THE SCOPE OF FLUORESCEIN ANGIOGRAPHY*

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Novotny and Alvis[1] first described a method of studying the retinal circulation using intravenous fluorescein with retinal photography.

Fluorescein angiography has added a new dimension to the study of anatomical details and pathological changes of the retinal microcirculation.

METHOD

The patient's pupils are dilated with Cyclomydril (cyclogyl 0·2%, phenylephrine hydrochloride 1% and polyvinyl pyrrolidone 3%) and a colour photograph of the fundus is taken. An assistant then injects 5 ml. of 10% fluorescein sodium into the antecubital vein.

*Date received: 6 June 1968.

The passage of the dye through the retinal vessels is then observed by the photographer, who needs to be dark-adapted to focus the camera satisfactorily. Serial photographs are taken at 2-second intervals, under direct observation.

Camera System[2]

The basic unit used was the Zeiss fundus camera which has been adapted for fluorescein photography by incorporating a high-power, rapid recycling, flash generator (Fig. 1). This generator has power increment stages of 120, 240, 480 and 840 watt-seconds, with a timing sequence of 0·6-, 0·8-, 1·0-, 1·2-, 1·5- and 2-second intervals. In order to obtain the most rapid working sequence at 0·6 seconds, the generator must be set at the minimum output of 120 watt-seconds. The recording camera is one which incorporates an automatic film advance with a time lag of camera release to complete shutter openings of 20 ± 5 msec.

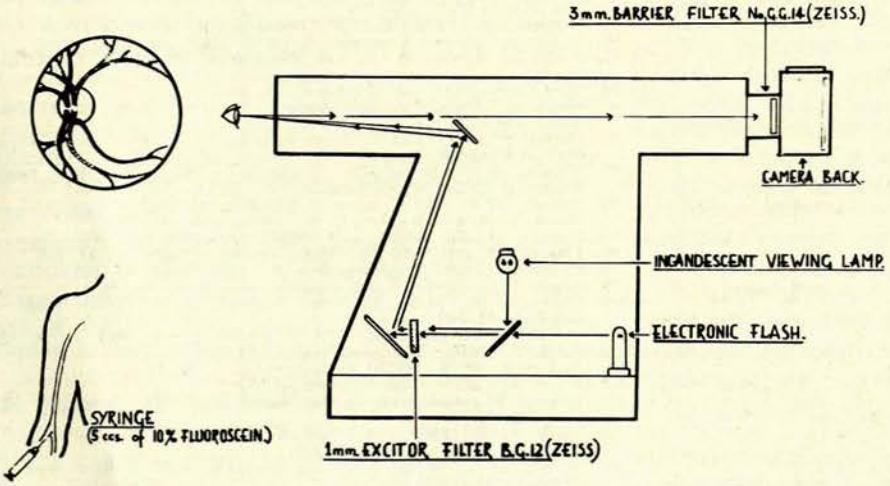

Fig. 1. Diagrammatic representation of camera system used with fluorescein angiography.

There is an illuminated instrument panel with a frame counter, clock and inscription area. The data from this panel are projected by means of a mirror and auxiliary lens as an 8 × 8-mm. image in the upper left corner of each frame. The camera lens system has also been modified by inserting an additional objective lens which is placed immediately in front of the camera shutter, leaving just enough clearance for a barrier filter. The objective lens gives improved results by

creating a larger field than normally obtained, with consequent illumination at the film plane. The exciting filter is fitted in the 7-mm. aperture of the rotating diaphragm wheel.

Film and Developing

The film used as a routine is 36 exposure Ilford HP4 (ASA 300). This is developed with Kodak D76 at 70°F for 30 minutes. This method of developing increased the contrast quality of the photopraphs.

Filter System

A 1-mm. Excitor Filter No. B.G. 12 (Zeiss) is interposed in the diaphragm disc between the flash and the eye, and a 3-mm. Barrier Filter No. GG 14 (Zeiss) in the magnification attachment of the robot camera. This is an absorption filter.

Normal Retinal Circulation[3]

The time taken from injection into the antecubital vein until visualization of the fluorescein at the disc is 12 - 30 seconds.

Distinct phases of the passage of the dyed blood through the retinal vessels are produced.

Early arteriolar phase. The retinal arterioles in the immediate vicinity of the disc rapidly fill within a second of the fluorescein appearing at the disc. The retinal background is dark.

Late arteriolar phase (Fig. 2). Two to three seconds after the injection the entire arteriolar tree fills and becomes fluorescent, but it is observed that the small arteriolar branches do not fill in the order of their distance from the disc. This is due to the fact that the wave-front of dye forms a parabolic surface and does not travel on a plane perpendicular to the main axis of the vessel.

Capillary phase. This phase is already developing during the late arteriolar phase and is evidenced by background fluorescence. At first the latter is patchy, but it then becomes generalized. Capillary nets may also be seen.

Early venous phase (Fig. 2). Smaller veins are filled during the early arteriolar phase. At the stage of late arteriolar filling, mural fluorescence is noted in the main retinal veins. This laminar flow stops at arteriovenous crossings, where there is presumably some turbulence present.

Late venous phase (Fig. 3). The arterioles lose their fluorescence 15 - 20 seconds after the first appearance. The brightness of the venous fluorescence then fades but does not disappear. Disc fluorescence may last for an hour and is probably due to greater capillary permeability at this site.

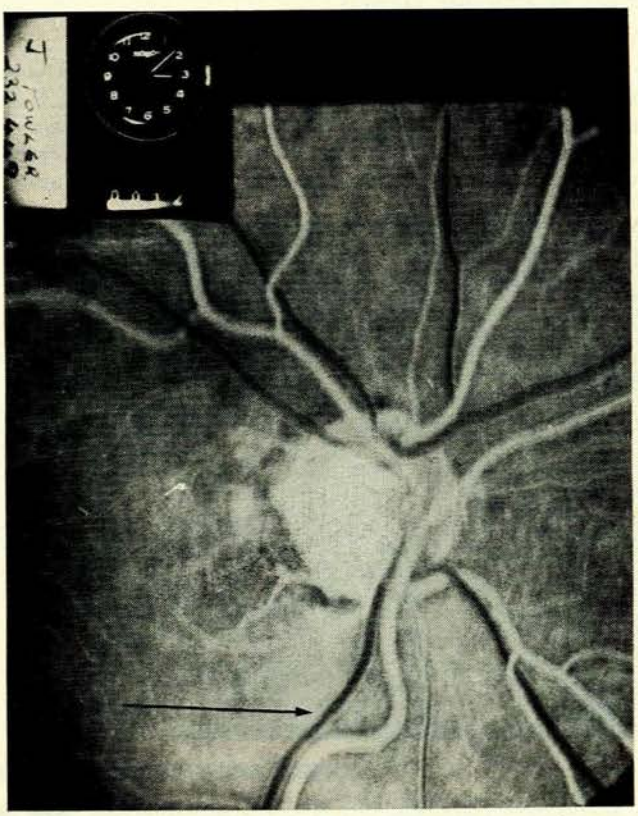

Fig. 2. J.F., aged 44 years. Late arteriolar phase—early venous phase. The arterioles fluoresce and there is background fluorescence. Laminar flow in the main retinal veins is noted (arrowed).

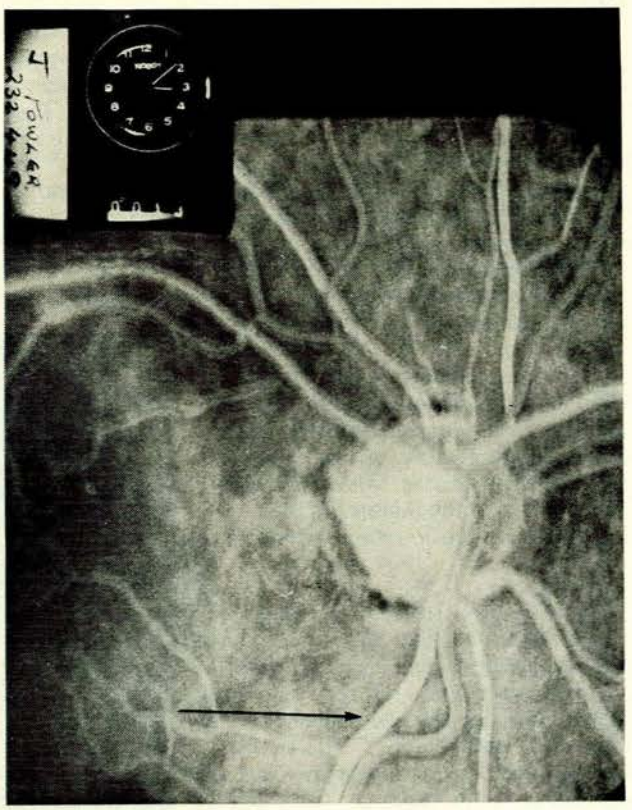

Fig. 3. Same patient as Fig. 2. Early venous phase—late venous phase. Laminar flow stops at arteriovenous crossing and entire vein fluoresces (arrowed).

Late-phase fluorescence.[4] Persistent fluorescent mottling then occurs and lasts until the end of the late venous phase. Its production is not completely understood and has been attributed to the slow rate of turnover of the fluorescein in the choroid, persistent staining of the sclera[5] and even altered tissue permeability disturbances of the overlying pigment epithelium.[6,7]

DISCUSSION

By means of a simple technique it is now possible to obtain increased visibility of the vessels and the blood flow and also to record the pattern of the retinal vasculature.

Apart from a yellowish discoloration of the skin and a bright yellow colour of the urine during the first few hours after the injection, the patient suffers no discomfort. To date, only one case of anaphylactic reaction (non-fatal) has been recorded.[8] This was in a hypersensitive individual suffering from hayfever, partial respiratory obstruction, food allergy and skin allergy. The rate of loss of fluorescein from the plasma is rapid, disappearing a few minutes after the injection of the dye.

A few conditions will be described to illustrate the practical applications of fluorescein angiography.

Hypertension

In the young hypertensive patient there is diffuse spasm of the retinal arterioles, while in the older patient, because of 'involutionary sclerosis',[9] irregularities of the vascular calibre are noted as well as segmental narrowing (Figs. 4 and 5). At the site of damaged, degenerate arterial walls there is fluorescent staining by selective absorption.[10] The dye may diffuse into the surrounding retina and into the vitreous. It is important to note that normal retinal vessels are almost impermeable to fluorescein.[10-12]

Micro-aneurysms can be demonstrated with fluorescein angiograms in association with 80% of soft exudates and also in relation to the haemorrhages of hypertension.[10]

Fluorescein studies suggest that multiple areas of increased diffusion of the dye from damaged vessels are a characteristic feature of the vascular pathology associated with soft exudates and are not minute infarcts related to occlusion in retinal arterioles.[9]

Diabetes

Vasculopathy such as irregularity and tortuosity of the veins is obvious (with fluorescein angiography). Micro-aneurysms which are not seen with the ophthalmoscope may be revealed with fluorescent photography.[13] The circulation through micro-aneurysms varies depending on its type, i.e. 'blow-out', 'loop' or 'onion layer'. At the sites of micro-aneurysms, leakage into the surrounding retina may occur. The neovascularization of *rete mirabile* and *retinitis proliferans* become obvious, and at the site of these new vessels, stasis of blood and transudation of the fluorescein occur.[14] The centre of hard exudates does not stain, but staining may occur at the periphery.[15]

Vascular Occlusion

Fluorescein photography is most helpful with vascular occlusion for it can reveal features otherwise not discernible with the ophthalmoscope, e.g. narrowing and beading of arterioles, disappearance of arteries and avascular areas of retina.[16,17]

It is possible to show that vascular occlusion (due to either an embolus or a thrombus) may not be complete. The field-loss in these cases is probably due to the blood supply of the segment of retina involved being cut off for a period long enough to cause permanent defect of the retinal function, and not due to complete arterial occlusion.

Retinal oedema is usually associated with vascular occlusion but it is of interest that there is no increased penetration of the dye into the area of retinal oedema. In fact, the oedema shadows the underlying fluorescein of the choroid.

Dollery *et al.*[18] injected very small beads of glass directly into the carotid arteries of pigs, causing retinal arterial occlusion. In this classical work they were able to demonstrate capillary circulation, and confirm the behaviour of fluorescein in relation to the arterial wall damage, i.e. that leaking occurs only where the vascular endothelium has been damaged by an embolus or a thrombus. In cases of malignant hypertension the leaking points occur at local areas of arteriolar necrosis.

Papilloedema

Fluorescein angiography is of particular value with pseudopapilloedema and plerocephalic papilloedema.[19] In the latter there is increased permeability of the vessels of the optic disc, and fluorescein diffuses into the extravascular space surrounding the disc and is maximal above

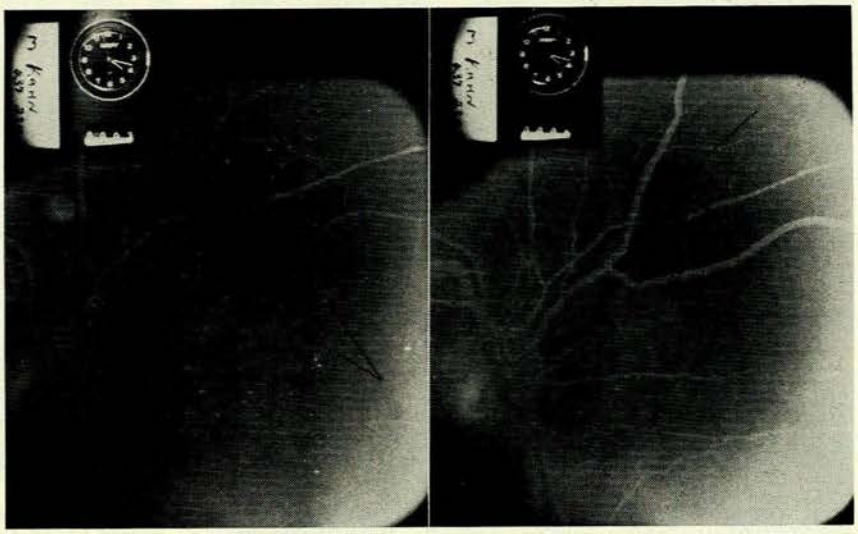

Fig. 4 *Fig. 5*

Fig. 4. Hypertensive patient aged 41 years. Late arteriolar phase—early venous phase. There is irregularity and tortuosity of the retinal arterioles due to involutionary sclerosis (arrowed). Fluorescence of the main retinal veins is noted (arrowed). *Fig. 5.* Same patient as Fig. 4. Early venous phase—late venous phase. The entire vein fluoresces and there is arteriovenous nipping (arrowed).

and below the disc (Figs. 6 and 7). Extravasation occurs particularly in the vicinity of the larger retinal vessels.[26]

Pseudopapilloedema due to hypermetropia and abnormal glial membranes of the disc show a normal pattern of flow and no leakage of dye at the disc.

Drüsen of the disc may simulate a swollen optic disc.

There are four types of drüsen at the disc: peripapillary drüsen, exposed drüsen, partially exposed drüsen and intrapapillary (or buried) drüsen.[20] The last form may be extremely difficult to diagnose, but in the remaining 3 forms, the margin of the drüsen fluorescein is well demarcated and is nodular. The disc fluorescence is of irregular density and there is no extension of the fluorescein along the retinal vessels, nor is there extravasation into the peripapillary space.

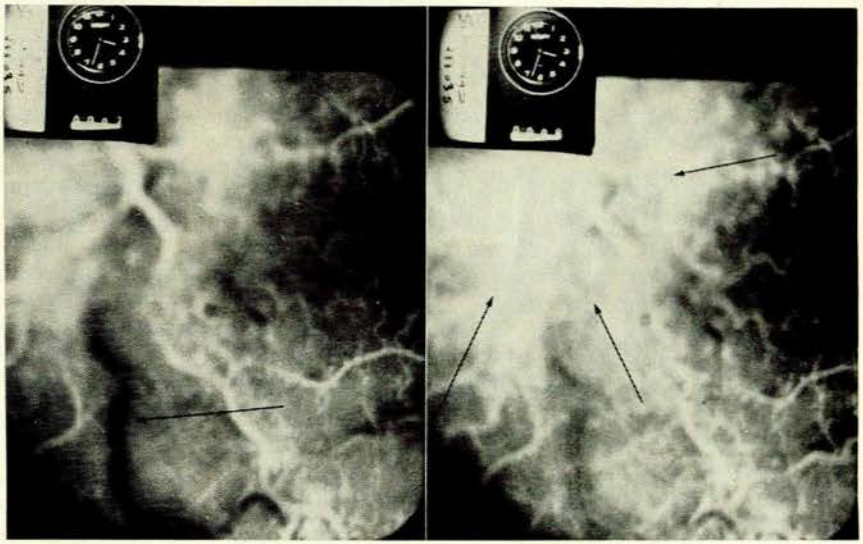

Fig. 6 *Fig. 7*

Fig. 6. E.S., aged 22 years, with central retinal vein thrombosis and papilloedema. Late arteriolar phase—early venous phase. There is extravasation of the dye in the peripapillary region and marked tortuosity of the veins is noted (arrowed).
Fig. 7. Same patient as Fig. 6. Late venous phase of Fig. 5, showing peripapillary extravasation of dye (arrowed).

Malignant Melanoma

It is often difficult to differentiate a benign naevus of the choroid from malignant melanoma, especially if the latter is flat and does not demonstrate an increased radioactive uptake. There is instant granular fluorescence of the naevus which fades after about 30 minutes, while in malignant melanoma the local build-up of the fluorescein is gradual, increasing in an irregular, blotchy pattern for at least 30 minutes and persisting for an hour or more.[21]

In addition, fluorescein angiography has been used to clarify the fundal picture of the blood dyscrasias, the vascular structure of the Von-Hippel-Lindau disease and the vascular disruptions around areas of choroidoretinitis.[22]

This is a preliminary report dealing with the scope of fluorescein photography. Its uses are protean, and to cope with the investigations and trials envisaged a special unit is being set up at Groote Schuur Hospital and the University of Cape Town.

SUMMARY

The scope of fluorescein angiography of the retinal circulation is reviewed and various conditions which illustrate the practical applications of the technique are described, as are the technical details and apparatus required.

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