adulthood in subjects with no retinal pathology. At higher spatial frequencies, sensitivity decreased with age beginning at age 40 to 50 years. They also demonstrated that when a low spatial frequency was drifted, the motion enhancement was markedly diminished in adults over 60 years, implying an impairment of temporal processing in the elderly. These authors suggested that decreased retinal illuminance characteristic of the aged eye could account for a large part of older adults' deficit in spatial vision, but appeared to play a little role in their deficit in temporal vision.

Loshin and White determined contrast sensitivity functions for a large group of patients with macular degeneration. They found a substantial loss of contrast sensitivity across all spatial frequencies, not just the high frequencies as indicated by Snellen visual acuity. In addition, they found that Snellen visual acuity measurements were somewhat variable and usually worse than would be predicted based on eccentricity alone. When compared with resolution acuity (calculated from the high-frequency cut-off of the CSF), the Snellen visual acuity of a patient with ARMD was considerably worse. From this data, the authors concluded that CSF is a useful tool in determining the visual characteristics of a patient with ARMD and that CSF information could be useful in predicting performance through an optical/low vision aid.

Lennerstrand and Ahlstrom studied contrast sensitivity in patients with ARMD. The researchers compared the subjective visual impairment of discrimination/mobility with the amount of reduction of Snellen visual acuity and contrast sensitivity. Contrast sensitivity was tested using two methods. One was the conventional method of presenting gratings of sinusoidal luminance profile on a TV monitor. The other consisted of printed charts with optotypes at different contrast levels. The study found that contrast sensitivity measurements correlated better than Snellen values of visual acuity to the subjective assessment of visual impairment in patients with ARMD. Contrast sensitivity was determined to be fairly well suited to identify patients with difficulties in orientation by means of
vision: e.g., the ability to move around in unfamiliar settings, recognize faces, and watch TV. Snellen visual acuity values were not helpful in prognosticating problems of visual orientation. On the other hand, contrast sensitivity was not correlated with the ability of visual discrimination: e.g., the ability to read printed text or subtitles on TV. In this respect, Snellen visual acuity measurements were found to be more useful. These data were later supported by Wilcox and Burdett.

Low contrast charts were used by Kleiner et al. to investigate the possibility that patients with drusen have visual deficits not detected by Snellen charts. The drusen group read fewer letters than the control group on all the charts tested. The difference increased as the contrast decreased. The results showed a loss of contrast sensitivity with increasing drusen. Low contrast charts may be useful for measuring visual loss not detected by the standard Snellen charts.

Richer presents contrast sensitivity evaluation as a part of a testing protocol for discerning subtle pathologic and functional changes in vision. Lu and Zhang reported that contrast sensitivity reduction at medium and high spatial frequencies of the fellow eyes in cases of unilateral ARMD suggested that CSF may be useful in the diagnosis of subclinical ARMD.

In three studies, Mayer et al. suggested that flicker sensitivity can be used as a predictive test for exudative ARMD. The stimulus was a foveal, long-wavelength, low spatial frequency 2.8 degree-circle in an equiluminant (photopic) surround. The authors speculated that sensitivity loss between 10 and 40Hz is a good predictor of which eyes will develop exudative ARMD.

AMSLER GRID

In 1953, Marc Amsler described the earliest symptoms of diseases of the macula. He reported that early functional symptoms of macular diseases consisted on the one hand of metamorphopsia and on the other hand of a relative scotoma. He designed the grid pattern that bears his name. The charts measure 10cm² and are most commonly lined at 5mm intervals.
chart is held at the recommended distance from the eye (28-30cm), each square subtends an angle of 1 degree.

The Amsler grid is a suprathreshold target and thus may fail to detect a relative scotoma. Wall and May\textsuperscript{57} reported that if the grid is viewed through 3 cross-polarizing filters creating low luminance conditions, the test is far more useful and provided a rapid and sensitive technique for the evaluation of the central 10 degrees of visual field in patients with maculopathies. This study supports an earlier study by Wall and Sadum\textsuperscript{58}.

ARMD could be considered a transition from normal retinal changes to pathological processes. In a pilot study by Cheng and Vingrys\textsuperscript{59}, the visual functions of 11 pre-ARMD and 11 early ARMD subjects were studied. In addition to compromised visual acuity, losses in central visual field, color vision, and visual adaptation, a low contrast Amsler grid proved to be the most sensitive to central field defects and that the desaturated panel D-15 gave many false positives among normal elderly subjects. The results also indicated foveal sparing in early ARMD.

PURPOSE OF THE STUDY

The main purpose of the present study is to develop a test or battery of tests that can be used by the clinical practitioner to identify at-risk patients for the development of ARMD. These tests concentrate in three areas:

1. Functional visual tests
2. Tests evaluating antioxidant protection including dietary intake and blood levels of antioxidants
3. Routine blood chemistry tests

A second purpose of this study is to provide normative data for a larger, nationwide study. The nationwide study is a multi-center, double-masked project on macular degeneration.

It is beyond the scope of this study to analyze all the data provided to the larger, nationwide project.
METHOD

Two groups of subjects, those with age-related macular degeneration and those without the condition ("normals"), were selected from volunteers who responded to newspaper articles, TV reports, and direct solicitations at senior citizen centers. Subjects were required to be age 50 or older and to have good general health. In the normals group, all subjects were required to be male in order to gender-match the subjects participating in the multi-center project. All subjects participated in a detailed screening interview. The interview was designed to exclude individuals who had systemic or ocular diseases with retinal manifestations, persons who had had cataract surgery within the last six months, individuals with glaucoma or IOPs greater than 26mmHg, persons on medications that cause retinal side effects, or individuals who were using a multivitamin/mineral supplement five or more times per week for two out of three years. A copy of the exclusion interview form is contained in Figure 1. All potential subjects were also given a dilated fundus examination to detect any other ocular conditions that might exclude them from the study. Those with severe and unstable cardiovascular disease, diabetes mellitus, chronic alcoholism/drug abuse, or those with previous laser photocoagulation for ARMD, advanced exudative ARMD, central serous retinopathy, optic atrophy, pathologic myopia, angoid streaks, macular hole, retinal vein occlusion, active uveitis, POHS, or other sight-threatening retinopathies, or other retinal degenerations were also excluded from the study. Following an explanation of the study, all subjects signed an informed consent form (See Appendix A). Each subject was paid ten dollars for each visit to the clinic to participate in the study. Twenty control subjects began the study; 18 completed. Three dry ARMD subjects began the study; two completed.

EYE EXAMINATION

All subjects participated in an eye examination every six months. The control subjects completed three eye examinations in the course of one year. The ARMD group completed four
FIGURE 1
EXCLUSION CHART

PATIENT'S NAME ___________________ DATE ____________

GENERAL EXCLUSION CRITERIA:

Multivitamin and/or mineral use
5 or more times per week
for 2 out of 3 years. Identify
all meds, vitamins, etc. currently
taking

Diabetes Mellitus and/or 10 or
more microaneurisms/
retinal hemorrhages in either eye

Severe and unstable Cardiovascular
disease or CHF

Chronic alcoholism or drug abuse

Personality Disorder or use of major
tranquilizers

OCULAR EXCLUSION CRITERIA:

Previous laser photocoagulation for ARM

Advanced exudative ARM in either eye

Central serous retinopathy

Optic atrophy

Surface wrinkling retinopathy severe
enough to produce folding and/or
increased tortuosity of retinal vessels

Pathologic myopia

Angold streaks

Macula hole

Retinal vein occlusion, active uveitis,
presumed ocular histoplasmosis syndrome,
other sight-threatening retinopathies, or
other retinal degenerations
Other ocular diseases, conditions, or previous retinal or ocular surgical procedures, the effects of which may now or in the future complicate assessment of the progression of ARM or cataract, i.e., ALT, RK, Trabeculectomy, cryo (except for a repair of a retinal hole), corneal transplant, radiation therapy, corneal or scleral laceration.

Uncomplicated cataract surgery 6 or more months before is acceptable.

Current or likely need for systemic or ocular medication that is toxic to the lens, retina, or optic nerve, i.e., Plaquenil, Chlorpromazine, Deferoxamine, Tamoxifen, Phenothiazines, ethambutol, or steroids, etc.

Glaucoma or IOP > 26 mmHg

Cataract surgery within 6 months
examinations in the course of eighteen months. The eye examination procedures for both groups were identical and included: best visual acuity through the patient's habitual lenses both at 6m and 40cm; pinhole if necessary to determine if reduced visual acuity was refractive in nature; slit lamp examination to evaluate the openness of the angle; intraocular pressure using Goldmann tonometry.

AMSLER GRID

Each patient's eyes were evaluated using an Amsler grid through threshold Stereo Optical's T.A.G. 100 polarized glasses worn over the habitual lenses. Room lights were standard 8-12 foot candles. The Amsler grid test was conducted monocularly. A drawing was made of any distortions or scotomas found and a numerical score was recorded to correspond to the coordinates of the boxes of the grid that were reported missing or distorted. When no distortions were found, the recording 0.0 was noted.

CONTRAST SENSITIVITY

Each subject was tested using the Vector Vision self-stick intermediate (6Hz) declining contrast test strip which was applied to the white, back side of the white on black Stereo Optical Amsler Grid test. The subject held the card 40cm from the eyes wearing the habitual lenses. The test was conducted monocularly. The subject identified the largest number test circle with vertical stripes that the subject could discriminate. Room illumination was standard room lighting.

PUPIL DILATION

Following the above tests, the subject's eyes were dilated using one drop of Paremyd solution on. The expected risks and effects of dilation were discussed with each subject prior to instillation of the drops.

HEIGHT, WEIGHT, FRAME SIZE, IRIS COLOR

Following instillation of the dilation drops, each subject was
weighed in kilograms on a standard sliding weight scale. Height was obtained by extending a rod from the scale to the top of the subject's head. Height was recorded in centimeters. From the subject's height, ideal body weight was calculated. Frame size was obtained visually and by asking the subject to compare his/her frame size against others of similar height and gender. Iris color was determined by observation and by asking the subject to identify his/her eye color. This data was not used in the present study, but was supplied to the Veterans Affairs Medical Center in North Chicago for inclusion in the multi-center study.

DARK ADAPTATION
Following the instillation of the dilation drops, each subject was seated in a dark room and a blindfold placed over both eyes for a period of 35 minutes. The researcher was present in the dark room with the subject to insure compliance.

NUTRITION QUESTIONNAIRE
During dark adaptation, the researcher used a standardized Veterans Administration nutrition questionnaire, Figure 2, to interview each subject. Information on occupation, date of birth, recreation/physical activity, allergies, medical diagnosis, current medications/multivitamin/mineral supplementation, smoking, alcohol consumption, phosphate beverage consumption, diet restrictions/status, and questions concerning digestion problems were obtained. The questionnaire was completed each six month visit. The data were not used in the present study, but were submitted for inclusion in the multi-center project.

FOVEAL RED THRESHOLD AUTOMATED PERIMETRY
Following 35 minutes of dark adaptation and with dilated pupils, each subject participated in a dark-adapted foveal red threshold test on the Humphrey Field Analyzer. The Humphrey Field Analyzer was modified to simulate a Tubinger perimeter. To set up the equipment for testing, the back and front of the instrument were removed to expose the internal bowl. Black cloth and tape were used
### VA Multicenter Optometry/Dietetic ARM Study

#### Admission/Nutrition Questionnaire

<table>
<thead>
<tr>
<th>Patient Code</th>
<th>Sex</th>
<th>Ht (In)</th>
<th>Wt (Lbs)</th>
<th>Body Frame Size</th>
<th>IBW (Lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M)</td>
<td>(F)</td>
<td>(S)</td>
<td>(M)</td>
<td>(L)</td>
</tr>
</tbody>
</table>

**Admission Date:** ____________________________

**Usual Wt (Lbs):** ____________________________

**Recent Wt Change?** gain ________ loss ________ Lbs

**Name:** ____________________________

**Last** ____________________________ **M**

**First** ____________________________ **F**

**SSN:** ____________________________

**Date Of Birth:** ____________________________

**Month** ____________________________ **Day** ____________________________ **Year** ____________________________

**Occupation:** ____________________________

**Recreation, Physical Activity:** ____________________________

**List Allergies:**

- **Food** ____________________________
- **Medication** ____________________________
- **Others** ____________________________

**Describe Symptoms Briefly:** ____________________________

**Medical Diagnosis: Primary** ____________________________

**Secondary Diagnosis:** ____________________________

**Current Medications:**

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Laxatives</th>
<th>Vitamins**</th>
<th>Anti-coagulants</th>
<th>Others</th>
</tr>
</thead>
</table>

**Dosage/Frequency** | **Prescribed:** yes | no

**Smoking:** yes ____ no ____ **packs per day** ________

**Alcohol intake:** yes ____ no ____ **ounces per day** ________

**Phosphate Beverages:** yes ____ no ____ **ounces per day** ________

**Dietary Restriction (Enter No. Applicable):**

1 - Reg 3 - Low NA 5 - Diabetic 7 - High Fiber 9 - Low Residue
2 - Mech 4 - Low Fat/Chol 6 - Wt Red 8 - Low Pro 10 - Vegetarian

**Nutritional Status (Enter One No.):**

1 - Normal 3 - Moderately Compromised
2 - Mildly Compromised 4 - Severely Compromised

**Per review with attending physician, patient can discontinue current vitamin supplement and begin OcuGuard, RD will alert OD or Gastroenterologist to the presence of side effects and monitor compliance during the first three months.**

**Completed By:** ____________________________ **Date:** ____________________________

R.D. Investigator
# VA Multicenter Optometry/Dietetic ARM Study

## Report of Changes and Problems

<table>
<thead>
<tr>
<th>Patient Code</th>
<th>Baseline</th>
<th>6 Month</th>
<th>12 Month</th>
<th>18 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: Mo/Day/Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% IBW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Digestion and Absorption

Enter No. Applicable

| Nausea: 0 None, 1 Mild, 2 Severe | | | |
| Diarrhea: 0 None, 1 Mild, 2 Severe | | | |
| Constipation: 0 None, 1 Mild, 2 Severe | | | |
| Vomiting: 0 None, 1 Mild, 2 Severe | | | |

### Distention and/or Bloating

Enter No. Applicable

| 0 None, 1 Mild, 2 Severe | | | |
| Excessive Gas: 0 None, 1 Mild, 2 Severe | | | |
| Malabsorption: 0 None, 1 Mild, 2 Severe | | | |

### Comments:

(May include problems with the Food Intake Record)

Baseline: 12 Month:

6 Month: 18 Month:

---

Completed By: R.D. Investigator

Date:
to remove all light leaks from entering the bowl. The small diamond fixation LED target was used and was neutralized using a neutral density filter. A 660nm filter was placed over the projection unit. A custom Goldman V target (1.72) 1 pt. was used. The internal light of the perimetry bowl was disconnected. The foveal threshold selection from the main menu was turned on. Calculated trial lenses, based on a target distance of 33cm, were put in place during the test. The test was performed monocularly and the patient's eye not being tested was patched. The foveal red threshold for each eye was measured using the ascending staircase method with a 200msec stimulus presentation. This method is the same as that established and used by Sunness\textsuperscript{38}. The results for each eye were recorded in decibels.

DILATED FUNDUS EXAMINATION

Following completion of the foveal red threshold test, each subject was sufficiently dilated to complete a dilated fundus examination, using direct ophthalmoscopy, 90D slit lamp examination of the posterior pole, and indirect ophthalmoscopy if necessary. Each subject's crystalline lenses were evaluated for cataract formation. Grades N0 through N4 were used to rate nuclear sclerosis and Grades C0 through C4 were used to designate the level of cortical spoking. Posterior subcapsular cataracts were noted, but not graded. The retina of each eye was evaluated for macular and disk abnormalities; findings were noted in the subject's chart.

FUNDUS PHOTOGRAPHY

Following the dilated fundus examination, 35mm slides were taken of each subject's retinae. Professional Kodak daylight 64ASA slide film was used. The fundus camera was set at 35 degrees angle of coverage and the flash setting was at 50. Three or more slides were taken of each eye. The film was processed by Kodak in Palo Alto or San Francisco. The slides were submitted to an independent professional optometric slide reader associated with the multi-center project. The slide interpreter had no knowledge of the subjects.
FOOD INTAKE DIARY AND CONSULTATION

Following the photography, subjects were seated in a consultation room. At that time, any findings of the examination were disclosed to the subject. A standardized Veterans Administration food intake diary, Figure 3, was presented to the subject with an explanation of how to complete the form and to return it to the researcher in the self-addressed envelope provided. The subjects were instructed to identify on the food intake diary all substances eaten or drunk. The diary was to be completed for three continuous three-day period to include a Friday, Saturday, and a Sunday within the next two weeks following that clinic visit. If the food intake diary was not returned, the researcher contacted the subject by telephone to request completion.

SUPPLEMENTATION TRIALS

The control group did not participate in this aspect of the study. The ARMD group of subjects were randomly selected to receive one of two unidentified capsule supplements. One capsule was a starch placebo; the other was an antioxidant vitamin/mineral nutrient supplement available without a prescription and manufactured by OcuguardR. The capsules were identical in packaging, taste, color, and smell. Which capsule was the placebo and which capsule was the active vitamin/mineral supplement was unknown to the researcher and to the subjects (double masked). The capsules were provided by an independent source not connected to the study. Each ARMD subject was instructed orally and in writing, Figure 4, how to use the capsules properly. The subjects were instructed to take one capsule in the morning with breakfast and one capsule in the evening with dinner. Two weeks following the ARMD subject's first visit to the clinic, the researcher telephoned the subject to check on compliance with the study requirements and to answer any questions. Refills of the supplement were available to the ARMD subjects at all times. If the ARMD subject experienced any adverse reactions to the supplements at any time, the subject was instructed to discontinue use and call the researcher immediately. None of the subjects experienced any adverse reactions to the supplements.
FIGURE 3
VA MULTICENTER OPTOMETRY/DIETETIC ARM STUDY
FOOD INTAKE RECORD

Record intake for three days.
Include a weekend and a weekday.

Patient Code __________
Date ________________

<table>
<thead>
<tr>
<th>MEALS</th>
<th>SPECIFY KIND</th>
<th>SERVING PORTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.M. Snack</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunch:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.M. Snack</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinner:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening Snack</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Review Completed By: __________________________
R.D. Investigator
THANK YOU FOR AGREEING TO PARTICIPATE IN THIS STUDY. WITH YOUR HELP WE WILL GAIN IMPORTANT INFORMATION THAT MAY HELP MANY PEOPLE IMPROVE THEIR SIGHT.

WE ASK THAT YOU FOLLOW THESE SIMPLE INSTRUCTIONS AT HOME DURING THE PROGRESSION OF THE STUDY:

1. TAKE YOUR ASSIGNED DIETARY SUPPLEMENTS TWICE PER DAY, ONE CAPSULE WITH BREAKFAST AND ONE CAPSULE WITH DINNER.

2. PERFORM THE AMSLER GRID AT HOME AS INSTRUCTED DURING YOUR FIRST VISIT TO PACIFIC UNIVERSITY.

3. WE WILL CHECK IN WITH YOU AFTER TWO WEEKS AND MONTHLY BY TELEPHONE TO SEE HOW YOU ARE DOING AND TO ANSWER ANY QUESTIONS.

IF, AT ANY TIME, YOU EXPERIENCE ANY ADVERSE REACTIONS TO THE DIETARY SUPPLEMENTS, DISCONTINUE USE AND CALL ONE OF THE RESEARCHERS AS SOON AS POSSIBLE:

DR. DIANE YOLTON: WORK: 357-6151, Ext. 2282
DR. SALISA WILLIAMS: WORK: 357-6151, Ext. 2530
FRAN TABOR, INTERN: HOME: 359-0742
BLOOD CHEMISTRY ANALYSIS
The subjects in the control group had their blood drawn once at
the conclusion of the study. Blood samples were drawn from the
ARMD subjects by a certified plebotomist at the beginning of the
study and at the conclusion of the study. Standard CBC/differential,
SMA6 and 12 serological tests were performed by a commercial
medical laboratory/hospital laboratory. The results of the test were
sent to the researcher by the laboratory.

AMSLER GRID
The ARMD subjects were given an identical Stereo Optical
Amsler Grid T.A.G. with polarized glasses as the one used in the
clinical visit. The polarized lenses were turned so that the minimal
amount of light entered the eye. The pins that rotated the polarizers
were removed by the researcher so the the polarizing angles could
not be changes by the subject. The ARMD subjects were given oral
and written instructions, Figure 4, on the proper use of the home
Amsler grid. ARMD subjects were instructed to call the researcher if
there were any changes in the appearance of the grid during the
course of the study.

RESULTS

Eighteen of the twenty control subjects and two of the three
ARMD subjects completed the study. The control ("normals") subjects
were followed for one year and the ARMD subjects were followed for
eighteen months.

The foveal red threshold automated perimetry test, nutritional
data from the food intake diaries, contrast sensitivity test,
Amsler grid test and blood chemistry tests were analyzed for
purposes of this study.

It should be noted that, because the ARMD group contained
only three participants, statistics comparing differences between the
control group and the ARMD group could not be conducted. A
minimum of seven subjects in each group are necessary to conduct a statistical analysis.

FOVEAL RED THRESHOLD AUTOMATED PERIMETRY

A comparison of the mean foveal red thresholds of 17 normals and weighted average of three ARMD patients over all trials is summarized in Table 1. One normal subject's data was dropped due to red/green color anomaly.

Table 1. Mean Foveal Red Thresholds in Decibels of the Normals and the ARMDs

<table>
<thead>
<tr>
<th></th>
<th>MEAN FOVEAL RED THRESHOLDS IN DECIBELS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
</tr>
<tr>
<td>NORMALS</td>
<td>25.3</td>
</tr>
<tr>
<td>ARMD</td>
<td>15.2</td>
</tr>
</tbody>
</table>

The results indicate that the foveal red thresholds of the normals were notably higher than those of the ARMD group.

CONTRAST SENSITIVITY

A comparison of the mean contrast sensitivity of 18 normals and the weighted average of three ARMD patients over all trials is shown in Table 2.

Table 2. Mean Contrast Sensitivity @ 6cc/degree of the Normals and ARMDs

<table>
<thead>
<tr>
<th></th>
<th>MEAN CONTRAST SENSITIVITY @ 6cc/Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMALS</td>
<td>8.0</td>
</tr>
<tr>
<td>ARMD</td>
<td>4.4</td>
</tr>
</tbody>
</table>

The results indicate that the normals are able to detect notably lower contrast targets than are the ARMDs.
Amsler Grid

A comparison of metamorphopsia of the normals and the ARMDs is indicated in Table 3.

Table 3. Amsler Grid Metamorphopsia in the Normals and ARMDs

<table>
<thead>
<tr>
<th></th>
<th>AMSLER GRID METAMORPHOPSIA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HORIZONTAL</td>
<td>VERTICAL</td>
<td>SCOTOMA</td>
</tr>
<tr>
<td>NORMALS</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ARMD</td>
<td>2.47</td>
<td>2.78</td>
<td>34.9</td>
</tr>
</tbody>
</table>

The results indicate that the normals did not experience any metamorphopsia, while the ARMD subjects showed horizontal and vertical distortion as well as scotomas.

Nutritional Data Analysis

In order to age-match the normal subjects of this study with the subjects in the larger multi-center project, the nutritional data of the five youngest control group members were dropped. The nutritional intake data were analyzed for the 13 remaining normals. The nutritional analysis was conducted by the Veterans Affairs Medical Center. The results are shown in Table 4.
Table 4. Nutritional Analysis of the "Normals" (Control) Group

<table>
<thead>
<tr>
<th></th>
<th>RDA</th>
<th>MEAN</th>
<th>%RDA</th>
<th>+/- %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (Kcal)</td>
<td>2250</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein g</td>
<td>63</td>
<td>102</td>
<td>162%</td>
<td>+62%</td>
</tr>
<tr>
<td>Carbo g</td>
<td>258</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat g</td>
<td>86.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude Fiber g</td>
<td>5.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet Fiber g</td>
<td>8.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron mg</td>
<td>10</td>
<td>20.2</td>
<td>202%</td>
<td>+102%</td>
</tr>
<tr>
<td>Selenium ug</td>
<td>70</td>
<td>132</td>
<td>189%</td>
<td>+89%</td>
</tr>
<tr>
<td>Zinc mg</td>
<td>15</td>
<td>8.83</td>
<td>59%</td>
<td>-41%</td>
</tr>
<tr>
<td>Magnesium mg</td>
<td>350</td>
<td>206</td>
<td>59%</td>
<td>-41%</td>
</tr>
<tr>
<td>Copper mg</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A RE</td>
<td>1000</td>
<td>1429</td>
<td>143%</td>
<td>+43%</td>
</tr>
<tr>
<td>Vitamin C mg</td>
<td>60</td>
<td>8.9</td>
<td>148%</td>
<td>+48%</td>
</tr>
<tr>
<td>Vitamin E mg</td>
<td>10</td>
<td>2.01</td>
<td>20%</td>
<td>-80%</td>
</tr>
<tr>
<td>Riboilavin mg</td>
<td>1.4</td>
<td>6.51</td>
<td>465%</td>
<td>+365%</td>
</tr>
<tr>
<td>Manganese mg</td>
<td>2.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium mg</td>
<td></td>
<td>2947</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium mg</td>
<td></td>
<td>3461</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium mg</td>
<td>800</td>
<td>719</td>
<td>90%</td>
<td>-10%</td>
</tr>
<tr>
<td>Phosphorous mg</td>
<td>800</td>
<td>1389</td>
<td>174%</td>
<td>+74%</td>
</tr>
<tr>
<td>H2O ml</td>
<td></td>
<td>1516</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamin mg</td>
<td>1.2</td>
<td>4.56</td>
<td>380%</td>
<td>+280%</td>
</tr>
<tr>
<td>Niacin mg</td>
<td>15</td>
<td>29.4</td>
<td>196%</td>
<td>+96%</td>
</tr>
<tr>
<td>Vitamin B6 mg</td>
<td>2.0</td>
<td>1.73</td>
<td>87%</td>
<td>-13%</td>
</tr>
<tr>
<td>Vitamin B12 mcg</td>
<td>2.0</td>
<td>4.17</td>
<td>209%</td>
<td>+109%</td>
</tr>
<tr>
<td>Folic Acid mcg</td>
<td>200</td>
<td>205</td>
<td>103%</td>
<td>+3%</td>
</tr>
<tr>
<td>Pant mcg</td>
<td></td>
<td>3.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chol mg</td>
<td>418</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>182C2 g</td>
<td>12.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18C3 g</td>
<td>0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono g</td>
<td>16.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PuFA g</td>
<td>11.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaFA g</td>
<td>28.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results indicate that the diets of the control subjects are deficient in zinc, magnesium, vitamin E, calcium, and vitamin B6. However, their diets appear to be rich in iron, riboflavin, phosphorous, thiamin, niacin, and vitamin B12.

No nutritional analysis data of the ARMD subjects was available.

**BLOOD CHEMISTRY ANALYSIS**

Blood chemistry values of the normals and the ARMDs were analyzed by the Veterans Affairs Medical Center. The results are shown in Table 5 (Normals) and Table 6 (ARMDs). Again, in order to age-match to the larger multi-center project, the blood chemistry values of the five youngest members of the control group were dropped from the analysis. The data of the 13 remaining normals for one blood test at the conclusion of the study was analyzed. A weighted average of the three ARMD patients for two blood chemistry tests, one at the beginning of the study and one at the conclusion of the study, was analyzed.
Table 5. Blood Chemistry Values of the Normals

<table>
<thead>
<tr>
<th>Test</th>
<th>Range of Values</th>
<th>Mean</th>
<th>+/- %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>60-110</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>8-25</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.5-1.5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>134-146</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.5-5.1</td>
<td>4.43</td>
<td></td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>92-109</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>CO₂ (mEq/L)</td>
<td></td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>2.6-4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.0-10.4</td>
<td>9.46</td>
<td></td>
</tr>
<tr>
<td>Total Protein (g/dl)</td>
<td>5.6-8.4</td>
<td>6.87</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4-5.4</td>
<td>3.99</td>
<td></td>
</tr>
<tr>
<td>Alk. Phosph. (U/L)</td>
<td>25-115</td>
<td>122</td>
<td>+6%</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>0-40</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>50-240</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>0-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tot. Bilirubin (mg/dl)</td>
<td>0.2-1.5</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>&lt;200</td>
<td>210</td>
<td>+5%</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>30-135</td>
<td>197</td>
<td>+46%</td>
</tr>
<tr>
<td>Uric Acid (mg/dl)</td>
<td>2.4-7.5</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Tot Lymph Count</td>
<td>630-3170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (cells/mm³)</td>
<td></td>
<td>6.87</td>
<td></td>
</tr>
<tr>
<td>RBC (10⁶/ul)</td>
<td>4.8-6.0</td>
<td>4.68</td>
<td>-3%</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14-18 m</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40-52 m</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>80-95 m</td>
<td>94.0</td>
<td></td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>27-32</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>Cell Type</td>
<td>Range</td>
<td>Value</td>
<td>% Change</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>32-36</td>
<td>33.9</td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>40-60</td>
<td>66.1</td>
<td>+10%</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>20-40</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4-8</td>
<td>7.27</td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1-3</td>
<td>2.66</td>
<td></td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0-1</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Blood Chemistry Values of the ARMDs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of Values</th>
<th>Mean</th>
<th>+/- %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>60-110</td>
<td>97.6</td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>8-25</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.5-1.5</td>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>134-146</td>
<td>140.8</td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.5-5.1</td>
<td>4.48</td>
<td></td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>92-109</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>CO2 (mEq/L)</td>
<td></td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>2.6-4.6</td>
<td>3.43</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.0-10.4</td>
<td>9.82</td>
<td></td>
</tr>
<tr>
<td>Tot. Protein (g/dl)</td>
<td>5.6-8.4</td>
<td>6.88</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4-5.4</td>
<td>4.04</td>
<td></td>
</tr>
<tr>
<td>Alk. Phosph. (U/L)</td>
<td>25-115</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>0-40</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>50-240</td>
<td>177.2</td>
<td></td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>0-40</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Tot. Bilirubin (mg/dl)</td>
<td>0.2-1.5</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>&lt;200</td>
<td>217.60</td>
<td>+8.8%</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>30-135</td>
<td>254.8</td>
<td>+88.7%</td>
</tr>
<tr>
<td>Uric Acid (mg/dl)</td>
<td>2.4-7.5</td>
<td>4.65</td>
<td></td>
</tr>
<tr>
<td>Total Lymph Count</td>
<td>630-3170</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (cells/mm$^3$)</td>
<td></td>
<td>7.62</td>
<td></td>
</tr>
<tr>
<td>RBC ($10^6$/ul)</td>
<td>4.8-6.0</td>
<td>4.40</td>
<td>-3.6%</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14-18 m</td>
<td>13.54</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40-52 m</td>
<td>40.90</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>80-95 m</td>
<td>93.16</td>
<td></td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>27-32</td>
<td>30.84</td>
<td></td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>32-36</td>
<td>33.14</td>
<td></td>
</tr>
</tbody>
</table>
A comparison of the blood chemistry values of the normals (Table 5) and the ARMDs (Table 6) indicates that, although both groups show high levels of triglycerides, the ARMD group shows a level almost double that of the controls. Although the normals show higher than usual levels of alkaline phosphatase and neutrophils, they also show higher than usual levels of these blood components than the ARMD group.

**DISCUSSION**

The present study represents an effort to develop a protocol testing method of identifying individuals who are likely candidates to develop age-related macular degeneration (ARMD). The subjects who participated in this study were part of a larger, nationwide, multi-center, double-masked study conducted by the Veterans Affairs Medical Center in North Chicago, Illinois. In that study, most participants were male and the average age was mid-seventies.

The "normals" control group in the present study consisted of 18 male subjects over the age of 50. In order to gender and age match the subjects in the larger study, the data of the five youngest members of the control group were not analyzed in the nutritional intake and blood chemistry analyses. However, in the analyses of contrast sensitivity, Amsler grid, and red foveal threshold automated perimetry, the data of all 18 normals is included.

Because of the small number of subjects in the ARMD group, statistical analyses could not be performed. This study analyzed the weighted averages of the three ARMD patients over all trials for the contrast sensitivity, Amsler grid, red foveal red threshold automated perimetry, and the blood chemistry analyses.
The foveal red threshold automated perimetry test appears to be an excellent tool for identifying who are likely individuals to develop ARMD in the future. Even without the benefit of statistical analysis, it is clearly evident that there is a significant drop in foveal sensitivity as ARMD develops. This finding supports those of earlier researchers, such as Sunness.\textsuperscript{39}

The results of the contrast sensitivity test also revealed a notable difference between the normals and the ARMDs. The ARMD subjects showed a reduced ability to distinguish targets of low contrast. Since the average age in the present study of the normals group was 68.1 years and that of the ARMD subjects was 75.6 years, the differences appear to be the result of ARMD rather than age. These data support the findings of Loshin and White\textsuperscript{48} and others who indicate a substantial loss of contrast sensitivity across all spatial frequencies with the development of ARMD.

The nutritional analysis was not completed for the ARMD subjects, so comparisons between the ARMD group and the "normals' control group could not be made. It is extremely interesting to note, however, that the normal group showed deficiencies in zinc, magnesium, vitamin E, calcium, and vitamin B6. Zinc and vitamin E are antioxidant vitamins/minerals that are known to be required to quench the free-radicals that may be responsible for the development of ARMD. It will be very interesting to learn whether any of the normals develop ARMD in the future.

The blood chemistry analysis showed that the triglyceride level of the ARMD subjects was almost double that of the control group, although both groups had about the same higher than usual cholesterol levels. There are no studies linking high triglyceride levels to ARMD. However, the Eye Disease Case Control Study\textsuperscript{30}, discussed above, does suggest that high serum cholesterol levels are indirectly linked with cardiovascular disease and ARMD.

In summary, this study should be regarded as a preliminary pilot study. The numbers of subjects in the ARMD group was too small for statistical analyses to be performed. In spite of this difficulty, however, notable differences between the "normals" control group and the ARMD group were observed. These data
suggest that further research is necessary. Perhaps if the ARMD group had been larger, the differences between the two groups would have withstood statistical scrutiny.

Based on the observations of this study, there appears to be a viable protocol for use by optometrists and ophthalmologists to determine who are likely individuals to develop ARMD in the future. The testing protocol recommended should include:

1. **Foveal Red Threshold Automated Perimetry.** The use of a 660nm filter over the projection unit; Goldman V target; neutral density filter over the small diamond; and removal of all light leaks should be employed. The patient should be dark-adapted and pupils dilated. This method was developed by Sunness in 1989 and appears to be an excellent predictor of future ARMD. The present study suggests that if the results of the foveal red threshold test start to drop below 20db, there is a likelihood that the patient may be developing ARMD.

2. **Contrast Sensitivity.** This test should employ the Vector Vision intermediate (6Hz) declining contrast test strip. The subject should be tested at 40cm from the eyes wearing habitual lenses. Contrast levels under 5.0 may suggest ARMD or other ocular disease.

3. **Amsler Grid.** This test should be performed using the Stereo Optical T.A.G. 100 polarized glasses worn over the habitual lenses. The test should be performed monocularity under minimal luminance conditions. Horizontal or vertical distortions or scotomas could be indicative of ARMD.

4. **Nutritional Data.** Analysis of food nutrients in the diet via food diaries analyzed over a period of time may suggest risk factors associated with the development of ARMD.
Since nutritional data of the normals could not be compared with the ARMDs, guidelines in this area will have to wait for the results of the multi-center study.

5. Blood Chemistry Analysis. Analysis of blood chemistry via the CBC and SMAC may suggest some risk factors for developing ARMD. Although the data of this study suggested that a high triglyceride level could be a risk factor, the number of subjects in the ARMD group is too small to draw any valid conclusion. The guidelines here will have to wait for the results of the multi-center study.

This study did establish that there is a strong suggestion that a testing protocol for identifying which patients are at risk for developing ARMD in the future can and should be developed. The predictability of these tests will likely be refined as part of the larger, nationwide, multi-center project of the Veterans Affairs Medical Center concludes. However, research in the area of ARMD needs to continue. As the population ages, more cases of ARMD are likely to occur. It is a challenge to researchers to find the causes, develop appropriate and cost-effective testing protocols, and the treatments necessary to bring the elusive eye disease under control.
REFERENCES


APPENDIX A

INFORMED CONSENT FORM

Pacific University College of Optometry

A. Title of Project: The Visual Function and Dietary Intake of Males of Age 50 or Older

B. Principal Investigators
   Fran L. Tabor, Intern
   359-0742
   and
   Dr. Diane P. Yolton, OD, PhD
   357-6151, ext. 2282

C. Location
   Pacific University Family Vision Clinic
   Forest Grove, Or 97116

D. Dates of Study
   1993-1994

Description of Study
The purpose of this study is to evaluate the dietary intake and specific visual functions of males 50 years of age and older who have healthy eyes and good general health. This study is part of a larger research project to determine whether an over-the-counter (OTC) multi-vitamin/mineral supplement taken twice daily can slow the progression of age related macular degeneration. The overall project includes other subjects from around the USA.

If selected for participation in this study, you will complete a food intake diary for three days (one weekday and one weekend) once at the beginning of the one-year research time period and once at the end of the study. You will visit the Family Vision Clinic at Pacific University three times: this visit, at six months and at one year from the start of the research time period. During each visit, your eyes will be evaluated for any changes that might have occurred during the last six months. During your visit, your eyes will be dilated and you will be dark-adapted for 40 minutes. Following dark adaptation, your eyes will be evaluated using a field analyzer test and a contrast sensitivity test, two standard tests which are administered during a routine vision exam. You will be informed if unusual conditions are detected.
Description of Benefits

You will be paid $10 for your participation in this study (a total of $30 for 3 visits). You will be paid in for form of cash or a check at the time of each visit.

If you have elected to participate in this study, you will have the advantage of close monitoring or your visual system at six-month intervals at no cost to you. However, this monitoring is not a complete eye exam. It is a screening test to determine whether your vision remains normal.

Description of Risks

During each visit to the clinic, your eyes will be dilated. The drops used to dilate your pupils for the exam may cause temporary blurring and/or light sensitivity for 2-4 hours after optometric procedures. Slight risks of allergic reactions to the medications used and a very slight risk of causing elevated pressure in the eye exist. You will be screened for susceptibility to these conditions prior to dilation. In addition, you will be warned not to drive or operate dangerous machinery while your eyes are dilated. Sunglasses will be provided to you to reduce possible sensitivity to light.

Confidentiality

Records of this project will be maintained in a confidential manner and no name-identifiable information will be released.

Compensation and Medical Care

If you are injured or become ill during this experiment, it is possible that you will not receive compensation or medical care from Pacific University, the researchers, or any organization associated with this study. All responsible care will be used during this study to prevent any injuries.
Offer to Answer Any Inquiries

The researchers are happy to answer any questions that you may have at any time during the course of the study. Please feel free to call Fran Tabor at 359-0742. If you are not satisfied with the answers you receive, you may call Dr. James Peterson at 357-0442.

During your participation in the project, you are not a Pacific University clinic patient or client for the purposes of the research. All questions should be referred directly to the researchers who will be solely responsible for any inquiries. As mentioned above, you will not be receiving complete eye, vision, or health care as a result of participation in this project. Therefore, you will need to maintain your regular program of eye, vision, and health care.

Freedom to Withdraw

You are free to withdraw your consent and to discontinue your participation in this study at any time without prejudice to you.

I have read and understand the above.

Printed Name --------------------------------------------

Signed ___________________________ Date ____________

Address ___________________________ Phone ____________

City ___________________________ State/Zip ____________

Name and telephone number of a person who will know that you are at Pacific University.

Name ___________________________ Phone ______________________