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Historical Perspectives on the Management of Macular Degeneration, Diabetic Retinopathy, and Retinal Detachment

Personal Reminiscences

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We were challenged and delighted when Dr. Sharon Solomon, guest editor of this Retina Supplement, invited us to reminisce about caring for patients with common retinal disorders before there was access to the diagnostic and therapeutic tools that are readily available today. We agreed to confine our remarks to 3 common, but serious, conditions: age-related macular degeneration (Dr. Fine), diabetic retinopathy (Dr. Goldberg), and retinal detachment (Dr. Tasman). Each of us completed our ophthalmology training about half a century ago. At that time, a patient who received any 1 of the 3 diagnoses was at considerable risk of severe and irreversible loss of vision. Most readers today will have little if any experience in evaluating and treating such patients without access to a plethora of diagnostic and therapeutic technologies, including intravenous fluorescein angiography, laser photocoagulation, optical coherence tomography, ophthalmic ultrasound, angioinhibitory drugs, vitrectomy, intraocular gases, and many others. We are both pleased and privileged that each of us has practiced our profession long enough to enjoy what the enormous technological developments of the past half century, as described in this article, have meant for our patients. *Ophthalmology 2016;123:S64-S77 © 2016 by the American Academy of Ophthalmology.*

Age-Related Macular Degeneration: A 48-Year Perspective

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In March 1968, I received an offer letter for a residency in ophthalmology at the University of Florida in Gainesville. I accepted the offer promptly. (Obviously this notification occurred before the beginning of the ophthalmology match.) One week later, I received a letter from Dr. Raymond Sever, a junior attending on the Retina Service, describing the large volume of patients and wide variety of pathologic features seen in each and every retina clinic. "Every day, we see two or three patients with senile macular degeneration," Sever wrote. Since I had not taken an ophthalmology elective in medical school, I had to look up "senile macular degeneration" (SMD); Sever's letter was my first exposure to the condition.

Fifteen months later, in July 1969, I began my residency. As Sever had stated, there were patients with macular degeneration in every retina clinic. Typically, the patient scheduled an appointment when there was sudden vision loss, often in the second eye and usually the result of a macular hemorrhage (Fig 1). After I had presented the patient, the senior retina attending, Dr. Melvin Rubin, would comment, "This is a typical Kuhnt-Junius lesion." Back to the library to learn that Junius and Kuhnt had described hemorrhagic macular lesions in 1926.[1] Thus, there was a name for the condition, but nothing could be done to ameliorate the problem.

So Kuhnt-Junius or senile disciform macular degeneration was what we called it. Only 2 years earlier, in 1967, Gass had reported that fundus fluorescein angiography (FA) could document the presence of subretinal neovascularization as the immediate underlying cause of the exudative macular detachment.[2] However, FA was not used routinely at that time to evaluate patients with exudative maculopathies. The most frequent indication for FA was in postoperative cataract patients; the purpose was to identify the presence of cystoid macular edema, or what then was called Irvine-Gass syndrome, as a possible explanation for impaired postoperative acuity.[3] Photocoagulation had not yet entered the therapeutic armamentarium to treat leakage in patients with exudative maculopathy, the one exception being central serous chorioretinopathy with focal leakage outside the fovea when the submacular fluid had not resolved spontaneously by the end of 3 months.

For the patients with senile disciform macular degeneration, or what we now call neovascular age-related macular degeneration (AMD), we counseled the patient that no

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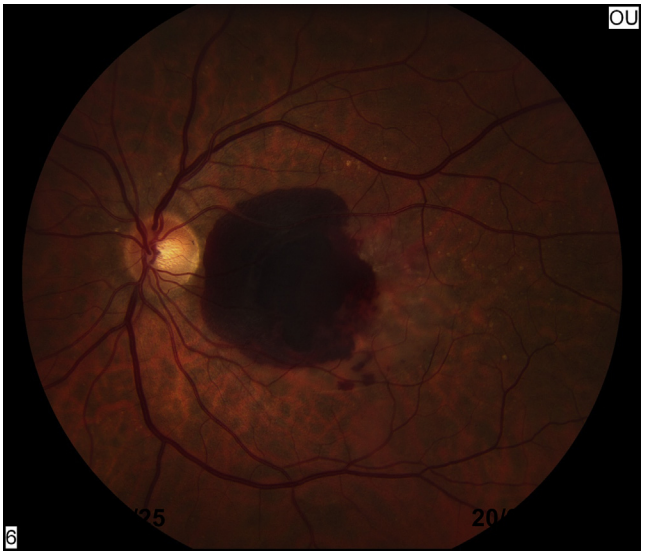

Figure 1. Fluorescein angiogram showing extrafoveal choroidal neovascularization in the left eye. Courtesy of Daniel F. Martin, MD.

effective treatment was available, reassured the patient that the condition would not lead to complete loss of vision, and referred the patient whose second eye was involved for a low-vision consultation, which typically meant a prescription for magnifying glasses. When it was the first eye that was involved, we discussed the possibility of second eye involvement, but it would be nearly a decade before the measurable risk factors for second eye involvement would be quantified and reported.

By the time I arrived at Johns Hopkins for a medical retina fellowship with Arnall Patz, MD, just over 3 years later, in September 1972, the evaluation of patients with exudative maculopathy had changed immensely. During that 3-year interval, argon laser photocoagulators had become commercially available, facilitating the slit-lamp delivery of coherent laser light to tiny areas of focal leakage in the posterior pole. As a consequence, FA was performed routinely in patients with recent vision loss resulting from exudative maculopathy (and macular edema) in an effort to determine whether potentially treatable focal leakage was present.

As is common whenever new medical technology becomes available, many investigators began performing and evaluating the outcomes of laser photocoagulation in patients with SMD and other exudative maculopathies whenever the FA disclosed an area of focal leakage outside the fovea.[4–8] (It would be several years before ophthalmologists abandoned the term *senile* in favor of AMD.) Laser courses in Baltimore, New York, and Palo Alto, California, were popular among retinal specialists and other ophthalmologists who wanted to learn about the indications for and the techniques of applying argon laser photocoagulation.

In addition to the paucity of information about treatment of AMD, there was astonishingly little information about its cause. After the Framingham Eye Study (FES) identified SMD (AMD) as the major cause of severe irreversible vision loss in the United States, interest developed in learning more about the condition.[9] In 1978, Harold Kahn, a biostatistician who worked on the FES while at the Office of Biometry and Epidemiology at the National Eye Institute and who was a visiting faculty member at the Johns Hopkins School of Hygiene and Public Health (now the Johns Hopkins Bloomberg School of Public Health), suggested to Leslie Hyman, a PhD student, that she select the epidemiology of SMD as her thesis topic. Hyman's case-control study identified a number of risk factors for the development of SMD, including older age, family history, cigarette smoking, hypertension, and reduced handgrip strength.[10,11] During that same interval, Neil and Susan Bressler, medical students working with me during an elective rotation, followed up on SMD patients with choroidal neovascularization (CNV) within the foveal avascular zone. They reported the natural history of these lesions and also described the ocular risk factors for the development of CNV in the fellow eye.[12] When they presented their findings at a research forum for medical students, a presentation that resulted in their receiving the Paul Ehrlich Award for best clinical research by Johns Hopkins medical students, the Hopkins Chief of Medicine and world-renowned geneticist, Victor McKusick, expressed astonishment that so little was known about the most prevalent cause of severe vision loss in the United States and the developed world!

After the initial report from the Diabetic Retinopathy Study (DRS) in April 1976, there was widespread recognition throughout the ophthalmic community that the randomized clinical trial was the gold standard for evaluating new treatments for major public health problems. Indeed, this recognition was almost as important as the principal finding from the DRS that pan-retinal photocoagulation had reduced by more than 50% the frequency of severe vision loss in treated versus untreated eyes with high-risk proliferative diabetic retinopathy.[13] Without question, publication of the DRS results facilitated the ophthalmic community's acceptance of many trials that would be initiated over the next several years.

Inspired by the impact of results from the DRS, I collaborated with Argye Hillis, PhD, a biostatistician, to prepare 2 proposals to assess argon laser photocoagulation in patients with extrafoveal CNV secondary to either SMD or ocular histoplasmosis (Fig 2). Eventually, these 2 proposals were merged into a single study—the Macular Photocoagulation Study—although eligibility criteria and other aspects of the protocol differed for each substudy.

Funded by the National Eye Institute in 1979, 224 patients at 12 clinical centers enrolled in the SMD portion of the Macular Photocoagulation Study over the next 3 years. In 1982, the data and safety monitoring committee recommended stopping the trial early because, after only 6 months of follow up, 60% of untreated eyes compared with 25% of laser-treated eyes had demonstrated 6 lines or more of vision loss. This outcome was reported in an expedited publication and also at a nationally attended press conference at the National Institutes of Health.[14] Unfortunately, this initial report about the benefit of argon laser treatment was to be disappointing for 2 reasons: (1) only a small proportion of SMD patients with exudative maculopathy had well-defined, extrafoveal CNV lesions and (2) there was a high