Studies by fluorescence photography of papilloedema in malignant hypertension¹

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Hyperaemia was noted to be an important feature of optic neuritis in 1860 by Graefe who described a 'swelling, reddening, and cloudiness of the optic disc which derives from my conception of mechanical hyperaemia'. Although a distinction in terms of aetiology is now made between papilloedema and true optic neuritis, Paton and Holmes (1911) noted almost identical ophthalmoscopic appearances in the two conditions. Duke-Elder (1940) attributed the increase of redness of the optic disc in papilloedema to the injection of small vessels. Michaelson and Campbell (1940) described an asymmetrical dense capillary network around the optic disc predominantly on its temporal side, and attributed papilloedema to leakage of plasma from this damaged peripapillary net. Niedermeier (1956) was able to demonstrate the leakage of methylene blue injected intravenously in white rabbits with experimental papilloedema. The presence of the peripapillary net was broadly confirmed by Ashton (1951) using an Indian ink injection technique, although some doubt on the layered pattern of this net was suggested by the trypsin digestion experiments of Touissant, Kuwabara, and Cogan (1961).

The purpose of the present paper is to describe the use of fluorescence angiography to investigate patients with papilloedema, and particular attention is paid to vascular abnormalities in the capillaries of the optic disc and leakage from them.

MATERIALS AND METHODS

In the present study, the photographic records of 36 patients with papilloedema, suspected papilloedema, or normal optic discs are reviewed. It forms part of a larger study which was begun in 1959 in order to document changing retinal pathology in hypertensive patients. Thirty-one of the patients in the group had hypertension and four who had normal optic discs were photographed because of diabetes mellitus. One patient with neurological papilloedema was also studied. All the patients had the optic fundi photographed using a modification by Dollery, Hodge, and Engel (1962) of the original retinal fluorescence technique of Novotny and Alvis

(1961). In 28 of 36 patients, 250 mg. doses of fluorescein were injected into the superior vena cava by a 1 mm. diameter polythene catheter inserted into a vein of the antecubital fossa. In eight patients, the right eye was photographed using a similar catheter positioned in the innominate artery via the brachial using the Seldinger technique. Through this catheter between 15 and 50 mg. of fluorescein was injected. Photographs were taken at intervals of 1 to 2 seconds in nearly all patients during the first transit of the dye through the retinal vessels. Late pictures were then taken after an interval of at least 10 minutes. The HPS film was developed by a standard technique (Dollery *et al.*, 1962). The unmodified Carl Zeiss fundus camera was also used to take colour transparencies of the optic disc on each occasion.

DENSITOMETRY The density of fluorescence of the optic disc was measured from the HPS negatives by means of a Joyce Loebel double-beam recording microdensitometer. In these measurements, the zero for the instrument was provided by the retina adjacent to the optic disc; the maximum deflection was noted and measured from a graph.

COLOUR PHOTOGRAPHS The colour transparencies were then inspected, and the optic disc appearances were classified (without knowledge of the densitometer readings) on the basis of a pink colour, loss of physiological cup, haziness of the disc surface with the retinal vessels surrounding in sharp focus, and blurring of the margin of the disc. When some, but not all, of the features were present, the papilloedema was considered doubtful. The presence of soft exudates was also noted. The gradings were:— 1 Normal optic disc, 2 papilloedema, 3 doubtful papilloedema with soft exudates, 4 doubtful papilloedema without soft exudates, and 5 soft exudates without papilloedema.

AREA OF OPTIC DISC FLUORESCENCE The geographical extent of the fluorescence was compared with that of the margins of the optic disc on the colour transparencies in five patients. This was done by projecting the fluorescence negative followed by the colour transparency on a screen and making drawings of the image at a fixed distance and magnification. The drawings were then traced onto graph paper and the areas of the optic disc and fluorescent zones together with that of any retinal oedema were determined by counting the squares.

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RESULTS

VASCULAR ABNORMALITIES The normal optic disc has only a few vessels visible on its surface by either colour or fluorescence photography (Fig. 1). The oedematous disc is pink or red but individual 'new' vessels cannot usually be identified on its surface. Fluorescence studies reveal intense vascularity of the nerve head under these circumstances. Most of the patients studied had papilloedema caused by malignant hypertension but similar changes were seen in a patient in whom papilloedema was associated with cerebral tumour.

Figure 2 is a print prepared from a colour transparency of the right optic fundus of a man aged 40 with malignant hypertension. The optic disc outline is hazy and irregular, and the original colour photograph showed pinkness of the disc with loss of the physiological cup characteristic of papilloedema. The retinal venules over the optic disc were in crisp focus while those lying in the adjacent retina were slightly blurred. Figure 3 shows a fluorescent photograph of the same area of the eye taken as the fluorescent dye first fills the arterioles. Note the dense network of minute blood vessels filling on the surface of the optic disc. Figure 4 is taken just over one second later. Again, the network of dilated capillaries is seen, and many of these cascade at random from the disc onto the surrounding retina. Bright pin-points of fluorescence at the optic disc margin represent capillary microaneurysms. There is only one tiny area of haemorrhage which appears as a dark streak inferior to the disc and well away from its margin. Figure 5 was taken 10 minutes after the dye injection and shows a general fluorescence spreading over the optic disc area. These changes, in varying degree, were seen in all the patients with malignant hypertension who had papilloedema. Similar changes, of a more advanced degree, were seen in a 39-year-old man with papilloedema due to secondary carcinomatous deposits in the brain. Figure 6 is a print made from a colour transparency of this patient's retina and Fig. 7 shows the fluorescent angiogram taken as the dye passes from the retinal arterioles into the vein. The most striking feature of this photograph was an extensive, irregular and intricate network of small vessels over the optic disc. These vessels are wider than normal retinal capillaries and they interlace and spiral at random, spilling over the edges of the optic disc onto the surrounding retina. Bright fluorescent dots are visible at the edge of this vascular network; these are capillary aneurysms which fill almost as soon as the retinal arterioles.

DENSITY OF LATE FLUORESCENCE Figure 8 shows the densitometry readings plotted out in such a way that

FIG. 1. Fluorescence photograph of a normal optic disc as the dye circulates through the arterioles into the veins. Only a few small vessels fill on the disc surface.

they can be compared with the appearance of the optic disc graded from colour transparencies of the optic fundus. If the late fluorescence densitometry readings of patients with papilloedema are compared with those of patients with normal optic discs, an almost complete separation is seen. Twenty-one out of 23 papilloedematous discs had a late fluorescence density of over 2.5 arbitrary units. By contrast, only one of 11 optic discs which were graded as normal has a reading of over 2.5. A statistical comparison of the means of the two sets of readings showed that the difference was highly significant ($P < 0.001$). Photographs of optic discs from patients with doubtful papilloedema were divided into those with soft exudates and those without. While the numbers in these groups is small, patients with doubtful papilloedema and soft exudates have readings which are slightly higher than those without soft exudates. A comparison of the means showed a statistically significant difference ($P = < 0.01$). Three patients had soft exudates with a clinically normal optic disc and the late fluorescence density varied from 1.3 to 2.2. Thus it fell within the normal group (patients without papilloedema or soft exudates). Those patients in whom fluorescein was injected by the arterial (innominate artery) route are marked with open circles in Figure 8. Although they are not strictly comparable owing to the greater local concentration of fluorescein injected into the right optic fundus, the density measurements follow the same pattern.

AREA OF FLUORESCENCE The areas of papilloedematous optic disc, retinal oedema (where present)

FIG. 2.

FIG. 2. *Print made from a colour photograph of a patient aged 40 with malignant hypertension. Note the swelling of the disc with blurring of its margins and dilatation of the veins.*

FIG. 3.

FIG. 3. *Fluorescence photograph of the same patient as in Fig. 2, taken three seconds after arterial injection of fluorescein. The arterioles are filling with dye (white lines) and early filling of abnormal capillary loops is seen over the swollen disc.*

FIG. 4.

FIG. 4. *Fluorescence photograph of the same area as Fig. 3, but L, two seconds later; there are numerous dilated capillary loops on the disc surface and aneurysms at the periphery.*

FIG. 5.

FIG. 5. *Fluorescence photograph of the same area as in Fig. 4, taken ten minutes after the first dye injection. The nerve head is diffusely fluorescent.*

FIG. 6. From a colour transparency of the optic disc of a man aged 39 with cerebral secondary deposits from a bronchial carcinoma of anaplastic type. There is severe papilloedema, the veins are dilated, and there are small haemorrhages at the edge of the disc.

FIG. 7. Fluorescence photograph of the same area as Fig. 6, taken four seconds after arterial injection of dye. The arterioles have filled and some dye is seen near the edge of the veins in which there is laminar flow. The whole nerve head is covered with dilated and tortuous capillaries. There are numerous aneurysms at the periphery of the swollen optic disc.

FIG. 8. Plot of the density of fluorescence in the nerve head of normal subjects, patients with papilloedema, doubtful papilloedema with and without soft exudates, and those with soft exudates but a normal disc.

and late fluorescence were compared in five patients by the projection technique. The results are set out in Table I and the disc area is normalized to 100 arbitrary units in each instance. The area of late fluorescence occupies a considerably larger area of the retina than that of the optic disc on the colour transparency. Figure 9 shows an example of tracings made from a hypertensive patient with severe papilloedema and retinal oedema. The area of fluorescence corresponds more nearly to the area of retinal oedema than to the optic disc. However, reference to Table I indicates that this is not always so, as the area of retinal oedema may be larger or smaller than the fluorescent area. It should be added that retinal oedema is a difficult feature to outline accurately from a simple retinal photograph.

The fluorescent photographs of six patients with papilloedema were examined in order to determine whether the late fluorescence predominated in the temporal side of the optic disc, that is, whether it follows the asymmetry of the peripapillary network of vessels (Michaelson and Campbell, 1940). In

TABLE I
AREA OF OPTIC DISC AND SURROUNDING OEDEMA IN COLOUR AND FLUORESCENCE PHOTOGRAPHS OF PATIENTS WITH PAPILLOEDEMA

Patient	Grade of Papilloedema	Area of Optic Disc Colour Photography	Fluorescent Area	Retinal Oedema Area Colour Photography
I.H.	++	100	1155	575
L.B.	++	100	307	494
C.O'D.	+	100	198	—
A.M.	+	100	260	325
W.B.	+++	100	468	325

FIG. 9. A tracing of the area of an optic disc measured from fluorescence and colour photographs from a patient aged 19 with malignant hypertension.

only two patients could any bias to the temporal side be seen.

An examination of the fluorescent photographs of the 11 patients with normal optic discs was made in order to detect any abnormalities of the capillaries, particularly in those patients who had fluorescence densitometry readings at the upper end of the scale. All of these patients showed optic disc capillaries of normal size and there were no aneurysms. The capillaries were strictly confined by the optic disc edge. Three of the patients had a tendency to concentrate fluorescein at the edge of the optic disc, and one of them had a densitometry reading of over 2.5 units.

The fluorescent photographs of eight patients with doubtful papilloedema were then examined, of whom four had soft exudates and four did not. Three of the four patients with soft exudates showed areas of fluorescence at the disc border suggesting capillary microaneurysms or capillary damage. In the four patients without soft exudates, one had a pinpoint of bright fluorescence on the optic disc surface and another at the disc border. Two of these patients had a faint halo of fluorescence surrounding the optic disc with small areas of fluorescein leakage well away from the optic disc. None of these four patients had soft exudates on colour photographs. One had a small flame-shaped haemorrhage, but not corresponding to the area of fluorescein leakage.

DISCUSSION

The principal contribution of fluorescence photography to the study of papilloedema has been the demonstration of some remarkable vascular abnormalities in the region of the optic disc: the most striking are capillary dilatation, aneurysm formation, and leakage from damaged vessels.

CAPILLARY ABNORMALITIES The presence of dilated spiralling vessels, filling at the same time as capillaries, which spill over the edge of the optic disc, raises the question of whether or not these are damaged capillaries which normally exist in the peripapillary area or new vessels such as those in diabetic retinopathy. In favour of the first suggestion is the histological dissection work of Michaelson and Campbell (1940), who described an intricate peripapillary network consisting of three layers of capillaries plus an additional superficial layer. In other areas of the retina there are but two layers, but the macula has three. Against this explanation are the facts that the fluorescent vessels do not show any bias towards the macula as does the network of Michaelson and Campbell, and the macula itself, with a triple layer of capillaries, does not show any preponderance of fluorescence. Furthermore, trypsin digestion work (Kuwabara and Cogan, 1960; Touissant *et al.*, 1961) casts doubt on the existence of layers in the capillary system. The vascular leakage and irregularity of their course lend some support to the view that they are newly formed.

The presence of microaneurysms in the optic disc region is shown by circular points of fluorescence. Haemorrhages in the peripapillary area probably arise from aneurysms in the peripapillary capillary network. Aneurysms are distinguished from leakage by disappearance of fluorescence after several seconds (Figs. 4 and 7) in contrast to points of leakage which persist and spread. The demonstration of microaneurysms in papilloedema is of interest because these also accompany soft exudate formation (Hodge and Dollery, 1964).

AETIOLOGY OF VASCULAR CHANGES The aetiology of the intense vascularity of the swollen nerve head is of considerable interest. The simplest explanation would be that these changes arise because of swelling caused by increased intracranial pressure. Pickering (1934) noted papilloedema in 12 out of 14 hypertensive patients with a cerebrospinal fluid pressure of over 250 mm. water. Kincaid-Smith, McMichael, and Murphy (1958), reviewing 197 patients with malignant hypertension, measured the cerebrospinal fluid pressure in 44 of these. While the mean pressure was found to be high at 205 mm. water, the pressures ranged from 70 mm. to 380 mm. water. These authors noted, in addition, that the papilloedema in one patient was worsening while the cerebrospinal fluid pressure was actually falling. Thus raised cerebrospinal fluid pressure is a common but not invariable association of papilloedema, and there may be some other mechanism such as direct damage to the arterioles supplying the optic disc. Soft exudates usually precede papilloedema in patients with hypertension

and these lesions are associated with damage to small arterioles and capillaries with increased leakage of fluorescence (Hodge and Dollery, 1964). Increased leakage of fluorescence is characteristic of abnormal vessels, and is seen in diabetic retinopathy with neovascularization or retinitis proliferans (Scott, Dollery, Hill, Hodge, and Fraser, 1964) as well as in hypertension.

The vascular changes are intense, for sheets of new vessels may spill off the disc onto the surrounding retina. However, areas of retina more distant than the optic disc appear normal apart from the dilatation of the veins. This suggests that the changes in the nerve head are not part of some general mechanism such as might occur if the retinal venous pressure was raised by obstruction to the venous outflow. The present evidence scarcely justifies the assertion that the new vessels provide the sole or even the main clue to the pathogenesis of swelling of the disc. Further evidence is needed about the relationship between structural and metabolic changes in the nerve head and alterations in cerebrospinal fluid pressure. While a raised cerebrospinal fluid pressure, communicated down the sheath of the optic nerve, may account for the swelling of the optic disc, it is not easy to see how this could cause the vascular change.

DOUBTFUL PAPILLOEDEMA The presence of relatively high fluorescent density in one or two of the patients with doubtful papilloedema (Fig. 8) and the apparent difference between the values with and without soft exudates prompted scrutiny of the capillaries on the optic discs in this group. Areas of leakage and a few capillary microaneurysms were seen in those with soft exudates, but there were also changes, though less marked, in those without soft exudates. It seemed likely that the gradation between papilloedema, doubtful papilloedema with soft exudates, and doubtful papilloedema without soft exudates were only differences of degree.

RETINAL OEDEMA AND PAPILLOEDEMA It is interesting to note that in patients with papilloedema, the area of late fluorescence greatly exceeds that of the optic disc as measured from conventional photographs. Part of this increased area may be due to retinal oedema. It seems likely that retinal oedema, where present, is produced by leakage from the peripapillary capillary network. The failure of the late fluorescence area to correspond closely to the retinal oedematous area is probably due to difficulties in defining retinal oedema on colour photographs. Occasionally, the retinal oedema area is surrounded by a boundary of hard exudates and it is perhaps significant that in Fig. 9, where hard exudates are present, the areas of retinal oedema and late fluorescence correspond.

DIAGNOSTIC APPLICATION The demonstration of abnormal capillaries on and around the optic disc, together with leakage of fluorescein, is of potential value in differentiating true from doubtful papilloedema, and as a research tool in estimating the vascular reactions in the optic nerve head in a variety of diseases.

SUMMARY

The technique of retinal fluorescence photography has been applied to 36 patients with papilloedema, suspected papilloedema, or normal optic discs. A grossly abnormal dilated plexus of capillaries on and around the optic disc has been shown in the papilloedematous patients. In addition there are microaneurysms in this area. Gross leakage occurs from these capillaries and the area of abnormal fluorescence greatly exceeds that of the optic discs as judged from colour photographs. The extent of vascular abnormalities was graded between 'doubtful papilloedema' on the one hand and increasing degrees of true papilloedema on the other.

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