RETINOPATHY IN A POPULATION-BASED STUDY*

BY *Ronald Klein,* MD

INTRODUCTION

SINCE THE INVENTION OF THE OPHTHALMOSCOPE IN 1852, RETINAL MICROANEURYSMS, blot hemorrhages, cotton-wool spots, and hard exudates have been observed.[1,2] Their appearance has been associated with a number of ocular and systemic conditions.[1,3,4] Although these retinal lesions were frequently observed in persons with diabetes,[5] it was not until the 1940s that it was commonly accepted that they could appear as a result of diabetes in the absence of other systemic conditions, such as hypertension or atherosclerotic vascular disease.[6,7] The appearance of these retinal lesions in persons with known diabetes characterizes diabetic nonproliferative retinopathy.[8,9]

Retinal microaneurysms, blot hemorrhages, cotton-wool spots, and hard exudates, along with changes in retinal arteriolar caliber and appearance, have also been associated with elevated blood pressure.[9-18] This association was first described in 1859 in patients with Bright's disease with severe hypertension and has since been described by numerous investigators.[18] In addition, retinal microaneurysms, blot hemorrhages, and cotton-wool spots have been described in patients with venous stasis retinopathy secondary to occlusive internal carotid artery disease.[19-21] These lesions have also been observed in a growing number of other systemic conditions as well and are thus not pathognomonic of any.[3,22]

The frequency of these retinal lesions in the general population and their diagnostic value for the presence of systemic disease other than diabetes is not certain. Studies by Ballantyne and Loewenstein[6] in the 1940s suggested that although lesions such as microaneurysms and blot hemorrhages could appear in nondiabetic patients with retinal vascular disease, this situation was considered to be rare. Friedenwald[7] studied the retinas of more than 76 nondiabetic persons and concluded that

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although capillary aneurysms may appear in patients without diabetes, they were not a usual manifestation of arteriosclerosis, malignant hypertension, or arteriolar hyaline degeneration.

In contrast, Ashton[23] and Cogan[24] found retinal microaneurysms to be frequent in the peripheral retinas of nondiabetic persons. Ashton stated that "microaneurysms are common lesions in the retinal capillary network and that they are by no means specific for diabetes."[23] Cogan described senescent changes in the peripheral capillaries of persons 50 years of age or older without diabetes.[24] The initial disappearance of endothelial cells was followed by the disappearance of mural cells, dilation of the vessels, shunt formation. and out-pouching of the capillaries with the formation of microaneurysms. He also described a similar gradual decrease in the cellularity of the rest of the retinal capillaries in the posterior polar area of the retina after the sixth decade of life, but could not differentiate whether this was due to an "aging" or a pathologic process. He noted that ischemia secondary to occlusion of the carotid artery or central retinal artery could lead to these changes at any time of life. Systemic hypertension and arteriosclerosis were less likely to cause histologic changes in these vessels.

Data from epidemiologic studies also suggest variability in the frequency of these retinal lesions in persons without diabetes.[16,17,25-27] No retinal exudates or hemorrhages were detected by ophthalmoscopy in 719 normotensive men 40 to 60 years of age examined in a Swedish study in 1950.[16] In another study in Gothenburg, Sweden, direct and indirect ophthalmoscopy and fundus photographs were used to detect the presence of hemorrhages and exudates and other signs of hypertensive retinopathy in a population-based cohort of 855 men who were 50 years of age.[25] The prevalence of retinal hemorrhages was 0.4% and that of exudates was 0%. At a 4-year follow-up examination of the same cohort, the prevalence of retinal hemorrhages in the 792 men who were reexamined was 0.9%; for retinal exudates (hard or soft not specified) it was 0.1%.[17]

In the Framingham Eye Study, ophthalmoscopic screening examinations revealed that 19 (0.8%) of those without a previous history of diabetes (n = 2375) had signs of retinopathy.[26] Fourteen of these 19 had a history of hypertension, 3 had branch vein occlusions, 1 had diabetes mellitus discovered at the time of follow-up examination, and 1 had no other pathologic disorder. In another recent study from Sweden, Nielsen[27] found a single red spot in the posterior pole in 2% of color fundus photographs of 185 "clinically healthy" persons 10 to 71 years of age.

The foregoing observations are limited. In the histopathologic studies, the eyes were selected by their availability after death, and in many cases

there was little information regarding premorbid pathology.[23,24,28] The study by Nielsen[27] was small and represented patients attending a clinic. The Framingham Eye Study and some of the earlier Swedish studies relied on a less sensitive technique, ophthalmoscopy, to detect retinopathy.[13,26] In addition, the Framingham Eye Study was done during the initial screening examination of a surviving cohort of participants from the Framingham Heart Study.[26] The Gothenburg study was limited to men who were 50 years of age.[17,25]

The purposes of this report are to describe the prevalences of various retinal lesions associated with diabetic retinopathy in a population of persons without diabetes mellitus or known retinal vascular diseases such as central or branch retinal venous occlusions; to examine the relationship of blood pressure and other factors to the presence of these lesions in persons without diabetes mellitus; and to examine the predictive value of these lesions for the presence of diabetes mellitus or hypertension. The data are from the large population-based Beaver Dam Eye Study.

METHODS AND MATERIALS

POPULATION

The Beaver Dam Eye Study population has been described in detail in previous reports.[29-31] In brief, a private census of the population of Beaver Dam, WI 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 43 to 84 years of age at the time of the census. Of the 6612 households that were identified by the census, 3715 contained at least one person satisfying the age criteria. These households had a total of 5833 individuals within the ages of 43 and 84 years. After completion of the census, 76 additional households with a total of 92 eligible persons were identified and are included in the population. Participants were examined over a 30-month period beginning March 1, 1988.

PROCEDURES

Letters describing the study and inviting participation were sent to those who were eligible. This was followed by a call from the study coordinator, who provided further information about the study and made an appointment for the examination. Persons who were not interested in participating in the examination were asked to respond (by telephone) to the same questionnaire that was administered at the time of the examination.

Of the 5925 eligible people, 4926 (83.1%) participated in the examination. Nonparticipants consisted of 226 persons (3.8%) who had died before the examination, 92 (1.6%) who had moved out of the area, 23 (0.4%) could not be located, 277 (4.7%) who permitted an interview only, and 381 (6.4%) who refused to participate. Comparisons between participants and nonparticipants have been presented elsewhere.[31]

The examination consisted of an explanation of the study, signing of an informed consent form, measurement of the blood pressure according to the Hypertension Detection and Follow-up Program protocol,[32] refraction and measurement of the visual acuity using a modification of the ETDRS protocol,[31,33] measurement of contrast sensitivity using Pelli-Robson charts,[34] a slit-lamp examination of the anterior segment, and measurement of the intraocular pressure using applanation tonometry. During dilation of the pupils, a structured interview was conducted by the examiners. Questions pertinent to this report are listed in the appendix. After completion of the questionnaire, the height and weight were measured. Direct and indirect ophthalmoscopy were then performed.

A photograph was taken of the lens of each eye using a Topcon SL5 Photoslit Lamp camera modified so that uniform photographs could be obtained for each eye of each participant. Retroillumination photographs of the lens were taken using a Neitz CR-T camera. A photograph was taken at the plane of the anterior lens capsule, and another at a more posterior plane. Kodak Ektachrome 200 ASA film was used. The photographs were graded in a masked fashion using the Wisconsin Age-Related Cataract Grading scheme.[35,36] Slit-lamp photographs were judged for severity of nuclear sclerosis by comparing them with a set of four standard photographs of increasingly severe nuclear sclerosis. The percentage area involvement by cortical cataract or posterior subcapsular cataract was estimated by the grade from the retroilluminated photographs of the lens.

Stereoscopic 30-degree color fundus photographs centered on the disc (Diabetic Retinopathy Study [DRS] Standard Field 1) and macula (DRS Standard Field 2) and a nonstereoscopic color fundus photograph of modified DRS Standard Field 3 (moved about 1/2 disc diameter nasally) of each eye were taken using Kodachrome ASA 25 film.[33] Additional fundus photographs were taken if any lesions were found outside these fields. The photographs were mounted in clear plastic sheets. The presence of retinal microaneurysms, blot hemorrhages, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, new vessels on the disc and elsewhere, and preretinal and vitreous hemorrhages were graded in a masked fashion using the modified Airlie House classification scheme.[37,38] The presence of other retinal disease, such as central

and branch retinal arterial or venous occlusion, retinal cholesterol emboli, and surface wrinkling retinopathy, was graded using a detailed protocol.[39]

The presence of retinal drusen; their type, size, area, and confluence; retinal pigment epithelial degeneration; increased retinal pigment; and signs of exudative macular degeneration or geographic atrophy was determined in the macular area of Field 2 using the Wisconsin Age-Related Maculopathy Grading Sceme.[39,40]

At the end of the examination, venous blood was drawn and urine collected. Serum glucose was determined using the hexokinase method, and whole-blood glycosylated hemoglobin was determined using affinity chromatography (Isolab, Inc, Akron, OH) from casual blood samples.[41,42] Serum total cholesterol and serum high-density lipoprotein (HDL) cholesterol were determined by enzymatic procedures.[43,44] Hematocrit and platelet counts were determined by using a Coulter counter method.[45,46] Protein levels in the urine were determined by means of a reagent strip (Labstix, Ames, Elkhart, IN).

DEFINITIONS

There were 395 people with a previous history of diabetes mellitus, treated with either insulin, oral hypoglycemic agents, and/or diet. There were 50 people with diabetes mellitus newly diagnosed at examination, defined as having no previous medical history of diabetes mellitus or use of hypoglycemic medications for diabetes mellitus and a glycosylated hemoglobin value that was greater than 2 standard deviations (SD) above the mean for a given age-sex group (43 to 54 years of age, men $> 9.5\%$ and women $> 9.6\%$; 55 to 64 years of age, men $> 9.4\%$ and women $> 10.0\%$; 65 to 74 years of age, men $> 9.6\%$ and women $> 9.6\%$; and 75 years of age or older, men $> 9.5\%$ and women $> 9.6\%$) and a random blood glucose level of > 200 mg/dl. Primary care physicians were consulted whenever the diagnosis was in doubt.

The age at diagnosis of diabetes was defined as the age at the time of the diagnosis of diabetes given by the participant or, if noninsulin-dependent diabetes mellitus was newly discovered, at the time of the examination.

Current age was defined as the age at the time of the examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures. The pulse pressure was computed by taking the difference between the mean systolic and the mean diastolic blood pressure. Hypertension was defined as a mean systolic blood pressure ≥ 160 mm Hg and/or a mean diastolic blood

pressure ≥ 95 mm Hg 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, stroke, emphysema, migraine, anticoagulant use, aspirin use, and glaucoma. 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. Average daily consumption of absolute alcohol, in ounces, was calculated as $(.04 \times 12 \times A + .15 \times 4 \times B + .45 \times 1.5 \times C)/7$, where A, B, and C were the average number of portions consumed each week of 12 oz of beer, 4 oz of wine, and 1.5 oz of distilled spirits, respectively. This variable is referred to as average consumption. Information about alcohol consumption during the week prior to the examination was also obtained and was expressed as ounces of ethanol per day as in the equation. This variable is referred to as recent consumption. For analyses of these variables, we defined an abstainer as having consumed no alcohol, a light drinker as having consumed .01 to .21 oz/day, a moderate drinker as having consumed .22 to .99 oz/day, and a heavier drinker as having consumed ≥ 1.00 oz/day. In addition, a person was defined as a nondrinker if he or she had never consumed alcoholic beverages, as an exdrinker if he or she had consumed alcoholic beverages in the past but not in the previous year, and as a current drinker if he or she had consumed alcoholic beverages in the previous year. This variable is referred to as drinking history.

Proteinuria was defined as urine protein concentration of 0.30 g/l or more as measured by a reagent strip. Anemia was defined as a hematocrit reading of < 37% in women and < 42% in men.

Cataract was defined as the presence, in at least one eye, of nuclear sclerosis severity level 3 and/or ≥ 5% of area of the lens involved by cortical opacity or posterior subcapsular cataract. Late cataract was defined as the presence in at least one eye of level 4 or 5 nuclear sclerosis or ≥ 25% of the lens area involved by either cortical opacity or posterior subcapsular cataract. Early age-related maculopathy was defined as the presence of soft indistinct drusen or the presence of any type of drusen in the presence of pigmentary abnormalities in the macular area (defined by a circle with a diameter of 6000 μ centered on the fovea) in the absence of late age-related maculopathy. Late age-related maculopathy was defined

as the presence of either signs of exudative macular degeneration or geographic atrophy.

STATISTICS

The Statistical Analysis System was used for calculating prevalence proportions, means, chi-square statistics, and *t*-tests.[47] Trends in proportions were tested for significance by the Mantel-Haenszel procedure.[48] To evaluate the relative influence of several variables on each specific lesion, stepwise logistic regression models were used.[47] An index is necessary to evaluate how well the independent variables explain the dependent variable. One such index is entropy. Entropy is a function of the log likelihood of the current model that is being considered, compared with a model in which no variables had been considered. This index might be considered analogous to the R^2 values for multiple linear regression and will be interpreted as such.

RESULTS

The diabetic status of the population is defined in Table I. Of the 4926 persons examined, the photographs of 88 (1.8%) could not be graded for retinopathy. In addition, 41 (0.8%) were excluded because of central or branch retinal venous occlusions, retinal detachments, macular edema due to a condition other than diabetes, or late age-related macular degeneration. This left 4797 persons for analysis (Table I). Retinal lesions thought to be consistent with diabetes were present in 10.4% (500) of these persons.

TABLE I: DIABETES STATUS IN THE BEAVER DAM EYE STUDY (1988-1990)

GROUP	FREQUENCY	%	FREQUENCY OF PERSONS WITH GRADABLE PHOTOGRAPHS OR NONEXCLUDABLE CONDITIONS	%
Diabetes present:				
Younger-onset taking insulin	19	0.4	18	0.4
Older-onset taking:				
Oral hypoglycemic agents or diet	277	5.6	266	5.5
Insulin	82	1.7	78	1.6
Oral hypoglycemic agents and insulin	17	0.3	16	0.3
Suspect	61	1.2	59	1.2
Newly diagnosed (at time of examination)	50	1.0	49	1.0
Diabetes not present	4420	89.7	4311	89.9
Total	4926	99.9	4797	99.9

Retinopathy was more frequent (37.0%) in persons with diabetes mellitus (n = 427). Among persons with diabetes, those diagnosed after 30 years of age and who were using insulin had the highest frequency of retinopathy (70.5%); those who were newly diagnosed (n = 49) had the lowest frequency (10.2%) (Table II).

Retinopathy was present in 7.8% (336 of 4311) of the nondiabetic population (Table II). Sixty-six (1.5%) of the nondiabetic population had retinal blot hemorrhages only, 221 (5.1%) had microaneurysms only (of whom 75.1% had only one, 15.0% had two, 5.2% had three, and 4.7% had four or more), 15 (0.3%) had soft exudates or intraretinal microvascular abnormalities (IRMA) present in the absence of retinal microaneurysms, and 34 (0.8%) had retinal microaneurysms with blot hemorrhages, hard exudate, cotton-wool spots, IRMA, or venous beading present. For purposes of the analyses, the latter two groups were combined and called "moderate to severe nonproliferative retinopathy group."

TABLE II: RETINOPATHY BY DIABETES STATUS IN THE BEAVER DAM EYE STUDY (1988-1990)

GROUP	NO.	RETINOPATHY PRESENT	
		NO.	%
Younger-onset insulin-dependent diabetes	18	12	66.7
Newly discovered NIDDM	49	5	10.2
Previously discovered NIDDM			
Using insulin	78	55	70.5
Using oral hypoglycemic agents or diet	266	80	30.1
Using insulin and oral hypoglycemic agents	16	6	37.5
Suspect	59	6	10.2
Diabetes not present	4311	336	7.8
Total	4797	500	10.4

NIDDM, non-insulin-dependent diabetes mellitus.

When retinopathy was present, it was more frequently bilateral (60.1%, 95 of 158) in persons with known diabetes mellitus as compared with the group without diabetes (9.5%, 32 of 336, $P < 0.0001$). When retinopathy was present in persons with diabetes, it was likely to involve microaneurysms associated with more severe retinopathic lesions (such as

cotton-wool spots, IRMA, or retinal new vessels); in persons without diabetes, retinopathy was more likely to involve the presence of only retinal microaneurysms or blot hemorrhages ($P < 0.001$, Table III). The average number of retinal microaneurysms found in eyes of diabetic persons (2.2, SD = 2.4) was significantly higher than the average number of microaneurysms found in nondiabetic persons (1.5, SD = 1.1, $P < 0.01$ by the Savage test).

TABLE III: RETINOPATHY SEVERITY BY DIABETES STATUS IN THE BEAVER DAM EYE STUDY (1988-1990)

GROUP	NO. WITH RETINOPATHY PRESENT	BLOT HEMORRHAGES ONLY (%)	MICROANEURYSMS ONLY (%)	MORE SEVER LESIONS*	
				LEVEL 30 (%)	LEVEL 40+ (%)
Diabetes not present	336	19.6	65.8	7.7	6.8
Diabetes present	158	6.3	29.7	27.8	36.1

*Microaneurysms and blot hemorrhages, hard exudates, soft exudates, IRMA, and/or venous beading. Level 30 defined as the presence of retinal microaneurysms and one or more of the following: retinal hemorrhages but total of hemorrhages and microaneurysms (H/MA) less than STD photograph 2 of DRS, or hard exudates less than STD photograph 3[49]; levels 40+ defined as presence of microaneurysms and soft exudates, IRMA, venous beading, retinal hemorrhages and microaneurysms ≥ STD 2, or signs of proliferative retinopathy.[49]

The positive predictive value of diabetes (the probability that a person actually has diabetes if specific retinopathy lesions are found by grading of the fundus photographs) for the presence of various lesions is presented in Table IV. The positive predictive value for diabetes of the presence of only retinal blot hemorrhages was 13.2% (10 of 76) and that of retinal microaneurysms was 17.3% (47 of 271). The positive predictive value for diabetes for presence of two or more microaneurysms (20.6%) was not statistically significantly different than for only one microaneurysm (12.8%). The positive predictive value for diabetes of more severe retinopathy (microaneurysms and the presence of more severe nonproliferative lesions, such as blot hemorrhages, hard exudates, cotton-wool spots, IRMA, or venous beading) was 64.4% (94 of 146); for proliferative retinopathy it was 100% (7 of 7). The remainder of the analyses are confined to the nondiabetic group and to lesions found in Diabetic Retinopathy Study Standard Fields 1 to 3.

TABLE IV: DISTRIBUTION OF BLOT HEMORRHAGES, MICROANEURYSMS, AND MORE SEVERE RETINOPATHY BY DIABETES STATUS AND POSITIVE PREDICTIVE VALUE IN THE BEAVER DAM EYE STUDY (1988-1990)

DIABETES GROUP	BLOT HEMORRHAGES ONLY	MICROANEURYSMS ONLY	MORE SEVERE RETINOPATHY	PROLIFERATIVE RETINOPATHY
Absent	66	221	49	0
Suspect	0	3	3	0
Newly diagnosed	0	2	3	0
Previously diagnosed	10	45	91	7
Total	76	271	146	7
Positive predictive value (%)	13.2	16.6	62.3	100.0

Single retinal microaneurysms, without other signs of retinopathy, were found in 3.7% of the nondiabetic population, and 1.2% had two or more microaneurysms in the same eye. The presence of two or more microaneurysms was associated with increasing age (Fig 1) and, after controlling for age, with a higher intraocular pressure ($P = 0.06$), higher hematocrit ($P = 0.003$), higher blood glucose level ($P = 0.03$), lower platelet count ($P = 0.01$), and a history of past heavy alcohol use ($P = 0.003$) compared to eyes with only one microaneurysm present (Figs 2 through 6).

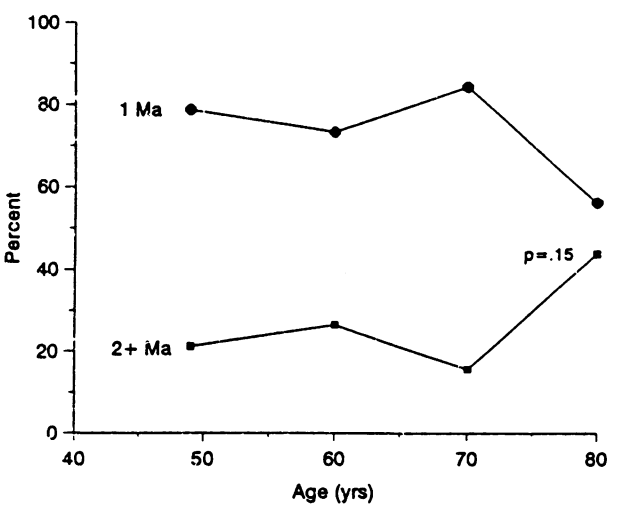

FIGURE 1
Relationship of frequency of number of microaneurysms (one or two or more) by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

The frequency of only blot hemorrhages or more severe nonproliferative retinopathy, but not microaneurysms only, was significantly (test of trend, $P < 0.001$ for blot hemorrhages only, $P < 0.001$ for more severe

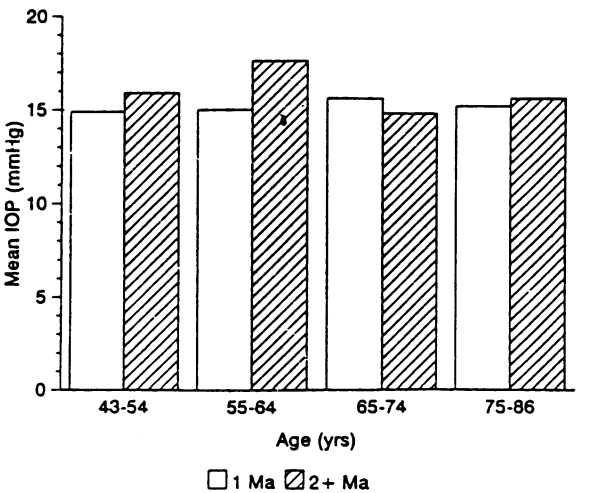

FIGURE 2
Relationship of mean intraocular pressure (IOP) to number of microaneurysms by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

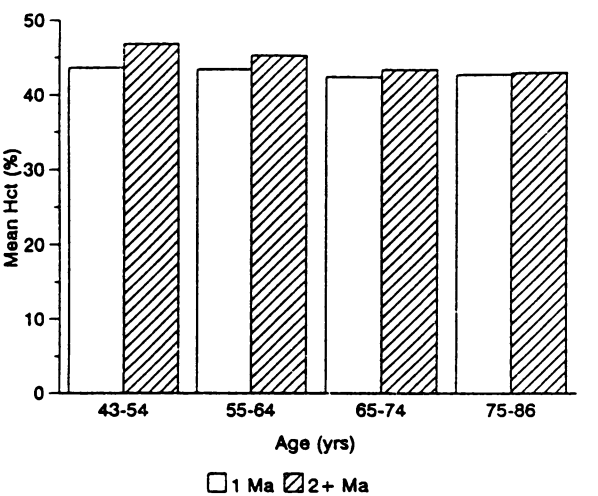

FIGURE 3
Relationship of mean hematocrit (Hct) to number of microaneurysms by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

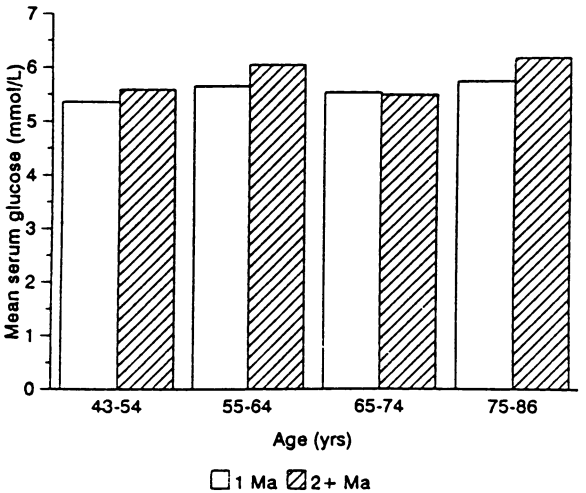

FIGURE 4
Relationship of mean serum glucose to number of microaneurysms by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

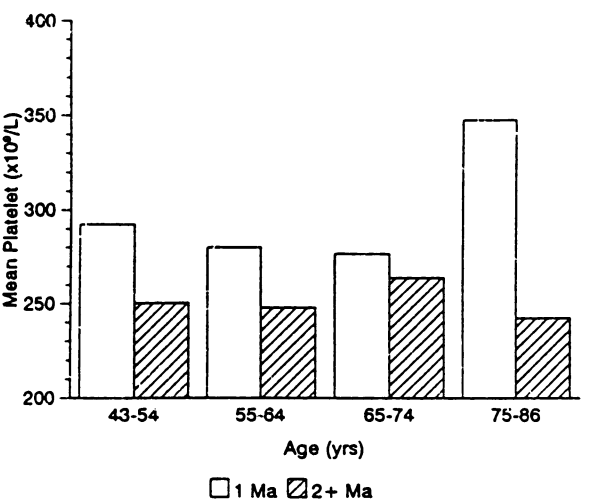

FIGURE 5
Relationship of mean number of platelets to number of microaneurysms by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

retinopathy) associated with increasing age in the nondiabetic population (Fig 7). Persons 75 years of age or older were 9.5 times (95% confidence interval [CI] 3.6, 25.1) as likely to have only blot hemorrhages present

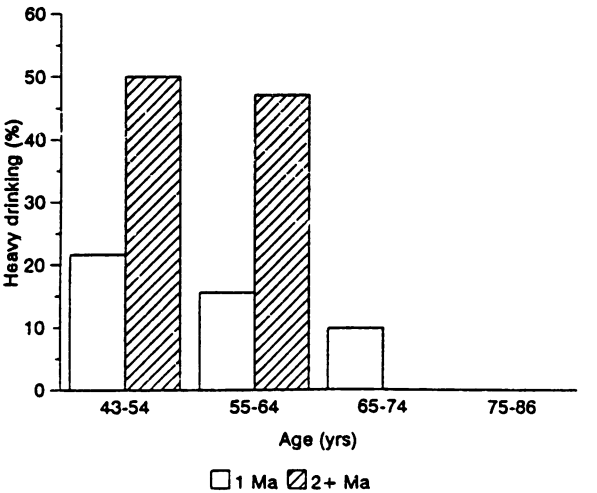

FIGURE 6
Relationship of heavy alcohol drinking to number of microaneurysms by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

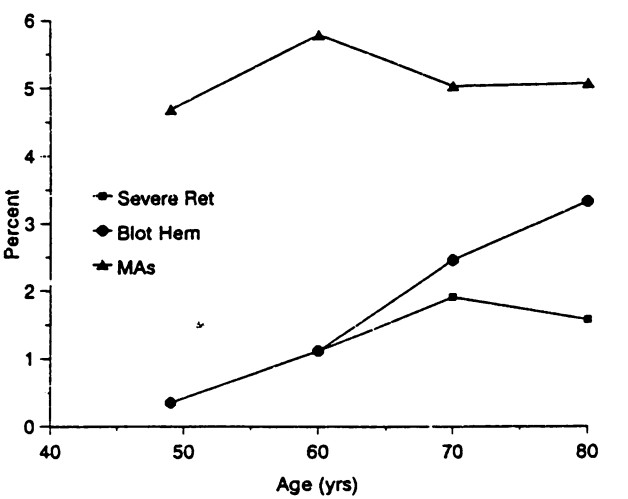

FIGURE 7
Relationship of microaneurysms (MAs), blot hemorrhages only (Blot Hem), or more severe retinopathy (Severe Ret) by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

and 4.5 times (95% CI 1.5, 13.2) as likely to have more severe retinopathy present as persons 43 to 54 years of age. Men had a significantly higher frequency of only microaneurysms present compared with women (Table V).

TABLE V: RELATIONSHIP OF VARIOUS CHARACTERISTICS TO PRESENCE OF

CHARACTERISTICS	NO. AT RISK	BLOT HEMORRHAGES ONLY % PRESENT	RR	95% CI	RETINAL MICROANEURYSMS ONLY % PRESENT	RR	95% CI
Sex: Female	2399	1.5	1.00	—	4.4	1.00	—
Male	1912	1.5	1.00	0.62-1.63	6.0	1.36	1.05-1.76
Systolic blood pressure (mm Hg) Quartiles							
1st (71-117)	1096	0.6	1.00	—	3.4	1.00	—
2nd (118-129)	1098	1.3	2.17	0.86-5.44	5.6	1.65	1.11-2.45
3rd (130-143)	1061	1.4	2.33	0.94-5.82	5.3	1.56	1.04-2.34
4th (144-248)	1055	2.8	4.67	2.01-10.82	6.4	1.88	1.27-2.78
Diastolic blood pressure (mm Hg) Quartiles							
1st (42-70)	1096	1.9	1.00	—	3.8	1.00	—
2nd (71-77)	1047	1.4	0.74	0.38-1.43	4.5	1.18	0.79-1.78
3rd (78-84)	1068	1.4	0.74	0.38-1.42	5.4	1.42	0.96-2.10
4th (85-127)	1099	1.4	0.74	0.38-1.42	6.7	1.76	1.22-2.55
Pulse pressure (mm Hg) Quartiles							
1st (11-40)	1027	0.7	1.00	—	4.0	1.00	—
2nd (41-50)	1095	0.6	0.86	0.30-2.46	5.8	1.45	0.99-2.13
3rd (51-62)	1082	1.4	2.00	0.83-4.84	4.5	1.12	0.75-1.69
4th (63-162)	1106	3.4	4.86	2.20-10.74	6.2	1.55	1.06-2.26
History of cardiovascular disease							
No	3547	1.4	1.00	—	5.0	1.00	—
Yes	764	2.0	1.43	0.81-2.52	5.9	1.18	0.86-1.62
History of emphysema							
No	4162	1.5	1.00	—	5.1	1.00	—
Yes	136	1.5	1.00	0.25-3.99	6.6	1.29	0.68-2.47
History of stroke							
No	4182	1.5	1.00	—	5.1	1.00	—
Yes	129	1.6	1.07	0.27-4.22	7.0	1.37	0.72-2.61
Migraine history							
No	3674	1.5	1.00	—	5.3	1.00	—
Yes	597	1.7	1.13	0.58-2.20	4.2	0.79	0.53-1.19
Anemia							
No	3845	1.4	1.00	—	5.0	1.00	—
Yes	454	2.4	1.71	0.90-3.26	5.9	1.18	0.80-1.75
Gross proteinuria							
No	4149	1.5	1.00	—	5.1	1.00	—
Yes	141	2.8	1.87	0.68-5.09	6.4	1.25	0.66-2.39
Smoking history							
Never	1914	1.8	1.00	—	4.7	1.00	—
Ex	1509	1.5	0.83	0.49-1.41	5.5	1.17	0.88-1.56
Current	885	0.9	0.50	0.23-1.08	5.4	1.15	0.82-1.62

RETINOPATHY IN NONDIABETIC BEAVER DAM POPULATION (1988-1990)

MORE SEVERE RETINOPATHY			ANY RETINOPATHY		
% PRESENT	RR	95% CI	% PRESENT	RR	95% CI
1.0	1.00	—	7.0	1.00	—
1.3	1.30	0.74-2.27	8.8	1.26	1.02-1.54
0.4	1.00	—	4.4	1.00	—
0.7	1.75	0.54-5.64	7.6	1.73	1.22-2.44
0.9	2.25	0.73-6.95	7.6	1.73	1.22-2.44
2.6	6.50	2.38-17.75	11.8	2.68	1.94-3.70
1.0	1.00	—	6.8	1.00	—
1.0	1.00	0.43-2.32	6.9	1.02	0.74-1.39
0.8	0.80	0.33-1.95	7.6	1.12	0.83-1.51
1.8	1.80	0.87-3.75	9.9	1.46	1.10-1.93
0.5	1.00	—	5.2	1.00	—
0.6	1.20	0.38-3.80	6.9	1.33	0.94-1.86
1.5	3.00	1.12-8.06	7.4	1.42	1.02-1.99
2.0	4.00	1.54-10.41	11.5	2.21	1.62-3.01
1.1	1.00	—	7.5	1.00	—
1.3	1.18	0.59-2.36	9.2	1.23	0.95-1.58
1.1	1.00	—	7.7	1.00	—
2.2	2.00	0.63-6.36	10.3	1.34	0.81-2.22
1.1	1.00	—	7.7	1.00	—
0.8	0.73	0.10-5.08	9.3	1.21	0.70-2.09
1.1	1.00	—	7.9	1.00	—
1.3	1.18	0.55-2.54	7.2	0.91	0.67-1.24
1.2	1.00	—	7.6	1.00	—
0.9	0.75	0.27-2.05	9.3	1.22	0.90-1.66
1.1	1.00	—	7.6	1.00	—
2.1	1.91	0.60-6.11	11.3	1.49	0.92-2.39
1.2	1.00	—	7.7	1.00	—
0.8	0.67	0.33-1.33	7.8	1.01	0.80-1.28
1.6	1.33	0.69-2.57	7.9	1.03	0.78-1.35

TABLE V: RELATIONSHIP OF VARIOUS CHARACTERISTICS TO PRESENCE OF

CHARACTERISTICS	NO. AT RISK	BLOT HEMORRHAGES ONLY % PRESENT	RR	95% CI	RETINAL MICROANEURYSMS ONLY % PRESENT	RR	95% CI
Alcohol history							
Nondrinker	2076	1.5	1.00	—	4.8	1.00	—
Drinker	2216	1.5	1.00	0.62-1.62	5.5	1.15	0.88-1.48
No heavy past history	3455	1.5	1.00	—	5.1	1.00	—
Heavy past history	712	1.7	1.13	0.61-2.11	5.5	1.08	0.77-1.51
Aspirin							
No	2969	1.3	1.00	—	5.5	1.00	—
Yes	1337	2.0	1.54	0.94-2.51	4.3	0.78	0.58-1.05
Anticoagulants							
No	4244	1.5	1.00	—	5.1	1.00	—
Yes	67	4.5	3.00	0.97-9.28	7.5	1.47	0.63-3.44
Education years							
<12 (completed)	1175	2.3	1.00	—	5.7	1.00	—
12	1912	1.3	0.56	0.33-0.97	5.3	0.93	0.69-1.26
13-15	619	1.0	0.44	0.18-1.04	4.4	0.77	0.50-1.19
≥16	601	1.5	0.65	0.31-1.38	4.2	0.74	0.47-1.15
Ocular							
Glaucoma history							
No	4214	1.5	1.00	—	5.2	1.00	—
Yes	89	1.1	0.73	0.10-5.34	1.1	0.21	0.03-1.52
Cataract							
Absent	1451	0.5	1.00	—	5.3	1.00	—
Early	2055	1.8	3.60	1.63-7.96	5.3	1.00	0.75-1.33
Late	628	2.2	4.40	1.80-10.76	4.6	0.87	0.57-1.32
Age-related maculopathy							
Absent	3545	1.4	1.00	—	4.9	1.00	—
Early present	728	2.2	1.57	0.90-2.74	6.5	1.33	0.97-1.81
Cholesterol embolus							
Absent	4290	1.5	1.00	—	5.1	1.00	—
Present	20	10.0	6.67	1.75-25.38	15.0	2.94	1.03-8.42
Surface wrinkling retinopathy							
Absent	4038	1.5	1.00	—	5.0	1.00	—
Present	272	1.5	1.00	0.37-2.70	7.7	1.54	1.00-2.37

RR, relative risk.

RETINOPATHY IN NONDIABETIC BEAVER DAM POPULATION (1988-1990) (CONT'D)

MORE SEVERE RETINOPATHY			ANY RETINOPATHY		
% PRESENT	RR	95% CI	% PRESENT	RR	95% CI
1.2	1.00	—	7.6	1.00	—
1.1	0.92	0.53-1.60	8.1	1.07	0.87-1.31
1.0	1.00	—	7.6	1.00	—
1.5	1.50	0.76-2.97	8.7	1.14	0.88-1.49
1.0	1.00	—	7.8	1.00	—
1.4	1.40	0.79-2.49	7.8	1.00	0.80-1.25
1.2	1.00	—	7.7	1.00	—
0	0	—	11.9	1.54	0.80-2.99
1.9	1.00	—	9.9	1.00	—
0.8	0.42	0.22-0.80	7.4	0.75	0.59-0.94
1.1	0.58	0.25-1.36	6.5	0.66	0.46-0.93
0.7	0.37	0.13-1.04	6.3	0.64	0.45-0.91
1.2	1.00	—	7.9	1.00	—
0	0	—	2.2	0.28	0.07-1.12
0.7	1.00	—	6.5	1.00	—
1.2	1.71	0.83-3.55	8.3	1.28	1.00-1.63
2.4	3.43	1.56-7.56	9.2	1.42	1.03-1.94
1.2	1.00	—	7.4	1.00	—
1.0	0.83	0.38-1.82	9.6	1.30	1.01-1.67
1.1	1.00	—	7.7	1.00	—
0	0	—	25.0	3.25	1.51-6.98
1.1	1.00	—	7.6	1.00	—
1.8	1.64	0.65-4.13	11.0	1.45	1.02-2.06

The hypertension status in the nondiabetic population is presented in Table VI. The frequency of retinopathy in nondiabetic persons with hypertension was 10.7%. These individuals were 1.7 times as likely to have any retinopathy present as those without hypertension. The frequency of retinopathy in persons with hypertension was consistently higher than in normotensive persons at all ages (Fig 8). The highest prevalence and most severe retinopathy were in persons with uncontrolled hypertension (Table VI). There were no differences in the frequen-

TABLE VI: HYPERTENSION STATUS IN NONDIABETIC POPULATION AND ITS RELATIONSHIP TO RETINOPATHY SEVERITY IN THE BEAVER DAM EYE STUDY (1988-1990)

HYPERTENSION STATUS	NO.	BLOT HEMORRHAGES ONLY (%)	MICROANEURYSMS ONLY (%)	MORE SEVERE RETINOPATHY (%)	ANY RETINOPATHY (%)
Normotensive	2831	1.2	4.3	0.7	6.3
Hypertensive	1480	2.2	6.7	1.9	10.7
Of those with hypertension:					
Antihypertensive medication(s), controlled	939	2.0	6.0	1.5	9.5
No antihypertensive medication(s), uncontrolled	302	2.0	6.6	3.0	11.6
Antihypertensive medication(s), uncontrolled	238	2.9	9.7	2.1	14.7
Not determined	1				

cy of any retinopathy between males (11.6%, 73 of 630) and females (10.1%, 86 of 850, $P = 0.37$) with hypertension. Higher systolic blood pressure and systemic hypertension were significantly related to all of the different types of retinopathy in the nondiabetic population (Tables V and VI). On the other hand, higher diastolic blood pressure was related only to an increased frequency of retinal microaneurysms (Table V). The positive predictive value of hypertension for blot hemorrhages when they were present alone was 48.5% (32 of 66); for retinal microaneurysms only it was 44.8% (99 of 221), for more severe nonproliferative retinopathy it was 57.1% (28 of 49).

Retinal cholesterol emboli were more frequent in eyes of older participants (Fig 9, test of trend by age $P < 0.001$). Nondiabetic females (0.2%, 5 of 2399) had a lower frequency than did males (0.8%, 15 of 1911, $P < 0.01$). Nondiabetic persons less than 65 years of age with hypertension had a significantly higher frequency (0.6%, $P = 0.05$) of retinal cholesterol emboli than did persons without hypertension (0.1%, Fig 10).

The frequency of any retinopathy in the presence of retinal cholesterol emboli was 25.0%. These individuals were 3.2 times as likely to have any retinopathy present as those without retinal cholesterol emboli present (Table V). In persons less than 75 years of age, the frequency of any retinopathy was more likely in nondiabetic persons with retinal cholesterol emboli than without such emboli (Fig 11). Females with such emboli had a similar frequency of retinopathy (20.0%) as did men (26.7%, $P =$

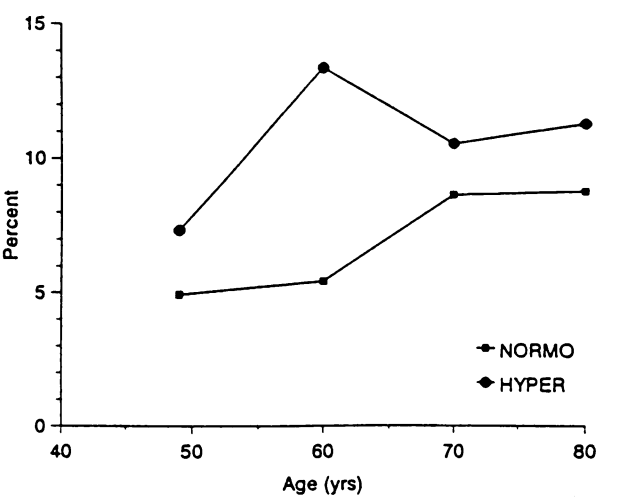

FIGURE 8
Relationship of any retinopathy to hypertension (normo = normotensive, hyper = hypertensive) by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

1.00). Persons without diabetes but with both retinal cholesterol emboli and hypertension had a significantly ($P < 0.01$) higher frequency of any retinopathy than did those with either condition alone or with neither

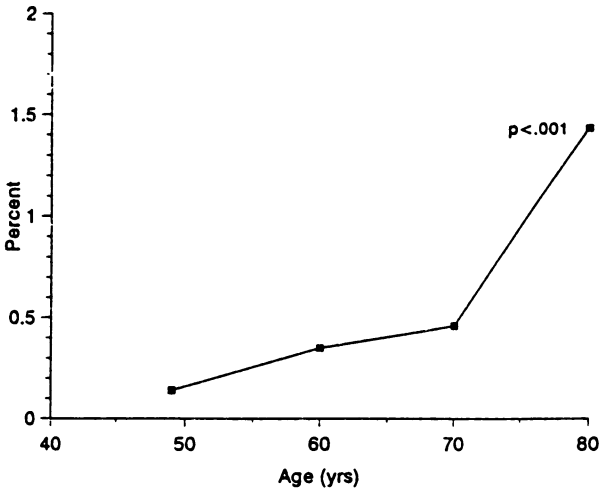

FIGURE 9
Relationship of retinal cholesterol emboli to age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

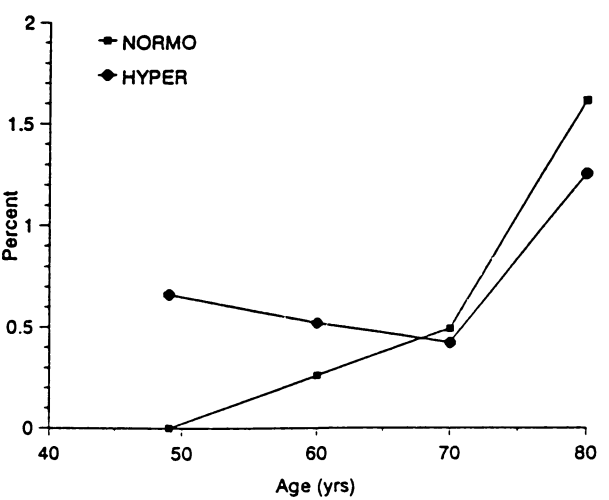

FIGURE 10
Relationship of retinal cholesterol emboli to hypertensive status (normo = normotensive, hyper = hypertensive) by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

condition (Fig 12). In the nondiabetic population, the presence of retinal cholesterol emboli was associated with an increased frequency of blot hemorrhages only or microaneurysms only.

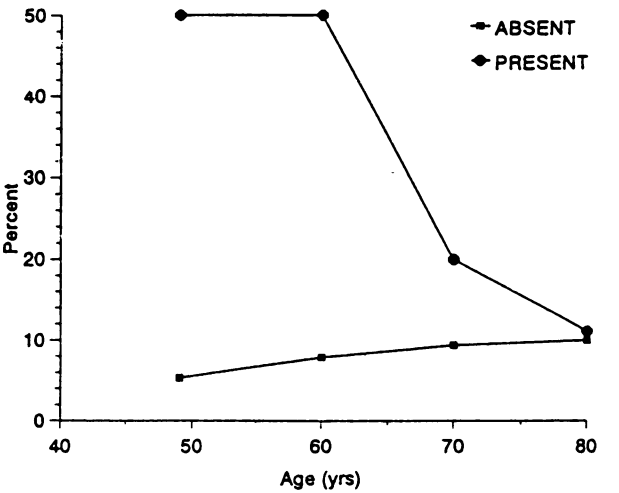

FIGURE 11
Relationship of retinopathy to retinal cholesterol emboli by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

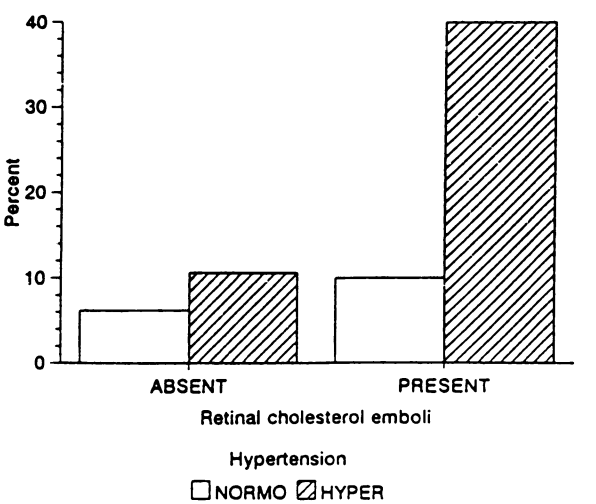

FIGURE 12
Relationship of retinopathy to retinal cholesterol emboli and hypertension in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

Tables V and VII show that few systemic and ocular characteristics were consistently related to the different types of retinopathy in this nondiabetic population. Nondiabetic persons using anticoagulants and aspirin were 3.0 times and 1.5 times as likely, respectively, to have retinal blot hemorrhages present as those not giving a history of current use of these medications at the time of examination. These relationships were found in nondiabetic persons 65 years of age or older (Fig 13). However, these relationships failed to reach a level of statistical significance ($P > 0.05$). Cataract severity appeared to be related to presence of only blot hemorrhages or more severe retinopathy. These relationships were not signifi-

TABLE VII: RELATIONSHIP OF RETINOPATHY LESIONS TO VARIOUS CHARACTERISTICS IN NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

CHARACTERISTIC	NO RETINOPATHY		BLOT HEMORRHAGES ONLY		MICROANEURYSMS ONLY		MORE SEVERE RETINOPATHY	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
Body mass index (kg/m^2)	27.9	5.2	28.1	4.8	27.8	4.6	27.3	4.6
Glycosylated hemoglobin (%)	5.7	0.7	6.0*	0.9	5.8	0.8	6.0*	1.0
Blood glucose (mmol/l)	5.48	0.79	5.63	0.93	5.62*	0.89	5.48	0.65
Hematocrit (%)	43.0	3.8	42.4	4.6	43.6*	4.0	44.0	4.4
Platelet count ($\times 10^9$/l)	290.3	75.1	275.0	81.3	280.6	103.2	279.3	65.1
Intraocular pressure (mm Hg)	15.3	3.3	15.4	3.7	15.4	3.3	15.3	3.2

*Significantly different ($P < 0.05$) from group with no retinopathy.

cant ($P > 0.40$), after controlling for age.

Some of these associations may be due to confounding with age or other factors. To evaluate the relative influence of several variables on the presence of the specific lesions, blot hemorrhages only, retinal microaneurysms only, one versus two or more microaneurysms, more severe retinopathy, or any retinopathy, stepwise logistic regression models were used. Thirty-one variables were entered into the models. The significant relationships are presented in Tables VIII through XII. The odds ratio estimates should be interpreted as follows. For example, the relative odds of having retinal microaneurysms are 12% higher for each increase of 10 mm Hg of diastolic blood pressure, 49% if hypertension is present, and 92% higher if a cholesterol embolus was present (Table IX). The entropy value for Table IX was 1.9%.

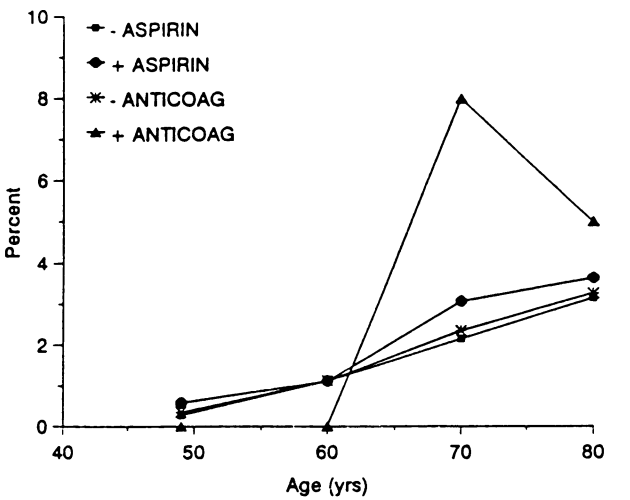

FIGURE 13
Relationship of retinopathy to anticoagulation or aspirin status ([−] = not taking, [+] = taking) by age in nondiabetic population in the Beaver Dam Eye Study (1988-1990).

TABLE VIII: CHARACTERISTICS ASSOCIATED WITH PRESENCE OF RETINAL BLOT HEMORRHAGES ONLY IN NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

CHARACTERISTIC	β	ODDS RATIO	95% CI	BLOT HEMORRHAGES MORE LIKELY IF
Age (10 yr)	.0549	1.73	1.34-2.24	Older
Systolic blood pressure (10 mm Hg)	.0152	1.16	1.04-1.30	Higher
Cholesterol embolus	.868	2.38	1.10-5.17	Present

Entropy = 6.2%.

TABLE IX: CHARACTERISTICS ASSOCIATED WITH PRESENCE OF RETINAL MICROANEURYSMS ONLY IN NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

CHARACTERISTIC	β	ODDS RATIO	95% CI	MICROANEURYSMS MORE LIKELY IF
Hypertension	.401	1.49	1.11-2.01	Present
Sex	.286	1.33	1.01-1.76	Male
Glucose (1 mmol/l)	.159	1.17	1.00-1.37	Higher
Cholesterol embolus	.650	1.92	1.05-3.50	Present
Diastolic blood pressure (10 mm Hg)	.0117*	1.12	0.99-1.28	Higher
Aspirin use history	−.282*	0.75	0.55-1.03	Does not use

*Of borderline significance with *P*-value = 0.08.
Entropy = 1.9%.

TABLE X: CHARACTERISTICS ASSOCIATED WITH FREQUENCY OF TWO OR MORE RETINAL MICROANEURYSMS COMPARED TO SINGLE RETINAL MICROANEURYSM IN NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

CHARACTERISTIC	β	ODDS RATIO	95% CI	TWO OR MORE MICROANEURYSMS MORE LIKELY IF
Blood glucose (1 mmol/l)	.429	1.54	1.04-2.26	Higher
Hematocrit (1%)	.143	1.15	1.05-1.27	Higher
Age at examination (10 yr)	.060	1.82	1.24-2.67	Older
Platelet count (100 × 10^9/l)	−.0054	0.58	0.35-0.96	Lower
Intraocular pressure (1 mm Hg)	.150	1.16	1.03-1.31	Higher
Systolic blood pressure (10 mm Hg)	−.021	0.81	0.66-1.00	Lower

Entropy = 16.4%.

TABLE XI: CHARACTERISTICS ASSOCIATED WITH PRESENCE OF MORE SEVERE RETINOPATHY IN NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

CHARACTERISTIC	β	ODDS RATIO	95% CI	SEVERE RETINOPATHY MORE LIKELY IF
Systolic blood pressure (10 mm Hg)	.0205	1.23	1.09-1.39	Higher
Age (10 yr)	.0427	1.53	1.15-2.04	Older
Hematocrit (1%)	.0880	1.09	1.01-1.18	Higher

Entropy = 6.1%.

TABLE XII: CHARACTERISTICS ASSOCIATED WITH PRESENCE OF ANY RETINOPATHY IN NONDIABETIC POPULATION IN THE BEAVER EYE DAM STUDY (1988-1990)

CHARACTERISTIC	β	ODDS RATIO	95% CI	RETINOPATHY MORE LIKELY IF
Systolic blood pressure (10 mm Hg)	.0113	1.12	1.05-1.19	Higher
Cholesterol embolus	.612	1.84	1.11-3.06	Present
Age (10 yr)	.0163	1.18	1.05-1.32	Older
Sex	.317	1.37	1.09-1.73	Male
Hypertension	.295	1.34	1.03-1.76	Present

Entropy = 2.9%.

DISCUSSION

Retinopathy was not uncommon in the Beaver Dam population, affecting 7.8% of the nondiabetic population. Retinopathy in our population was nearly ten times more frequent than previously reported in the Framingham nondiabetic population.[26] The higher frequency of retinopathy found in persons without diabetes in Beaver Dam compared with the population studied in Framingham may be due, in part, to the difference in the sensitivity of the methods of detection used in the two studies. In Beaver Dam, retinopathy was detected by stereoscopic fundus photographs using the modified Airlie House classification scheme, which is more sensitive than direct ophthalmoscopy, the method used in the Framingham Eye Study.[49,50] The prevalence reported in Beaver Dam is also significantly higher than that reported in a Swedish group by Nielsen.[27] This may be due to the older age of the Beaver Dam group compared with the Swedish group, which included people as young as 10 years of age. In Beaver Dam, increasing age was associated with a higher prevalence of retinopathy. The prevalence of lesions in 43- to 54-year-old men in Beaver Dam (6.8%) was higher than in 50-year-old Gothenburg men (0.4%).

The prevalence of retinopathy in Beaver Dam was significantly lower than previously found in histopathologic studies.[23,24] This may be due to the different techniques used to detect retinopathy. Microscopy is a more sensitive method than is grading of color fundus photographs for the detection of very small or hyalinized microaneurysms. The higher frequency of microaneurysms also may be due, in part, to examination of sections including the retinal periphery in the histopathologic studies; grading of retinopathy in our study was confined to fundus photographs of the posterior pole. Most of the retinopathy found in the histopathologic studies was detected in the far periphery of the retina.

Our findings confirm previous observations of a higher prevalence and more severe retinopathy in persons with diabetes mellitus compared with

persons without diabetes.[26,51,52] The prevalence and severity of retinopathy found in diabetic persons in the Beaver Dam Eye Study are comparable to those previously reported in the Wisconsin Epidemiological Study of Diabetic Retinopathy and in other studies of persons with non-insulin-dependent diabetes.[53-56]

Although microaneurysms or blot hemorrhages in the absence of other, more severe lesions, such as hard exudates, cotton-wool spots, and IRMA, were frequent in people with diabetes in the Beaver Dam Eye Study population, these lesions were not strong predictors of the presence of diabetes mellitus in the whole population studied. Lorentzen[57] has previously stated, "Such an observation (solitary microaneurysms) should always give occasion to an examination with view to the presence of diabetes mellitus, especially by means of an oral glucose tolerance test." However, in Beaver Dam, the positive predictive values for diabetes mellitus of 17% when only retinal microaneurysms were present and 13% when only retinal blot hemorrhages were present suggest that when these lesions are found in asymptomatic persons without known diabetes mellitus, no further effort should be made to diagnose the presence of diabetes. The higher positive predictive value for diabetes when more severe retinopathy is present (62% when retinal microaneurysms with blot hemorrhages, hard exudates, IRMA, or cotton-wool spots were present and 100% when proliferative retinopathy was present) suggests that further medical evaluation to diagnose diabetes mellitus may be beneficial.

Our findings confirm the previous relationship between high blood pressure and the presence of microaneurysms, blot hemorrhages, or signs of more severe nonproliferative retinopathy.[10-12,18,58,59] In the nondiabetic Beaver Dam population, 11% of those with systemic hypertension had retinopathy present, compared with 6% of those without hypertension. The highest frequency of retinopathy was found in people treated with antihypertensive medications (15%) whose blood pressure was poorly controlled. No other population-based prevalences of retinopathy in nondiabetic hypertensive groups are available for comparison.

The predictive value for hypertension was 45% when only microaneurysms were found and 48% when only blot hemorrhages were found. The predictive value of these lesions for hypertension in nondiabetic subjects in the Framingham Eye Study was 74% (14 of 19). The presence of these lesions in people with hypertension may carry ominous consequences if the high blood pressure is not treated.[11,60,61] Breslin and associates[60] studied hypertensive Mayo Clinic patients in a period prior to the widespread use of antihypertensive medications. They found that patients with

retinopathy and hypertension had a significantly poorer 10-year survival rate (those with only retinal hemorrhages, without exudates, 20%; those with retinal hemorrhages and exudates, 18%) than an age- and sex-matched normotensive population (86%). This is consistent with some[10,11,62] but not all[13,58,63] earlier observations by others of increased cardiovascular disease and stroke associated with retinopathy in hypertensive patients. If poorer survival in persons with hypertension is related to an increased risk of developing cardiovascular disease and stroke, then the finding of retinopathy in nondiabetic hypertensive persons may be another marker of severity of hypertension over time, rather than casual blood pressure measurements alone. These data suggest the need for closer monitoring of the blood pressure and examination of the fundus of hypertensive nondiabetic persons with retinopathy. Persons with uncontrolled hypertension and retinopathy may be in need of more intensive medical intervention to control blood pressure.

The presence of retinal blot hemorrhages, microaneurysms, or more severe signs of nonproliferative retinopathy in persons without diabetes may also be a sign of atherosclerotic disease affecting retinal blood flow. These signs have been reported in eyes of persons with venous stasis retinopathy secondary to occlusion of the internal carotid artery.[19,20] This is supported by the finding in the Beaver Dam Eye Study of the strong relationship between the presence of retinal cholesterol emboli and retinal microaneurysms or blot hemorrhages. Other population-based epidemiologic studies that measure carotid patency and flow and use fundus photography, such as the Atherosclerosis Risk in Communities Study, should permit assessment of the predictive value of these retinal lesions for atherosclerotic vascular disease.[64]

The inverse relation between aspirin and retinal microaneurysms found in the nondiabetic group suggests a possible protective effect of aspirin. In the Beaver Dam Eye Study the reason for aspirin use was not ascertained. It is possible that those using aspirin were taking it to prevent cardiovascular disease; and that its use provided "protection" against progression of atherosclerotic carotid artery and the development of retinopathy.[65,66]

While hypertension was common to persons with either retinal blot hemorrhages or retinal microaneurysms, there were differences between persons with either lesion. Those without diabetes with blot hemorrhages were older and were more likely to be taking an anticoagulant medication or to be taking aspirin (although these relationships were of borderline significance). It is possible that the blot hemorrhages were the result of the anticoagulant effect. However, the hemorrhages may also be a result

of ischemic changes secondary to atherosclerotic carotid artery disease, for which these medications might have been prescribed. Nondiabetic persons with higher serum glucose levels were more likely to have retinal microaneurysms present and, when present, to have more of them. This may have resulted from misclassification of persons with diabetes as not having diabetes. It is unlikely due to the presence of impaired glucose tolerance, because recent studies have failed to demonstrate an increased risk of retinopathy in the presence of this condition.[56,67]

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 relationships. For example, we found no relationship between smoking behavior and the presence of the retinal lesions. If nondiabetic persons in the population who smoked and who had retinopathic lesions present 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 likely that the association of blot hemorrhages and anticoagulant medications or aspirin may have been a result of increased risk of hemorrhage from these medications; however, the initiation of anticoagulant treatment may have been in response to finding retinal blot hemorrhages in symptomatic persons with atherosclerotic carotid artery disease.

Second, the retinal lesions might have been present as a result of conditions in nondiabetic persons that were not asked about in the study, such as acquired immune deficiency syndrome, disseminated lupus erythematosus, and aplastic anemia. However, these conditions are very rare in this population and would not be expected to account for the frequency of the retinopathic lesions found in the nondiabetic group.

Third, misclassification of diabetes status may have occurred. Diabetes diagnosis was based on history, doctors' records, specific medication use, and blood glucose and glycosylated hemoglobin values at the time of the examination. Persons who did not fit either definition (having or not having diabetes) were considered to be "diabetes suspects" and were not included in the analyses. This was done to reduce the possibility of misclassification regarding diabetes status. However, if persons with diabetes were misclassified as not having diabetes, it could lead to an overestimate of the prevalence of retinopathy in the nondiabetic population. This might, in part, account for the association of blood glucose and retinal microaneurysms in the nondiabetic group. It is more likely that people with impaired glucose tolerance, a more common condition in this age-group, and more difficult to detect, would be included in the non-

diabetic group. However, recent studies have shown that this group has a risk of retinopathy similar to those without diabetes.[55,56] Misclassification of some normotensive persons as hypertensive is also possible, because the classification was based, in part, on three measurements of the blood pressure during a single examination. This type of misclassification would probably weaken the significant relationship found between hypertensive status and the presence of retinopathy in nondiabetic persons.

Fourth, a potential bias due to selective recall is possible, but probably unlikely. Most persons were unaware of the end point, retinopathy, which was asymptomatic and determined objectively by masked gradings of fundus photographs.

Fifth, the sample size may have limited the evaluation of relationships between relatively rare conditions such as retinal cholesterol emboli, which may appear and disappear very rapidly, and the presence of retinopathy. These relationships might be best studied using a case-control design.

CONCLUSIONS

This study provides precise estimates of the prevalence of retinopathy across a wide age range in persons without diabetes. The findings suggest that retinopathy is common, affecting 7.8% of the nondiabetic population. Retinal microaneurysms or blot hemorrhages in the absence of other, more severe signs of nonproliferative retinopathy are poor predictors of diabetes mellitus. However, in nondiabetic persons they were associated with increased blood pressure, retinal cholesterol emboli, and other systemic factors.

REFERENCES

1. Duke-Elder S, Dobree JH: Diseases of the retina, in *System of Ophthalmology*, Vol 10. St Louis, CV Mosby, 1967.
2. James WA: Historical aspects of diabetic retinopathy, in EA Friedman, FA L'Esperance (eds): *Diabetic Renal-Retinal Syndrome*. New York, Grune & Stratton, 1950, pp 27-42.
3. Gass JDM: *Stereoscopic Atlas of Macular Diseases*, 3rd ed. St Louis, CV Mosby, 1987.
4. Wise GN, Dollery CT, Henkind P: *The Retinal Circulation*. New York, Harper & Row, 1971.
5. Juler HE: *A Handbook of Ophthalmic Science and Practice*. Philadelphia, Henry Lea's Son & Co, 1884, chap 7.
6. Ballantyne AJ, Loewenstein A: The pathology of diabetic retinopathy. *Trans Ophthalmol Soc UK* 1943; 63:95-115.
7. Friedenwald JS: Diabetic retinopathy. *Am J Ophthalmol* 1950; 33:1187-1189.
8. Davis MD, Norton EWD, Myers FL: The Airlie Classification of diabetic retinopathy, in MF Goldberg, SL Fine (eds): *Symposium on the Treatment of Diabetic Retinopathy*. Arlington, VA, US Dept of Health, Education and Welfare, 1969, pp 7-37; PHS Publication No. 1890.

9. Early Treatment Diabetic Retinopathy Study Research Group: Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS Report No. 12. *Ophthalmology* 1991; 98:823-833.
10. Friedenwald H: Pathological changes in the retinal blood-vessels in arterio-sclerosis and hypertension. *Trans Ophthalmol Soc UK* 1930; 50:452-531.
11. Keith NM, Wagener HP, Barker NW: Some different types of essential hypertension: Their course and prognosis. *Am J Med Sci* 1939; 197:332-343.
12. Wagener HP, Clay GE, Gipner JF: Classification of retinal lesions in the presence of vascular hypertension. *Trans Am Ophthalmol Soc* 1947; 45:57-73.
13. Bechgaard P, Porsaa K, Vogelius H: Ophthalmological investigations of 500 persons with hypertension of long duration. *Br J Ophthalmol* 1950; 34:409-424.
14. Wexler D, Branower G: Retinal capillary lesions in malignant hypertension. *Arch Ophthalmol* 1950; 44:539-548.
15. Kirkendall WM, Armstrong ML: Vascular changes in the eye of the treated and untreated patient with essential hypertension. *Am J Cardiol* 1962; 9:663-668.
16. van Buchem FSP, Heuvel-Aghina JWM, Heuvel JEA: Hypertension and changes of the fundus oculi. *Acta Med Scand* 1964; 176:539-548.
17. Svärdsudd K, Wedel H, Aurell E, et al: Hypertensive eye ground changes: Prevalence, relation to blood pressure and prognostic importance. *Acta Med Scand* 1978; 204:159-167.
18. Walsh JB: Hypertensive retinopathy: Description, classification, and prognosis. *Ophthalmology* 1982; 89:1127-1131.
19. Hedges TR: Ophthalmoscopic findings in internal carotid artery occlusion. *Am J Ophthalmol* 1963; 55:1007-1012.
20. Kearns TP, Hollenhorst RW: Venous-stasis retinopathy of occlusive disease of the carotid artery. *Mayo Clin Proc* 1963; 38:304-312.
21. Sarkies NJC, Shilling JS, Russel RWR: Fluorescein angiography in carotid disease. *Trans Ophthalmol Soc UK* 1986; 105:489-493.
22. Friedman AN: The retinal lesions of acquired immune deficiency syndrome. *Trans Am Ophthalmol Soc* 1984; 82:447-491.
23. Ashton N: Retinal micro-aneurysms in the non-diabetic subject. *Br J Ophthalmol* 1951; 35:189-212.
24. Cogan DG: Development and senescence of the human retinal vasculature. *Trans Ophthalmol Soc UK* 1963; 83:465-489.
25. Aurell E, Tibblin G: Hypertensive eye-ground changes in a Swedish population of middle-aged men. *Acta Ophthalmol* 1965; 43:355-361.
26. Leibowitz HM, Krueger DE, Maunder LR, et al: The Framingham Eye Study monograph. *Surv Ophthalmol* (Suppl) 1980; 24:335-610.
27. Nielsen NV: The normal fundus fluorescein and the normal fundus photograph. *Acta Ophthalmol* (Suppl) 1986; 180:1-30.
28. Sugi K: Studies on the pathological changes in the retinal vessels of human eyes, using the trypsin digestion method. *Jpn J Ophthalmol* 1966; 10:252-266.
29. Campbell JA, Palit CD: Total digit dialing for a small area census by phone, in *American Statistical Association*. 1988 Proceedings of the Section on Survey Research Methods, 1988, pp 549-551.
30. Linton KLP, Klein BEK, Klein R: The validity of self-reported and surrogate-reported ocular disease in the Beaver Dam Eye Study. *Am J Epidemiol* 1991; 134:1438-1446.
31. Klein R, Klein BEK, Linton KLP, et al: The Beaver Dam Eye Study: Visual acuity. *Ophthalmology* 1991; 98:1310-1315.
32. Hypertension Detection and Follow-up Program Cooperative Group: The hypertension detection and follow-up program. *Prev Med* 1976; 5:207-215.
33. Early Treatment Diabetic Retinopathy Study: *Manual of Operations*. Baltimore, ETDRS Coordinating Center, Dept of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 1985, chaps 12, 18.

34. Pelli DG, Robson JG, Wilkins AJ: The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci* 1988; 2:187-199.
35. Klein BEK, Klein R, Linton KLP, et al: Assessment of cataracts from photographs in the Beaver Dam Eye Study. *Ophthalmology* 1990; 97:1428-1433.
36. Klein BEK, Magli YL, Neider M, et al: Wisconsin System for Classification of Cataracts from photographs. NTIS Accession No. PB90-138306, 1990. Available from National Technical Information Service, Springfield, VA.
37. Klein BEK, Davis MD, Segal P, et al: Diabetic retinopathy: Assessment of severity and progression. *Ophthalmology* 1984; 91:10-17.
38. Klein R, Klein BEK, Magli YL, et al: An alternative method of grading diabetic retinopathy. *Ophthalmology* 1986; 93:1183-1187.
39. Klein R, Davis MD, Magli YL, et al: *Wisconsin Age-Related Maculopathy Grading System*. Madison, Dept. of Ophthalmology, University of Wisconsin School of Medicine, 1991. US Dept of Commerce. Available from: National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161. Accession #PB91-184267/AS.
40. ———: The Wisconsin age-related maculopathy grading system. *Ophthalmology* 1991; 98:1128-1134.
41. Stein MW: D-glucose determination with hexokinase and glucose-6-phosphate dehydrogenase, in HC Bergmeyer (ed): *Methods of Enzymatic Analysis*. New York, Academic Press, 1963, p 177.
42. Klenk DC, Hermanson GT, Krohn RI, et al: Determination of glycosylated hemoglobin by affinity chromatography: Comparison with colorimetric and ion-exchange methods, and effects of common interferences. *Clin Chem* 1982; 28:2088-2094.
43. Allain CC, Poon LS, Chan CGS, et al: Enzymatic determination of total serum cholesterol. *Clin Chem* 1974; 20:470-475.
44. Lopes-Virella MF, Stone P, Ellis S, et al: Cholesterol determination in high-density lipoproteins separated by three different methods. *Clin Chem* 1977; 23:882-884.
45. Koepke JA, Protextor TJ: Quality assurance for multichannel hematology instruments: Four years' experience with patient mean erythrocyte indices. *Am J Clin Pathol* 1981; 75:28.
46. Bessmen JD, Williams LJ, Gilmer PR: Mean platelet volume. *Am J Clin Pathol* 1981; 76:289-293.
47. SAS Users Guide: *Statistics*, version 5. Cary, NC, SAS Institute, 1985, pp 403-432, 795-800.
48. Mantel N: Chi-square tests with one degree of freedom: Extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc* 1963; 58:690-700.
49. Diabetic Retinopathy Study Research Group: Report 7: A modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 1981; 21:210-226.
50. Klein R, Klein BEK, Neider MW, et al: Diabetic retinopathy as detected using ophthalmoscopy, a nonmydriatic camera and a standard fundus camera. *Ophthalmology* 1985; 95:485-491.
51. Ashton N: Diabetic micro-angiopathy. *Adv Ophthalmol* 1958; 8:1-84.
52. Pettit DJ, Knowler WC, Lisse JR, et al: Development of retinopathy and proteinuria in relation to plasma glucose concentration. *Lancet* 1980; 2:1050-1052.
53. Kornerup T: Studies in diabetic retinopathy: An investigation of 1,000 cases of diabetes. *Acta Med Scand* 1955; 153:81-101.
54. Nilsson SE, Nilsson JE, Frostberg N, et al: The Kristianstad Survey II. *Acta Med Scand* (Suppl) 1967; 469:1-42.
55. Klein R, Klein BEK, Moss SE, et al: The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; 102:527-532.
56. Klein R, Barrett-Connor ED, Blunt BA, et al: Visual impairment and retinopathy in people with normal glucose tolerance, impaired glucose tolerance and newly diagnosed NIDDM. *Diabetes Care* 1991; 14:914-918.

57. Lorentzen SE: Micro-aneurysms of unknown nature observed ophthalmoscopically. *Acta Ophthalmol* 1959; 37:279-289.
58. Dimmitt SB, Eames SM, Goslin P, et al: Usefulness of ophthalmoscopy in mild to moderate hypertension. *Lancet* 1989; 1:1103-1106.
59. Ashton N: The eye in malignant hypertension. *Trans Am Acad Ophthalmol Otolaryngol* 1972; 76:17-40.
60. Breslin DJ, Gifford RW Jr, Fairbairn JF II: Essential hypertension: A twenty-year follow-up study. *Circulation* 1966; 33:87-97.
61. ———: Prognostic importance of ophthalmoscopic findings in essential hypertension. *JAMA* 1966; 195:335-338.
62. Gunn M: An ophthalmoscopic evidence of general arterial disease. *Trans Ophthalmol Soc UK* 1898; 18:356-381.
63. Pickering GW: *High Blood Pressure*. London, Churchill Livingstone, 1955.
64. Heiss G, Sharett AR, Barnes R, et al: Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC Study. *Am J Epidemiol* 1991; 134:250-256.
65. Candelise L, Landi G, Perrone P, et al: A randomized trial of aspirin and sulfin pyrazone in patients with TIA. *Stroke* 1982; 13:175-179.
66. Barnett HJM: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978; 299:53-59.
67. McCartney P, Keen H, Jarrett RJ: The Bedford Survey: Observations on retina and lens of subjects with impaired glucose tolerance and in controls with normal glucose tolerance. *Diabete Metab* 1983; 9:303-305.

APPENDIX*

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 ever said you had a *heart attack* (myocardial infarction, or coronary thrombosis, or coronary occlusion)?
5. Did a doctor ever tell you that you 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?
7. Have you ever had *migraine* headaches (with vomiting or light flashes, or severe enough to keep you in bed)?

Hypertension

8. 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)?
9. Are you now taking water pills (diuretics)?

Emphysema

10. Have you ever been told by a doctor that you have had emphysema?

Surgery

Did you have any of the following surgery?

11. Surgery to the brain or neck to correct or prevent a stroke?
12. Surgery on your heart?
13. Was it a coronary bypass?
14. Have you had an amputation of an arm or leg, toe or finger?
15. 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?

16. Digitalis, Digoxin, or Lanoxin for your heart?
17. Nitroglycerin, Nitro-Bid, Isordil, etc, for angina?
18. Aspirin or aspirin products regularly, that is at least twice a week for more than 3 months?

Cigarette Smoking

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

Alcohol Consumption

24. Have you had any beer or ale in the past month?
25. Have you had any beer (ale) during the past year?
26. During the average week how many 12-oz bottles or cans of beer do you usually drink?
27. Have you had any wine in the past month?
28. Have you had any wine during the past year?
29. During the average week how many 4-oz glasses of wine do you usually drink?
30. Have you had any liquor in the past month, that is, things like brandy, whiskey, vodka, gin, schnapps, cocktails, or liqueurs?
31. Have you had any liquor in the past year?
32. During the average week, how many $1\frac{1}{2}$-oz glasses of liquors do you usually drink?
33. Was there a time in your life when you drank alcoholic beverages?

34. Has there been a period in your life when you drank quite a bit more than you do now?
35. Has there ever been a time in your life when you drank four or more alcoholic beverages daily?

Income

36. Which of these income groups best represents your total household personal income (including your husband's or wife's income) for the past year? Please include all income, such as from employment, rent, social security, disability, or retirement that you may be receiving.

Education

37. What was the highest year of school or college you completed?

*Partial list used for analyses.