Perspective

Looking Back: Fluorescein Angiography and Optical Coherence Tomography and the First Century of the *American Journal of Ophthalmology*

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THIS PERSPECTIVE FOLLOWS AN EARLIER ARTICLE BY Feibel,[1] which reviewed the development of ophthalmic photography as seen in the first 100 years of the *American Journal of Ophthalmology* (hereafter: the *Journal*). Here I will review fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) as presented to the readers of the *Journal* over the last 100 years. As in Feibel's review, no effort has been made to analyze every article, nor is there any claim to this being a complete history of FFA and OCT. What follows is simply an attempt to show the reader some of the interesting work that has found its way into the *Journal* during that time span. The reader will appreciate the clinical orientation of these publications.

FUNDUS FLUORESCEIN ANGIOGRAPHY

THE HISTORY OF FFA IS VERY TIGHTLY INTERWOVEN WITH the *Journal*. The *Journal* has, at times, been criticized for one incident—the rejection of Alvis and Novotny's seminal 1961 paper on using photography to document the findings of FFA. I too knew this story from early on in my training. I will try to place that event in its proper perspective here, one that may well persuade the reader of the very positive influence of publications in the *Journal* on the development and use of FFA from the earliest days onward.

The first ophthalmic uses of fluorescein were summarized by Schatz and associates in 1978[2] and by Same in 1993.[3] Fluorescein, first synthesized in 1871, was used by Ehrlich 10 years later to study aqueous circulation. He injected the dye into a rabbit intravenously and within minutes saw it flowing in the anterior chamber. In 1930 it was realized that a blue filter might make the dye more visible to the observer. In 1939 Sorsby realized that seeing the dye flow through the retinal vessels in a human could be used to study various diseases.[4]

In 1958 the *Journal* published the first of 2 innovative papers, both from Stanford University. Chao and Flocks used trypan blue injected into the carotid artery of a cat.[5] They watched the flow of the dye through the retinal vasculature (Figure 1[5]; all figures in this article were previously published in the *Journal*). A stopwatch was used to time this rapid event. The authors presciently noted that fluorescein might be a better dye, and that "the study of retinal circulation time might be of value in such pathologic conditions as retinitis pigmentosa, diabetic retinopathy and macular degeneration." The paper was the first to publish a photograph of dye coursing through a retina. In 1959 the Stanford group published their follow-up paper.[6] They now used intravenously administered fluorescein and a movie camera in place of a fundus photography camera (Figure 2[6]). Again studying the cat eye, the authors could see and capture the retinal image in 6 of 10 cats studied (Figure 3[6]). The paper was the first anywhere in the ophthalmic literature to publish images of fluorescein dye in the retina. As in the prior publication, the authors noted that the technique could be useful for the study of "retinal disease on the retinal circulation." Two problems were apparent. Sometimes there was not enough light to obtain an adequate image when using cats. Two attempts to perform the study on humans failed for the same reason. The second problem was that of the complexity of the cinephotography equipment.

In 1960 the *Journal* again published an article on fluorescein, this time on humans and this time using the dye in the clinic to specifically diagnose disease. Maclean and Maumenee reported a series of patients with choroidal hemangiomas.[7] They noted the difficulty of making an accurate diagnosis and the need to differentiate this benign lesion from choroidal melanoma. Two of the 8 patients studied were examined with intravenous fluorescein. The first (seen in 1955) was studied at the slit lamp and "a dozen small spots in the central portion of the tumor fluoresced." The second patient (seen in 1958) was examined with the

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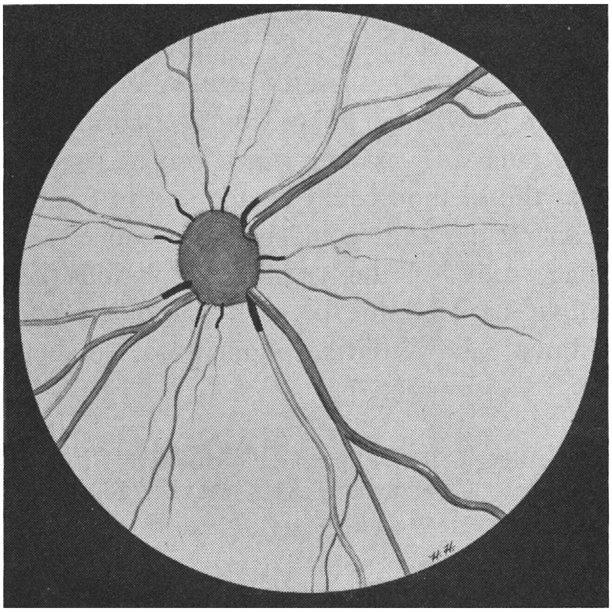

FIGURE 1. Trypan blue dye in a cat retina. [Figure previously published in Chao P, Flocks M. The retinal circulation time. *Am J Ophthalmol* 1958;46(1, part 2):8-10.]

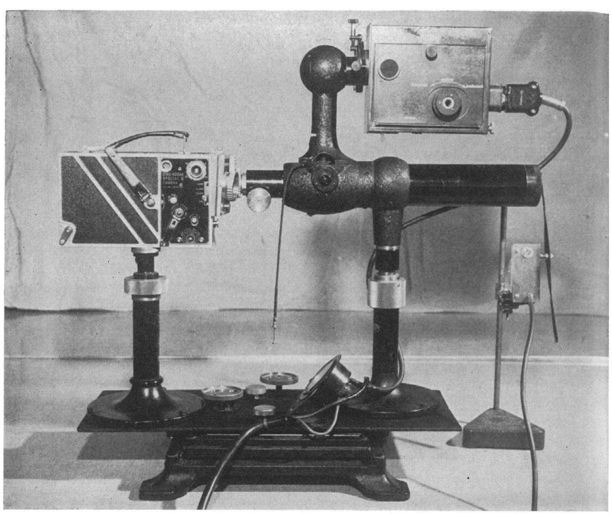

FIGURE 2. Apparatus for fundus cinephotography. [Figure previously published in Flocks, M, Miller J, Chao P. Retinal circulation time with the aid of fundus cinephotography. *Am J Ophthalmol* 1959;48(1, part 2):3-10.

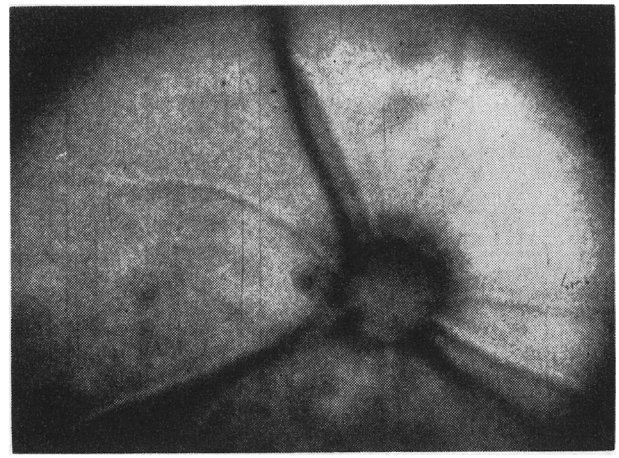

FIGURE 3. Fluorescein entering the cat retinal arteries (white vessels). [Figure previously published in Flocks, M, Miller J, Chao P. Retinal circulation time with the aid of fundus cinephotography. *Am J Ophthalmol* 1959;48(1, part 2):3-10.]

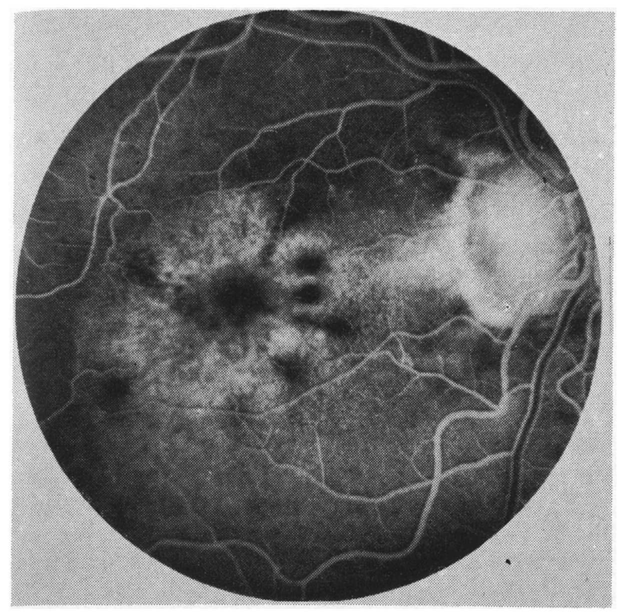

FIGURE 4. First fluorescein photograph of a human in the *Journal*: fluorescein staining of the macula of a patient with an optic nerve pit. [Figure previously published in Johnson AW, Smith JL, Hart LM. Macular changes with pit of optic disc: fluorescein photography. *Am J Ophthalmol* 1963;55(5):1070-1072.]

indirect ophthalmoscope using a cobalt blue filter. The "tumor mass fluoresced beautifully." No attempt was made to photograph or in any other way capture was what seen by the examiner at the time of the procedure. The authors noted that the test was hardly foolproof, as "other lesions such as amelanotic melanomas, disciform degeneration of the macula and other chorioretinal lesions" also fluoresced. Thus, the *Journal* published the first report on the use of fluorescein to study human retinal disease.

The story of how photography was incorporated into FFA is well known to many ophthalmologists. In 1959, 2 medical students at Indiana University, David Alvis and Harold Novotny, were looking for a research project within the Department of Internal Medicine, chaired by John Hickam, MD. Alvis, who became a comprehensive ophthalmologist (Novotny became a psychiatrist), published his memories

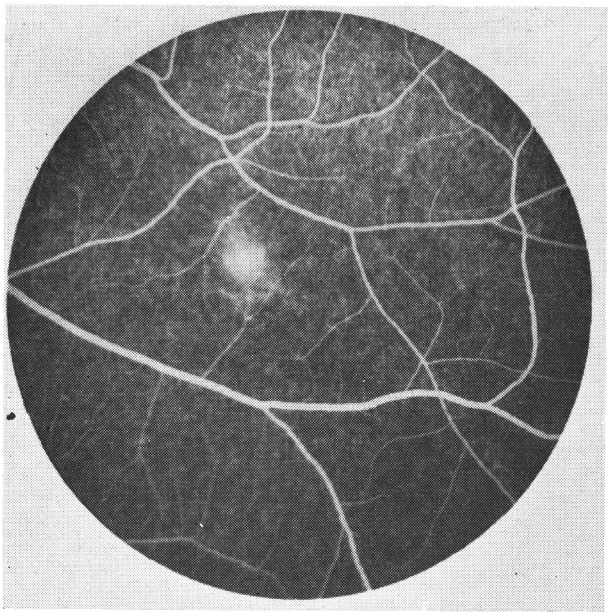

FIGURE 5. Fluorescein staining of a choroidal lesion in an owl monkey. [Figure previously published in Smith JL, Singer JA. Experimental ocular histoplasmosis: VI. Fluorescein fundus photographs of choroiditis in the primate. *Am J Ophthalmol* 1964;58(6):1021-1026.]

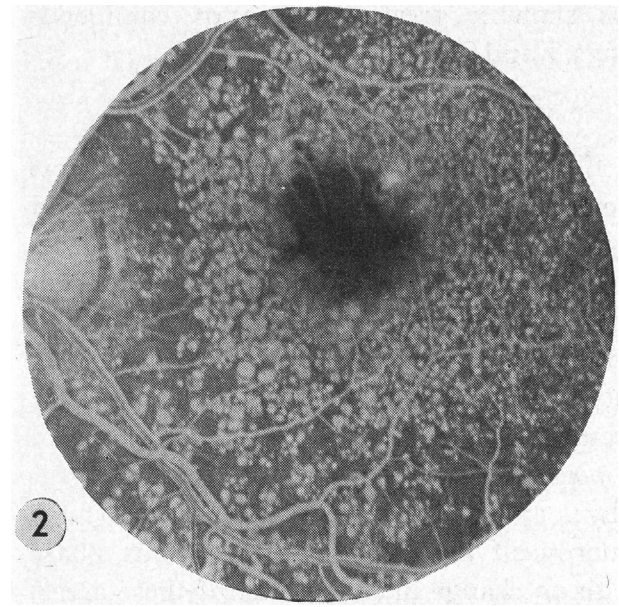

FIGURE 7. The "dotlike fluorescent spots" seen in a 48-year-old woman with drusen. Interestingly, the authors described the photograph as being taken during the "arterial" phase. [Figure previously published in Ernest JT, Krill AE. Fluorescein studies in fundus flavimaculatus and drusen. *Am J Ophthalmol* 1966;62(1):1-6.]

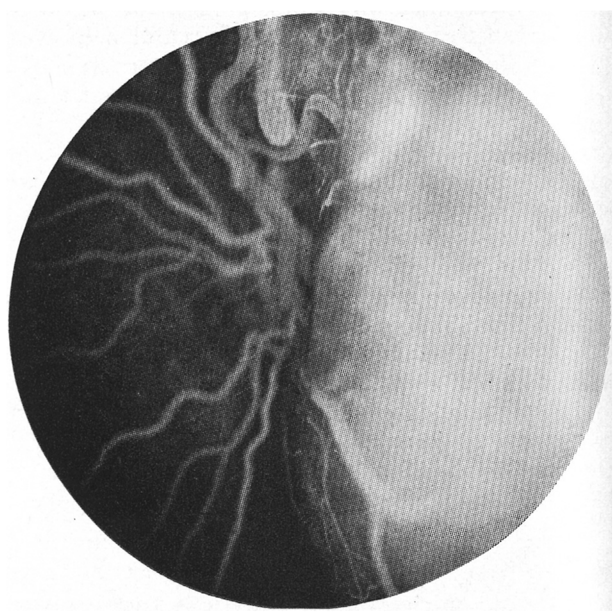

FIGURE 6. Intense fluorescein staining of a retinoblastoma. [Figure previously published in Wetzig PC, Jepson CN. Fluorescein photography: in the differential diagnosis of retinoblastoma. *Am J Ophthalmol* 1966;61(2):341-343.]

of the events in 1982.[8] Hickam had a research grant to study oxygen saturation in retinal arteries using photography and the 2 students were put to work. After learning photographic technique, Novotny noted that the human crystalline lens seemed to give off a peculiar light. Alvis said that "for no apparent reason I suggested that this light could be fluorescent." This led the two to research the literature and come across the Stanford group's articles in the *Journal*. The 2 students realized the need for the exciting and emitting of wavelengths of light entering and coming from the retina. They overcame the lack of adequate light for photography by using very fast 35mm film and developing it in a specific manner. The students' very first attempt (photographed by Novotny, with Alvis as the patient) succeeded in showing fluorescein coursing through the retinal vessels. They studied numerous patients with diabetes and hypertension using their new technique.

The finding was quickly appreciated as important by Hickam, but also by Fred Wilson, chairman of the ophthalmology department. The 2 students were encouraged to prepare a manuscript for publication. The paper was submitted to the *Journal* but rejected. Alvis later recalled that the rejection letter said that the "work was not original enough" and made reference to the Stanford group's articles in the *Journal*. Since the work had been done in the internal medicine department, Hickam called a friend who edited the journal *Circulation*. The article, with only the 2 medical students' names attached, was published in July of 1961 and included the first photographs of fluorescein dye in the human retina.[9]

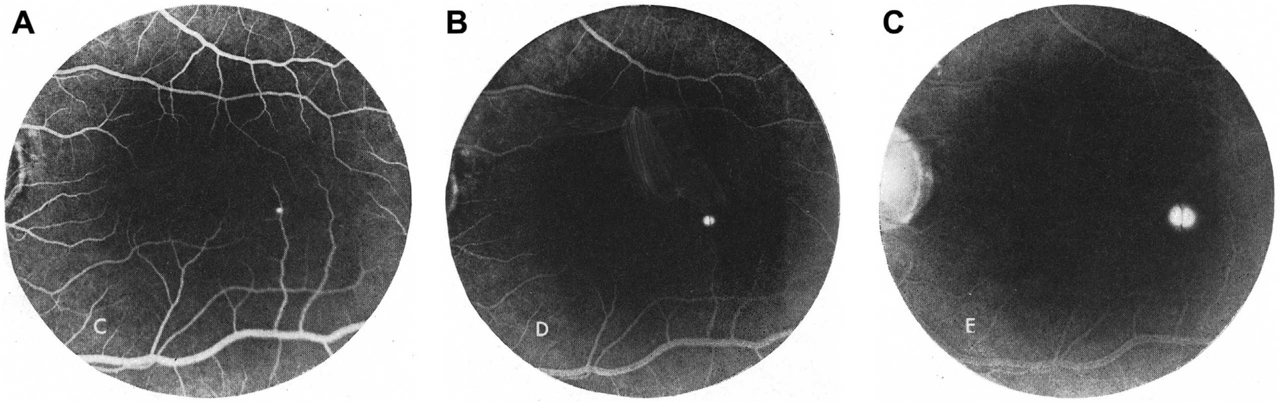

FIGURE 8. (A-C) Hyperfluorescent spot enlarges and is clearly under a retinal blood vessel in this case of idiopathic central serous choroidopathy. [Figures previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: II. Idiopathic central serous choroidopathy. *Am J Ophthalmol* 1967;63(3, part 2):587/15-615/43.]

Why was this article rejected by the *Journal*? *Why* did the *Journal* say that the work was not original enough? Perhaps the reviewers did not understand that photographic FFA would be simpler to perform and would be a more accessible technique for the ophthalmic community and become the mainstay of retinal imaging for the next 5 decades? It may be that there was some lack of regard for a paper coming from 2 medical students working in an internal medicine department. We will never know the complete story. Suffice to say that in 1968 the *Journal*'s editor when the article had been rejected, Derrick Vail, MD, directly and publicly apologized for the rejection to Alvis in Miami at the First International Symposium on Fluorescein Angiography.[8]

Interestingly, the *Journal* actually *had* published Alvis and Novotny's work, or at least an abstract of their findings. In April of 1960 Novotny presented a paper on FFA using photography at the Midwest Section of the Association for Research in Ophthalmology (renamed the Association for Research in Vision and Ophthalmology in 1970).[10] The published abstract from the talk can be found within a section of the *Journal*'s July 1960 issue entitled "Ophthalmic Research" and succinctly describes the technique.[11] Even in this brief discussion the finding of the various phases of the dye passing through the retinal circulation are clearly presented. Two aspects of this abstract are interesting. First, the publication is in the very same issue as the Maclean and Maumenee paper on choroidal hemangiomas. Second, the meeting was held in Indianapolis, where Alvis and Novotny were enrolled in medical school. Perhaps the easy availability of the forum was the main reason why the two decided to give an oral presentation of their findings.

The first article in the *Journal* with fundus fluorescein photographs was published in 1963. J. Lawton Smith, then working at Duke University, wrote on the macular damage caused by optic nerve pits.[12] FFA was used to study macular anatomy (Figure 4[12]). The authors concluded that the FFA showed that there was increased blood flow to the macula when optic nerve pits were present. Looking at the arterial-venous stage FFA photograph today, one would conclude that the changes are secondary to prior long-standing secondary serous macular detachment.

Shortly thereafter, Smith (later to become one of the world's preeminent neuro-ophthalmologists) co-wrote an article on FFA in the squirrel monkey.[13] This work, done at the University of Miami, included the contributions of Johnny Justice, who went on to become one of the most renowned ophthalmic photographers ever. In 1964 Smith continued his experimental work, publishing a paper on an owl monkey model of focal choroiditis created by injecting *Histoplama* organisms into the animal's vitreous humor.[14] FFA was used to document the lesions (Figure 5[14]).

Improving the technique of FFA was an important issue in the first half of the 1960s. Various *Journal* papers were published on such matters. Ferrer described her technique allowing for more frequent photographs (the original method required a 12-second pause between photographs to allow the camera to recharge) and for a way to more accurately define the exact amount of time that had elapsed from injection of the dye to when each photograph was taken.[15]. Others contributed ideas on better filters to capture more of the emitted light.[16] Such papers, combined with work published elsewhere, allowed for better, brighter, and more rapid sequence photography during the study. This allowed for better analysis of the early stages of dye flow through the retinal circulation.

Ophthalmologists began to publish more of their use of the new technique in clinical care. Wetzig and Jepson, 2 private practitioners in Colorado Springs, performed FFA on an anesthetized 20-month-old child with a tumor appearing to be retinoblastoma.[17] They noted the intense fluorescence of the tumor mass (Figure 6[17]) and stated that this phenomenon, which they realized also occurred

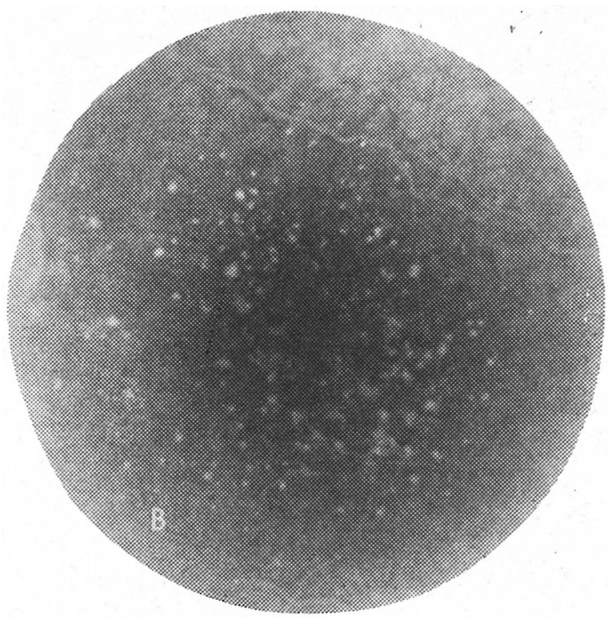

FIGURE 9. Drusen studied angiographically. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: IV. Fluorescein angiographic study of senile disciform macular degeneration. *Am J Ophthalmol* 1967;63(3, part 2):645/73-659/87.]

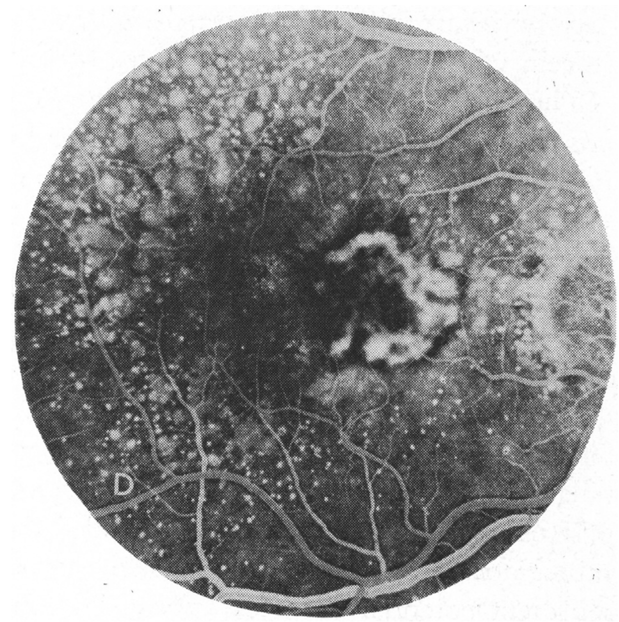

FIGURE 11. Neovascularization shown with fundus fluorescein angiography. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: IV. Fluorescein angiographic study of senile disciform macular degeneration. *Am J Ophthalmol* 1967;63(3, part 2):645/73-659/87.]

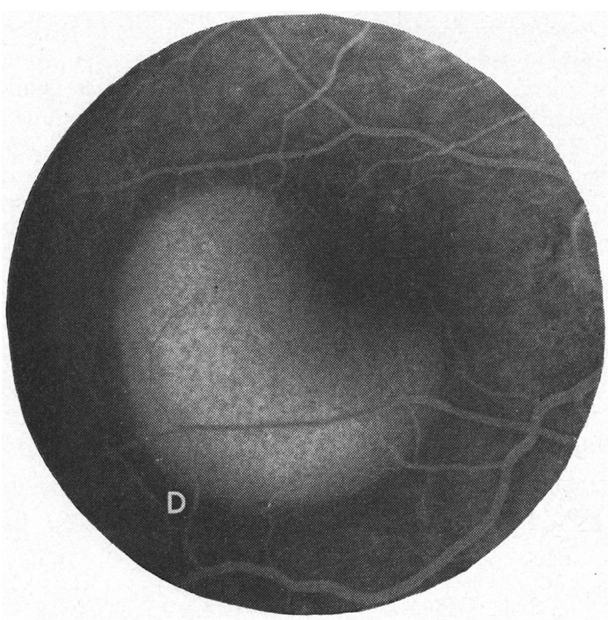

FIGURE 10. Serous detachment of the retinal pigment epithelium studied with fundus fluorescein angiography. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: IV. Fluorescein angiographic study of senile disciform macular degeneration. *Am J Ophthalmol* 1967;63(3, part 2):645/73-659/87.]

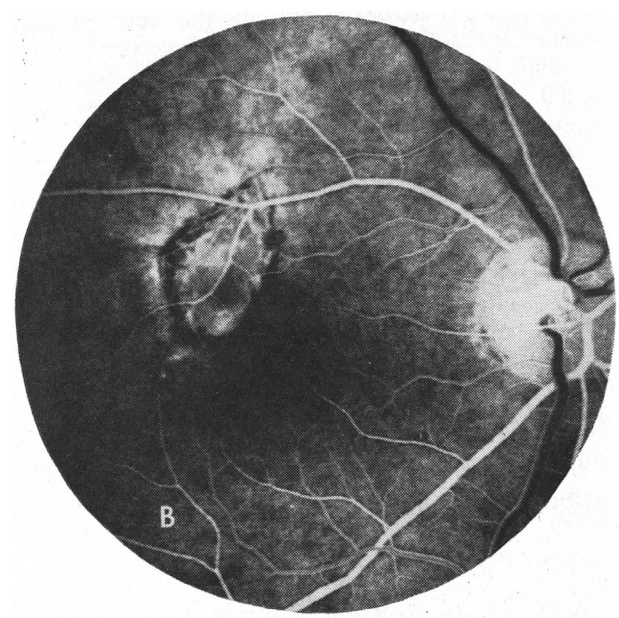

FIGURE 12. Early photograph from fundus fluorescein angiography showing "serous detachment overlying oval choroidal lesion" in a patient with presumed ocular histoplasmosis syndrome. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: V. Disciform macular degeneration secondary to focal choroiditis. *Am J Ophthalmol* 1967;63(3, part 2):661/89-687/115.]

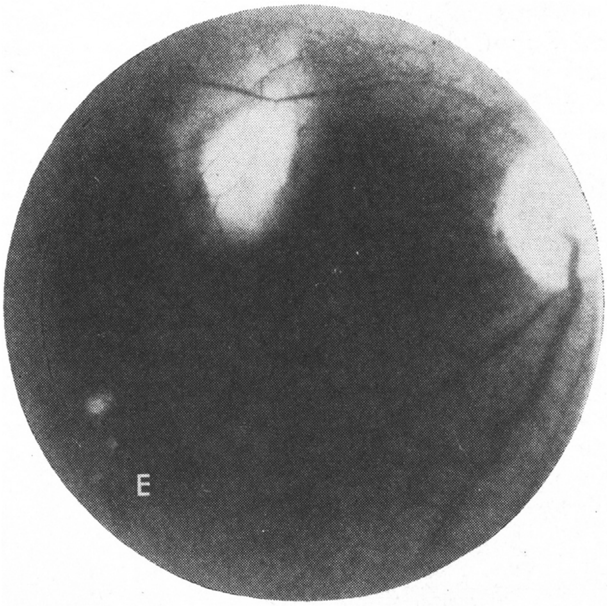

FIGURE 13. Late photograph from fundus fluorescein angiography showing "serous detachment overlying oval choroidal lesion" in a patient with presumed ocular histoplasmosis syndrome. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: V. Disciform macular degeneration secondary to focal choroiditis. *Am J Ophthalmol* 1967;63(3, part 2):661/89-687/115.]

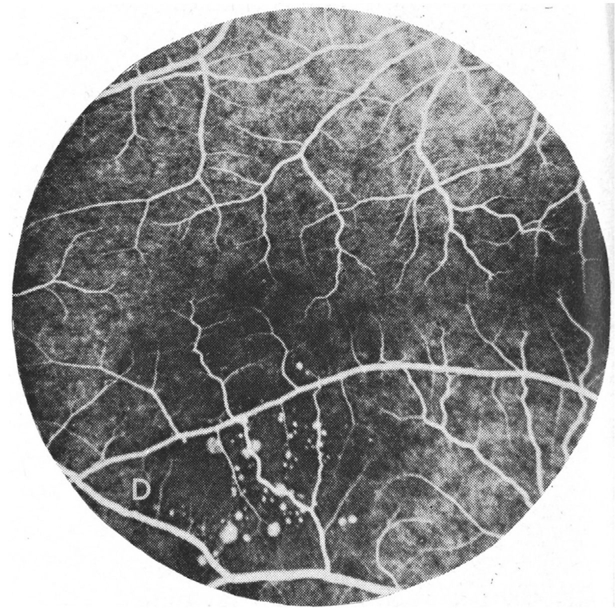

FIGURE 14. Late-stage fundus fluorescein angiography of choroidal nevus showing blockage and overlying staining of drusen, typical for the lesion. [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: VI. Disciform detachment secondary to heredodegenerative, neoplastic and traumatic lesions of the choroid. *Am J Ophthalmol* 1967;63(3, part 2):689/117-714/142.]

in choroidal melanoma, might be of help in making the accurate diagnosis of retinoblastoma.

Ernest and Krill, working at the University of Chicago, used FFA to further study patients with fundus flavimaculatus and drusen.[18] They noted "dotlike fluorescent spots" (Figure 7[18]) in the 2 patients with drusen, aged 48 and 42. Today we might call this condition basal laminar drusen.

March of 1967 marks an important time in the history of the *Journal* and of the study of retinal disease. A supplemental issue was published that month, in addition to the usual one. The supplement was made up of 6 separate articles, all by 1 physician, J. Donald M. Gass of the Bascom Palmer Eye Institute, a part of the University of Miami. There were no coauthors. These 6 articles spanned almost 140 pages of text in the *Journal*. Gass combined his astute clinical observations with FFA and histopathology to attempt to understand the pathophysiology of various macular diseases. Some of the articles used hand-drawn schematic figures to help Gass explain how certain events occurred and which level of the retina was affected. These 6 articles would become the basis for Gass' *Stereoscopic Atlas of Macular Diseases: A Fundoscopic and Angiographic Presentation*, first published in 1970.[19] Gass had arrived at Bascom Palmer in 1963, when a fundus and fluorescein camera was already there, as was the experienced photographer Johnny Justice. Gass began to use and study FFA patterns in various macular

FIGURE 15. Early fluorescence of a choroidal hemangioma (before the retinal arteries are fully filled). [Figure previously published in Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: VI. Disciform detachment secondary to heredodegenerative, neoplastic and traumatic lesions of the choroid. *Am J Ophthalmol* 1967;63(3, part 2):689/117-714/142.]

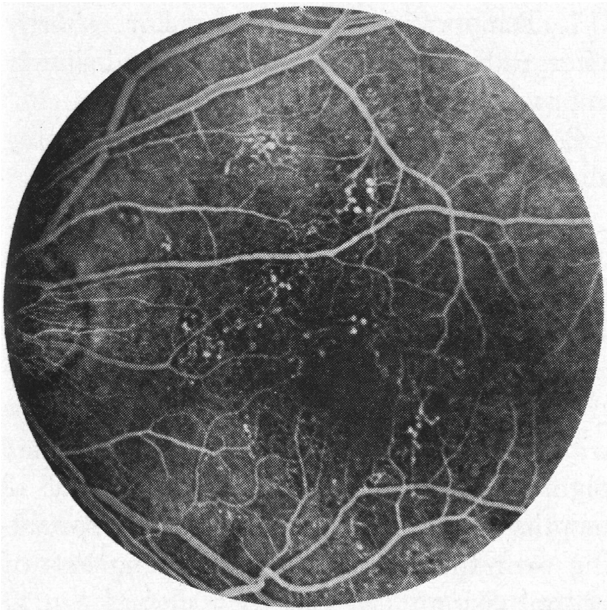

FIGURE 16. Macular capillary damage in a patient who had undergone radiation treatment to the face several years before. [Figure previously published in Chee PHY. Radiation retinopathy. *Am J Ophthalmol* 1968;66(5):860-865.]

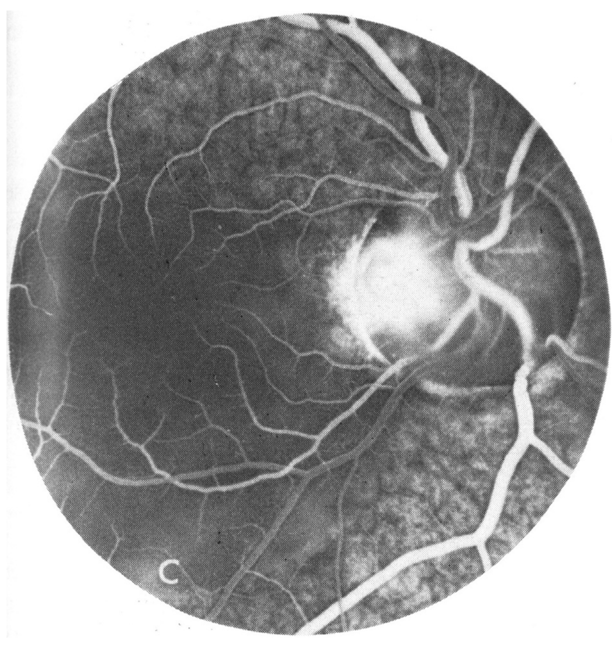

FIGURE 17. Fluorescein staining of the optic nerve pit; note lack of dye in the subretinal space. [Figure previously published in Gass JDM. Serous detachment of the retina: secondary to congenital pit of the optic nervehead. *Am J Ophthalmol* 1969;67(6):821-841.]

FIGURE 18. "Venous phase revealing underlying fluorescein channels, double circulation" in a choroidal melanoma. [Figure previously published in Edwards WC, Layden WE, Macdonald R. Fluorescein angiography of malignant melanoma of the choroid. *Am J Ophthalmol* 1969;68(5):797-808.]

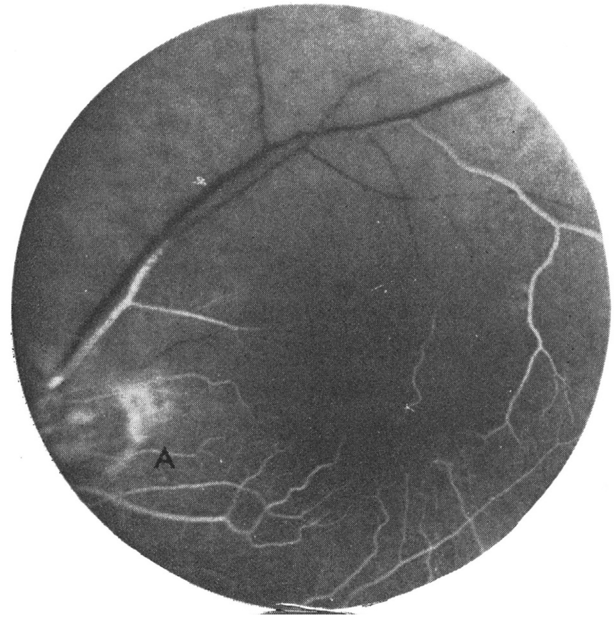

FIGURE 19. Fluorescein staining of the superotemporal artery at the point of obstructon with a "granular column of dye" distally. The authors also noted dye traveling upward in the macular capillaries across the median raphe. [Figure previously published in David NJ, Gilbert DS, Gass JDM. Fluorescein angiography in retinal arterial branch obstructions. *Am J Ophthalmol* 1970;69(1):43-55.]

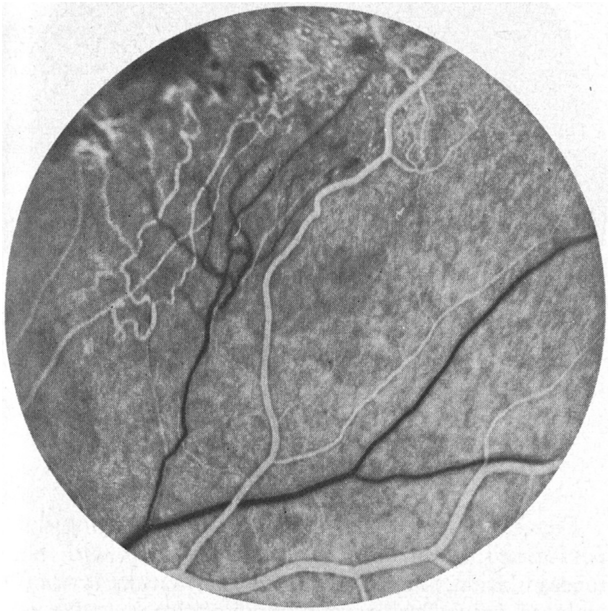

FIGURE 20. Arterial phase photograph showing new vessel formation and arteriovenous communication in a patient with Eales disease. [Figure previously published in Theodossiadis G. Fluorescein angiography in Eales' disease. *Am J Ophthalmol* 1970;69(2):271-277.]

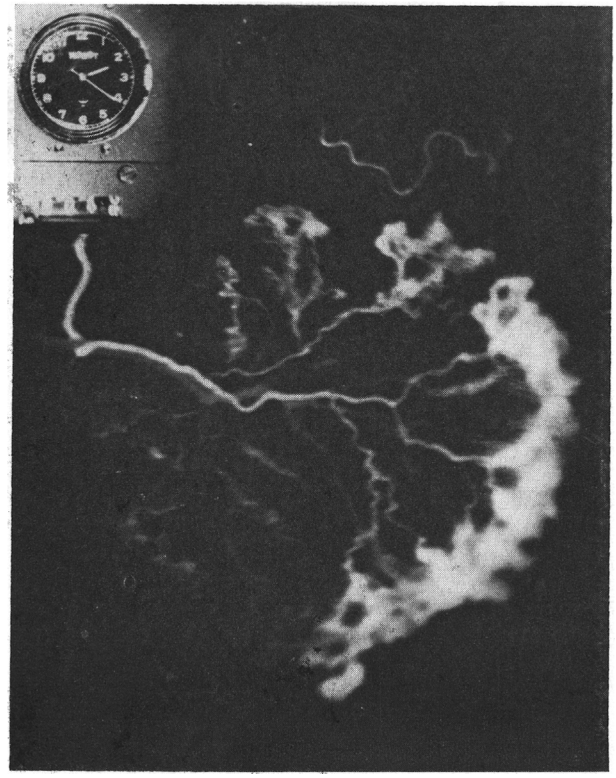

FIGURE 21. Early arteriovenous phase of a sea-fan seen in sickle cell retinopathy. [Figure previously published in Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol* 1971;71(3):649-665.]

diseases and posterior segment tumors. He had spent a year after his residency at the Wilmer Eye Institute as an ophthalmic pathology fellow at the Armed Forces Institute of Pathology. There he had the chance to study many eyes that were enucleated with a misdiagnosis of melanoma or other tumors. This likely sparked his interest in trying to find better ways to differentiate various conditions from neoplasms (written communication, Anita Agarwal, MD, July, 2018).

Writing in the *Journal* in 2004, Lawrence Yannuzzi and associates from New York City appropriately stated that Gass' "brilliant and original work" published in this supplemental issue was the origin of the medical retina subspecialty. Additionally, Yannuzzi and associates noted the extreme importance of fundus imaging as the "fundamental basis for clinical research, teaching, and patient care."[20]

Gass' first article described in detail the pathogenesis of macular scarring secondary to serous and hemorrhagic macular detachment, something he called "disciform degeneration."[21] He stated that the subsequent articles in the supplement would use FFA to help prove his contentions. The second article focused on what Gass called "idiopathic central serous choroidopathy."[22] Using FFA, Gass illustrated the leak in the pigment epithelium allowing fluid to build up under the retina (Figure 8A-C[22]). Numerous cases and schematic drawings were included and mention was made of using photocoagulation to seal the leak and stop the disease process.

Gass used clinical and histopathologic findings to describe disciform degeneration in aging ("senile") degeneration in his third article.[23] Here he proposed the key role of neovascularization developing under the retinal pigment epithelium in allowing the development of serous and hemorrhagic macular detachment. The fourth article used FFA to confirm his findings.[24] Gass used FFA to show the reader how the stages of the disease process could be better understood, how early stages could be diagnosed, how the process could be differentiated from malignancy, and how the photographic study could guide photocoagulation treatment. First Gass showed drusen as an early stage of the process (Figure 9[24]) and that these hyperfluorescent spots would not leak in the later stages of FFA. A description of serous detachment of the pigment epithelium was presented (Figure 10[24]) with the admonition that this could otherwise be confused with a choroidal neoplasm. Examples of hemorrhagic macular detachment were given where the FFA was again helpful in differentiating the finding from neoplasm. Finally, Gass showed FFA evidence of "new vessels growing under the pigment epithelial space" (Figure 11[24]) and later stated that photocoagulation of the lesion might "prevent the often disastrous effect of serous and hemorrhagic macular detachment." Gass predicted future problems with

FIGURE 22. Enlarged foveal avascular zone seen in patient with sickle cell retinopathy and occlusion of macular capillaries. [Figure previously published in Ryan SJ. Occlusion of macular capillaries in sickle cell hemoglobin C disease. *Am J Ophthalmol* 1974;77(4):459-461.]

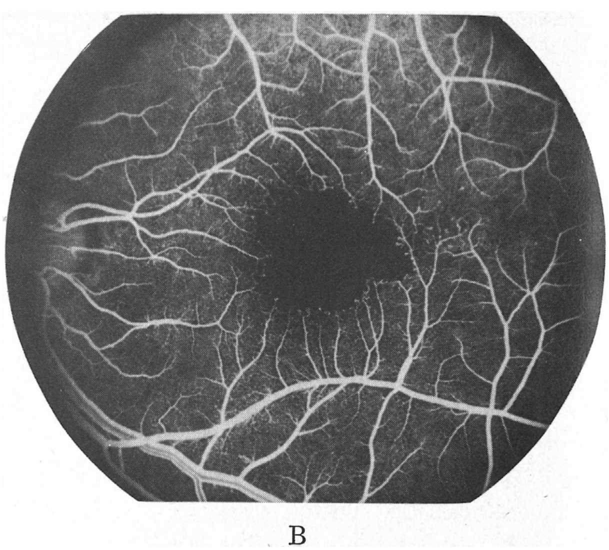

FIGURE 23. Temporal nonperfusion in a 2-month-old with retinopathy of prematurity. [Figure previously published in Cantolino SJ, O'Grady GE, Herrera JA, Israel C, Justice J, Flynn JT. Ophthalmoscopic monitoring of oxygen therapy in premature infants. *Am J Ophthalmol* 1971;72(2):322-331.]

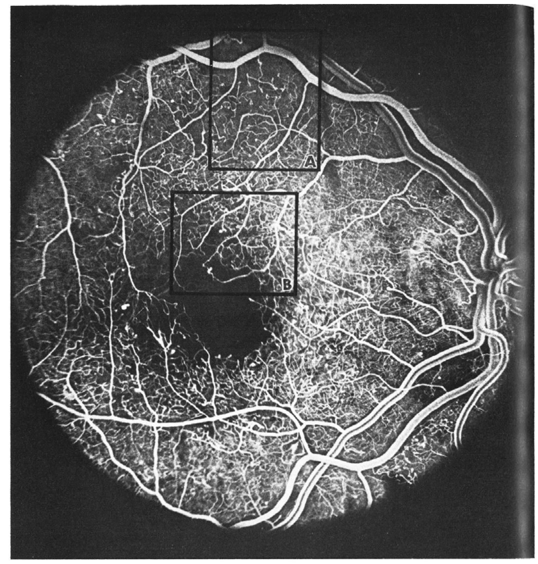

FIGURE 24. Capillary nonperfusion seen in boxes A and B in a patient with diabetic retinopathy. [Figure previously published in Kohner EM, Henkind P. Correlation of fluorescein angiogram and retinal digest in diabetic retinopathy. *Am J Ophthalmol* 1970;69(3):404-414.]

FIGURE 25. Plasma layering of fluorescein dye (arrow) in patient with cavernous hemangioma of the retina. [Figure previously published in Gass JDM. Cavernous hemangioma of the retina: A neuro-cutaneous syndrome. *Am J Ophthalmol* 1971;71(4):799-814.]

treatment, stating that "the choroidal disease in the macular region of many elderly patients is so diffuse that photocoagulation is impractical."

Gass' fifth article focused on other etiologies of disciform scarring, including presumed ocular histoplasmosis and other conditions that could cause choroidal scarring.[25] Gass carefully avoided stating that neovascularization was

FIGURE 26. A fluorescein conference in the late 1970s showing (Left) a projection of the angiogram contact sheet, (Middle) a photograph from the angiogram, and (Right) fundus photograph. [Figure previously published in Nyberg WC, Benson WE. A new technique for fluorescein conferences. *Am J Ophthalmol* 1977;84(5):734.]

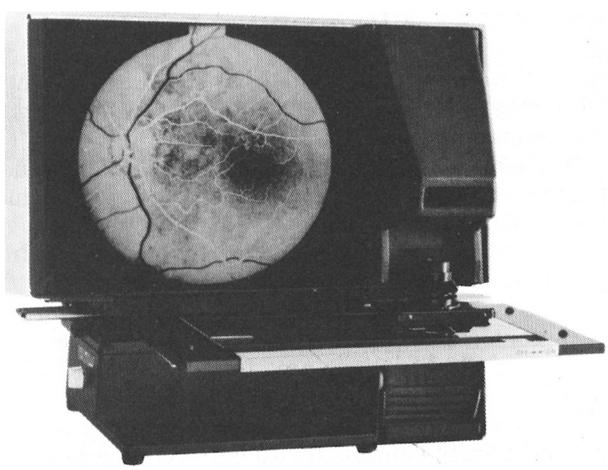

FIGURE 27. A desktop viewer. [Figure previously published in Kraushar MF. Viewing fluorescein films while performing laser treatment. *Am J Ophthalmol* 1980;89(5):747-748.]

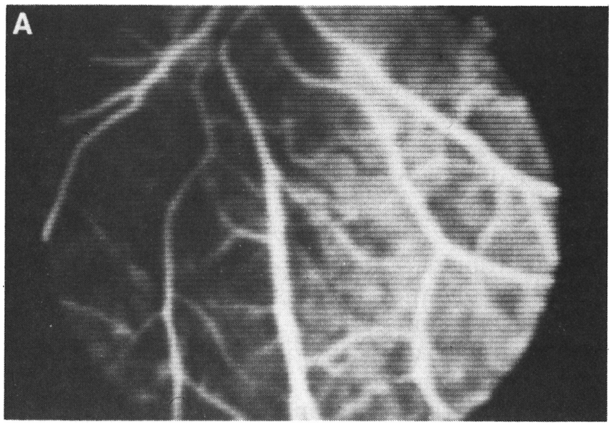

FIGURE 28. A digitized image from a fundus fluorescein angiography. [Figure previously published in Feldman EL. Digital fluorescein tele-angiography. *Am J Ophthalmol* 1987;104(1):91-93.]

present because of a lack of histopathologic proof but realized the similarities in the process of events with patients with aging degeneration. Some of the cases presented include FFAs that certainly seem to show what is now termed a choroidal neovascular membrane (Figures 12 and 13[25]). Again, photocoagulation was proposed as a possible treatment.

In Gass' final article in the issue, he reviewed less common conditions such as angioid streaks, degenerative myopia, Best disease, trauma, focal neoplasms, and choroidal nevi.[26] The FFA characteristics of nevi in contradistinction to melanomas were clearly made (Figure 14[26]).

Gass reviewed differences in the FFA findings of choroidal melanoma and choroidal metastatic tumors in detail. Choroidal hemangomas were discussed in detail as well. Gass highlighted the prominent early fluorescence of these tumors (Figure 15[26]). Interestingly, Gass did not reference the work by Maclean and Maumenee published in the *Journal* in 1960.

More and more publications appeared in the *Journal* after Gass' papers. In 1968 Wise and associates showed that FFA could help guide laser photocoagulation treatment for various retinal conditions.[27] They felt that FFA was quite helpful in treating central serous retinopathy but much less so for "disciform degeneration." In that same year, Krill and associates described FFA studies of patients with diseases affecting mainly the retinal pigment epithelium, such as Best disease and choroideremia.[28] Chee showed the late effect of radiation on the retina (Figure 16[28]) and the possible benefits of treating the damage with photocoagulation.[29]

In 1969 Gass again published important findings in the *Journal*. He described the clear benefits of FFA in patients with serous retinal detachments and optic nerve pits.[30] He showed that the subretinal fluid was not coming from the choroid, retina, or optic nerve blood vessels (Figure 17[30]). Gass theorized that the "subretinal fluid may be

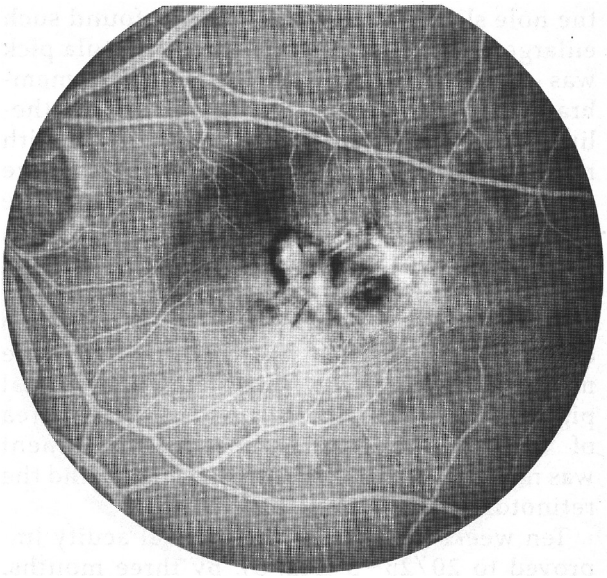

FIGURE 29. A recurrent subretinal neovascular membrane in a patient just prior to the lesion being surgically extracted. [Figure previously published in Thomas MA, Kaplan HJ. Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome. *Am J Ophthalmol* 1991;111(1):1-7.]

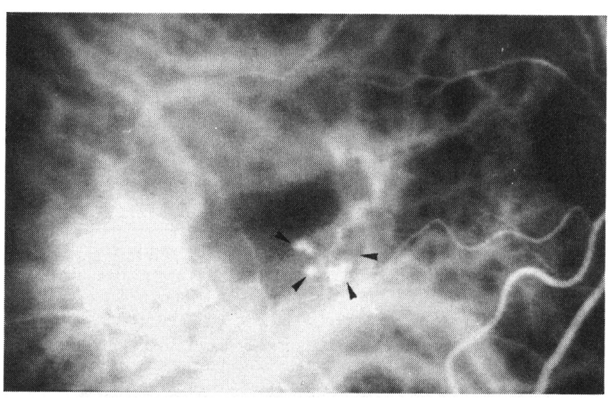

FIGURE 30. Early-phase indocyanine green angiogram showing a choroidal neovascular membrane (arrows) in patient with angioid streaks. [Figure previously published in Quaranta M, Cohen SY, Krott R, Sterkers M, Soubrane G, Coscas GJ. Indocyanine green videoangiography of angioid streaks. *Am J Ophthalmol* 1995;119(2):136-142.]

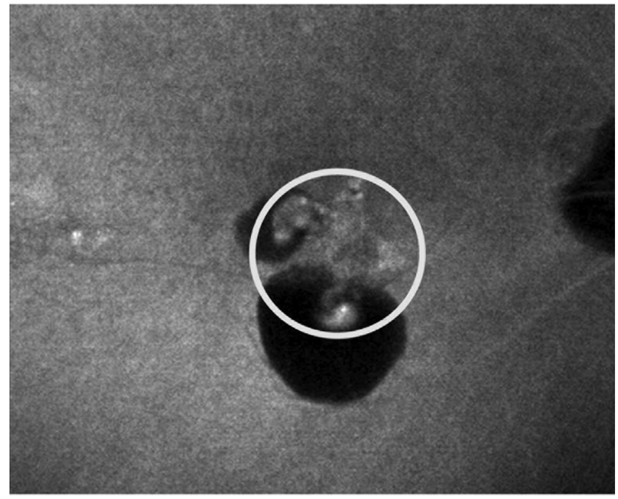

FIGURE 31. Indocyanine green angiogram showing mapping (circle) area to be treated with photodynamic therapy in a patient with polypoidal choroidal vasculopathy. [Figure previously published in Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography: guided photodynamic therapy of polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007;144 (1):7-14.e1.]

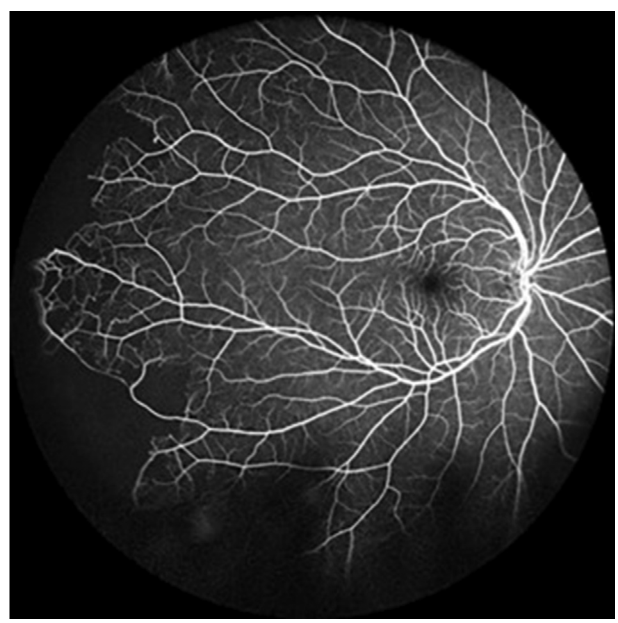

FIGURE 32. Peripheral capillary dropout in a patient with hemoglobin SS disease. [Figure previously published in Pahl DA, Green NS, Bhatia M, Lee MT, et al. Optical coherence tomography and ultra-widefield fluorescein angiography for early detection of adolescent sickle retinopathy. *Am J Ophthalmol* 2017;183:91-98.]

cerebrospinal fluid or vitreous fluid entering the subretinal space via the optic pit." He felt that lightly applied laser photocoagulation of the peripapillary retina adjacent to the pit could hasten fluid resorption and used this treatment modality on some of the patients reported.

Edwards and associates contributed to a growing body of work on the role of FFA in diagnosing choroidal melanomas in 1969.[31] They pointed out the often-seen "double circulation" (Figure 18[31]) in such tumors. Other papers during this time continued to expand on the various

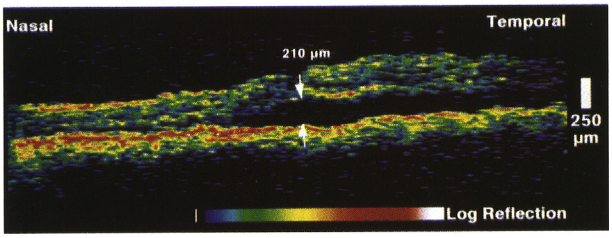

FIGURE 33. Early optical coherence tomography showing subretinal fluid in a patient with idiopathic central serous chorioretinopathy. [Figure previously published in Hee MR, Puliafito CA, Wong C, et al. Optical coherence tomography of central serous chorioretinopathy. *Am J Ophthalmol* 1995;120(1):65-74.]

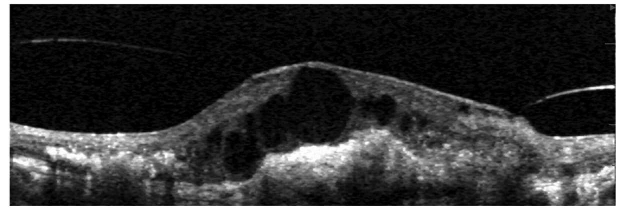

FIGURE 35. Spectral-domain optical coherence tomography of patient with vitreomacular adhesion and neovascular age-related macular degeneration. [Figure previously published in Mojana F, Cheng L, Bartisch D-U, et al. The role of abnormal vitreoretinal adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. *Am J Ophthalmol* 2008;146(2):218-227.]

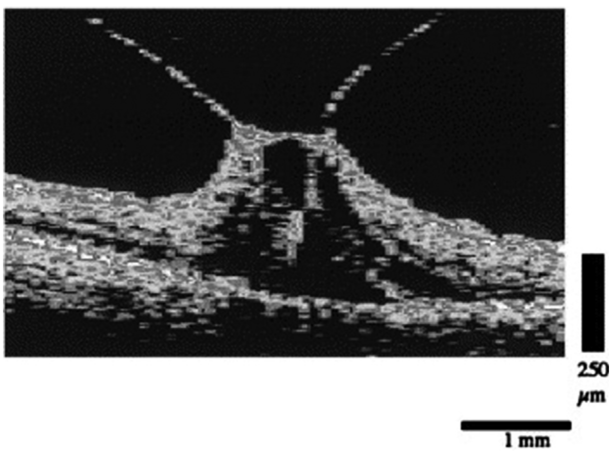

FIGURE 34. An early optical coherence tomography image of vitreomacular traction. [Figure previously published in Uhino E, Uemura A, Doi N, Ohba N. Postsurgical evaluation of idiopathic vitreomacular traction syndrome by optical coherence tomography. *Am J Ophthalmol* 2001;132(1):122-123.]

diseases that could be better understood with FFA. In 1979 David and associates showed how retinal branch artery obstructions could be better understood with FFA in 1970 (Figure 19).[32] Others published articles in the early 1970s illustrating findings in patients with Eales disease (Figure 20[33]), retinitis pigmentosa, hyperviscosity syndrome and macular holes.[33–36] Goldberg used FFA to beautifully describe the various stages of sickle cell retinopathy and developed a classification system for the disease (Figure 21).[37] A few years later Ryan added to the understanding of the disease by publishing a case of sickle cell retinopathy with occlusion of macular capillaries (Figure 22).[38] Cantolino and associates in Miami used FFA to show the marked nonperfusion seen in the temporal retina of infants with retinopathy of prematurity (then called retrolental fibroplasia). Despite the technical difficulties in photographing infants in a neonatal intensive care unit, high-quality images were obtained (Figure 23).[39]

Kohner and Henkind used Gass' method of combining clinical findings with FFA and histopathology to study capillary nonperfusion in diabetic retinopathy.[40] The nonperfusion seen clinically (Figure 24[40]) was confirmed to be caused by acellular capillaries found postmortem. Gass used the combination technique in describing cavernous hemangioma of the retina.[41] Three cases of what had heretofore been considered an incredible rare condition were described. The clusters of "saccular aneurysms filled with dark venous blood" created a near-pathognomonic FFA finding of "plasma layering" where only the upper portion of the aneurysms stained with fluorescein dye (Figure 25[41]).

As more and more patients were studied with FFA, the rate and type of adverse reactions to the dye became better understood. In a comprehensive analysis of the subject, Stein and Parker reviewed the literature and added 9 cases of their own.[42] They concluded that there was a 0.6% chance of a reaction to intravenous fluorescein dye and that two thirds of these were of the allergic type. However, most of the remainder had more severe reactions. The authors concluded that it was imperative to have an emergency tray and oxygen nearby when performing FFA. Later articles reported an 8% rate of nausea after FFA and showed that anaphylaxis could occur even after oral administration of fluorescein.[43,44]

Throughout the 1970s articles appeared in the *Journal* describing the FFA findings in more and more retinal conditions. Gass showed that nicotinic acid, used orally at that time to treat elevated cholesterol, caused a form of cystoid macular edema where essentially no dye leakage occurred.[45] Bos and Deutmann described a new condition, acute macular neuroretinopathy.[46] Patients acutely developed vision loss with dark wedge-shaped flecks in the retina. The presence of a normal FFA helped separate the condition from various previously-described diseases. FFA proved useful to Marmor and Byers when they recommended that various previously described conditions could best be lumped together and called "pattern dystrophy of the pigment epithelium."[47]

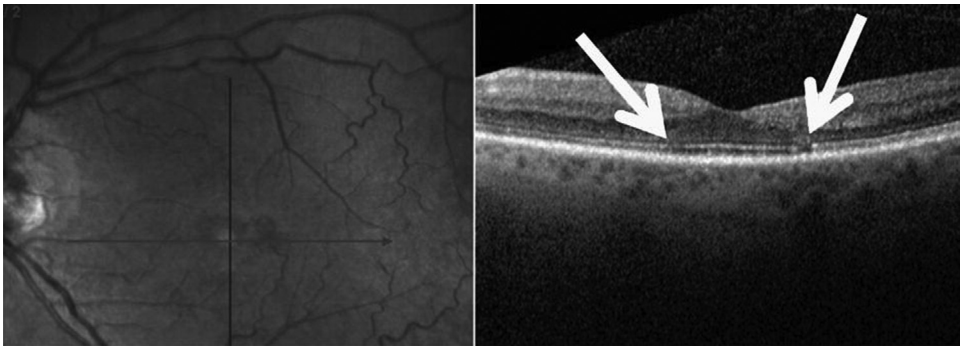

FIGURE 36. Spectral-domain optical coherence tomography showing discontinuities (arrows) in the inner segment–outer segment junction of a patient with hydroxychloroquine toxicity. [Figure previously published in Browning DJ. Impact of the revised American Academy of Ophthalmology guidelines regarding hydroxychloroquine screening in actual practice. *Am J Ophthalmol* 2013;155(3):418-424.]

In the late 1970s several articles dealt more with the logistics of FFA. One study showed a way to develop film in just 90 seconds rather than the more typical 30- to 45-minute time frame.[48] Another showed an inexpensive way to show a fluorescein angiogram and a color fundus photograph side by side at conferences (Figure 26[49]). Such conferences, first popularized by Gass, had become both a standard form of teaching resident physicians and a mainstay of retinal meetings. Another paper described a technique of having a highly magnified view of a fluorescein angiogram available on a desktop viewer so as to guide the ophthalmologist while perfoming retinal laser photocoagulation (Figure 27[50]).

In 1987 Edward Feldman of Boston presented the idea of converting a standard angiogram into a digital image.[51] He realized that this would allow for enhancement of the images, telephone transmission of the study for review offsite, and creating a national data bank of angiograms that could be useful for clinical research and trials. An example of an angiogram converted to digital form was included (Figure 28[51]).

The early 1990s were a time of exciting progress in macular surgery. Writing in the *Journal*, Thomas and Kaplan first introduced the technique of using vitrectomy to remove subretinal neovascular membranes, initially in patients with presumed ocular histoplasmosis syndrome.[52] The technique used a recent FFA of the affected eye. A photograph from the arteriovenous phase of the study was projected on a screen in the operating room, inverted to match the surgeon's view of the retina. This photograph was used as a guide showing the extent of the lesion and where a retinotomy could be made to perform the extraction (Figure 29[52]).

In the mid-1990s a new form of retinal angiography was introduced. Indocyanine green (ICG) dye was substituted for, or used in addition to, fluorescein, allowing for a better analysis of the underlying choroidal vasculature. Researchers working with Soubrane and Coscas in France

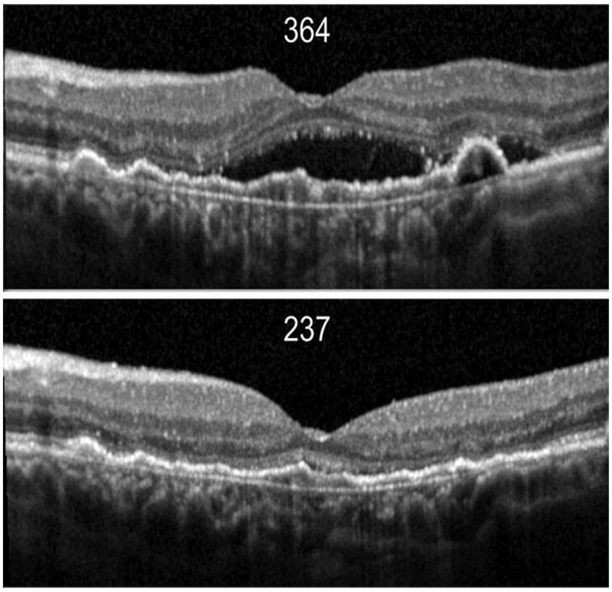

FIGURE 37. Optical coherence tomography after 1 and 3 injections of aflibercept for neovascular age-related macular degeneration, showing resolution of subretinal fluid and decreased central macular thickness (number). [Figure previously published in Bakall B, Folk JC, Boldt, HC, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol* 2013;156(1):15-22.e1.]

published the first article in the *Journal* using this technique, which required videoangiography and a scanning laser ophthalmoscope. The images were then digitalized for further review (Figure 30).[53] Numerous other articles followed showing benefits of ICG in studying patients with various retinal and choroidal conditions.

In 2002 Staurenghi and Flower showed that ICG angiography could be used to identify and treat the feeder vessel of a choroidal neovascular membrane.[54] The apparent

FIGURE 38. An infant studied with a hand-held spectral-domain optical coherence tomography unit. [Figure previously published in Scott AW, Farsiu S, Enyedi L, Wallace DK, Toth CA. Imaging the infant retina with a hand-held spectral-domain optical coherence tomography device. *Am J Ophthalmol* 2009;147(2):364-373.e2.]

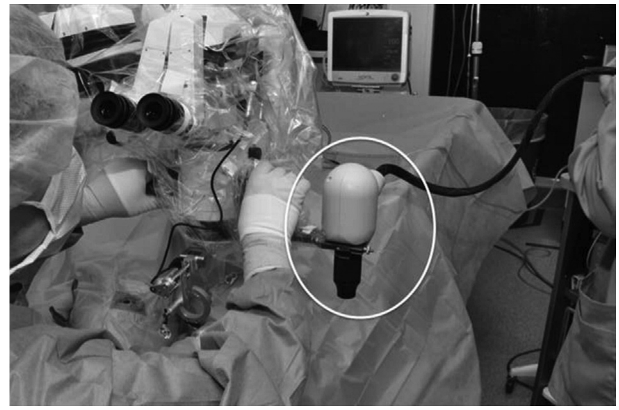

FIGURE 39. A microscope-mounted portable spectral-domain optical coherence tomography unit (circled). [Figure previously published in Ehlers JP, Dupps WJ, Kaiser PK, et al. The prospective intraoperative and perioperative ophthalmic imaging with optical coherence tomography (PIONEER) study: 2-year results. *Am J Ophthalmol* 2014;158(5):999-1007.e1.]

efficacy of the technique was tempered by the extreme complexity (and presumably cost) of the system. The clear benefits of ICG guiding treatment with the new technique of photodynamic therapy for patients with polypoidal choroidal vasculopathy was made apparent in a 2007 study from Japan (Figure 31).[55]

Over time it became apparent that ICG angiography would not replace FFA and was generally only useful in certain specific conditions, mainly those primarily involving the choroidal circulation. Yannuzzi, writing in the *Journal* in 2011, pointed out that various issues such as higher cost, fewer trained photographers, and a lack of clinical experience at many retinal centers diminished the popularity of ICG angiography.[56]

FFA was still the most important component of retinal imaging in the early 2000s. It had a key role in the diagnosis, treatment guidance, and follow-up in patients with neovascular age-related macular degeneration treated with verteporfin in photodynamic therapy in those years. The results of a trial showing efficacy of treatment in patients with “occult” or subfoveal early-onset “classical” choroidal neovascularization was published in the *Journal* in 2001.[57]

FFA began to change in a substantial way in the early 2000s. Rather than using film, studies were accomplished with digital systems. In the clinic, physicians grappled with difficulties in obtaining a stereoscopic view, something easily done when viewing sequential photographs on film. However, stereoscopic images had never been published in most academic journals. Publications in the *Journal* did not state if the angiographic images published came from conventional or digital systems. It is impossible for me to tell which articles used digital rather than photographic images during this transition. The newer systems allowed for immediate viewing of images by clinicians, educating patients about their disease, and easy storage and retrieval.

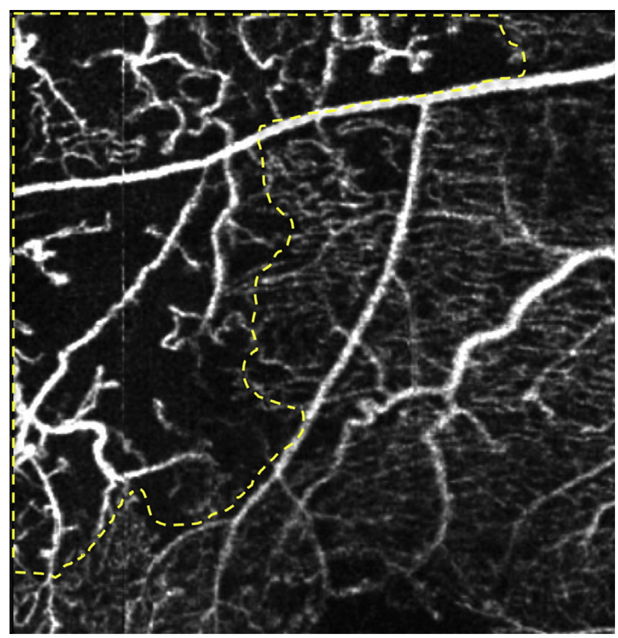

FIGURE 40. An optical coherence tomography angiogram showing capillary nonperfusion (within yellow dotted line) in a patient with diabetic maculopathy. [Figure previously published in Ishibazawa A, Nagaoka T, Takahashi A, et al. Optical coherence tomography angiography in diabetic retinopathy: a prospective study. *Am J Ophthalmol* 2015;160(1):35-44.e1.]

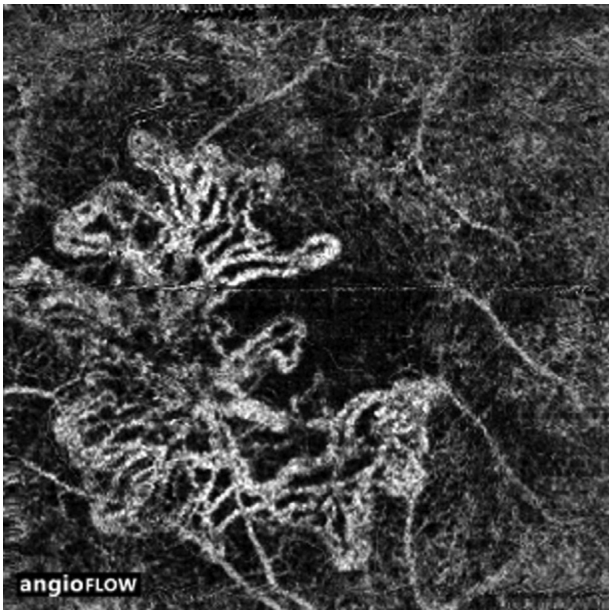

FIGURE 41. Optical coherence tomography angiogram of choroidal neovascularization in age-related macular degeneration. [Figure previously published in Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2015;160(4):739-748.]

One new development that found its way into the *Journal* was that of wide-field and ultra-wide-field FFA. These techniques were especially helpful in diagnosing and understanding peripheral retinal vascular disease (Figure 32).[58]

With the introduction of OCT (see below), the number of FFAs performed by ophthalmologists decreased substantially.[59] Virtually all articles published in the *Journal* in recent years that included FFA have also used other imaging systems to illustrate the posterior segment findings being studied. This has been termed "multimodal imaging."

OPTICAL COHERENCE TOMOGRAPHY

THE DEVELOPMENT OF OCT HAS ADDED AN IMPORTANT new tool for the retinal specialist to use in daily clinical practice and in research settings. Collaborative work between physicians and scientists in Boston created a new technique that allowed for "noninvasive cross-sectional imaging of internal structures of biologic tissues by measuring their optical reflections."[60] This could create a cross-sectional image of the posterior vitreous, retina, and underlying structures. By 1994 the Tufts group presented clinical findings.[61]

One year later the *Journal* published its first article describing OCT findings. The Tufts group described cases of idiopathic central serous chorioretinopathy studied with the new technique. Today these images of neurosensory macular detachment (Figure 33) may seem primitive, but the obvious benefits of a noninvasive, rapidly performed test were already apparent.[62] Within the next 10 years myriad articles appeared describing the gamut of retinal diseases. Vitreomacular traction syndrome became a much more widely diagnosed condition and OCT proved helpful in both detection of the condition (Figure 34) and in following patients after vitrectomy surgery performed to release the adhesion.[63] In these early years studies were performed with time-domain scanning.

Spectral-domain OCT replaced time-domain scanning in most *Journal* articles by 2008. Among other advantages, the newer scans were faster and allowed for higher resolution of the retinal layers with less motion artifacts. Soon, many papers compared the 2 techniques. In 2009 Keane and associates declared that the new technology was superior in detecting intraretinal and subretinal fluid, something of great benefit to aid in the new anti–vascular endothelial growth factor drug treatments for neovascular age-related macular degeneration.[64] The authors accurately predicted that spectral-domain OCT would likely become "standard of care for retina specialists in the near future."

The detailed images obtained with spectral-domain OCT allowed for studying more subtle conditions, such as vitreomacular adhesions in patients with age-related macular degeneration (Figure 35).[65] Screening patients for hydroxychloroquine toxicity was enhanced with the new technology (Figure 36).[66] Perhaps the most common reason to perform OCT imaging was to monitor residual intraretinal and subretinal fluid as part of the protocol of sequential intravitreal anti–vascular endothelial growth factor treatment for neovascular age-related macular degeneration and diabetic macular edema (Figure 37).[67]

A handheld device was devised to study infants and young children (Figure 38).[68] Another innovative adaption was that of using an OCT unit intraoperatively during vitreous microsurgery (Figure 39).[69] The authors presented one of the first large case series showing the utility of the device in increasing the ability to accurately remove membranes from the retinal surface, published in the *Journal* in 2014.

Within the last few years OCT angiography (OCT-A) added additional information about retinal disease. OCT-A allowed for a way to image vascular flow in the posterior segment without dye injection. The need for the patient to fixate for a longer period of time than standard OCT testing has limited the study in patients with poor central vision.

The usefulness of OCT-A was rapidly made apparent in many *Journal* articles beginning in 2015. For instance, the ability to find areas of capillary nonperfusion in patients with diabetic maculopathy was shown in an early article (Figure 40).[70] Another article showed the ability to find choroidal neovascularization in patients with age-related macular degeneration (Figure 41).[71] Parodi and associates showed that OCT-A could detect choroidal

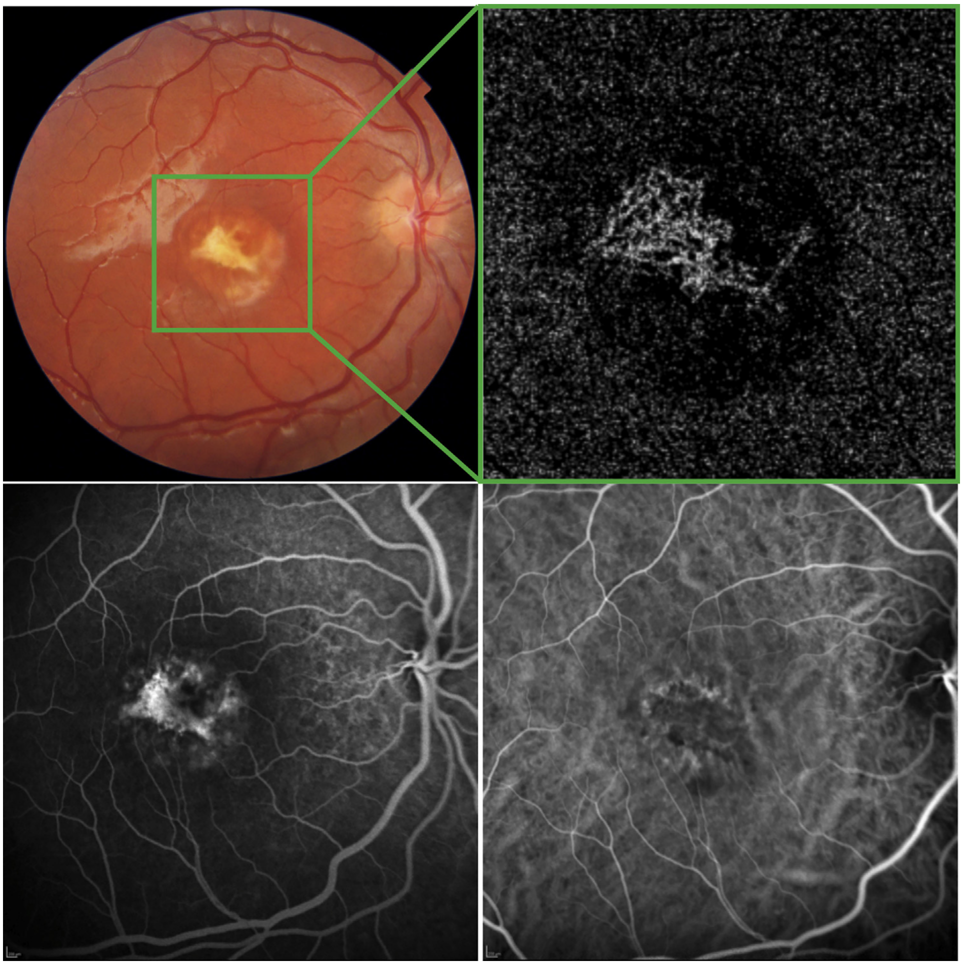

FIGURE 42. Choroidal neovascularization in a patient with Best vitelliform macular dystrophy (Top left) is best seen with optical coherence tomography angiography (Top right) compared to fundus fluorescein angiography (Bottom left) or indocyanine green angiography (Bottom right). [Figure previously published in Parodi MB, Romano F, Cicinelli MV, et al. Retinal vascular impairment in Best vitelliform dystrophy assessed by means of optical coherence tomography angiography. *Am J Ophthalmol* 2018;187:61-70.]

neovascularization better than either FFA or ICG angiography in patients with Best vitelliform macular dystrophy (Figure 42).[72]

An additional refinement, swept-source OCT, added further clarity in studying vitreoretinal interface changes as well as better resolution of deeper retinal pathology. Articles appeared showing the benefit of this diagnostic tool in such conditions as retinal surface neovascularization in proliferative diabetic retinopathy and in retinal changes caused by intermediate uveitis.[73,74]

CONCLUSION

IN REVIEWING MORE THAN 6 DECADES OF ARTICLES IN THE *Journal* I am left with the deep appreciation for the clinicians and scientists that have worked relentlessly to improve our ability to diagnose and thereby treat retinal diseases. The clinical orientation of the *Journal* insures the ophthalmic community that future relevant diagnostic tools will be published in a manner helpful to the practicing ophthalmologist.

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REFERENCES

1. Feibel RM. Looking back: ophthalmic imaging from the first century of the American Journal of Ophthalmology. Part one: photography and ultrasonography. *Am J Ophthalmol* 2018; 195:xx–lv.
2. Schatz H, Burton TC, Yanuzzi LA, Rabb MF. Interpretation of Fundus Fluorescein Angiography. Saint Louis: C. V. Mosby; 1978:3–9.
3. Same PJ. Landmarks in the historical development of fluorescein angiography. *J Ophthalmic Photogr* 1993;15(1):17–23.
4. Sorsby A. Vital staining of the retina: preliminary clinical note. *Br J Ophthalmol* 1939;23(1):20–24.
5. Chao P, Flocks M. The retinal circulation time. *Am J Ophthalmol* 1958;46(1, part 2):8–10.
6. Flocks M, Miller J, Chao P. Retinal circulation time with the aid of fundus cinephotography. *Am J Ophthalmol* 1959;48(1, part 2):3–10.
7. Maclean AL, Maumenee E. Hemangioma of the choroid. *Am J Ophthalmol* 1960;50(1):3–11.
8. Alvis DL, Julian KG. The story surrounding fluorescein angiography. *J Ophthalmic Photogr* 1982;5(1):6–8.
9. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. *Circulation* 1961;24(1):82–86.
10. Marmor MF, Ravin JG. Fluorescein angiography: insight and serendipity a half century ago. *Arch Ophthalmol* 2011;129(10): 943–948.
11. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood of the human eye (abstract). *Am J Ophthalmol* 1960;50(11):176.
12. Johnson AW, Smith JL, Hart LM. Macular changes with pit of optic disc: fluorescein photography. *Am J Ophthalmol* 1963; 55(5):1070–1072.
13. Smith JL, Reynolds DH, Rane L, Justice J. The fundus oculi in the squirrel, owl and marmoset monkey: a study with fluorescein angiography. *Am J Ophthalmol* 1964; 57(3):431–435.
14. Smith JL, Singer JA. Experimental ocular histoplasmosis: VI. Fluorescein fundus photographs of choroiditis in the primate. *Am J Ophthalmol* 1964;58(6):1021–1026.
15. Ferrer OM. Serial fluorescein fundus photography of retinal circulation: a description of technique. *Am J Ophthalmol* 1965;60(4):587–591.
16. Hodge JV, Clemett RS. Improved method for fluorescence angiography of the retina. *Am J Ophthalmol* 1966;61(6): 1400–1404.
17. Wetzig PC, Jepson CN. Fluorescein photography: in the differential diagnosis of retinoblastoma. *Am J Ophthalmol* 1966; 61(2):341–343.
18. Ernest JT, Krill AE. Fluorescein studies in fundus flavimaculatus and drusen. *Am J Ophthalmol* 1966;62(1):1–6.
19. Gass JDM. Stereoscopic Atlas of Macular Disease; A Fundoscopic and Angiographic Presentation. Saint Louis. C.V. Mosby; 1970.
20. Yannuzzi LA, Ober MD, Slakter JS, et al. Ophthalmic fundus imaging: today and beyond. *Am J Ophthalmol* 2004;137(3): 511–524.
21. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: I. General concepts and discussion. *Am J Ophthalmol* 1967;63(3, part 2). 573/1-585/13.
22. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: II. Idiopathic central serous choroidopathy. *Am J Ophthalmol* 1967;63(3, part 2). 587/15-615/43.
23. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: III. Senile disciform macular degeneration. *Am J Ophthalmol* 1967;63(3, part 2). 617/645-644/72.
24. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: IV. Fluorescein angiographic study of senile disciform macular degeneration. *Am J Ophthalmol* 1967;63(3, part 2). 645/673-659/87.
25. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: V. Disciform macular degeneration secondary to focal choroiditis. *Am J Ophthalmol* 1967;63(3, part 2). 661/689-687/115.
26. Gass JDM. Pathogenesis of disciform detachment of the neuroepithelium: VI. Disciform detachment secondary to heredodegenerative, neoplastic and traumatic lesions of the choroid. *Am J Ophthalmol* 1967;63(3, part 2). 689/117-714/142.
27. Wise GW, Campbell CJ, Wendler PF, Rittler MC. Photocoagulation of vascular lesions of the macula. *Am J Ophthalmol* 1968;66(3):452–459.
28. Krill AE, Newell FW, Chisti MI. Fluorescein studies in diseases affecting the retinal pigment epithelium. *Am J Ophthalmol* 1968;66(3):470–484.
29. Chee PHY. Radiation retinopathy. *Am J Ophthalmol* 1968; 66(5):860–865.
30. Gass JDM. Serous detachment of the retina: secondary to congenital pit of the optic nervehead. *Am J Ophthalmol* 1969;67(6):821–841.
31. Edwards WC, Layden WE, Macdonald R. Fluorescein angiography of malignant melanoma of the choroid. *Am J Ophthalmol* 1969;68(5):797–808.
32. David NJ, Gilbert DS, Gass JDM. Fluorescein angiography in retinal arterial branch obstructions. *Am J Ophthalmol* 1970; 69(1):43–55.
33. Theodossiadis G. Fluorescein angiography in Eales' disease. *Am J Ophthalmol* 1970;69(2):271–277.
34. Krill AE, Archer D, Newell FW. Fluorescein angiography in retinitis pigmentosa. *Am J Ophthalmol* 1970;69(5):826–835.
35. Luxenburg MN, Mausolf FA. Retinal circulation in hyperviscosity syndrome. *Am J Ophthalmol* 1970;70(4):588–598.
36. Aaberg TM, Blair CJ, Gass JDM. Macular holes. *Am J Ophthalmol* 1970;69(4):555–562.
37. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol* 1971;71(3): 649–665.
38. Ryan SJ. Occlusion of macular capillaries in sickle cell hemoglobin C disease. *Am J Ophthalmol* 1974;77(4):459–461.
39. Cantolino SJ, O'Grady GE, Herrera JA, Israel C, Justice J, Flynn JT. Ophthalmoscopic monitoring of oxygen therapy in premature infants. *Am J Ophthalmol* 1971;72(2):322–331.
40. Kohner EM, Henkind P. Correlation of fluorescein angiogram and retinal digest in diabetic retinopathy. *Am J Ophthalmol* 1970;69(3):403–414.
41. Gass JDM. Cavernous hemangioma of the retina: A neurocutaneous syndrome. *Am J Ophthalmol* 1971;71(4):799–814.
42. Stein MR, Parker CW. Reactions following intravenous fluorescein. *Am J Ophthalmol* 1971;72(5):861–868.
43. Schatz H, Farkos WJ. Nausea from fluorescein angiography. *Am J Ophthalmol* 1982;93(3):370–371.

44. Kinsella FP, Mooney DJ. Anaphylaxis following oral fluorescein angiography. *Am J Ophthalmol* 1988;106(6):745–746.
45. Gass JDM. Nicotinic acid maculopathy. *Am J Ophthalmol* 1973;76(4):500–510.
46. Bos PJM, Deutman AF. Acute macular neuroretinopathy. *Am J Ophthalmol* 1975;80(4):573–584.
47. Marmor MF, Byers B. Pattern macular dystrophy of the pigment epithelium. *Am J Ophthalmol* 1977;84(1):32–44.
48. Merin LM. Rapid access fluorescein angiography. *Am J Ophthalmol* 1978;86(1):136–137.
49. Nyberg WC, Benson WE. A new technique for fluorescein conferences. *Am J Ophthalmol* 1977;84(5):734.
50. Kraushar MF. Viewing fluorescein films while performing laser treatment. *Am J Ophthalmol* 1980;89(5):747–748.
51. Feldman EL. Digital fluorescein tele-angiography. *Am J Ophthalmol* 1987;104(1):91–93.
52. Thomas MA, Kaplan HJ. Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome. *Am J Ophthalmol* 1991;111(1):1–7.
53. Quaranta M, Cohen SY, Krott R, Sterkers M, Soubrane G, Coscas GJ. Indocyanine green videoangiography of angioid streaks. *Am J Ophthalmol* 1995;119(2):136–142.
54. Staurenghi G, Flower RW. Clinical observations supporting a theoretical model of choriocapillaris blood flow in the treatment of choroidal neovascularization associated with age-related macular degeneration. *Am J Ophthalmol* 2002;133(6):801–808.
55. Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography: guided photodynamic therapy of polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007;144(1):7–14.e1.
56. Yannuzzi LA. Indocyanine green angiography: a perspective on use in the clinical setting. *Am J Ophthalmol* 2011;151(5):745–751.e1.
57. Verteporforin in Photodynamic Therapy Study Group. Verteporforin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization-verteporforin in photodynamic therapy report 2. *Am J Ophthalmol* 2001;131(5):541–560.
58. Pahl DA, Green NS, Bhatia M, et al. Optical coherence tomography and ultra-widefield fluorescein angiography for early detection of adolescent sickle retinopathy. *Am J Ophthalmol* 2017;183:91–98.
59. Schneider EL, Mruthyunjaya P, Talwar N, et al. Retinal fluorescein angiography and fundus photography use in the management of neovascular macular degeneration and macular edema during the past decade. *Invest Ophthalmol Vis Sci* 2014;55(1):542–549.
60. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science* 1991;254:1178–1181.
61. Puliafito CA. A brief history of optical coherence tomography: a personal perspective. *Ophthalmic Surg Lasers Imaging* 2008;39(4 Supplement):56–57.
62. Hee MR, Puliafito CA, Wong C, et al. Optical coherence tomography of central serous chorioretinopathy. *Am J Ophthalmol* 1995;120(1):65–74.
63. Uhino E, Uemura A, Doi N, Ohba N. Postsurgical evaluation of idiopathic vitreomacular traction syndrome by optical coherence tomography. *Am J Ophthalmol* 2001;132(1):122–123.
64. Keane PA, Bhatti RA, Brubaker JW, Liakopoudos S, Sadda SR, Walsh A. Comparison of clinically relevant findings from high-speed Fourier-domain and conventional time-domain optical coherence tomography. *Am J Ophthalmol* 2009;148(2):242–248.
65. Mojana F, Cheng L, Bartisch D-U, et al. The role of abnormal vitreoretinal adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. *Am J Ophthalmol* 2008;146(2):218–227.
66. Browning DJ. Impact of the revised American Academy of Ophthalmology guidelines regarding hydroxychloroquine screening in actual practice. *Am J Ophthalmol* 2013;155(3):418–424.
67. Bakall B, Folk JC, Boldt HC, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol* 2013;156(1):15–22.e1.
68. Scott AW, Farsiu S, Enyedi L, Wallace DK, Toth CA. Imaging the infant retina with a hand-held spectral-domain optical coherence tomography device. *Am J Ophthalmol* 2009;147(2):364–373.e2.
69. Ehlers JP, Dupps WJ, Kaiser PK, et al. The prospective intraoperative and perioperative ophthalmic imaging with optical coherence tomography (PIONEER) study: 2-year results. *Am J Ophthalmol* 2014;158(5):999–1007.e1.
70. Ishibazawa A, Nagaoka T, Takahashi A, et al. Optical coherence tomography angiography in diabetic retinopathy: a prospective study. *Am J Ophthalmol* 2015;160(1):35–44.e1.
71. Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2015;160(4):739–748.
72. Parodi MB, Romano F, Cicinelli MV, et al. Retinal vascular impairment in Best vitelliform dystrophy assessed by means of optical coherence tomography angiography. *Am J Ophthalmol* 2018;187:61–70.
73. Pan J, Chen D, Yang X, et al. Characteristics of neovascularization in early stages of proliferative diabetic retinopathy by optical coherence tomography angiography. *Am J Ophthalmol* 2018;192:146–156.
74. Wintergerst MWM, Pfau M, Mueller PL, et al. Optical coherence tomography in intermediate uveitis. *Am J Ophthalmol* 2018;194:35–45.