The Epidemiology of Eye Disease: From Glycemia to Genetics
The Friedenwald Lecture

Ronald Klein and Barbara Eden Kobrin Klein

Shortly after the invention of the ophthalmoscope by Helmholz in 1851, characteristics defining diabetic retinopathy were described. In 1884, retinopathy was thought to be rare, with a very unfavorable prognosis for vision. Its treatment at that time was entirely directed toward the diabetes. Harry Friedenwald, Jonas Friedenwald’s father, attributed retinopathy to diabetes However, in 1930, in the Doyne Memorial Lecture, he attributed retinopathy to arteriosclerosis, high blood pressure, and high cholesterol, not hyperglycemia. He joined a growing group of clinicians in the period after the discovery of insulin who had come to a similar conclusion based on their observation of retinopathy in some diabetic patients despite seemingly good glycemic control and the absence of retinopathy in those with poor glycemic control. Jonas Friedenwald, 20 years later in his Francis Proctor Lecture, described a series of histopathological studies that demonstrated that lesions characterizing retinopathy were specific to diabetes and distinguishable from retinopathy of atherosclerosis or malignant hypertension. However, he wrote: “It is clear that the retinopathy bears no relation to the blood sugar. . . .” By 1979 when we began our research, diabetic retinopathy was considered the leading cause of legal blindness in persons 25 to 74 years of age. The relationship between hyperglycemia and retinopathy had still not been resolved. Kelly West, in his 1978 textbook, Epidemiology of Diabetes and Its Vascular Lesions, wrote: “The extent to which the level of hyperglycemia determines the risk of retinopathy is not at all clear. This is the most important issue at hand and deserves high priority in epidemiologic research.”

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was funded by the National Eye Institute in 1979 (R01 EY03083), with primary aims to (1) describe the prevalence and severity of retinopathy and visual loss in persons with diabetes and their relationship to other systemic complications and mortality; (2) quantitate the association of risk factors with retinopathy; and (3) provide information on healthcare delivery and quality of life in persons with diabetes. The study design and methods have been described in detail in previous reports. In brief, 452 of the 457 physicians who provided primary care to diabetic patients in an 11-county area in southern Wisconsin (Health Service Area 1) participated in the study. The tenets of the Declaration of Helsinki were followed, institutional human experimentation committee approval was granted, and informed consent was obtained from each subject. The 452 physicians kept lists of all their diabetic patients for whom they provided primary care from July 1, 1979, to June 30, 1980. During this 1-year period, 10,135 diabetic patients were identified. A sample of 2990 persons was selected for the baseline examination. This sample was composed of two groups. The first consisted of all patients with diabetes diagnosed before 30 years of age who took insulin (1210 patients); this group will be referred to as “younger onset.” The second group consisted of a probability sample of 1780 persons of the 5431 patients who met the eligibility criteria of having diabetes diagnosed at 30 years of age or older and who had the diagnosis confirmed by a casual or a postprandial serum glucose level of at least 11.1 mM or a fasting serum glucose level of at least 7.8 mM on at least two occasions. This group will be referred to as “older onset.” The latter group was stratified by duration of disease (<5 years, 576 persons; 5–14 years, 579 persons; and >15 years, 625 persons). Of these, 824 were taking insulin and 956 were not.

Of the 2990 eligible patients, 2366 (79.1%) participated in the baseline examination from 1980 through 1982 (Fig. 1). The younger-onset cohort was re-examined in 1984 to 1986, 1990 to 1992, 1994 to 1996, and 2000 to 2002, whereas the older-onset cohort was re-examined in 1984 to 1986 and 1990 to 1992 and interviewed in 1994 to 1996 (Fig. 1). The main reason for nonparticipation was death. Comparisons between participants and nonparticipants have been presented elsewhere. Stereoscopic photographs of the Diabetic Retinopathy Study’s seven standard fields were taken of each eye. Objective masked grading of retinopathy according to standard protocols assured reproducible assessment and classification of the severity of retinopathy. In the WESDR, 71% of younger-onset persons had retinopathy, 23% had proliferative retinopathy, and 10% had Diabetic Retinopathy Study high-risk characteristics for severe visual loss (DRS-HRC). Data from the WESDR also showed that diabetic retinopathy was infrequent before puberty. When adjustment was made for other factors, such as duration of diabetes, glycemic control, and blood pressure, younger-onset subjects who were postmenarchal in the WESDR were 3.2 times as likely to have diabetic retinopathy as those who were premenarchal. In the older-onset group, 50% had retinopathy, 5% had proliferative retinopathy (PDR), and 2% had DRS-HRC. Six percent of the younger- and 5% of the older-onset subjects had clinically significant macular edema (CSME). Based on these data, it was estimated that the burden of proliferative retinopathy with HRC and/or CSME in the 5.8 million persons with known diabetes in the United States was approximately 400,000.

In younger- and older-onset persons, both the frequency and severity of retinopathy (Fig. 2) and CSME (Fig. 3) increased with increasing duration of diabetes. In the younger-onset group, the prevalence of retinopathy during the first 5 years after the diagnosis of diabetes was 14%, and in all cases, it was
In contrast, in younger-onset persons with diabetes for 20 or more years, 53% had signs of proliferative retinopathy, and 11% had signs of CSME. After diagnosis of diabetes, retinopathy was more frequent in the older-onset groups than in the younger-onset group (Fig. 2). In the first 5 years after diagnosis of diabetes, 33% of the older-onset group had retinopathy, 2% had proliferative retinopathy (Fig. 2), and 3% had CSME (Fig. 3). However, after 20 years or more of diabetes, fewer older-onset people had proliferative retinopathy (22% versus 53%) than did younger-onset people. These findings, in part, provided the rationale for the development of guidelines for dilated eye examination by eye doctors experienced in detection and treatment of diabetic retinopathy: at the time of diagnosis in older-onset persons and yearly thereafter and after 5 years’ duration of diabetes in younger-onset persons and yearly thereafter.

In the WESDR, only 67% of persons with proliferative retinopathy with DRS-HRC for severe visual loss or CSME had been seen by an ophthalmologist within 2 years of the study examination. The frequency of having an eye examination in the past year was associated with having health insurance—specifically, with coverage of costs of an eye examination in both younger- and older-onset persons (Fig. 4). Moreover, the reasons most frequently given by study subjects for not having an eye examination were that they had no problems with their eyes, were too busy, or were not told they needed an eye examination (Figs. 5, 6). These observations had important healthcare implications. They provided the rationale for the development of the National Eye Institute’s National Eye Health Education Program to educate diabetic patients and their doctors on the need for dilated eye examinations. They also identified lack of health insurance and inability to afford such care as major barriers for receiving care for diabetic patients in the United States at the time.

One of the main aims of the WESDR was to address the question of whether hyperglycemia is related to the incidence and progression of diabetic retinopathy. This question remained unanswered when we began our study. Data from the WESDR showed that glycosylated hemoglobin was associated with the incidence and progression of diabetic retinopathy, progression to PDR, and the incidence of CSME. Furthermore, the incidence and progression (Fig. 7) in each quartile of glycosylated hemoglobin was similar in both younger- and older-onset participants. This suggested that it was the level of glycemia and not the type of diabetes that is important in determining the risk of progression of retinopathy—an important finding, in that many persons with older-onset diabetes were thought to have less severe diabetes, and so hyperglycemia was often left poorly treated. The relationship of glycosylated hemoglobin to progression of retinopathy was found at any stage of retinopathy before the proliferative phase and at any duration of diabetes. This suggested that there is no “point of no return”—that is, lowering levels of glycosylated hemoglobin at any duration of diabetes or at any severity of nonproliferative retinopathy would reduce the risk of progression. In addition, there was no evidence that there is a threshold level of glycosylated hemoglobin below which lowering it further fails to have a beneficial effect on the risk of progression of
retinopathy. In the WESDR, in addition to the relation of glycemia to retinopathy, a 1% increase in glycosylated hemoglobin was also associated with a 25% to 40% higher risk of incident visual loss, gross proteinuria, lower-extremity amputation, and ischemic heart disease death in both the younger- and older-onset groups.\textsuperscript{33–35}

However, epidemiologic studies such as the WESDR cannot determine whether reduction of glycosylated hemoglobin would result in lowered risk of progression of retinopathy and other complications with an acceptable risk–benefit ratio. These questions were addressed by two large randomized therapeutic trials of metabolic control: the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS). These prospective clinical trials demonstrated the efficacy of intensive treatment of diabetes in preventing diabetic retinopathy and other microvascular complications.\textsuperscript{36,37} The DCCT data suggested that if intensive therapy for the 120,000 persons with type 1 diabetes in the United States who met DCCT criteria could maintain a hemoglobin A\textsubscript{1c} level of 7.2% for life, there would be a gain of 920,000 years of sight.\textsuperscript{38} However, the WESDR and other community-based studies have suggested that few persons with type 1 diabetes are able to achieve this level of glycemic control (Klein R, unpublished data, 2005).\textsuperscript{39}

Data from the WESDR have shown associations of high blood pressure, lipid levels, and the presence of gross proteinuria with retinopathy and are published elsewhere.\textsuperscript{19,40–44} In summary, the WESDR has provided population-based estimates of the prevalence and incidence of diabetic retinopathy. The associations of glycemia and other traditional risk factors with the incidence and progression of retinopathy have been quantitated, and the findings have shown the need for better general medical and eye care delivery for persons with diabetes. These findings have resulted in the development of guidelines and health education programs directed at prevention, and earlier treatment, of diabetic retinopathy. We have begun the 25-year follow-up of the younger-onset cohort, with the primary goals being to describe the long-term co-incidence and progression of complications, measure nontraditional risk factors (e.g., markers of inflammation, endothelial dysfunction, and cellular adhesion), and assess the effect of retinopathy and other complications on quality of life and depression.

We explored many other eye conditions of aging using epidemiologic approaches. Some of these were also interests of Jonas Friedenwald and others and grew out of our own experiences in ocular manifestations of chronic systemic diseases and in other intrinsic eye conditions. The Beaver Dam Eye Study was designed to investigate these conditions in a representative adult population. This study was designed in the 1980s and was funded by the National Eye Institute, to begin in 1987. Critical to the success of the study was the census of the population of the city and township of Beaver Dam, Wisconsin, that was performed from 1987 to 1988.\textsuperscript{45} This was essential because valid prevalence and incidence estimates rely on the accurate enumeration of the population at risk. The census gave an accurate count of the population and, in addition, confirmed addresses for follow-up contact and scheduling as
well as providing some information about participants and nonparticipants in the study.

Beginning in March 1988, we invited all 5924 enumerated persons in the target age range (43–84 years of age) to participate in the baseline study evaluation. There were 4926 persons who completed the baseline examination. Questionnaire data were obtained for many additional participants.

At the time of the prevalence (baseline) examination, nuclear cataract was found in 17%, cortical cataract in 16%, and posterior subcapsular cataract in 5% of the population (Table 1). Late stages of age-related macular degeneration (AMD) were found in 2% and early stages in approximately 16% of the population. Definite glaucoma was found in 2% and probable glaucoma in an additional 2%. No age group was spared, and there were consistent increases in prevalence with increasing age for all these conditions. Best corrected visual acuity was obtained at the baseline examination to estimate visual function of the population. Approximately 5% of the population had any visual impairment (vision 20/40 or poorer in the better eye), and 0.5% had severe impairment (20/200 or worse in the better eye). However, as anticipated, the frequency of these functional endpoints was uncommon in the youngest age group and increased with increasing age (Table 1).

Even when persons with advanced cataract or late stages of AMD were not included, there was a change in visual function with age. We found other ocular conditions to be relatively common, such as diabetic retinopathy (10.4% of those with diabetes), retinopathy in nondiabetic persons (8% of those without diabetes; those with diabetes had on average more severe retinopathy), and refractive errors (myopia: 28% in women, 24% in men; hyperopia: 49% in women and men). In addition to specific ocular conditions, we have collected data on important ocular traits. In particular, we have quantitative measures of intraocular pressure, optic disc and cup diameters, retinal arteriole and venule diameters, and lens thickness. More recently, we have measured axial length, anterior chamber depth, and corneal curvature. These measurements have permitted the description of population distributions of these characteristics and have facilitated further investigations of the relationship of these characteristics to ocular and systemic diseases.

Another exciting aspect of the Beaver Dam Eye Study has been investigating the possible role of genetics in the ocular conditions and traits that we have documented. The path to this avenue of investigation stems from the family histories that we obtained at the baseline study evaluations. We asked study participants the names and ages of their siblings and parents. As it turned out, many of these family members were also part of the Beaver Dam Eye Study sample (they lived in the Beaver Dam Eye Study catchment area). Initially we were able to...
identify 564 sibships. Based on these sibships and the phenotype data, we found that there was evidence of genetic effects on nuclear sclerosis,\textsuperscript{54} cortical cataract,\textsuperscript{55} and age-related maculopathy.\textsuperscript{56} These findings were followed up by a genome-wide scan in 325 persons in sibships who manifested these conditions with a specified degree of severity. For AMD, 10 regions suggestive of linkage were observed on chromosomes 3, 5, 6, 12, 15, and 16. After further fine-mapping, we found that a region on chromosome 12 near D12S346 showed the strongest indication of linkage, and three other regions on chromosomes 5, 6, and 15 were also appropriate for mapping.\textsuperscript{57} Data from that subset for cortical cataract indicated that seven different regions on chromosomes 1, 2, 4, 6, and 15 and 16 were suggestive of linkage. After fine-mapping, significant evidence of linkage remained on chromosome 6.\textsuperscript{58}

We were subsequently able to expand the pedigrees based on interviews. These pedigrees included siblings, parents, first cousins, and avuncular relationships. To be a member of a pedigree, an individual had to have been eligible to be a participant in the Beaver Dam Eye Study. We identified 2785 persons in 602 families in the population. A sample of the family diagrams is shown in Figure 8. Family aggregation of intraocular pressure,\textsuperscript{59,60} cup-to-disc ratio,\textsuperscript{59} refractive error,\textsuperscript{61} nuclear sclerosis,\textsuperscript{62} cortical opacities, AMD, lens thickness, retinal arteriole, and venule diameters\textsuperscript{63} were all significant. The heritability of several of the traits is shown in Figure 9. A genome-wide scan of the entire family set in Beaver Dam has been completed, and these data are currently being analyzed. Several regions appear to be linked to each of the traits, and there appear to be overlapping signals in many cases. Further laboratory analyses are planned for finer mapping and further linkage analyses for most traits, to facilitate association studies for a few of these traits. The underlying concept for the etiology of these complex diseases and traits is that they result from the complement of vulnerability genes, some with time-dependent expression, and environmental exposures at critical times. Further, there may be variability in time or expression of a phenotype. Aside from the investigation of potential causal inference of these studies, they have also provided clinical insights. For example, we observed that if an older sibling had exudative macular degeneration at baseline, his or her younger sibling was approximately 10 times as likely to have the same lesion develop 5 years later than those whose older siblings did not have this condition (Table 2). If the older sibling had a specific cataract type, the younger sibling was also at increased risk of the same lesion 5 years later, but the odds were much less than for exudative macular degeneration.\textsuperscript{59} The odds of development of all these conditions increase when the sample is limited to nonsmokers, suggesting that smoking, an environmental risk factor of significant importance for macular degeneration and nuclear cataract, somewhat obscures the genetic effects on these legions.

Our approach to understanding both disease distribution and the association of those diseases with risk indicators and potential causal risk factors is to perform carefully designed observational studies (Fig. 10). The growth of understanding of disease causation is a succession of ever-evolving steps in a cycle wherein well-designed studies incorporate accurate measurement of the disease or trait. Care is also taken to define risk factors previously identified in the laboratory or in other studies in humans. Next, appropriate and rigorous statistical analyses of the findings, including the evaluation of interactive effects when possible, are necessary. The analyses may enable us to characterize the disease and define categories further and may, in turn, facilitate the identification of novel potential risk factors. In time, other studies will follow on these to refine phenotypes and to consider new risk factors. In this way, we expand our knowledge and understanding of diseases that plague us and begin to develop potential preventive strategies.

### References


### Table 2. Odds of Incident Age-Related Ocular Disorders 5 Years after Similar Lesion Is Found in Older Sibling

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exudative AMD</td>
<td>10.32</td>
<td>0.83–128.58</td>
</tr>
<tr>
<td>Nuclear cataract</td>
<td>1.65</td>
<td>0.91–2.99</td>
</tr>
<tr>
<td>Cortical cataract</td>
<td>1.62</td>
<td>0.92–2.85</td>
</tr>
<tr>
<td>Posterior subcapsular cataract</td>
<td>1.95</td>
<td>0.48–7.95</td>
</tr>
</tbody>
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* Odds ratio (OR) from generalized estimating equations model adjusted for age of each sibling. CI, confidence interval.

† 0.05 < P < 0.10.


