The Story Surrounding Fluorescein Angiography

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During the winter of my senior year at Indiana University School of Medicine, 1959, I considered finding a job which would both expose me to medical research as well as internal medicine. I applied to the Department of Internal Medicine and was told that the only vacancy would be working directly for the Chairman, John B. Hickam, M.D., who had a research grant to study by photographic methods the oxygen saturation in retinal arterioles. I reluctantly decided that this was better than nothing because I thought I was interested in gastroenterology.

Harold Novotny, a junior medical student at the time, was also employed for the same purpose. We started Dr. Hickam's research project by learning how to operate the Zeiss Fundus Camera. This was the first model available with an electronic flash. Next we learned how to process film, and to make prints. After much practice with a model eye we were allowed to photograph patients.

One day Harold Novotny was observing the crystalline lens of a patient, and he commented that the lens appeared to give off an unusual type of light he had not been aware of before. For no apparent reason I suggested that this light could be fluorescent. Harold responded by saying that fluorescent blood or blood vessels would be beautiful to observe and that he wondered if they could be photographed. I suggested that we research the problem prior to presenting it to Dr. Hickam for his approval. Harold went to the Medical Center pharmacy and discovered that an injectable form of fluorescein was commercially available. I reviewed the *Index Medicus* and discovered that cinematography and angiography had been performed in cats but not in humans. Dr. Hickam was enthusiastic about our idea and offered many helpful suggestions.

The most important suggestion he gave us was that we needed to know the exciting and emitting wavelengths of light

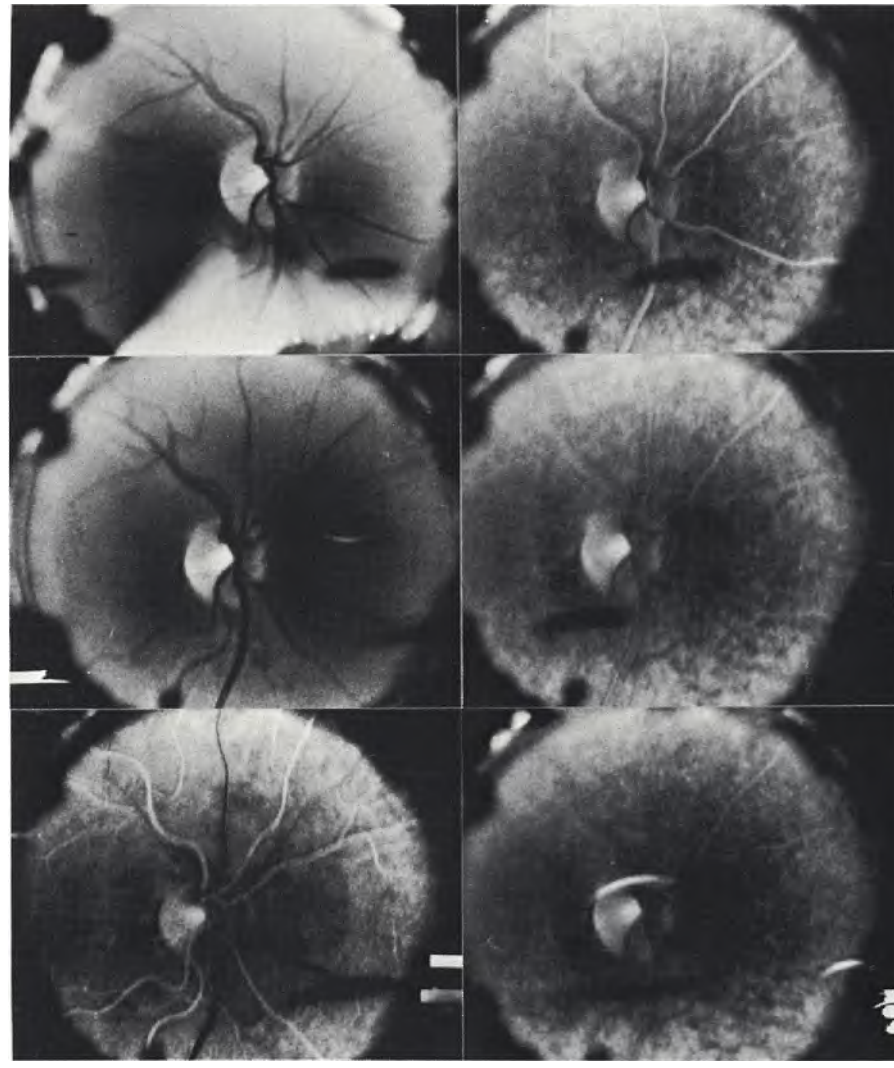

Fig. 1: First human fluorescein angiogram. 1959, match sticks were used to show sequence of prints. The "patient" is Dr. Alvis.

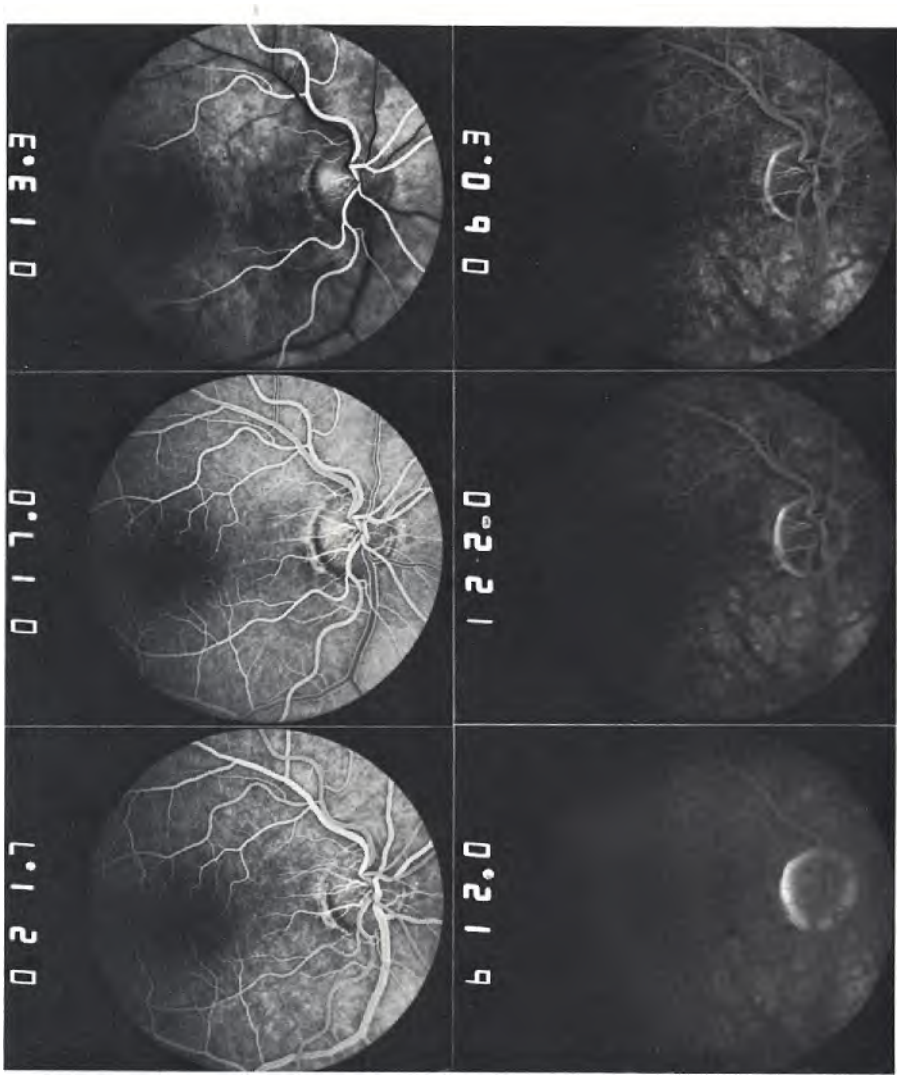

Fig. 2: Comparison fluorescein angiogram done in April, 1981. Photographs show marked improvement in image quality. Again the "patient" is Dr. Alvis.

from fluorescein as it circulated in human blood. Eli Lilly and Company, the pharmaceutical manufacturer, provided the spectrofluorometer for the light determinations. I supplied the blood.

The optimal exciting wavelength was 490 nm in the blue range of the visible spectrum; and the maximal emitting wavelength was 520 nm in the green. We found that Kodak Wrattan filters # 47 and # 58 could appropriately be placed within the optical system of the camera to produce the desired blue and green light.

Because our light requirements were greater than the Zeiss fundus camera power pack could supply at its greatest setting, Dr. Hickam suggested we find the fastest 35mm film available and force develop it, if possible, to obtain enough contrast in our negatives for good prints. Ansco Super Hypan film was selected because when it was force developed for 10 min at 70°F with UFG Ethol developer, an ASA rating of 2400 was obtained.

The first attempt to do an angiogram was of my right eye. We were successful on the first try (Fig. 1). A copy of these first pictures is now among the archives of the Ophthalmic Photographers' Society and has been included in this paper with a comparison set of prints done in 1981 (Fig. 2).

Dr. Hickam was pleased with our efforts and suggested that Harold and I present our work to Dr. Fred M. Wilson, Sr., Chairman, Department of Ophthalmology, Indiana University Medical Center. Dr. Wilson received this discovery enthusiastically, and requested that we duplicate the same facilities in the Ophthalmology Department.

Dr. Hickam had always been interested in the devastating vascular complications of diabetic and hypertensive retinopathy. He put the word out that two medical students would like to photograph these complications for their research project. We had an immediate, unlimited supply of patients.

This discovery almost was not published. Neither Harold nor I had ever written an article for publication. We wrote and re-wrote it. Both Dr. Hickam and Dr. Wilson were very generous with their time in editing our manuscript.

When our revisions were completed to the satisfaction of both Dr. Wilson and Dr. Hickam, we submitted the text and

photographs to the *American Journal of Ophthalmology* for publication. Soon thereafter we received a rejection notice stating that our work was not original. The editorial board cited the article by Chao and Flocks" as their reason for refusing publication. Neither Doctors Novotny, Hickam, Wilson, nor Alvis had any idea what the retinal circulation time in cats had to do with the fluorescence we were reporting for the first time in humans.

Dr. Hickam came to our rescue by calling the editor of the journal *Circulation.* This individual was a personal friend and long-time colleague of Dr. Hickam. The editor was courteously told that we had information worthy of publication and that we had been refused publication by one of ophthalmology's leading journals. Dr. Hickam's intervention on behalf of his two medical students worked. Our article, "A Method of Photographing Fluorescence in Circulating Blood in the Human Retina" appeared in *Circulation,* volume XXIV, July 1961.2

Following graduation Dr. Novotny and I went our separate paths. He entered psychiatry, and I entered ophthalmology. Coincidently, each of us pursued our graduate training at Wayne State University, Detroit, Mich.

As a resident in ophthalmology I tried to interest my instructors at Wayne State in establishing facilities for fluorescein angiography. The support was not forthcoming. One night at a social gathering for staff and residents, four years after publication of our article, I was asked by my ophthalmology professor why I had not pursued fluorescein angiography during my residency. For reasons that I did not understand at that time he could not remember that I had asked him several times for his support in this project. I had an idea how Orville and Wilbur Wright must have felt when they finally received support for their heavier-than-air machine which was thought to be unworkable.

In February 1968 I was asked to be an honored guest of the Horatio Ferrer Eye Institute in Miami, Fla. The First International Symposium on Fluorescein Angiography was being held, and I was to be honored. I elected not to show my original slides because of their poor quality when compared to the quality of those by other participants. I was asked to relate to those in attendance the story surrounding the development of fluorescein angiography. Included in my remarks was the rejection slip from the *American Journal of Ophthalmology*. Dr. Derrick Vail, who was editor of the *Journal* and a participant in the symposium, apologized to me for not publishing the article. This was a gracious gesture on his part, and I readily accepted his apology.

Twenty years after the publication of our original fluorescein article, Mr. Julian and I thought a comparison of the original techniques and photographs with a recent angiogram would be appropriate.

Improvement in equipment now provides more technical ease for the photographer as well as superior photographs. For example, matched filters without light leakage may be swung into position without opening the side of the fundus camera. The modern day flash power packs provide enough power for photographs as often as twice per second instead of one picture every twelve seconds. Photographs may now be numbered on the film instead of using match sticks on the exposed printing paper to show the sequence. Camera backs of all types are now interchangeable with the Zeiss Fundus Camera so that adapting devices are no longer necessary. Foot controls and synchronized timing devices make photography and appropriate timing much more easy and accurate.

Of primary importance to me as a patient is the increased comfort during and after photography. One percent Mydriacyl and 2 $^{1}/_{2}$% Mydfrin have been found to provide adequate pupillary dilation instead of the stronger combination of 1% Cyclogyl and 10% Neosynephrine. Ten cubic centimeters of a 5% fluorescein solution followed by a 10-cm^3 bolus saline administered through a reusable 18-gauge needle was much more unpleasant than 5 cm^3 of 10% fluorescein given through a disposable 19-gauge needle. Because the timed sequences have been standardized, the patient may now rest during the photographic session.

Paradoxically, I must now refer patients to other ophthalmologists for fluorescein angiography because I do not perform it myself. Yet I have had the pleasure of observing the plethora of new clinical knowledge, advances in photographic equipment, and talented photographers drawn into ophthalmology as the result of this simply discovery. When one of my patients returns to my office following fluorescein angiography, he or she never fails to mention the expert technicians and complex equipment. I, in turn, laughingly refer the patient to the original pictures of my right eye hanging on the wall of my examining room and tell the patient he has experienced living ophthalmic history.

References

1. Chao, P.; Flocks, M.: The Retinal Circulation Time. *Amer. J. Ophthalmol.* 46:8, 1958.
2. Novotny, Harold R.; Alvis, David L.: A Method of Photographing Fluorescein in Circulating Blood in the Human Retina. *Circulation* **XXIV:82, 1961.**

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About the author—Dr. Alvis was graduated with Phi Beta Kappa honors from DePauw University in 1956. He attended Indiana University School of Medicine from which he was graduated with Alpha Omega Alpha honors in 1960. One year of a rotating internship at Indiana University Medical Center was followed by a three-year ophthalmology residency at Wayne State University, Detroit, Mich. **In** the private practice of ophthalmology since 1966, Dr. Alvis was a volunteer instructor in the glaucoma' clinic, Wishard Memorial Hospital, Indiana University School of Medicine.