THE EPIDEMIOLOGY OF EPIRETINAL MEMBRANES*

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INTRODUCTION

EPIRETINAL MEMBRANES ARE FREQUENTLY FOUND IN EYES OF OLDER individuals and occasionally lead to decreased vision.[1-10] Most of the information regarding the prevalence and factors associated with epiretinal membranes comes from case-series reports of patients attending retina clinics or from histopathologic studies of eye bank eyes.[1-15] These studies have suggested a higher frequency of epiretinal membranes in eyes with retinal vascular disease, rhegmatogenous retinal detachment, vitreal inflammatory diseases, and cataract surgery than in eyes without these conditions. Histopathologic, immunochemical, and cell culture studies of epiretinal membranes removed at vitrectomy have led to a limited understanding of the pathogenesis of this condition.[16-23]

There have been no population-based epidemiologic data describing the prevalence of epiretinal membranes or systemic and ocular factors that may be associated with this condition. The purposes of this report are to describe the prevalence of epiretinal membranes and associated risk factors and to examine the relationship of epiretinal membranes to visual acuity in a large population.

MATERIALS AND METHODS

POPULATION

The Beaver Dam Eye Study population has been described in detail in

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previous reports.[24-27] In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987, to May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver Dam and being aged 43 to 84 years at the time of the census. A total of 5,924 individuals were eligible, 4,926 of whom participated in the examination phase between March 1, 1988, and September 14, 1990.

Nonparticipants consisted of 226 persons (3.8%) who died before the examination, 100 (1.7%) who moved out of the area, 18 (0.3%) who could not be located, 276 (4.7%) who permitted an interview only, and 378 (6.4%) who refused to participate. Comparisons between participants and nonparticipants have been presented elsewhere.[26]

PROCEDURES AND DEFINITIONS

The parts of the examination pertinent to this report consisted of a standardized refraction and measurement of the visual acuity using the Humphrey 530 refractor.[26] The refraction obtained was placed in a trial lens frame and the best-corrected visual acuity was remeasured using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol with a modified chart R at a distance of 2 m.[27] If the best-corrected visual acuity was 20/40 or worse, an ETDRS refraction was performed and the visual acuity was remeasured. Visual acuity was not obtainable in both eyes for 29 persons and in the left eye for two. For each eye, the visual acuity was recorded as the number of letters correctly identified (range, 0 [<20/200] to 70 [20/10]). Impaired vision was defined as best-corrected visual acuity of 20/40 or worse and included eyes that were blind (visual acuity of 20/200 or worse). Legal blindness was defined as best-corrected visual acuity of 20/200 or worse in the better eye.

Blood pressure (BP) was measured with a Hawksley random-zero sphygmomanometer (Hawksley & Sons, Ltd, West Sussex, England) according to the Hypertension Detection and Follow-up Program protocol.[28] After dilation of the pupils, a structured interview was conducted by the examiners. Questions pertinent to this report are listed in Appendix A.

Nonfasting blood specimens also were obtained from participants. Serum glucose levels were determined using the hexokinase method, and plasma glycosylated hemoglobin was determined using affinity chromatography (Isolab Inc, Akron, OH).[29,30]

Stereoscopic fundus 30-degree color photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (standard field 2) and a nonstereoscopic fundus color photograph temporal to but including the fovea of each eye were taken.[31] Additional fundus photographs were

taken if any lesions were found outside these fields.

The presence of epiretinal membranes was graded in a masked fashion using the Wisconsin Age-Related Maculopathy Grading scheme.[32-35] A grid consisting of three circles concentric with the center of the macula and four radial lines was superimposed over one member of the stereoscopic pair of field 2. The radius of the innermost circle corresponded to 500 μm in the fundus of an average eye, and the radii of the middle and outer circles corresponded to 1,500 and 3,000 μm, respectively. Nine subfields were defined by the grid: the central subfield (within the inner circle); the inner superior, nasal, inferior, and temporal subfields (between the inner and middle circles); and the outer superior, nasal, inferior, and temporal subfields (between the middle and outer circles).

Epiretinal membranes, which vary in appearance from a "glinting, water-silk, and shifting light reflex"[4] to a more opaque, grayish appearance on the inner retinal surface, were graded in each subfield as being absent, questionable, present with cellophane reflex only, or present with cellophane reflex and with retinal folds. For each eye, the maximum grade was determined and used in defining the epiretinal severity levels as follows: level 1, absent or questionably present; level 2, present with cellophane reflex but no retinal folds in two or fewer subfields; level 3, present with cellophane reflex but no retinal folds in three or more subfields; and level 4, present with cellophane reflex and retinal folds. The epiretinal membrane severity level for a participant was derived by giving the eye with the higher level greater weight. This scheme provided a seven-step scale (1/1, 2/<2, 2/2, 3/<3, 3/3, 4/<4, 4/4). For purposes of classification, if the epiretinal membrane could not be graded in an eye, the participant was considered to have a score equivalent to that in the other eye.

Grading for age-related maculopathy was performed in a masked fashion using a standardized protocol, The Wisconsin Age-Related Maculopathy Grading scheme.[33-35] This system permits the assessment of the presence and severity of up to 14 lesions associated with age-related maculopathy. More detailed descriptions of these lesions appear elsewhere.[33-35] For this report, three lesions characterizing early age-related maculopathy were assessed: soft indistinct drusen (≥63 μm, decreasing density from center to periphery, and lack of sharp edges), retinal pigment epithelial degeneration, and increased retinal pigment (the presence of granules or clumps of gray or black pigment in or beneath the retina). Early age-related maculopathy was defined as the presence in the macular area of either soft indistinct drusen or hard or soft drusen plus pigmentary abnormalities (increased retinal pigment or retinal pigment epithelial degeneration) in the absence of signs of late age-related maculopathy. Late age-related maculopathy was defined

as the presence of signs of exudative age-related macular degeneration or pure geographic atrophy. Exudative macular degeneration was defined as the presence of a retinal pigment epithelial detachment or serous detachment of the sensory retina, retinal or subretinal pigment epithelial hemorrhage, and/or subretinal fibrous scars. Pure geographic atrophy was defined by the presence of geographic atrophy and the absence of exudative macular degeneration. For purposes of analyses, two categories were used: absent (or questionable) and present.

The presence of retinal microaneurysms only, blot hemorrhages only, hemorrhages and/or microaneurysms, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, new vessels on the disc and elsewhere, and preretinal and vitreous hemorrhages was graded in a masked fashion using an abbreviation of the modified Airlie House classification scheme.[36,37] Retinopathy was defined as the presence of any of the retinal lesions described.

Arteriolar narrowing was graded using a standard photograph from the Wisconsin Age-Related Maculopathy Grading protocol in which focal narrowing of small arterioles in the posterior pole (field 2) involves a total length of one-third disc diameter.[33] Arteriolar narrowing was graded as absent, questionable, less than the standard, and greater than or equal to the standard for all arterioles more than one-half the disc diameter from the disc in all three standard fields. When there were multiple but separate areas of focal arteriolar narrowing, the composite length of involvement was compared with the standard. For purposes of analyses, two categories were used: absent (or questionable) and present.

Arteriovenous nicking was graded for all arteriovenous crossings that were more than one-half the diameter from the disc in all three fields using an abbreviation of the modified Airlie House classification scheme.[36,37] Arteriovenous nicking was graded as present if there was a decrease in the diameter of the venule on both sides of the arteriole that was crossing it. The presence of other retinal disease, such as central and branch retinal arterial or venous occlusion, retinal cholesterol emboli, and macular holes, was graded using a detailed protocol.[33]

Fundus photographs were graded in a masked fashion for the presence of macular holes (sharply defined round or oval full-thickness holes involving the foveal area, usually surrounded by detachment of the retina). For purposes of analyses, two categories were used: absent (or questionable) and present.

A slit-lamp camera (Topcon SL-5, Topcon America Corp, Paramus, NJ) was used to take photographs, which were graded for the presence and severity of nuclear sclerosis.[38] Anterior and posterior retroillumination pho-

tographs of the lens were taken with a Neitz CR-T camera (Tokyo Optical Corp Ltd, Tokyo, Japan) and graded for the presence and severity of cortical and posterior subcapsular opacities. Details of the standardized grading systems have been reported previously.[39,40]

For the purposes of this paper, nuclear sclerotic cataract was defined as present if the photograph of the lens was graded as more opaque than standard 3 (levels 4 or 5 in a five-step scale of severity). Grading of the Neitz photographs was designed to determine the area of the lens involved with cortical and posterior subcapsular opacities. The measuring grid used divided the red reflex photographs into a central circular area and eight sectors of equal size that were defined by clock hours. The grader estimated the area involved with cortical and posterior subcapsular opacity in each of the fields, including information from both anterior and posterior photographs for cortical opacity. For purposes of presentation of the data, cortical opacity was considered to be present if on grading of the retroillumination photograph, 5% or more of the lens surface area was affected; posterior subcapsular opacity was considered to be present if 5% or more of the surface area of any of the eight sectors or the central circle of the lens was involved.

The procedures in detecting and defining open-angle glaucoma have been presented elsewhere.[32,41] In brief, a visual field screening test of each eye using a Henson CFS 2000 perimeter was performed. In those eyes that failed the screening test, full perimetric testing was performed. Intraocular pressure was measured according to a standard protocol using a Goldmann applanation tonometer. Stereoscopic fundus photographs of field 1 were used for grading of optic discs and cups according to a detailed standardized protocol. A standardized history was obtained. Subjects were asked whether they had ever been told that they had glaucoma, were taking medicines for glaucoma, or had had surgery for glaucoma.

The presence of at least two of the three following criteria was necessary for inclusion as a definite case of glaucoma: an abnormal visual field, a cup-to-disc ratio of at least 0.8 or asymmetry of at least 0.2 between the eyes, or an intraocular pressure ≥22 mm Hg. A history of taking drops for or having had surgery for glaucoma (excluding glaucoma secondary to rubeosis iridis, trauma) with or without any of the previous criteria defined an individual as a probable case. Because these groups had similar distributions of age, sex, and other risk indicators, they are combined in these analyses.[41]

Current age was defined as the age at the time of the examination. The mean systolic BP was the average of the two systolic BP measurements, and the mean diastolic BP was the average of the two diastolic BP measurements. Hypertension was defined as a mean systolic BP of 160 mm Hg or

greater, and/or a mean diastolic BP of 95 mm Hg or greater, and/or history of hypertension with use of antihypertensive medication at the time of examination. A person was defined as having a positive history if he or she responded positively to the questions regarding cardiovascular disease or stroke.

There were 395 people who had a history of diabetes mellitus and were being treated with insulin, oral hypoglycemic agents, or diet. In 50 people, diabetes mellitus was newly diagnosed at examination, (ie, the subjects had no previous medical history of diabetes mellitus or use of hypoglycemic medications for diabetes mellitus and a glycosylated hemoglobin value greater than 2 SD above the mean for a given age-sex group and a randomly measured blood sugar value of >200 mg/dl). Primary care physicians were consulted whenever the diagnosis was in doubt.

Cigarette smoking status was defined as follows: subjects were classified as having never smoked if they reported having smoked fewer than 100 cigarettes in their lifetime; as ex-smokers if they had smoked more than this number of cigarettes in their lifetime but had stopped smoking before the examination; and as currently smoking if they had not stopped. A person was defined as a nondrinker if he/she had never consumed alcoholic beverages, as an ex-drinker if he/she had consumed alcoholic beverages in the past but not in the previous year, and as a current drinker if he/she had consumed alcoholic beverages in the previous year.

STATISTICS

SAS was used for calculating prevalence proportions, means, chi-square statistics, and *t*-tests.[42] Age-adjusted prevalences were calculated by the direct method by using the Beaver Dam population as the standard population.[43] Significance of trend in proportions was tested by the Mantel-Haenszel procedure.[44] Multiple logistic regression models were performed. The method of Liang and Zeger[45] was used to assess multivariate relationships with data regarding epiretinal membrane status from both eyes. This repeated measures method adjusts the coefficients for the lack of independence of the two measurements.

RESULTS

Of the 4,926 persons examined, 4,639 had both eyes, 72 had only the right eye, and 91 had only the left eye that could be graded for the presence of epiretinal membranes (Fig 1). An epiretinal membrane was present in at least one eye in 11.8% (565/4,802) of the population. Epiretinal membranes were present in both eyes in 2.4% (110/4,639) of people. The frequency of

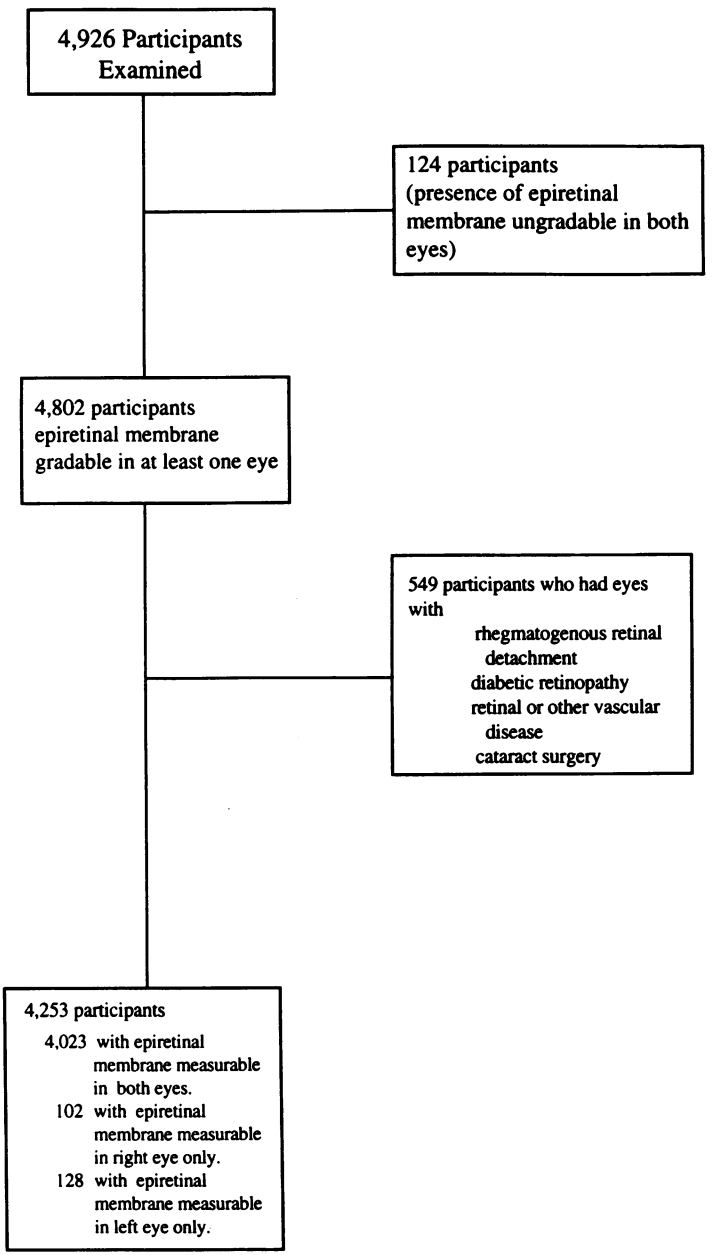

FIGURE 1
Study population.

TABLE I: EPIRETINAL MEMBRANE BY AGE, SEX, AND EYE IN THE BEAVER DAM EYE STUDY (1988-1990)

SEX	AGE (YR)	NO AT RISK	MEMBRANE WITHOUT RETINAL FOLDS			MEMBRANE WITH RETINAL FOLDS (%)
			NONE OR QUESTIONABLE (%)	MEMBRANE ≤2 SUBFIELDS (%)	MEMBRANE >2 SUBFIELDS (%)	
Right eye						
Females	43-54	785	97.8	0.9	0.6	0.6
	55-64	684	92.7	3.7	2.2	1.5
	65-74	712	88.1	3.8	5.3	2.8
	75+	437	90.9	3.2	3.0	3.0
	Total	2618	92.7	2.8	2.7	1.8
Males	43-54	710	98.3	0.9	0.3	0.6
	55-64	611	93.6	3.3	2.1	1.0
	65-74	519	86.5	4.2	6.7	2.5
	75+	253	88.9	3.2	4.7	3.2
	Total	2093	92.9	2.7	3.0	1.5
Total		4711	92.8	2.7	2.8	1.7
Left eye						
Females	43-54	788	98.6	1.0	0.4	0.0
	55-64	686	94.0	2.5	2.3	1.2
	65-74	721	87.2	4.3	5.3	3.2
	75+	443	91.7	2.7	3.4	2.3
	Total	2638	93.1	2.6	2.7	1.6
Males	43-54	710	99.0	0.4	0.4	0.1
	55-64	608	92.8	4.1	2.1	1.0
	65-74	519	85.4	5.8	6.6	2.3
	75+	255	89.8	1.6	6.7	2.0
	Total	2092	92.7	3.0	3.2	1.2
Total		4730	92.9	2.7	2.9	1.4

epiretinal membranes in right eyes (7.2%, 341/4,711) was similar to that in left eyes (7.1%, 334/4,730, P=.75). The correlation between eyes was significant (r=.28; P=.0001).

The prevalence of epiretinal membranes increased with increasing age until 75 years (Table I). There was an increased odds of epiretinal mem-

branes without retinal folds (5.57; 95% confidence interval [CI], 3.69 to 8.40) and of epiretinal membranes with retinal folds (7.01; 95% CI, 3.41 to 14.43) in those people 75 years of age or older compared with those 43 to 54 years of age. Epiretinal membranes involving three or more subfields and epiretinal membranes associated with retinal folds were most frequent in eyes of persons 65 to 74 years of age. After adjusting for age, the frequency of epiretinal membranes was similar in males (7.6%) and females (7.3%; P=.84) for right eyes. No relation between sex and epiretinal membranes was found for left eyes (data not shown).

The prevalences of epiretinal membranes in eyes with and without specific retinal diseases (eg, retinal detachment, retinal vascular disease), diabetic retinopathy, and cataract surgery are as shown in Table II. Age-adjusted frequencies of epiretinal membranes were higher in eyes with these conditions than in eyes without them. The highest frequency of epiretinal membranes was in eyes with proliferative diabetic retinopathy present. After adjusting for age, the frequency of epiretinal membranes was significantly higher in eyes with proliferative diabetic retinopathy or those that had undergone cataract surgery (Fig 2).

Eyes with rhegmatogenous retinal detachment, diabetic retinopathy, other retinal diseases (retinal vascular occlusions, photocoagulation in the absence of diabetes, and presumed ocular histoplasmosis), and/or cataract surgery were excluded to allow examination of eyes without known predisposing causes of epiretinal membranes (Fig 1). This left 4,023 people with both eyes, 102 with only the right eye, and 128 with only the left eye in which fundus photographs for epiretinal membrane were gradable in the absence of the excluded conditions.

The overall prevalence of epiretinal membranes in this remaining group was 10.9% (464/4,253). Prevalence of epiretinal membranes in at least one eye varied with age from 2.7% in those 43 to 54 years old to 12.8% in those 75 years or older. Age-adjusted frequencies were similar in males (11.6%) and females (11.2%, P=.85). Frequencies were similar in right and left eyes (Fig 3 and Table III).

After controlling for age using logistic regression analyses, epiretinal membranes were less common in eyes with early maculopathy (odds ratio [OR], 0.76; 95% CI, 0.58 to 1.00) or any age-related maculopathy (OR 0.69; 95% CI, 0.53 to 0.90) and in eyes with cortical (OR, 0.65; 95% CI, 0.49 to 0.86) or nuclear sclerotic cataract present (OR, 0.58; 95% CI, 0.43 to 0.77) and were more common in eyes with arteriovenous nicking (OR, 1.80; 95% CI, 1.00 to 3.25) (Figs 4 and 5). There was no relationship with posterior subcapsular cataract, refractive error, arteriolar narrowing, or glaucoma (Figs 4 and 5).

TABLE II: PREVALENCE OF EPIRETINAL MEMBRANE IN EYES WITH OR WITHOUT RETINAL DISEASE, DIABETIC RETINOPATHY, AND CATARACT SURGERY IN THE BEAVER DAM EYE STUDY (1988-1990)

	RIGHT EYE				LEFT EYE			
OCULAR CONDITIONS	NO AT RISK	CRUDE PREVALENCE (%)	AGE-ADJUSTED PREVALENCE (%)	*P* VALUE‡	NO AT RISK	CRUDE PREVALENCE (%)	AGE-ADJUSTED PREVALENCE (%)	*P* VALUE‡
Retinal disease*								
Absent	4666	7.2	7.3		4690	7.0	7.1	
Present	30	16.7	29.0	.18	26	11.5	13.1	.72
Diabetic retinopathy†								
Absent	277	5.9	6.1		288	6.1	5.0	
Nonproliferative	116	8.6	7.1	.45	121	9.1	9.5	.30
Proliferative	3	33.3	13.0	.20	4	50.0	39.5	.002
Cataract surgery								
Absent	4518	6.6	6.7		4550	6.1	6.3	
Present	189	23.3	21.9	<.001	177	30.5	28.3	<.001

*Retinal disease includes history of retinal detachment, branch vein occlusion, central vein occlusion, or panretinal or local photocoagulation in people without diabetes, and presumed ocular histoplasmosis.
†Refers to retinopathy status in people with diabetes.
‡Determined using Mantel-Haenszel statistic.

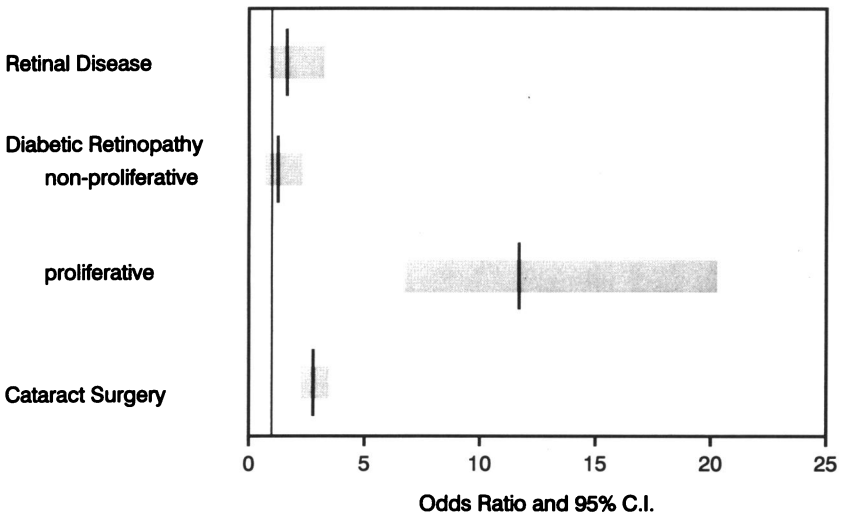

FIGURE 2
Relationship of age-adjusted prevalence of epiretinal membrane and retinal disease, diabetic retinopathy, and cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratios of having epiretinal membrane in eyes with retinal disease, diabetic retinopathy, or cataract surgery versus those without.

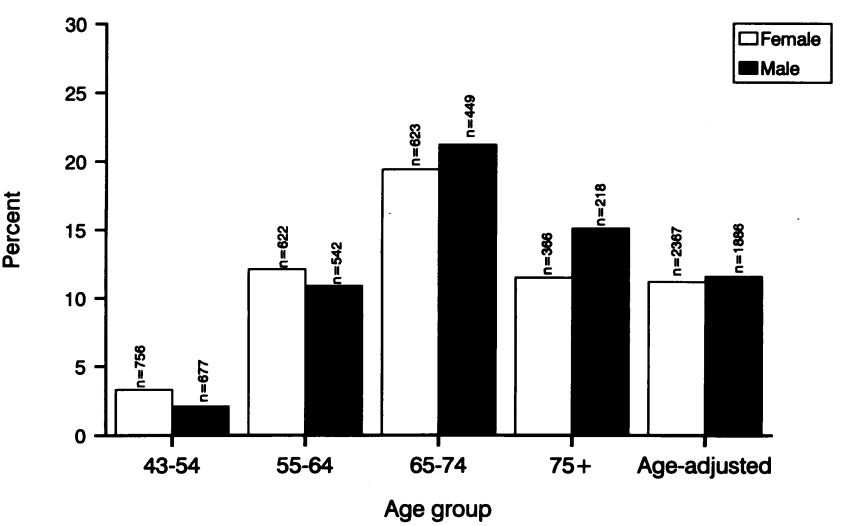

FIGURE 3
Age-adjusted prevalence of epiretinal membrane by gender and age after excluding eyes with retinal disease, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990).

TABLE III: EPIRETINAL MEMBRANE IN EYES IN THE ABSENCE OF RETINAL DISEASE,* DIABETIC RETINOPATHY, AND CATARACT SURGERY BY AGE, SEX, AND EYE IN THE BEAVER DAM EYE STUDY (1988-1990)

SEX	AGE (YR)	NO AT RISK	NONE OR QUESTIONABLE	MEMBRANE WITHOUT RETINAL FOLDS		MEMBRANE WITH RETINAL FOLDS
				MEMBRANE ≤2 SUBFIELDS	MEMBRANE >2 SUBFIELDS	
Right eye						
Females	43-54	748	98.3	0.9	0.5	0.3
	55-64	612	92.5	4.1	2.3	1.1
	65-74	605	88.9	3.5	4.6	3.0
	75+	327	92.1	2.8	2.1	3.1
	Total	2292	93.4	2.7	2.3	1.6
	Age-adjusted	2292	93.3	2.7	2.3	1.7
Males	43-54	671	98.4	0.8	0.3	0.6
	55-64	533	94.2	3.0	1.9	0.9
	65-74	430	87.4	4.0	6.3	2.3
	75+	199	90.5	3.5	3.0	3.0
	Total	1833	93.7	2.5	2.5	1.4
	Age-adjusted	1833	93.1	2.7	2.7	1.5
Total		4125	93.5	2.6	2.4	1.5
Left eye						
Females	43-54	750	98.5	1.1	0.4	0.0
	55-64	614	94.3	2.6	2.1	1.0
	65-74	611	87.2	4.4	5.2	3.1
	75+	333	96.4	0.9	0.6	2.1
	Total	2308	94.1	2.3	2.2	1.4
	Age-adjusted	2308	94.1	2.3	2.1	1.4
Males	43-54	671	99.6	0.3	0.2	0.0
	55-64	535	92.9	4.3	1.9	0.9
	65-74	439	85.9	5.5	6.2	2.5
	75+	198	91.4	1.5	5.6	1.5
	Total	1843	93.5	2.8	2.7	1.0
	Age-adjusted	1843	92.9	2.9	3.1	1.1
Total		4151	93.8	2.6	2.4	1.2

*Retinal disease defined as retinal vascular disease, retinal detachment, photocoagulation in the absence of diabetic retinopathy, or presumed ocular histoplasmosis syndrome.

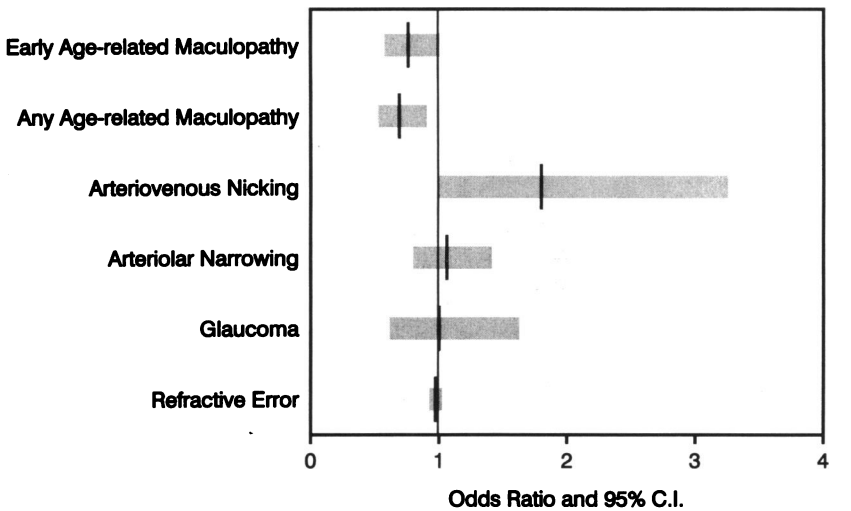

FIGURE 4
Relationship of age-adjusted epiretinal membrane and ocular abnormalities after excluding eyes with retinal disease, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratio of having epiretinal membrane in eyes with ocular abnormalities versus those without.

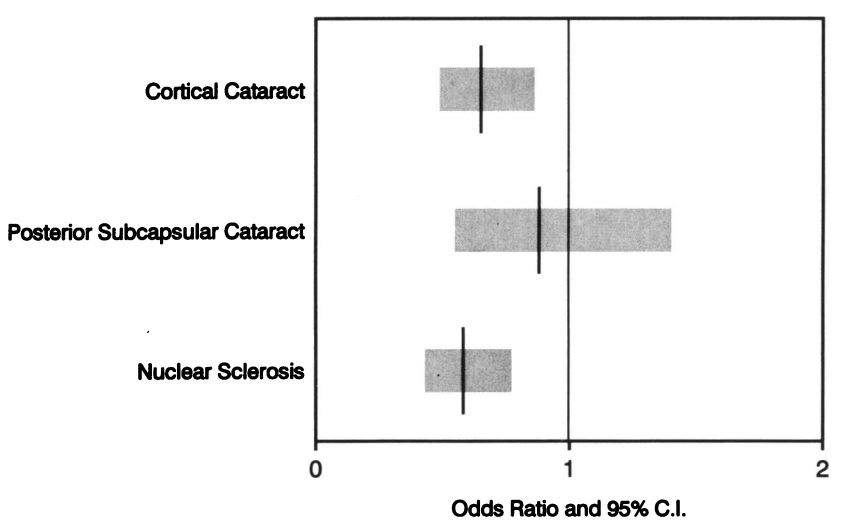

FIGURE 5
Relationship of age-adjusted epiretinal membrane and cataract type after excluding eyes with retinal diseases, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratios of having epiretinal membrane in eyes with cataracts versus those without.

Because the inverse relationship with cataract may result from the difficulty of detection of these membranes by grading fundus photographs with poor quality due to the presence of cataract, we reexamined the relationship of cataract to epiretinal membranes in eyes in which the photographs were judged to be fair to good. There was a statistically significant association of epiretinal membrane and cataract in the left eye (OR, 0.54; 95% CI, 0.38 to 0.79) but not in the right eye (OR, 0.75; 95% CI, 0.52 to 1.07).

Neither the presence nor severity of epiretinal membranes was related to hypertension, history of cardiovascular disease, history of smoking, or history of alcohol consumption (Figs 6 and 7).

We examined the relationships of the presence of epiretinal membranes to retinopathy in people without diabetes. Retinopathy was present in 4.4% (180/4,070) of right eyes (blot hemorrhages only were present in 32 right eyes, microaneurysms only were present in 115 right eyes, and mild to moderately severe retinopathy consisting of microaneurysms with blot hemorrhages, hard exudates, soft exudates, intraretinal microvascular abnormalities, or venous beading was present in 33 right eyes) and 4.6% (188/4,097) of left eyes (blot hemorrhages only were present in 33 left eyes, microaneurysms only in 124 left eyes, and mild to moderately severe retinopathy in 31 left eyes) of people without diabetes. After controlling for age, the frequency of retinopathy was higher in eyes with epiretinal membranes compared with eyes without them (OR, 1.42; 95% CI, 1.01 to 1.97) (Table IV).

Macular holes were infrequent in the population. When present, they were more frequent in eyes with epiretinal membranes compared with eyes without epiretinal membranes (Table IV). This relationship remained after controlling for age (OR, 16.10; 95% CI, 5.37,48.42).

The relationship of epiretinal membranes to visual acuity is presented in Table V. Other causes of loss of vision, aside from age-related cataract and maculopathy, were excluded from these analyses. While correcting for age, the visual acuity was significantly but minimally decreased only in eyes with level 3 or 4 epiretinal membranes involving the central subfield. The relationship of epiretinal membranes to visual impairment was not significant (Table VI and Fig 8).

DISCUSSION

Most information about the frequency of epiretinal membranes has been derived from studies of select groups attending specific clinics in which patients with severe disease may be overrepresented.[1-10] The Beaver Dam Eye Study provides unique data on the presence and severity of epiretinal

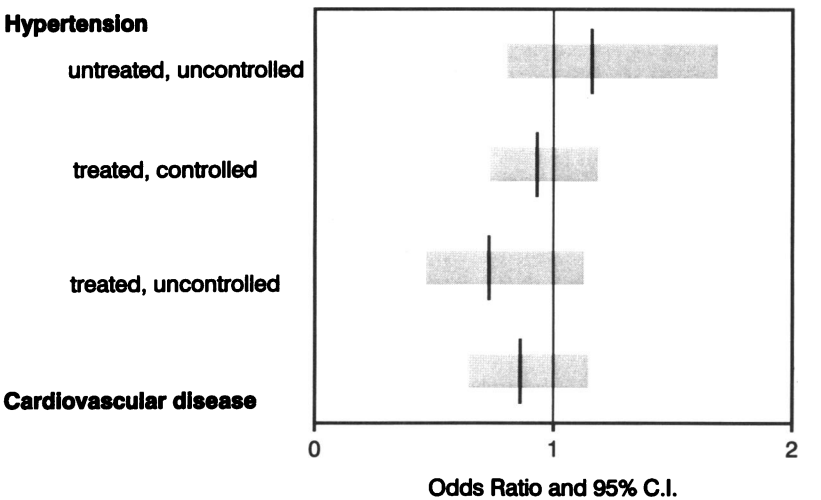

FIGURE 6
Relationship of age-adjusted epiretinal membrane with hypertension and cardiovascular disease after excluding eyes with retinal diseases, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratios of having epiretinal membrane in hypertensive versus normotensive participants, and in people with cardiovascular disease versus those without.

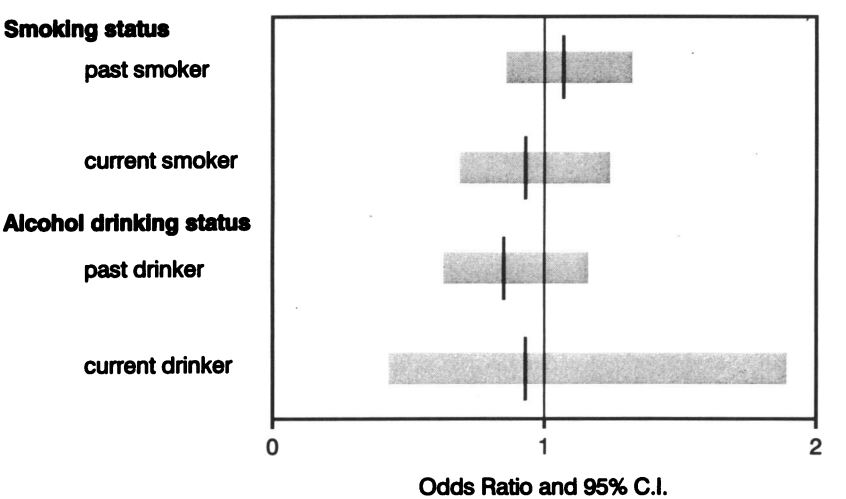

FIGURE 7
Relationship of age-adjusted epiretinal membrane with smoking and alcohol drinking status after excluding eyes with retinal diseases, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratios of having epiretinal membrane in smokers versus nonsmokers, and in alcohol drinkers versus nondrinkers.

TABLE IV: RELATIONSHIPS OF EPIRETINAL MEMBRANE TO RETINOPATHY IN ABSENCE OF DIABETES AND TO MACULAR HOLES IN THE BEAVER DAM EYE STUDY (1988-1990)

		RETINOPATHY IN ABSENCE OF DIABETES		MACULAR HOLE	
EPIRETINAL MEMBRANE	AGE (YR)	NO AT RISK	%	NO AT RISK	%
Right eye					
Absent	43-54	1393	2.8	1395	0.0
	55-64	1061	4.9	1069	0.0
	65-74	901	5.3	914	0.3
	75+	451	4.7	481	0.4
	Age-adjusted	3806	4.3°	3858	0.1†
Present	43-54	4	8.3	24	0.0
	55-64	77	9.1	77	1.3
	65-74	119	5.9	121	1.7
	75+	44	9.1	45	0.0
	Age-adjusted	264	8.0°	267	0.8†
Left eye					
Absent	43-54	1405	3.3	1407	0.0
	55-64	1069	4.0	1076	0.0
	65-74	902	5.7	910	0.1
	75+	465	6.7	502	0.0
	Age-adjusted	3841	4.7‡	3895	0.03§
Present	43-54	14	0.0	14	0.0
	55-64	73	9.6	73	2.4
	65-74	140	4.3	140	0.7
	75+	29	13.8	29	6.9
	Age-adjusted	256	6.0‡	256	2.0§

°P=.05.
†P=.01.
‡P=.28.
§P=.0001.

membranes using standardized protocols for the recording and grading of these lesions with stereoscopic fundus photographs.

Epiretinal membranes (11.8%) were common in the population and increased with increasing age. The relationship with age is likely due to the increased frequency in older people of conditions such as posterior vitreous detachment, cataract surgery, and retinal diseases that may cause epiretinal membranes. On the basis of the Beaver Dam data, we estimate that there are 30 million people 43 to 86 years of age in the United States with epiretinal membranes in at least one eye, 6.8 million of whom have membranes associated with retinal folds.

The higher frequency of epiretinal membranes in eyes with proliferative diabetic retinopathy, other retinal vascular diseases, rhegmatogenous retinal detachment, or cataract surgery than in eyes without these conditions is

TABLE V. RELATIONSHIP OF EPIRETINAL MEMBRANE TO VISUAL ACUITY BY EYE IN PEOPLE WITHOUT RETINAL VASCULAR DISEASES, CATARACT SURGERY, AND DIABETIC RETINOPATHY IN THE BEAVER DAM EYE STUDY (1988-1990)

EPIRETINAL MEMBRANE	AGE-ADJUSTED MEAN VISUAL ACUITY (MEAN ± SD)	*P* VALUE*	AGE, CATARACT, AND ARM ADJUSTED MEAN VISUAL ACUITY (MEAN ± SD)	*P* VALUE*
Right eye				
Level 1: absent/questionable	53.6 ± 9.5	—	53.6 ± 3.9	—
Level 2: membrane ≤2 subfields				
Central subfield not involved	53.2 ± 3.0	.75	53.2 ± 3.1	.18
Central subfield involved	48.5 ± 2.2	.07	48.5 ± 1.4	.12
Level 3: membrane >2 subfields				
Central subfield not involved	53.1 ± 2.5	.52	53.1 ± 3.2	.6
Central subfield involved	49.8 ± 2.2	<.001	48.4 ± 3.1	<.001
Level 4: retinal folds				
Central subfield not involved	45.6 ± 3.3	<.001	45.6 ± 4.0	<.001
Central subfield involved	52.2 ± 2.6	.08	51.7 ± 4.1	.05
Left eye				
Level 1: absent/questionable	54.3 ± 4.0	—	54.7 ± 4.0	—
Level 2: membrane ≤2 subfields				
Central subfield not involved	55.1 ± 2.6	.004	55.1 ± 2.9	.21
Central subfield involved	56.0 ± 3.1	.47	56.0 ± 2.2	.41
Level 3: membrane >2 subfields				
Central subfield not involved	49.7 ± 2.2	<.001	49.7 ± 2.6	<.001
Central subfield involved	46.5 ± 3.3	<.001	46.0 ± 2.8	<.001
Level 4: retinal folds				
Central subfield not involved	44.0 ± 2.4	<.001	43.4 ± 2.7	<.001
Central subfield involved	51.0 ± 2.6	<.001	51.0 ± 3.4	<.001

*Mean visual acuity in eyes with epiretinal membranes was compared with mean visual acuty in eyes in which epiretinal membranes were absent or questionable.
†ARM, age-related maculopathy.

consistent with data from previous case-series.[1-4,15,46-50] Posterior vitreous detachment, distortion of the retina with edema, and ischemic changes of the retina—factors associated with these conditions—have been suggested as possible etiologic factors.[4] Less is known regarding the etiology of epiretinal membranes in the absence of these conditions. Histopathologic studies suggest that separation of the posterior vitreous from the retina is an important factor in the pathogenesis of these membranes.[1-3,18]

Consistent with previous studies, we found no systemic factors or diseases other than diabetes with proliferative retinopathy associated with epiretinal membranes. In Beaver Dam, there was a relationship of epiretinal mem-

TABLE VI: FREQUENCIES OF IMPAIRED VISION IN EYES WITH AND WITHOUT EPIRETINAL MEMBRANE, BEAVER DAM EYE STUDY (1988-1990)

	43-54 YR				55-64 YR				65-74 YR				75+ YR				AGE-ADJUSTED			
	20/200-20/40		<20/200		20/200-20/40		<20/200		20/200-20/40		<20/200		20/200-20/40		<20/200		20/200-20/40		<20/200	
EPIRETINAL MEMBRANE	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%	NO AT RISK	%
Absent																				
OD*	1385	1.3	1390	0.4	1058	2.1	1063	0.5	903	7.0	911	0.9	467	21.2	479	2.5	3813	6.3	3843	0.9
OS*	1400	1.1	1402	0.1	1064	1.9	1070	0.6	904	5.3	906	0.2	486	21.4	498	2.4	3854	5.7	3876	0.6†
Present																				
OD	24	0	24	0	77	6.5	77	0	120	5.8	121	0.8	44	6.8	45	2.2	265	4.4	267	0.6
OS	14	7.1	14	0	71	2.8	73	2.7	138	3.6	140	1.4	27	14.8	29	6.9	250	6.3	256	2.2†

*Visual acuity was not available in 15 right eyes, 19 left eyes.

†P=.001, impaired visual acuity was more frequent in left eyes in which epiretinal membranes were present compared with left eyes in which epiretinal membranes were absent.

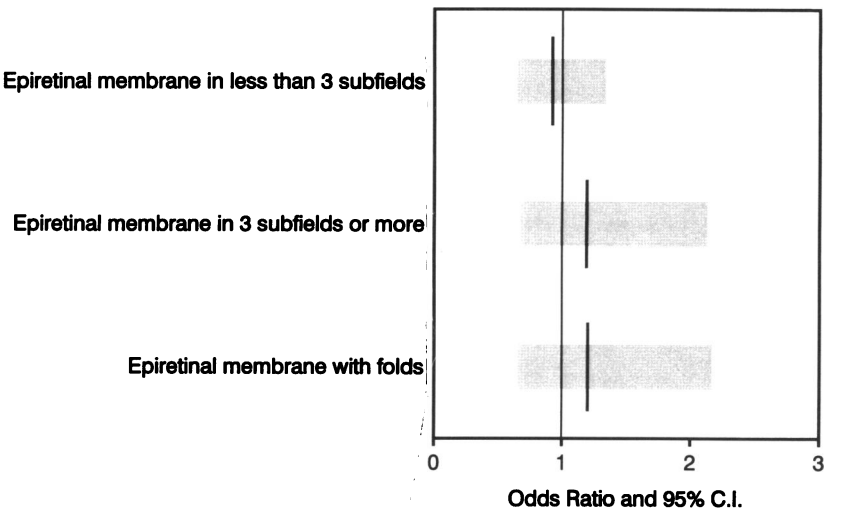

FIGURE 8
Relationship of age-adjusted epiretinal membrane and visual impairment after excluding eyes with retinal disease, diabetic retinopathy, or cataract surgery in the Beaver Dam Eye Study (1988-1990). Odds ratios of having impaired vision in eyes with epiretinal membrane versus those without.

branes with arteriovenous nicking but not with hypertension. Wise,[4] in a large case series, reported an association of retinal arteriosclerosis with epiretinal membranes. In Beaver Dam, neither narrowing of the retinal arterioles nor a history of cardiovascular disease was associated with the presence of epiretinal membranes.

There was a lower frequency of epiretinal membranes in eyes with nuclear or cortical cataract than in eyes without these types of cataract. The reasons for this are not clear. Difficulty in detection of epiretinal membranes owing to poorer photographic quality associated with more severe cataracts may explain, in part, the inverse relationship of epiretinal membranes and nuclear sclerotic cataract. However, this relationship remained even when the fundus photographs were of fair to good quality. There was also a lower frequency of epiretinal membranes in eyes with early age-related maculopathy compared with eyes without these lesions. The reason for this relationship is not apparent.

In the Beaver Dam population, eyes with more severe idiopathic epiretinal membranes involving the central subfield of the macular area had slightly poorer visual acuities than eyes without these membranes. However, the frequency of visual impairment was similar. This is consistent with the

observation that in the absence of other ocular conditions, epiretinal membranes are usually not associated with visual symptoms.[2,3] Data from patients seen in a retina clinic indicate that there is little change in the visual acuities in eyes with idiopathic epiretinal membranes over an average of 2½ years follow-up.[10]

Epiretinal membranes were associated with a higher frequency of macular holes. This was not unexpected, as these membranes may play a role in the pathogenesis of some of these holes.[1-3] However, Smiddy and associates[18] suggested that when epiretinal membranes were present, there was little risk of progression to a full-thickness macular hole, because there was usually a complete posterior vitreous detachment present in these eyes.

There are a number of relative limitations regarding conclusions drawn from this study. First, it is cross-sectional. Selective mortality may have resulted in the failure to find important relationships. For example, we found no relationship between smoking behavior and the presence of epiretinal membranes. If people in the population who smoked and who had epiretinal membranes were at increased risk of death and were not examined, there would be less likelihood of finding a relationship if it existed. In addition, antecedent-consequent relationships cannot be determined from these data. For example, it is possible, that the association of epiretinal membranes and macular holes may have been a result of increased risk of developing macular holes in eyes with epiretinal membranes; however, macular holes may be associated with the development of epiretinal membranes.

Second, epiretinal membranes may be related to conditions not determined in the study, such as posterior vitreous detachment. Third, misclassification of presence of epiretinal membrane status may have occurred, especially in poorly focused retinal photographs with media opacities. This may explain, in part, the decrease in prevalence of epiretinal membranes in people 75 years of age or older, in whom more severe cataracts are present.

Fourth, the sample size may have limited the evaluation of relationships between relatively infrequent conditions such as posterior subcapsular cataracts and epiretinal membranes.

CONCLUSIONS

This study provides precise estimates of the prevalence of epiretinal membranes across a wide age range in the population. The findings suggest that epiretinal membranes are common, affecting 11.8% of the population. They are associated with cataract surgery and proliferative diabetic retinopathy. Besides age, no systemic factor was associated with the presence of epireti-

nal membranes. The presence of epiretinal membranes was not associated with significant decreases in visual acuity.

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DISCUSSION

DR ALEXANDER IRVINE. The authors are to be praised for drawing yet more valuable information from the Beaver Dam Study. It is amazing how much has been learned from this one well-planned study—information regarding cataracts, age-related macular degeneration, diabetic retinopathy, glaucoma, and now epiretinal membranes. The Beaver Dam Study is unique in that its inclusion of the total population avoids the selection biases inherent in all practice-based studies.

The authors have demonstrated that epiretinal membranes, sufficient to be detected on fundus photography are present in 11% to 12% of the population, and that only a very small proportion of them ever progress or affect visual acuity.

Epiretinal membranes have increased incidence in patients who have had retinal vascular disease, retinal detachment, or cataract surgery. In the great majority of patients in this study, however, none of those conditions were present and the major factor affecting prevalence was age.

The new knowledge that the authors have imparted to us is of practical clinical value in that it reassures us regarding the benign behavior of most epiretinal membranes and it warns us that in a patient with decreased vision and an epiretinal membrane that produces just a "cellophane sheen" without retinal wrinkling, we must search for another cause for the decreased acuity.

The authors suggest that the incidence of posterior vitreous detachment may, in large part, explain the increased incidence of epiretinal membranes with increasing age. I wonder if they think the same mechanism might explain the increased incidence with cataract extraction.

I also wonder what the sensitivity of fundus photographs is in detecting epiretinal membranes. It seems that at times, when one is looking with the indirect ophthalmoscope, the sharply defined area of "cellophane" light reflex appears and disappears depending on the angle of incidence of the light. Similarly, with fundus photos one may see the reflex clearly in one photo and not in another, depending on the incidence of the light. Thus, I would feel that the 12% incidence reported here must be a minimal figure, and the true incidence may be even greater. I would ask the authors whether they had many cases in which certain fundus photographs showed the membrane and yet other photos from the same macula did not. This question regarding the sensitivity of the fundus photographic technique, however, only strengthens the authors' findings regarding the high prevalence and generally benign nature of epiretinal membranes.

In summary, I would like to praise the authors for contributing to our knowledge regarding spontaneous epiretinal membranes. I would ask them whether they feel

the increased incidence of posterior vitreous detachment may explain the increased incidence of epiretinal membranes following cataract extraction and what they feel the sensitivity of the photographic technique is in detecting epiretinal membranes.

DR HUGH TAYLOR. I would like to again compliment Drs Klein and colleagues. I think theirs a landmark study.

I was impressed with the relative decrease in frequency of epiretinal membranes in the oldest age group. I wondered whether there may be a biologic reason for this or if it were an artefact. Certainly, the detection of these membranes in a large part was based on the changes in the macular light reflex which will be susceptible to change by a number of factors including lens opacity. Although the analysis was performed looking at good quality photographs, data were also collected on the presence of the severity of lens opacities on a semicontinuous scale and I wonder if an analysis had been done either controlling or adjusting for lens opacity. One way of examining this would be a regression analysis. Another factor that could influence the macular reflex would be the changes in the surface topography of the macula which may occur in the presence of age-related macular degeneration. I would be interested to know if an analysis had been performed to look for that. So my specific question is whether the age-specific decrease in epiretinal membranes is a true biologic phenomena or due to a detection artefact?

DR ROBERT DREWS. Dr Klein's data seems to indicate that there are fewer cellophane membranes in patients who have cataract and more cellophane membranes once the cataracts are removed. Perhaps part of the answer is that the cataract itself makes detection of such diaphanous pathology difficult—until the cataract is removed and a clear view of the fundus is obtained. Both patient and surgeons are occasionally disappointed. In this study, did the aphakic patient group include all aphakic patients or only patients who did not have other ocular problems that might predispose to cellophane membrane?

DR J. BROOKS CRAWFORD. Patients with neurofibromatosis 2 have meningiomas, acoustic neuromas and posterior subcapsular cataracts. They also have peculiar retinal lesions. Thanks to the generosity of Drs Eagle and Egbert, Dr Hoyt and I have had the chance to examine four eyes in two patients with neurofibromatosis 2. What has been surprising is that they have multiple defects in the internal limiting membrane of the retina associated with atypical epiretinal proliferations. My question to the authors is: In their study, did they happen to come across any patients with neurofibromatosis 2, and if so, did they have any of the retinal lesions that have been described?

DR ARIAH SCHWARTZ. In response to Dr Taylor's question and also to the decreased incidence in the older age groups we have observed a certain number of patients in whom there is a partial vitreous detachment down to the level of the macula causing an epiretinal sheen. Then when the vitreous detaches completely from that area the

apparent sheen of the macula will disappear. I wonder whether in the older age groups with an increased incidence of posterior vitreous detachment this might partially explain this finding.

DR W. RICHARD GREEN. In examining surgical specimens of secondary epiretinal membranes, it seems clear that fibrous astrocytes are the predominant cell type. Fibrous astrocytes gain access to the inner surface of the retina through defects in the internal limiting membrane. In the case of macular epiretinal membranes, this occurs in the center of the fovea where the internal limiting membrane is attenuated and absent. In a study of over 100 idiopathic epiretinal membrane, Smiddy and associates observed retinal pigment epithelium to be the principle cell type. From your studies there appears to be no differences that would explain why there are RPE in the idiopathic epiretinal membranes and fibrous astrocytes in the secondary epiretinal membranes. Dr Klein, do you have any thoughts on this matter?

DR W. BANKS ANDERSON. Dr Klein, if I understand you correctly you said that epiretinal membranes in the study were associated with AV nicking. Gutman, Zegarrm, and Gas have found that after branch retinal vein obstruction epiretinal membranes are common. Actually I think the percentage is about what you showed in this population. Both vein obstruction and AV nicking have been associated with hypertension and in your study you showed a negative correlation with hypertension. How do you explain that?

DR RONALD KLEIN. I want to thank Dr Irvine for his comments and the comments of all the discusants.

First, Dr Irvine asked about the sensitivity of detecting small epiretinal membranes by grading fundus photographs. We took stereoscopic fundus photographs of three fields as defined by the Diabetic Retinopathy Study: field 1, which is centered on the disc; field 2, which is centered on the fovea; and field 3, which is temporal to the macular. Viewing the stereoscopic pairs of photographs of fields 1, 2, and 3 probably increases the sensitivity of detecting subtle membranes, because the different angles of the incident light in each of the stereoscopic pairs increases the chance of seeing reflections from the epiretinal membrane. However, it is likely that some small and very subtle membranes are missed. As we only measure epiretinal membranes by grading fundus photographs, we have no way of determining the sensitivity. Dr Irvine's second question is about the role of posterior vitreous detachment in explaining the higher frequency of epiretinal membranes in eyes after cataract surgery compared to phakic eyes. I cannot address this issue because we did not measure the presence of posterior vitreous detachments in the study. It is likely that the higher frequency of posterior vitreous detachment after cataract surgery explains, in part, the association of cataract surgery and epiretinal membrane that we report.

Dr Taylor asked whether changes in the contour of the retina in eyes with early age-related maculopathy might explain the inverse association of epiretinal mem-

branes when this condition is present. I do not know. Dr Taylor also asks whether the presence of cataracts might decrease the sensitivity of detection of the membranes causing a detection bias. It is likely that the sensitivity of detection of membranes is decreased when cataracts are present. Even though we separated eye with fair to good photoquality from eyes with poor photoquality in the presence of cataract and still found a decreased prevalence of epiretinal membranes in the presence of fair to good photoquality and cataract, it is likely that subtle decreases in the clarity of the photographs may result in this finding.

Dr Drews asked whether the increased frequency of epiretinal membranes in eyes which had undergone cataract surgery is due to presence of other retinal conditions. When we reanalyzed the data excluding retinal conditions associated with epiretinal membranes, we still found higher frequencies of epiretinal membranes in eyes after cataract surgery compared to phakic eyes.

Dr Crawford describes an interesting observation of higher frequency of epiretinal membranes and neurofibromatosis 2. We did not examine this relation in the population.

Dr Schwartz's observation may, in part, account for the decreasing frequency of epiretinal membranes in the oldest age group. The higher frequency of cataract and early age-related maculopathy in the oldest age group in our population also may account for this observation.

Dr Green's comments on specific cellular types and etiologies of epiretinal membranes are important. Our classification of membranes are based on their appearance in color fundus photographs in the central area of the retina. We cannot tell specific cell types present in the epiretinal membranes we describe. More detailed classifications of the membranes, based on a series of clinicopathologic observations, might be helpful in future epidemiologic studies of these membranes.

Dr Anderson asks about why we find a positive association of epiretinal membranes and arteriovenous nicking and an inverse relationship with hypertension. He also asks whether we found any relationship of epiretinal membranes with hypertension and/or AV nicking if we controlled for branch vein occlusions. It is possible that the relationship with hypertension. Our data suggest that the relationships with epiretinal membranes are most likely due to local ocular changes, such as in the vitreous or retina, rather than to systemic factors. There were few eyes with analyses or removing them (as we did in the analyses) did not change the relationships reported.

Dr Anderson asks about why we find a positive association of epiretinal membranes and arteriovenous nicking and an inverse relationship with hypertension. He also asks whether we found any relationship of epiretinal membranes with hypertension and/or AV nicking if we controlled for branch vein occlusions. It is possible that the relationship with AV nicking is a chance finding, as we do not find a relationship with hypertension. Our data suggest that the relationships with epiretinal membranes are most likely due to local ocular changes, such as in the vitreous or retina, rather than to systemic factors. There were few eyes with branch vein occlusions in the study. Leaving such eyes in the analyses or removing them (as we did in the analyses) did not change the relationships reported.

APPENDIX A

Glaucoma

1. Have you ever been told by a physician that you have glaucoma, that is, high pressure in your eyes?
2. Are you currently taking drops for glaucoma?

Cardiovascular Disease

3. Have you ever had *angina,* that is, pressure (or pain) in the chest on exertion due to heart disease?
4. Has a doctor said you had a *heart attack* (myocardial infarction, or coronary thrombosis, or coronary occlusion)?
5. Did a doctor tell you that had a *stroke* or a brain hemorrhage?

Diabetes

6. Has a doctor *ever* said you had *diabetes*, sugar in your urine, or *high blood sugar*?
   How old were you when you learned this?
   Are you currently:
   Following special diet for your diabetes?
   Taking pills for your diabetes?
   Taking insulin injections?
   Losing or controlling your weight?

Hypertension

7. Has a doctor ever told you that you had *high blood pressure*?
   Are you currently taking any medication for this?
   What are the names of the blood pressure pills you are taking (or last took)?
8. Are you now taking water pills (diuretics)?

Surgery

Did you have any of the following surgery?

9. Surgery to the brain or neck to correct or prevent a stroke?
10. Surgery on your heart?
11. Was it a coronary bypass?
12. Have you had an amputation of an arm or leg, toe or finger?
13. Was it due to poor circulation?

Medication History

Have you ever taken any of the following types of medication? If so, do you still take them?

14. Digitalis, digoxin, or Lanoxin for your heart?
15. Nitroglycerin, Nitro-Bid, Isordil, etc, for angina?

Cigarette Smoking

16. Have you smoked more than 100 cigarettes in your lifetime?
17. About how many months or years have you smoked (or did you smoke) cigarettes?
18. Do you *smoke* now?
19. How many months or years ago did you stop?
20. How many cigarettes *per day* (are you smoking now or did you usually smoke before you stopped)?

Alcohol Consumption

21. Have you had any beer or ale in the past month?
22. Have you had any beer (ale) during the past year?
23. During the average week how many 12-oz bottle or cans of beer do you usually drink?
24. Have you had any wine in the past month?
25. Have you had any wine during the past year?
26. During the average week how many 4-oz glasses of wine do you usually drink?
27. Have you had any liquor in the past month? That is things like brandy, whiskey, vodka, gin, schnapps, cocktails, or liqueurs?
28. Have you had any liquor in the past year?
29. During the average week, how many 1½-oz glasses of liquors do you usually drink?
30. Was there a time in your life when you drank alcoholic beverages?
31. Has there been a period in your life when you drank quite a bit more than you do now?
32. Has there ever been a time in your life when you drank four or more alcoholic beverages daily?

*Partial list used for analyses.