Chapter 2

LITERATURE REVIEW

2.1 EPIDEMIOLOGY OF AGE-RELATED CATARACT

2.1.1 Blindness From Cataract

Cataracts are the leading cause of blindness worldwide, accounting for visual loss in about half of the world's estimated 23 million persons with best corrected acuities of 3/60 or worse.[1] The number of cataract blind is expected to increase dramatically in coming decades as the number of elderly in the world's population increases. In the absence of more widespread availability of cataract surgery in the developing world, or the identification of interventions that retard the development or progression of cataracts, population projections suggest that the number of cataract blind could reach close to 40 million by the year 2025.[1]

While cataract blindness is largely a problem in the developing world, where access to surgical intervention is often limited, blindness registry data collected by several US states as recently as 1970 suggested that cataracts were the third leading cause of blindness and accounted for about 9 percent of all blindness in the United States.[2] The prevalence of cataract blindness (best corrected visual acuity of 6/60 or less in the better eye or visual field limited to 20 degrees in its widest diameter) was 13.5 per 100,000 and the incidence was 1.7 per 100,000 in 1970. Many changes in cataract management, including an extremely large increase in the number of cataract operations since 1970, have apparently reduced the number of cataract blind in developed countries.[3] However, a recently published survey from East Baltimore indicated that unoperated age-related cataract was the leading cause of blindness in blacks, accounting for almost one-third of all blindness in this population.[4]

2.1.2 Cataract Prevalence

Data from the Framingham Eye Study (FES) indicated that age-related lens changes, ranging from mild early changes (vacuoles, water clefts, spokes and lamellar separations) to later changes (cortical cuneiform opacities, nuclear sclerosis, posterior subcapsular opacities, aphakia), were present in 42 percent of persons aged 52-64.[5] The prevalence of these changes increased to 91 percent for persons aged 75-85.

In the same study, age-related cataract (cortical cuneiform opacities, nuclear sclerosis, posterior subcapsular opacities, or aphakia accompanied by a reduction in visual acuity to 6/9 or worse) ranged from 4 percent at age 52-64 to 50 percent at age 75-85.[6]

Eye examinations conducted during the 1971-72 National Health and Nutritional Examination Survey (NHANES) showed that approximately 60 percent of persons in the age group

65-74 years had lens opacities.[7] The prevalence of lens opacities causing a decrease in vision to 6/7.5 or worse was 28 percent in persons aged 65-74.

2.1.3 Cataract Incidence

Few incidence data are available for age-related cataract. Podgor, Leske, and Ederer have used age-specific prevalence data from the Framingham Eye Study to estimate 5-year incidence rates for lens opacities and cataract.[8] For lens opacities, the 5-year incidence estimates for ages 55, 60, 65, 70, and 75 were 10, 16, 23, 31, and 37 percent, respectively. For cataract (visual acuity of 6/9 or worse and lens opacities that could entirely account for the visual loss), the corresponding incidence estimates were 1, 2, 5, 9, and 15 percent, respectively. These estimates assume that the lens opacities are not reversible and not accompanied by a differential mortality.

Using data collected during a re-examination of the survivors of the original Framingham Eye Study, the 13.6-year incidence of lens opacities among persons free of opacities at baseline was 50 percent for persons aged 55-59 years at baseline.[9] The incidence rate increased to more than 80 percent for persons aged 70-74 at baseline. Incidence rates for the same age groups for lens opacities accompanied by a reduction in visual acuity to 6/9 or worse were approximately 20 percent and more than 60 percent, respectively.

2.1.4 Risk Factors for Age-Related Cataracts

2.1.4.1 Demographic

Age. Increasing age is by far the strongest known risk factor for cataract. Data from the Model Reporting Area suggested that the prevalence of cataract blindness increased from 17/100,000 for persons aged 45-64 to 488/100,000 for persons over age 85.[2] In the Framingham Eye Study, the prevalence of cataract rose from 4 percent at age 52-64 to 50 percent at age 75-85.[6] More than 90 percent of persons aged 75-85 have age-related lens changes.[5]

Sex. The combined evidence from several studies suggests a small excess risk of cataract for women compared with men.[10] A higher risk of cortical cataract may explain the 10-20 percent excess risk of cataract among women.[11,12]

Race. Data from one study, the 1971-72 NHANES suggest that cortical and nuclear cataracts are more commonly found in blacks than whites.[11] Data from a large urban survey indicate that cataracts are the leading cause of blindness in blacks, accounting for about one-third of all blindness.[4]

Geographic. Reports of a higher prevalence of cataract in tropical areas compared with nontropical areas are hard to evaluate because of differences in survey methodology. However, prevalence rates adjusted for age and sex have been reported for the Punjab plains of India that were almost three times higher than the comparable FES rates.[13] For persons in the Punjab aged 75-85, more than 80 percent had age-related cataracts with vision reduced to 6/9 or worse. A survey in

Nepal reported an almost threefold increase in the prevalence of cataract at an altitude of 185 meters compared with sites at more than 1,000 meters.[14] In this study, higher elevations had less sunlight than lower elevations because of tall neighboring mountains, and there was a strong positive association between increasing hours of sunlight exposure and cataract. In population-based studies conducted by the same examination team, the age- and sex-adjusted prevalence of cataract was 60 percent higher in Tibet (alt. 4,000 m) compared with Beijing, China (alt. 50 m).[15]

2.1.4.2 Medical

Diabetes. Data from two population-based surveys have shown a marked excess prevalence of age-related cataract in diabetics less than 65 years old (relative risk of 4.02 and 2.97, respectively); after age 70 the excess appears to be less.[16] The Lens Opacities Case-Control Study reported an increased risk of posterior subcapsular, cortical, and mixed cataracts (OR = 1.56) in diabetics.[17]

Family History. There is a long-standing clinical impression of a familial relationship for cataract, but few data are available to substantiate this impression. Two case-control studies have recently reported an increased risk of cataract for persons with a family history of cataract.[12,17]

Drugs. Many drugs are suspected of having cataractogenic potential.[7] Implicating evidence is strong for some drugs such as corticosteroids, but less strong for others. Drugs that may have cataractogenic potential include phenothiazines, miotic cholinergic compounds, cancer chemotherapy agents, various photosensitizing drugs, diuretics, major tranquilizers, gout medications, cholesterol-lowering medications, and many others.[7,18] For the most part, the cataracts that are suspected to be caused by these agents are similar in appearance to age-related cataracts.

There have been contradictory reports about whether aspirin or aspirin-like analgesics protect against the formation of cataract. While some observational studies have reported a protective effect for aspirin,[19,20] other observational studies[21,22] and two clinical trials of physicians[23,24] seem to have excluded any large protective effect of low aspirin usage on cataract formation.

2.1.4.3 Environmental

Nutrition. Theoretical considerations and laboratory data have made it tempting to speculate that nutritional status may play a role in the development of cataract. However, observational epidemiologic studies have provided no conclusive data about the relationship between nutrient intake and the development of cataract. Two[17,25] of three large case-control studies that used food-frequency interviews to estimate dietary intake of selected nutrients reported a decreased risk of cataracts in persons with a higher intake of a number of micronutrients. One of the studies[17] also reported a decreased risk of cataracts among persons who used multiple vitamin supplements regularly. A smaller case-control study found fewer cataracts in persons taking supplementary vitamin C or supplementary vitamin E, but no protective effect for persons taking multivitamin preparations.[26] One additional observational study reported that subjects with "high" plasma levels of at least two of three vitamins with antioxidant characteristics (vitamin E, vitamin C, or carotenoids) were at reduced risk of cataract compared with subjects with low levels of these vitamins.[27] No association was found between the risk of cataract and erythrocyte levels of superoxide dismutase and glutathione peroxidase, enzymes important in antioxidant systems of red blood cells as well as the lens. Limitations of observational studies, in particular the possibility of

unadjusted confounding, make it difficult to reach conclusions about the importance of nutritional factors in cataractogenesis. An editorial summarizing data on the relationship between nutrition and cataract is included as Appendix D.[28]

Radiation. Ultraviolet radiation, a part of the sunlight spectrum that is absorbed efficiently by the lens, can be used to produce cataracts in laboratory animals.[29,30] Several ecologic studies have reported an association between cataracts and sunlight or ultraviolet light exposure.[31,32] These studies have suggested that persons living in areas of greater sunlight/UV exposure have a higher prevalence of cataracts than persons living in areas of lesser exposure. A weakness of these studies is their inability to control for potential confounding variables: Persons living in different areas differ not only in their UV exposures, but also in their exposures to a variety of other factors. One nonecologic study that attempted to quantify individual, lifetime UV exposure reported that fishermen with the highest amount of exposure were at increased risk of cortical and posterior subcapsular cataracts.[33,34]

Energy from other parts of the electromagnetic spectrum can damage the lens.[7] High dose exposures to ionizing, infrared, and microwave radiation are capable of inducing lens opacities. The cumulative effect of low-dose exposures to such forms of radiation, which occur far more frequently than high-dose exposures, is unknown. The difficulty in measuring individual long-term exposure to the various energy sources and the absence of unique features for cataracts induced by such exposures have complicated such studies.

Smoking. Observational studies have reported that current history of cigarette smoking increases the risk of nuclear, but not cortical, cataract.[17,35] Risk decreased among those who had stopped smoking.

A large number of other factors have been reported to increase the risk of cataract.[7] These include myopia, systemic hypertension, severe diarrhea, renal failure, and various biochemical markers. The mix of associations reported by many studies has contributed to a growing consensus that the development of age-related cataract is not related to a single overwhelmingly important exposure but is a complex multifactorial process.

2.2 EPIDEMIOLOGY OF AGE-RELATED MACULAR DEGENERATION

AMD is the leading cause of registered blindness in both England[36] and the United States.[2] Although certain personal characteristics and environmental factors have been shown to be associated with AMD, the etiology of this disorder remains unknown.

It is clear that the risk of AMD increases with age especially after the fifth decade. As the average life span of the population increases, the incidence and prevalence of blindness from this disease will undoubtedly increase unless successful means of prevention or treatment can be found. Epidemiologic approaches to identify possible risk factors for AMD are necessary first steps in developing the means to prevent this disease.

2.2.1 Prevalence of Age-Related Macular Degeneration Causing Legal Blindness

Blindness registries are a source of data that have been used to estimate the prevalence of AMD severe enough to cause legal blindness. They have been utilized for this purpose in England and Wales,[36] the United States[2], and Canada.[37]

Two unknowns limit the usefulness of data from these sources. First, these data reflect only those who register as legally blind. These registrants may represent as few as half of those who are actually legally blind.[2,37] With an unknown proportion of those legally blind registering, no good method of estimating the prevalence of blindness exists. Second, the classification of cause of blindness is not done in a standardized way. These two severe shortcomings apply to all three of the blindness registries mentioned above.

Keeping these caveats in mind, one may cautiously review these data to obtain some idea of the proportion of blind persons who have AMD. Exhibit 2-1 shows the proportion of the registered blind with the four leading causes of blindness in the three registries. The large differences in proportions of blind persons with AMD are probably due to the two unknown variables stated above; however, it is impossible to rule out the possibility that these are true differences in different populations.

The data from England and Wales compiled by Sorsby[36] show a dramatic increase in the number of persons blind from AMD in older segments of the population (Exhibit 2-2). Although females outnumber males by about 50 percent in each age group, this difference reflects a similar increased proportion of females in these age groups in the population[36] and demonstrates the problem of looking at "numerator" data alone. In a followup study,[38] Sorsby reports on individuals 65 years old or younger. While AMD is the leading cause of blindness among all registered blind in England and Wales, it is not even one of the top 10 causes in this younger age group.

The Model Reporting Area study conducted in 16 US states[2] is more difficult to summarize with respect to the proportion of blind persons with AMD. Throughout the report of this study, retinal disease is summarized in the following three categories: prenatal cause of retinal disease, diabetic retinopathy, and other retinal disease. Cases of AMD are pooled with all retinal disease other than that having prenatal or diabetic etiologies. The Model Reporting Area study provides summary data that show that AMD comprises approximately two-thirds of this "other retinal disease" category, but we do not know the proportion of AMD in this category within specific age or sex subgroups. These data, summarized in Exhibit 2-3, show that the "other retinal disease" category increases in number with increasing age, but we can only presume that this increase is due largely to AMD. No significant sex differences are apparent in this "other retinal disease" category. Age- and sex-specific data for AMD are not available from the Canadian study.

In summary, the data from all three registries identify AMD as a leading cause of blindness, and two of these registries demonstrate a strong association between age and blindness from AMD.

2.2.2 Prevalence of Age-Related Macular Degeneration

There are two population-based studies that include data on the prevalence of AMD. The Framingham Eye Study[39,40] provides data from comprehensive, standardized ophthalmic examinations performed on 2,631 persons, aged 52-85, who are or had been residents of Framingham, Massachusetts. This study group comprised two-thirds of the surviving members of the cohort that had participated in the Framingham Heart Study. Specific definitions are provided for each of the manifestations of AMD. These include pigment disturbance in the macula; drusen, perimacular circinate exudates; and serous, hemorrhagic or proliferative elevation of the pigment epithelium. If the etiology of any of these lesions was designated by the examining ophthalmologist as "age-related," and the vision in that eye was 20/30 or worse, the eye was classified as having AMD. Examining ophthalmologists also categorized AMD as being either of the "dry type" or the "exudative type." Prevalence estimates (Exhibit 2-4) were derived from data on individuals who lived in the local Framingham area (84 percent of this group was examined). The assumption is made that the prevalence of AMD in subjects who were not examined or who were not classified for AMD was similar to the prevalence observed in those who were examined and classified. Notable are the marked increase in prevalence of AMD with age and the 50-percent higher prevalence of this disease in females compared with males.

In addition to information on the prevalence of AMD, the Framingham Eye Study also provides information on the proportion of the population with each specific manifestation of AMD. Drusen were seen in approximately 25 percent of the population regardless of sex or age. The size of the drusen was also considered. When the size was specified, about 90 percent of eyes had small drusen. Large drusen were seen in only about 10 percent of all eyes with drusen, but this rate increased from 9 percent of the eyes with drusen in persons less than 65 years old to 17 percent in persons older than 74 years. Large drusen were also seen more commonly in eyes with many drusen. Only 2.7 percent of eyes with less than 10 total drusen had large drusen while 37 percent of eyes with 10 or more drusen had large drusen. This may be a reflection of the tendency for drusen to coalesce as described by Sarks.[41]

Changes in the retinal pigment epithelium were seen in approximately one-third of eyes in the Framingham Eye Study. The proportion and severity of these changes were clearly associated with increasing age.

In the Framingham Eye Study, eyes with only drusen or RPE atrophy comprise the "dry" group, which has also been termed the "atrophic" group. Eyes with fluid beneath the retina either from an RPE detachment or from hemorrhage or exudate caused by subretinal neovascularization are categorized as "exudative" or "wet" cases of AMD. Eyes with disciform scars are also categorized in this group since the scar was presumably caused by subretinal hemorrhage. However, all eyes with geographic atrophy are classified as "dry", although some undoubtedly resulted from RPE detachments which, if present at the time of the examination, would have been classified as exudative. Exhibit 2-5 shows the relative proportion of the "dry" and "exudative" forms of AMD. The "dry" form represents approximately 90 percent of the cases of AMD identified by type, and there is little evidence that the relative proportion of "exudative" disease increased with age.

The 1971-72 NHANES provides the other set of data from which prevalence estimates of AMD can be made.[42] Standardized examinations of persons selected from probability samples of

noninstitutionalized US populations were conducted between April 1971 and October 1972. Although the original study design is excellent, only 70 percent of the selected population received eye examinations. In addition, the assessment of AMD may be unreliable because of the large number of examiners with diverse levels of experience and training. Bearing this in mind, it is still useful to look at the adjusted prevalence rates calculated for AMD in this study.[42] Exhibit 2-6 presents the age-specific rates for drusen, RPE or pigmentary changes, and macular degeneration (drusen or pigmentary changes with visual acuity of 20/25 or worse). These data show that the finding of some drusen is relatively common in middle age, but the biggest increase in the diagnosis of AMD occurs after age 65. The extent to which this may be due to decreased visual acuity secondary to cataract in eyes with drusen is uncertain. The fact that drusen exist commonly in middle age but blindness from AMD is most frequent over age 65 suggests that drusen may predate visual loss by many years. AMD was found in 8.5 percent of those aged 65-74, which is similar to the 11-percent ratio obtained for this age group in the Framingham Eye Study.

In summary, current prevalence rates for blindness caused by AMD are not available, but estimates from existing studies show that AMD is not only a leading cause of blindness, but also increasing rapidly among persons older than 65. With an increasingly aged population, AMD may be the leading cause of blindness in the United States in the coming decades unless methods of prevention or treatment become available.

2.2.3 Incidence of Age-Related Macular Degeneration

Few incidence data are available for AMD. Podgor, Leske, and Ederer[8] have used age-specific prevalence data from the Framingham Eye Study to estimate 5-year incidence rates for AMD. These are 0.9, 0.9, 2.5, 6.7, and 10.8 percent for ages 55, 60, 65, 70, and 75, respectively.

Using unpublished data collected during a re-examination of the survivors of the original Framingham Eye Study from 1986-88, the 7-year incidence of advanced AMD is estimated to be 1 to 2 percent among patients with few or no drusen, 2 to 6 percent among patients with multiple small or intermediate drusen, and 7 to 14 percent among patients with at least one large drusen. Recent findings from the Macular Photocoagulation Study[43] indicate that, in persons with advanced AMD in one eye, the 7-year incidence of advanced AMD in the fellow eye is between 21 and 42 percent.

2.2.4 Risk Factors

The Framingham Eye Study[40,43] is the first source of information on possible risk factors for AMD. The Framingham Heart Study cohort had been followed for approximately 25 years prior to the initiation of eye examinations in the Framingham Eye Study. The Framingham Heart Study data provided information on 667 variables that could be evaluated for possible associations with the ocular findings from the Framingham Eye Study, including AMD. With this large number of variables, it is likely that some of the associations found are due to chance alone. However, as Kahn et al[44] point out, consistent findings from other studies will help sort out the real from the chance associations. The prevalence studies of blindness[36,2,45] are only useful for finding associations of AMD with age, sex, or race. NHANES has broader potential usefulness, but this source has not been exploited fully.

Finally, there have been three case-control studies. The study by Hyman et al[46] is the largest such study and involved 162 cases and 175 age- and sex-matched controls. The other two case-control studies, one by Delaney and Oates[47] and the other by Maltzman, Mulvihill, and Greenbaum[48] suffer from relatively small sample sizes (50 and 30 age- and sex-matched cases and controls, respectively) and difficulties with selection of the control groups. However, consistency among the case-control studies, even with small sample sizes, tends to add credence to any proposed associations. The combined data, including the Framingham Eye Study, provide the best current information on risk factors associated with AMD.

2.2.4.1 Demographic

Age. The prevalence studies discussed in the previous section all document the marked association of AMD with age. This relationship exists in all studies and exists for both AMD and each of the lesions known to be associated with AMD. Age-related changes similar to AMD have also been demonstrated in both rats[49] and monkeys.[50] Age is such a strong factor that it must be accounted for in any comparative study of AMD.

Sex. The Framingham Eye Study[41] found that AMD was approximately 50 percent more prevalent in women than in men in each of the fairly broad age groups studied (Exhibit 2-4). However, in an analysis of the Framingham data by Sperduto and Seigel[5], which was based only on the presence of lesions of age-related macular disease seen at the eye examination and not requiring decreased visual acuity, there was no increased prevalence of either the mild or more severe age-related macular changes among females compared with males. They did find an increase in the prevalence of lens changes among females, which may account, at least in part, for the increased female prevalence of AMD changes with visual acuity of 20/30 or worse.

Similarly, the Model Reporting Area data[2] do not demonstrate an increase of female registered blind compared with male registered blind in the "retinal-other" category, and an analysis of the NHANES data by Klein and Klein[51] shows no increase in females compared with males with either AMD or the presence of drusen or RPE changes (Exhibit 2-7).

Interestingly, each of the three case-control studies of AMD[46-48] had approximately 50 percent more females than males as did two of the largest case series studied.[52,53] Some of this excess can be explained by the increased prevalence of females in the elderly population, but the magnitude of this effect is impossible to determine in these studies. A large autopsy series, however, showed more males than females with AMD.[54]

Of all these studies, selection biases are likely to be least important in the Framingham Eye Study and the NHANES. Based on the reanalysis of the Framingham Eye Study data by Sperduto and Seigel[5] and the analysis of the NHANES,[51] it would appear that females do not have an excess risk of developing AMD.

Race. Gregor and Joffe[55] "consecutively" examined 1,000 blacks and 380 whites over age 50 for the presence of drusen, RPE changes, and disciform macular degeneration. All individuals in the study were hospital outpatients, the blacks from two South African hospitals and the whites from Moorfields Eye Hospital, London. Drusen and RPE changes were twice as common among the whites, and disciform degeneration was seen in only one black African (0.1 percent) compared

with 3.5 percent of the whites. Chumbley[56] also reported a low prevalence of AMD in Rhodesian blacks (1 percent of adults over age 65). The clinical impression in the United States is that AMD is rare in blacks.[57] In the autopsy series done by Green and Key,[53] 86 percent of the individuals with AMD were white, although only 58 percent of all patients autopsied at The Johns Hopkins Hospital during that time period were white.

The NHANES data[51], however, show no increase in the prevalence of AMD in whites compared with blacks (Exhibit 2-7). Information from this recent study has therefore raised doubts about the impression that males are at lower risk than females of developing AMD and that blacks are at lower risk than whites.

2.2.4.2 Medical

Blood pressure. The Framingham Eye Study[44] found a positive association between the presence of AMD and elevated diastolic blood pressure taken approximately 25 years earlier during the first Framingham Heart Study examination (Exhibit 2-8). At the first examination, all persons in the Framingham Heart Study were between ages 30 and 62, and the presence of the diastolic hypertension at this examination is likely to predate the existence of the disease AMD.

Delaney and Oates[47] found that their cases of AMD were more likely to be receiving treatment for hypertension than their controls.

Hyman et al[46] in their case-control study, found no association of AMD with current systolic or diastolic blood pressure, history of hypertension, current use of antihypertensive medications, or any combination of these factors. They did find an association of AMD with a number of cardiovascular diseases that are known to be associated with hypertension. It may be that the ability to identify hypertension as a risk factor for AMD in this study was compromised by the inability to determine if hypertension was present prior to the onset of AMD and by the increasing general prevalence of hypertension in the aging population. If hypertension is a risk factor for the development of AMD, it may be that it takes many years of exposure to this factor before the disease becomes apparent.

Hyperopia. The three case-control studies have all shown an association between AMD and hyperopia.[46-48] The control group in each of these studies might be enriched in the proportion of myopes compared with the general population because the controls were all selected from ophthalmologic office practices. If this imbalance is true, it would explain the apparent association. This is especially a problem in retinal specialty practices.[47,48] The study by Hyman et al[46] was based on general ophthalmologic practices, and the percentage of myopes in the control group of this study (17.7 percent) compares quite closely with the population frequency of myopia for people over age 52 in the Framingham Eye Study (17 percent). This information, along with the positive findings in all three case-control studies, adds strength to the credibility of this association and suggests that hyperopes are more likely to have AMD.

Iris color. As discussed previously, there is a clinical impression among ophthalmologists that blacks are less likely to develop AMD than whites. However, the evidence for this suggestion is conflicting and the one population-based study does not confirm this observation.[57] Since the amount of pigment in the retinal pigment epithelium is related to race and also is correlated with the

amount of pigment in iris epithelial cells, an attempt was made by Hyman et al[46] to study iris color as a risk factor. In that study, one observer classified the iris color of all cases and controls (Exhibit 2-9). The smaller proportion of AMD in patients with brown eyes (9.2 percent) compared with the proportion of the control group with brown eyes (26.4 percent) suggests that individuals with brown eyes may be at lower risk of developing AMD. Even if this association proves to be true, it remains to be seen whether increased pigment protects against AMD or whether it is simply correlated with some other factor that is responsible for the observed association.

2.2.4.3 Environmental

Nutrition. Nutritional factors are speculated to have an important role in preventing or delaying the development of AMD. Interest in zinc stemmed from its high concentrations in the retinal pigment epithelium and the retina. One case-control study and a randomized clinical trial have examined the role of zinc in the development and progression of AMD. The results from the 2 studies are contradictory; the case control study showing cases of AMD with higher zinc levels than controls without AMD[58] and the clinical trial suggesting a protective effect.[59] One hundred fifty one participants in this randomized, controlled clinical trial were enrolled. Each had at least drusen in both eyes and many participants had one or more of the following lesions in one or both eyes; geographic atrophy, pigment mottling, or RPE detachment. Although this was a randomized trial, and a statistically significant beneficial effect of therapy with oral zinc was found, the difference in the study arms appears to be enhanced by the higher than expected progression rate in the control group rather than a much lower than expected rate of progression in the treated group. The pilot nature of the study warrants that this nutrient be further investigated before a preventive effect of zinc is accepted.

Animal studies have shown deficiencies of vitamin A or E may be associated with AMD,[60] but these associations have not been adequately assessed in human populations. A review of the role of nutrition in the development of AMD is provided in Appendix D.

Cigarette smoking. In a case series of 114 patients with at least one eye blind from AMD, Paetkau et al[61] noted that the mean age at onset of blindness in the first eye was 64 years in current smokers compared with 71 years in the group that had never smoked. Confounding factors such as increased mortality in the smoking group cannot be accounted for since there are no controls, but their cases as a group had a higher percentage of smokers overall compared with a survey of a comparable group of Canadians.

Hyman et al[46] also noted an association of smoking with AMD. However, this association was only present in males and was actually reversed in females.

The association of smoking with AMD was not found in the Framingham Eye Study[44] or noted in the two small case-control studies.[57,48] Therefore, the evidence demonstrating an association between smoking and AMD must be considered equivocal.

2.2.4.4 Other Risk Factors

Family history. A family history of AMD has been thought to increase one's risk of developing the disease. Numerous pedigrees and other family information have been used to

document this clinical impression.[62-68] The study by Hyman et al[46] also identified family history of AMD as a risk factor, an association that was present for both parental and sibling history.

Other risk factors. As part of the Framingham Eye Study[44] an attempt was made to identify associations between ophthalmic disease such as AMD and any of 667 variables selected from the Framingham Heart Study data. The authors of the Framingham Eye Study stress the need to corroborate these findings, which may be due to a combination of real and chance associations. In addition to the risk factors previously mentioned, the Framingham Eye Study identified associations between AMD and the following risk factors: height, decreased vital capacity, left ventricular hypertrophy, history of lung infection, and decreased handgrip strength. The study by Hyman et al[46] attempted to replicate all of these observations except for vital capacity and left ventricular hypertrophy. Of the remaining variables, they found a positive association only with handgrip strength. Although they did not test for left ventricular hypertrophy, they did find a positive association between AMD and a history of cardiovascular disease. Their inability to replicate associations of AMD with height or a history of lung infection does not rule out the possibility that these factors are associated with AMD, but it does make such associations less likely.

Exhibit 2-10 summarizes the positive associations reported in any of the three published case-control studies of AMD or the Framingham Eye Study. Negative associations reported in the studies by Delaney and Oates[47] and by Maltzman, Mulvihill, and Greenbaum[48] should be accepted with caution since their power to assess negative associations is severely limited by small sample sizes.

In addition to the associations listed in Exhibit 2-10, some investigations have suggested that AMD is associated with elevated lipids.[69-71] However, controls were not used in these studies, and the Framingham Eye Study did not find this association. Animal studies have suggested that prolonged exposure to sunlight[49,72] may be associated with the development of AMD. This association has not been adequately investigated in human populations.

2.2.5 Etiology of Blindness from Age-Related Macular Degeneration

Visual loss can result from the atrophic or exudative form of AMD; however, the exudative form is more likely to reduce vision to 20/200 or worse. Among persons with AMD in the case-control study reported by Hyman et al[46] exudative maculopathy accounted for the visual loss in 66 (88 percent) of the 75 legally blind eyes.

Patients with exudative disease in one eye and drusen in the other eye are at particularly high risk of developing exudative disease in the second eye. The risk of blindness in the second eye may be as high as 12 percent per year.[73-77] Recently published results of the Macular Photocoagulation Study,[78] which demonstrate a beneficial effect of argon laser photocoagulation in certain patients with exudative AMD, provide hope that we can reduce the number of persons who will become legally blind from this disorder.

Photocoagulation is the only form of treatment that has been shown to be effective for AMD. Unfortunately, only certain types of neovascular membranes associated with the exudative type of AMD are amenable to treatment. This means that many persons with AMD are untreatable, either because the neovascularization is under the fovea or because their visual loss is caused by the

atrophic form of the disease. These limitations of photocoagulation underscore the need to identify risk factors, search for methods of preventing AMD, and evaluate new prevention and treatment methods.

2.2.6 Summary

AMD is a leading cause of visual loss in the United States, England, and probably many other industrialized countries. The clinical manifestations of this disease include drusen, atrophy of the retinal pigment epithelium, serous detachment of the retinal pigment epithelium, subretinal neovascularization, and disciform scars. Standardized techniques for defining the manifestations of AMD are necessary for epidemiologic study of this disease. Such standardization is facilitated by the use of fundus photographs.

The Framingham Eye Study provides the best prevalence data on AMD. The rapid increase in prevalence of this disease after the fifth decade of life is demonstrated in this study and is consistent with other studies. In fact, increasing age has the strongest association with AMD of any of the risk factors considered to date. Many other possible risk factors have been identified, but further investigation is necessary to verify these associations.

2.3 REFERENCES

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Exhibit 2-1. PROPORTION OF REGISTERED BLIND FROM THE FOUR LEADING CAUSES OF BLINDNESS

Cause of Blindness	England and Wales Registered 1955-1962 (n = 60,309) %	United States Registered 1970 (n = 8,353) %	Canada Living Registrants 1964 (n = 24,605) %
Senile macular degeneration	26	13	5
Cataract	23	12	15
Glaucoma	12	11	10
Diabetic retinopathy	7	11	5

Source:

Sorsby A: Reports on public health and medical subjects. No. 114. London: Her Majesty's Stationery Office, 1966.

Graham PA, Wallace J, Walsby E, et al: Evaluation of postal detection of registrable blindness. *Br J Prev Soc Med* 22:238, 1968.

Sorsby A: Reports on public health and medical subjects. No. 128. London: Her Majesty's Stationery Office, 1972.

Exhibit 2-2. NUMBER OF REGISTERED BLIND DUE TO SENILE MACULAR DEGENERATION IN ENGLAND AND WALES (1955-1962)

Age (years)	Male	Female	Total
50-59	23	36	59
60-69	293	412	705
70+	5,411	9,432	14,843

Source:

Sorsby A: Reports on public health and medical subjects. No. 114. London: Her Majesty's Stationery Office, 1966.

Exhibit 2-3. AGE-SPECIFIC NUMBER AND RATE OF ALL ADDITIONS TO MODEL REPORTING AREA REGISTERS FOR RETINAL DISEASES, 14 MODEL REPORTING AREA STATES, AVERAGE 1969 AND 1970 (*AVERAGE ANNUAL RATE PER 100,000*)

MALE

	Total		Retinal Disease				Other	
			Prenatal		Diabetic			
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total	680	3.7	162	0.9	172	0.9	346	1.9
<5	7	0.4	5	0.3	0	0.0	2	0.1
5-19	59	1.0	42	0.7	1	0.0	16	0.3
20-44	145	2.5	54	0.9	50	0.8	41	0.7
45-64	226	6.2	54	1.5	89	2.4	83	2.3
65-74	87	9.5	5	0.5	26	2.8	56	6.1
75-84	118	29.8	2	0.5	6	1.5	110	27.8
>85	38	42.2	0	0.0	0	0.0	38	42.2

FEMALE

	Total		Retinal Disease				Other	
			Prenatal		Diabetic			
Age (years)	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total	905	4.7	140	0.7	292	1.5	473	2.5
<5	6	0.4	4	0.3	0	0.0	2	0.1
5-19	45	0.8	36	0.7	0	0.0	9	0.2
20-44	112	1.8	45	0.7	34	0.6	33	0.5
45-64	271	6.9	44	1.1	155	3.9	72	1.8
65-74	156	12.9	6	0.5	72	6.0	78	6.5
75-84	205	33.0	5	0.8	28	4.5	172	27.7
>85	110	66.7	0	0.0	3	1.8	107	64.8

Source:

Graham PA, Wallace J, Walsby E, et al: Evaluation of postal detection of registrable blindness. *Br J Prev Soc Med* 22:238, 1968.

Exhibit 2-4. PREVALENCE OF SENILE MACULAR DEGENERATION BY AGE AND SEX: FRAMINGHAM EYE STUDY (1973-1975), LOCAL AREA ONLY

Age (years) and sex	Total persons screened	Percent with senile macular degeneration
Total	2,477	8.8
Men	1,043	6.7
Women	1,434	10.3
Age 52-64	1,293	1.6
Men	573	1.2
Women	720	2.0
Age 65-74	787	11.0
Men	318	8.8
Women	469	12.6
Age 75-85	397	27.9
Men	152	24.4
Women	245	30.1

Source:

Kini MM, Leibowitz HM, Colton T, et al: Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham Eye Study. *Am J Ophthalmol* 85:28-34, 1978.

Exhibit 2-5. TYPE OF SENILE MACULAR DEGENERATION BY AGE, FRAMINGHAM EYE STUDY (1973-1975)

Age (years)	Type of Senile Macular Degeneration			
	Dry %	Exudative %	Combination %	Questionable or unknown
< 65	88.2 (n = 15)	5.9 (n = 1)	0 (n = 0)	5.9 (n = 1)
65-74	77.1 (n = 54)	7.1 (n = 5)	1.4 (n = 1)	14.3 (n = 10)
> 74	79.5 (n = 97)	4.1 (n = 5)	3.3 (n = 4)	13.1 (n = 16)
Total	79.4 (n = 166)	5.3 (n = 11)	2.4 (n = 5)	12.9 (n = 27)

Source:

Kini MM, Leibowitz HM, Colton T, et al: Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham Eye Study. *Am J Ophthalmol* 85:28-34, 1978.

Exhibit 2-6. PREVALENCE RATE (PER 1,000) OF DRUSEN, PIGMENTARY CHANGES, AND MACULAR DEGENERATION BY AGE (1971-1972)

Age (years)	Drusen	Pigmentary changes	Macular degeneration
25-34	14	12	3
35-44	41	13	11
45-54	63	13	19
55-64	72	13	30
65-74	99	28	85
All ages	30	12	13

Source:

Ganley J, Roberts J: Eye conditions and related need for medical care among persons 1-74 years of age, United States, 1971-72. Vital and Health Statistics, Series 11. No 228. Washington, DC: DHHS Publication No. (PHS) 83-1678, March 1983.

Exhibit 2-7. NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY: UNITED STATES PREVALENCE RATES OF SENILE MACULAR DEGENERATION (1971-1972) BY AGE, RACE, AND SEX

	Age (years)			
	45 - 64		65 - 75	
Race and sex	Number	Prevalence rate (%)	Number	Prevalence rate (%)
White				
Male	531	2.3	612	9.6
Female	561	2.3	654	6.9
Black				
Male	156	3.8	193	9.3
Female	165	2.4	184	11.4

Source:

Klein B, Klein R: Cataracts and macular degeneration in older Americans. *Arch Ophthalmol* 100:571-573, 1982.

Exhibit 2-8. ASSOCIATION BETWEEN SENILE MACULAR DEGENERATION IN FRAMINGHAM EYE STUDY (1973-1975) AND DIASTOLIC BLOOD PRESSURE ON EXAM 1, FRAMINGHAM HEART STUDY (1948-1952)

Sex and age (years) at eye exam	Mean Diastolic Pressure			
	Negative senile macular degeneration		Positive senile macular degeneration	
	Number	mmHg	Number	mmHg
Men				
52-64	282	82	5	84
65-74	96	86*	15	96*
75-84	16	84	32	84
Women				
52-64	348	79*	11	88*
65-74	107	84*	44	89*
75-84	16	88	56	90

* $p < 0.05$ for difference between positive and negative for senile macular degeneration.

Source:

Kahn HA, Leibowitz HM, Ganley JP, et al: The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. *Am J Epidemiol* 106:33-41, 1977.

Exhibit 2-9. DISTRIBUTION OF CASES AND CONTROLS BY IRIS COLOR

Iris color	Senile macular cases (%) (n = 162)	Controls (%) (n = 175)	Odds ratio	p*
Brown (dark)	9.2	26.4		
Medium pigment	49.4	39.7	3.6	0.002
Blue (light)	41.4	33.9	3.5	

* The p value is based on the chi-square test for independent samples.

Source:

Hyman LG, Lilienfeld AM, Ferris FL III, et al: Senile macular degeneration: A case-control study. *Am J Epidemiol* 118:213-227, 1983.

Exhibit 2-10. STUDIES OF SENILE MACULAR DEGENERATION CASES AND CONTROLS, REPORTED ASSOCIATIONS OF RISK FACTORS AND SENILE MACULAR DEGENERATION

Risk factors	Framingham Eye Study	Hyman et al	Delaney & Oates ↕	Maltzman et al ↕
Hyperopia	*	+	+	+
Decreased handgrip strength	+	+	*	*
Iris color (blue or medium)	*	+	*	*
Elevated systemic blood pressure	+	-	+	-
Family history of senile macular degeneration	*	+	-	*
Decreased vital capacity	+	*	*	*
Left ventricular hypertrophy	+	*	*	*
Short height	+	-	*	*
History of lung infection	+	-	-	*
Cigarette smoking	-	+	*	-
History of cardiovascular disease	*	+	*	*
Chemical work exposure	*	+	*	*

* Not studied.
\+ Positive association found.
\- No significant association found.
↕ Negative results difficult to interpret due to small sample size.

Sources:

Leibowitz HM, Kreuger DE, Maunder LR, et al: The Framingham Eye Study Monograph. *Survey Ophthalmol* 24 (Suppl):335-610, 1980.

Hyman LG, Lilienfeld AM, Ferris FL III, et al: Senile macular degeneration: A case-control study. Am J Epidemiol 118:213-227, 1983.

Delaney WV, Oates RP: Senile macular degeneration: A preliminary study. *Ann Ophthalmol* 14:21-24, 1982.

Maltzman BA, Mulvihill MN, Greenbaum A: Senile macular degeneration and risk factors: A case-control study. *Ann Ophthalmol* 11:1197-1201, 1979.