Macular and perimacular vascular remodelling in sickling haemoglobinopathies

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Peripheral retinal vascular changes in patients with sickling haemoglobinopathies (Welch and Goldberg, 1966; Goldberg, 1971a, b; Condon and Serjeant, 1972a, b, c) include both non-proliferative and proliferative lesions. Dynamic vascular remodelling of the peripheral vasculature of the retina has also been documented (Galinos, Asdourian, Woolf, Stevens, Lee, Goldberg, Chow, and Busse, 1975). Reports of posterior pole changes in patients with sickling haemoglobinopathies have described these changes as either acute, such as central retinal artery occlusion and macular arteriolar occlusions (Knapp, 1972; Acacio and Goldberg, 1973; Ryan, 1974), or as chronic manifestations of vascular occlusions, including microaneurysm-like dots, dark and enlarged segments of terminal arterioles, hairpin-shaped venular loops, and pathological avascular zones (Stevens, Busse, Lee, Woolf, Galinos, and Goldberg, 1974). Visual function may or may not be affected as a result of these vascular changes (Goldberg, 1973; Stevens and others, 1974).

This paper further documents these posterior pole changes and characterizes their evolution as determined prospectively over a long follow-up period.

Patients and methods

During the last three years the Sickie Cell Eye Clinic screened over 400 patients with sickling haemoglobinopathies. The purpose was to identify patients with early stages of proliferative retinopathy. Fluorescein angiography was performed whenever there was the least suspicion of retinopathy.

Since macular changes were found in some 20 per cent of the clinic's population (Stevens and others, 1974) more attention and careful evaluation have been given to the study of the posterior pole. Kodachrome photographs and fluorescein angiograms of the posterior pole were taken in all patients at four-month intervals.

Fluorescein angiography was performed in the manner of Novotny and Alvis (1961) using a Zeiss Fundus-Flash III camera. Kodachrome II film was used for colour photography; angiograms were taken with Kodak Tri-X film processed in Kodak D-11 (1:1 dilution) for nine minutes at 70°F. Spectrotech exciter and barrier filters were used.

After the injection of fluorescein (10 per cent fluorescein sodium solution), through an indwelling paediatric scalp vein needle inserted near the patient's antecubital fossa, phase angiograms of the macular area were taken at the rate of one frame per second. The fine capillary network of the posterior pole was selectively focused. Repeat injections of small increments of 1 to 1.5 ml were given as needed to maintain a high degree of fluorescent contrast within the macular capillary network. Careful attention was also given to the region of the horizontal vascular 'raphe', which is similar in location to the horizontal nerve fibre raphe (Vrabec, 1966). Many vertically orientated arterioles appear to terminate along this vascular raphe.

Patients with posterior pole abnormalities were investigated for colour vision abnormalities and visual field changes. Pseudoisochromatic charts, the Farnsworth D-15 panel, Farnsworth-Munsell 100-hue test, and the Nagel anomaloscope were used in assessing colour vision. The tangent screen, Goldmann perimeter, and Amsler grid were used to detect visual field changes. More recently we used static perimetry to assess minute visual field abnormalities.

Results

One hundred consecutive patients with various haemoglobinopathies underwent selective fluorescein angiography of the macular area and the area of the temporal raphe. Altogether 41 of the patients had homozygous sickle-cell disease (HbSS), 36 had sickle cell-haemoglobin C disease (HbSC), 15 had sickle cell-thalassaemia disease (HbS-thal), seven had sickle cell trait (HbAS), and one had homozygous haemoglobin C disease (HbCC). A total of 29 patients had abnormalities of the macular area, the temporal raphe area, or both. Of the patients with abnormal maculae 13 (44.8 per cent) had HbSS, 13 (44.8 per cent) had HbSC,

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FIG. 1 *Case 1. Fluorescein angiogram of right eye before acute obstructive episode of normal macular vasculature*

and three (10.4 per cent) had HbS-thal. Of the patients with different haemoglobinopathies 31.7 per cent of HbSS, 36.1 per cent of HbSC, and 20 per cent of HbS-thal patients had abnormal maculae. All HbAS patients and the single HbCC patient had normal macular angiograms.

CASE REPORTS

Case 1

A 26-year-old Black woman with sickle cell-haemoglobin C disease (haemoglobin S 52 per cent; haemoglobin C 48 per cent) was admitted to the Eye and Ear Infirmary in February 1974 because of vitreous haemorrhage in the left eye. Eight months previously

she had been found to have stage I retinopathy (peripheral arteriolar occlusions) (Goldberg, 1971b) in the left eye. On admission her general physical examination was normal. Blood pressure was 105/80 mmHg. Her fasting serum glucose level, oral glucose tolerance test, and serological tests for syphilis were normal.

Her visual acuity was 20/20 in the right eye and 20/70 in the left. Slit-lamp examination of the anterior segment revealed minimal conjunctival sickling sign (Paton, 1962) and stromal atrophy of both irides (Galinos, Rabb, Goldberg, and Frenkel, 1973). Ophthalmoscopy of the right eye showed extensive areas of stage I and II retinopathy. The macular area looked normal. Ophthalmoscopy of the left eye showed a recent vitreous haemorrhage occupying the lower temporal quadrant with extensive sea fan neovascularization extending from

FIG. 2 Case 1. Right fundus on day cotton-wool patches developed (four days after Fig. 1). Salmon-patch haemorrhage evident at 9 o'clock meridian. Multiple occluded silver-wire vessels present at superotemporal quadrant

12 to 3 o'clock with evidence of recent haemorrhage. After 24 hours of complete bed rest fluorescein angiography confirmed the presence of stage I and II retinopathy in the right eye with normal macular vasculature (Fig. 1). The left eye showed perfusion and leakage of dye from the previously photocoagulated sea fans.

On the fifth hospital day ophthalmoscopy of the right eye showed cotton-wool patches of the posterior pole (Fig. 2) with one of the patches extending to the superior border of the fovea. The patient had no visual symptoms. Vision was still 20/20. Visual field testing on the tangent screen and with the Goldmann perimeter was normal. Amsler grid testing indicated no scotomas. Colour vision testing was normal with the Ishihara plates and the D-15 panel test. By fluorescein angiography multiple arteriolar occlusions corresponded to the areas of the cotton-wool patches (Figs 3 and 4).

At the macular area a single capillary bridged the superior aspect of the foveal avascular zone (FAZ). Forty-eight hours after this acute episode ophthalmoscopy showed no remarkable change. Fluorescein angiography showed persistent closure of all the previously closed arterioles (Fig. 5a). The single capillary at the superior border of FAZ was not perfusing at this time (Fig. 5b). Retrograde filling of one of the occluded vessels was evident. There was no change in the visual acuity, visual fields, and colour discrimination.

Two months later the patient complained of blurred vision in the right eye, which now had visual acuity of 20/50. There was evidence of a recent vitreous haemorrhage from a newly developed equatorial neovascularization at the 11 o'clock meridian. Fluorescein angiography, which the vitreous haemorrhage obscured somewhat, showed reperfusion of all the previously occluded arteri-

FIG. 3 Case 1. Fluorescein angiogram of right fundus 48 hours after cotton-wool patches developed. An arteriolar occlusion corresponds to each cotton-wool patch

oles in the macular region except one (Fig. 6). The capillary at the superior border of the FAZ was reperfusing, and three newly developed venular loops were directed into areas of non-perfused retina (Fig. 6). Five months after the initial acute episode and three months after her last visit visual acuity in the right eye was 20/20. Ophthalmoscopy showed the vitreous haemorrhage to have resorbed completely. The cotton-wool patches had also resorbed (Fig. 7). Their locations could be identified as dimpled facets, probably representing localized areas of retinal atrophy. On fluorescein angiography all except one of the previously occluded arterioles perfused. The capillary beds surrounding the areas of venular loops were more prominent and were directed into areas of capillary bed drop-out (Fig. 8). One capillary clearly separated the FAZ from the

adjacent avascular area. One week later, fluorescein angiography showed further changes in the character of the venular loops (Fig. 9).

Case 2

A 30-year-old Black man with sickle-cell anaemia (S 95.4 per cent, A₂ 1.7 per cent, F 2.9 per cent) was first seen at the Eye and Ear Infirmary in December 1972 as a screening patient with no visual complaints. Best corrected vision was 20/20 in the right eye and 20/25+ in the left. Both conjunctivas showed fairly numerous sickling signs (Paton, 1962). By ophthalmoscopy the right posterior pole appeared normal. Ophthalmoscopy of the left posterior pole showed several terminal arteriolar segments which were larger

FIG. 4 Case 1. Fluorescein angiogram of right posterior pole on day cotton-wool patches developed. Longer arrows indicate site of arteriolar occlusions. Dependent vascular beds not perfused. Shorter arrow indicates single capillary bridging superior aspect of FAZ. A, arteriole; V, venule

and darker than normal, suggesting obstructed vascular segments. The peripheral retina in both eyes was pale and vessels were thin and sparse. A fibrovascular nodule was seen in the left equatorial zone at the 9 o'clock position.

Fluorescein angiography of the left macular region showed a normal-looking FAZ. Just temporal to the FAZ were three non-filling terminal branches corresponding to the dark segments described above (Fig. 10). The capillary bed surrounding these vessels was sparse. Fluorescein angiography of the right macular area was normal. Visual field testing on the Goldmann perimeter and the tangent screen showed no scotomas, and the responses to the pseudoisochromatic plates and the Farnsworth D-15 panel were normal. Static perimetry with the Goldmann perimeter through the area temporal

to the macula showed an absolute scotoma which had not been found with ordinary kinetic perimetry with the Goldmann apparatus or the tangent screen.

Fasting serum glucose level and oral glucose tolerance test were normal, and results of serologic tests for syphilis were normal.

At follow-up examination on 9 April 1974 his visual acuity was the same. The previously dark-coloured arteriolar segments in the left fundus were of normal colour. An arteriolar segment in the right fundus looked darker in colour, suggesting occlusion. By fluorescein angiography the previously occluded vessels in the left eye were perfusing again (Fig. 11) but the capillary meshwork round them remained sparse. In the right eye the dark arteriolar segment seen on ophthalmoscopy was non-perfusing with a sparse capillary meshwork

FIG. 5 Case 1. Fluorescein angiograms of right posterior pole 48 hours after acute episode. (a) Shows persistent closure of all involved arterioles (longer arrows). Shorter arrow indicates non-perfusion of single capillary bridging superior border of FAZ. R indicates retrograde filling of one of occluded vessels; A, arteriole; V, venule. (b, opposite) Enlarged view of FAZ showing non-perfusion of single capillary bridging superior border of FAZ (arrow). Compare with Fig. 4

round it. The perifoveal capillary meshwork was also wider than normal, suggesting true capillary loss.

On 18 April the left eye showed no change ophthalmoscopically or angiographically. Ophthalmoscopy of the right eye showed the previously dark arteriolar segment to be of normal colour. Fluorescein angiography showed reperfusion of this previously occluded vessel. However, there was a capillary occlusion at the temporal aspect of the FAZ exaggerating the wide perifoveal capillary mesh.

Case 3

A 24-year-old Black man had sickle-cell anaemia

(S 93.3 per cent, F 3.4 per cent, A₂ 3.3 per cent) which had been diagnosed at the age of 4. His visual acuity had always been poor and had been much reduced for over 10 years. When first seen in February 1973 in the screening programme at the Eye and Ear Infirmary his best corrected visual acuity was 20/200 in the right eye and 20/400 in the left eye. The conjunctivas showed the sickling sign (Paton, 1962). By ophthalmoscopy both eyes manifested optic atrophy, paucity of the nerve fibre layer on red-free examination, apparently sheathed and possibly occluded macular arterioles, peripheral arteriolar and venular sheathing, and atrophic-looking peripheral retinal tissue.

Fluorescein angiography of the macular regions of

(5b)

both eyes showed avascular zones at the centres of the maculae that incorporated and were two to three times larger than the normal FAZ. The blood vessel meshwork surrounding these zones consisted mostly of arterioles and venules connected by large anastomoses. There was loss of the normal fine capillary architecture of these areas. Several non-filling segments were noted at the terminal ends of some arterioles. Kinetic perimetry on the Goldmann perimeter showed a central scotoma of 3 degrees on the right and one of 12 degrees on the left. With the left eye the patient made eight errors on the pseudoisochromatic plates and showed a deutan defect on the Farnsworth D-15 panel. With the right eye his response to the colour tests was normal.

On 27 April 1973 ophthalmoscopy of the left fundus showed a dark-looking segment of the superior temporal arteriole (Fig. 12). Fluorescein angiography showed the dark segment to be occluded (Fig. 13a); there were several small vascular occlusions seen ophthalmoscopically. Ophthalmoscopy of the right fundus showed a dark vascular segment of the lower temporal arteriole, and fluorescein angiography showed occlusion of that

FIG. 6 Case 1. Fluorescein angiogram of right posterior pole two months after acute episode. Vitreous haemorrhage partially obscures view. Longer thicker arrows indicate site of arteriolar occlusions, all except one of which have reopened. Shorter arrow indicates reperfusion of the single capillary at superior border of FAZ. Thinner arrows with L indicate venular loops. A denotes arteriole; V, venule

FIG. 8 Case 1. Fluorescein angiogram of right posterior pole five months after acute episode. All previously occluded vessels are reperfusing except one (longer thicker arrow). Venular loops (thinner arrows with L) more prominent than previously noted. Shorter arrow indicates perfused capillary at superior border of FAZ. A denotes arteriole; V, venule

segment (Fig. 14a). On 28 May 1974, there was no change in his visual acuity. The previously dark-looking segment in each eye was of normal colour by ophthalmoscopy. Fluorescein angiography showed perfusion of the previously occluded vascular segments (Figs 13b, 14b).

Ophthalmoscopy on 17 June showed a dark vascular segment of the superior temporal arteriole which was larger than the previously noted one. Fluorescein angiography showed occlusion of the previously occluded vessel, but the site of occlusion was more proximal than the previous one and there was an unsuspected small terminal vascular occlusion of the lower temporal arteriole (Fig. 13c). Ophthalmoscopy of the right eye showed a dark vascular segment at the site of the previous occlusion. Fluorescein angiography indicated reocclusion of the same segment. There was evidence of retrograde filling of the distal segment of this occluded arteriole (Fig. 14c).

Case 4

A 35-year-old Black woman with sickle-cell anaemia (S 97 per cent, A₂ 3 per cent) was screened at the Eye and Ear Infirmary on 29 March 1974. She had no visual complaints, although she had been hospitalized on several occasions for painful crises. Her blood pressure

was normal. Fasting blood glucose and two-hour postprandial glucose levels were normal, as were the results of serologic tests for syphilis.

Vision was 20/20 in both eyes with no refractive error. The anterior segments were normal. By ophthalmoscopy both fundi showed generalized tortuosity of the retinal vessels. The macular areas looked normal. Fluorescein angiography of the right macular area showed an irregularly shaped FAZ (Fig. 15a, b) due to arteriolar occlusion at the 2 and 3 o'clock positions with loss of the nasal arcade of the FAZ. Fluorescein angiography of the left macular area showed a round, regular FAZ which was smaller than the right one (owing to loss of capillaries in the right macula). Kinetic visual fields done on the Goldmann perimeter were normal with no scotomas. Colour vision testing with the pseudoisochromatic plates, Farnsworth D-15 panel, Farnsworth-Munsell 100-hue panel, and the anomaloscope gave normal results.

Four months later there was no change in visual acuity or ophthalmoscopic appearance. By fluorescein angiography of the right macular area the FAZ was smaller than at the previous examination. This was owing to reopening of the occluded vessels at the 2 and 3 o'clock positions and the formation of an arcade at the nasal border of the FAZ. A small capillary which was occluded previously was open at this time (Fig. 15c).

FIG. 7 Case 1. Right posterior pole five months after acute episode. Cotton-wool patches have resorbed

FIG. 12 Case 3. Left fundus showing optic atrophy and a dark-looking segment of upper temporal arteriole (arrow)

(9a)

FIG. 9 Case 1. *Fluorescein angiograms of right posterior pole one week after Figs 7 and 8. (a) Venular loop (open arrow) is supplied by retrograde filling. (b) After complete filling venular loop shows change in shape from previous week. (c, opposite) Enlarged view of posterior pole shows single capillary (solid arrow) bridging FAZ (arrow). A indicates arteriole; V, venule*

(9b)

(9c)

The macular vasculature of the left eye was unchanged.

At examination on 25 February 1975 visual acuity was still 20/20 with no change in her visual field or colour status. Fluorescein angiography of the right macular area showed no change since the previous examination.

Case 5

An 18-year-old Black man with sickle cell-haemoglobin C disease (S 58 per cent, C 42 per cent), was seen at the Eye and Ear Infirmary on 15 June 1973 as a screening patient with no ocular symptoms. Best corrected visual acuity was 20/20 in each eye. There was no conjunctival sickling sign and no iris atrophy. Ophthalmoscopy of the right eye showed a sharply looping terminal venule $1\frac{1}{2}$ disc diameters temporal and slightly inferior to the macula. The left fundus was normal. By fluorescein angiography the vasculature around the FAZ in the right eye was normal. Temporal and slightly inferior to the fovea a terminal venule looped sharply towards a small area where the capillary bed was sparse (Fig. 16a). There were no definite vascular occlusions. The fluorescein appearance of the left macular area was normal. On 12 November 1973 ophthalmoscopy of the right eye showed dark terminal segments of the lower temporal raphe area. Fluorescein angiography confirmed occlusion of these terminal vascular segments (Fig. 16b). There was a small, unsuspected vascular occlusion at the superior border of the temporal raphe. The left eye was normal. Kinetic perimetry with the Goldmann perimeter and Amsler grid showed no scotomas. Colour vision testing was normal. Fluorescein angiography on 19 November 1973 showed reperfusion of all the occluded vessels. After that the patient was lost to follow-up.

Case 6

A 35-year-old Black woman with sickle cell-haemoglobin C disease (S 54 per cent, C 46 per cent), was seen at the Eye and Ear Infirmary with a history of transient blurring vision in the left eye of several weeks' duration. Best corrected visual acuity was 20/25-2 in each eye. The conjunctivas showed minimal sickling sign (Paton, 1962). The vitreous in the left eye showed peripheral yellowish material suggesting old haemorrhage. The equatorial region of both eyes showed several sea fan neovascular formations.

Fluorescein angiography of the right macular area showed a normal FAZ. The spaces of the surrounding capillary meshwork varied more in size than normal (Fig. 17a, b). Temporal to the FAZ there was a pathological avascular zone (PAZ) twice as large as the FAZ. The borders of the PAZ showed tiny beads of fluorescence (Fig. 17a). Fluorescein angiography of the left macular area showed an enlarged, irregularly shaped FAZ with beads of fluorescence at its superior and temporal borders (Fig. 18a).

The tangent screen and Amsler grid examinations showed no scotomas. The patient had normal responses to the pseudoisochromatic plates and Farnsworth-Munsell 100-hue panels.

Examination one year later showed no ophthalmoscopic change in the macular areas. Fluorescein angiography of both maculae showed more loss of capillaries surrounding the FAZ (Figs 17c; 18b, c). There was no change in her visual acuity, fields, or colour discrimination.

Case 7

A 45-year-old Black man with sickle cell-haemoglobin C disease (S 53.2 per cent, C 46.8 per cent) was first seen at the Ear and Eye Infirmary on 16 January 1974 as a screening patient. Best corrected visual acuity was 20/30 in each eye. The conjunctivas showed no sickling sign and there was no iris atrophy. Ophthalmoscopy of the right eye showed a neovascular tuft at the 1 o'clock equatorial meridian. The left eye showed several sea fan neovascularizations extending circumferentially around the equator. Both maculae had abnormal vascular patterns with enlarged foveal avascular areas.

Fluorescein angiography of the right macula disclosed an abnormally shaped FAZ with loss of the vascular arcade at the 10 o'clock meridian of the FAZ (Fig. 19). There was a small venular loop directed into the FAZ. The left macular area showed an abnormally shaped FAZ with loss of the vascular arcade at the 7 o'clock meridian (Fig. 20).

Kinetic visual field testing with the Goldmann perimeter and the Amsler grid manifested no scotomas. Colour vision testing with the pseudoisochromatic plates, Farnsworth D-15, and Farnsworth-Munsell 100-hue panels was normal. During the second year of follow-up the appearance of the left macular area did not change and the character of the venular loop in the right macular area changed somewhat (Fig. 19b).

Discussion

Acute vascular changes at the posterior pole in sickle patients have been characterized by central

(10a)

FIG. 10 Case 2. Fluorescein angiograms of left posterior pole. (a) Arrows indicate three non-filling terminal segments of same arteriole at temporal raphe. (b) Enlarged view of same area. A indicates arteriole

(10b)

FIG. 11 Case 2. Fluorescein angiogram of left posterior pole 16 months after initial examination. Previously occluded vessels are perfused (arrows)

retinal artery occlusions and peripapillary and macular arteriole occlusions (Kabakow, Weimokly, and Lyons, 1955; Conrad and Penner, 1967; Knapp, 1972; Acacio and Goldberg, 1973; Ryan, 1974). Patients with acute vascular occlusion, especially central retinal artery occlusion, usually seek medical advice because of sudden and profound visual loss. Such acute occurrences must be uncommon, however, since only scattered cases have been reported. Branch artery occlusion affecting the macular vessels usually produces central scotomas or loss of vision. Occlusion of fine arteriolar twigs surprisingly may produce no visual disturbances and is therefore not brought to the ophthalmologist's attention. The assessment of the true incidence of these lesions thus becomes difficult.

Chronic abnormalities of the posterior pole have also been reported. Condon and Serjeant (1972a, b, c) reported dilated capillaries and a few microaneurysms of the posterior pole of 10 to 40 per cent of patients, producing no visual symptoms. Since the recognition of chronic macular abnormalities in about 20 per cent of our clinic's population we have examined more carefully the posterior pole of all patients admitted to the clinic using both red-free and direct ophthalmoscopy and selective fluorescein angiography, focusing on the macular vasculature and the area immediately temporal to it.

Out of 100 consecutive patients studied since our initial communication, including some of the originally reported cases, 29 showed some form of posterior pole abnormality—13 with SS haemoglobin, 13 with SC, and three with S-thal. Although vascular occlusions have been reported in patients with AS haemoglobin (Kabakow and others, 1955; Conrad and Penner, 1967), we found no abnormalities in the seven AS patients studied. The posterior pole changes were characterized as microaneurysm-like dots, dark and enlarged segments of arterioles, hairpin-shaped venular loops, pathological avascular zones (PAZ), and widening and irregularities of the foveal avascular zone (FAZ).

In most cases kinetic visual field testing with the tangent screen and Goldmann perimeter did not show any scotomas, even in the presence of large areas of pathological avascular zones. Such preservation of visual function despite lack of normal retinal perfusion has also been described in ischaemic diabetic maculopathy (Kohner, 1971; Bresnick, De Venecia, Myers, and Davis, 1975). Recently we have found that small relative and absolute scotomas can be detected with static perimetry, the scotomas corresponding to these pathological avascular zones.

Colour vision seems to be surprisingly well preserved in these patients with posterior pole abnormalities. Although some patients did have colour vision defects, most were normal.

(13a)

(13b)

FIG. 13 Case 3. Fluorescein angiograms of left posterior pole. (a) Dark segment seen ophthalmoscopically is non-perfusing. Three small occlusions also evident (arrows). FAZ is two to three times larger than normal. (b) One year later: all previously occluded vessels are perfusing (arrows). (c, opposite) One month later: superior temporal arterioles reoccluded (upper arrow). Site of occlusion is more proximal. Small arteriolar occlusion is evident in a terminal segment of inferotemporal arteriole (lower arrow). A indicates arteriole

(13c)

The discrepancy between the angiographic appearance of the posterior pole vasculature and normal visual function (normal visual acuity, colour vision, and fields) suggests that there may be a considerable redundancy of the blood supply to the macula from either adjacent retinal vascular arcades, the choroid, or both.

Our current tests for evaluating macular function may not be as sensitive for detecting early, minute visual function abnormalities, and thus the need for more sophisticated tests is emphasized. However, with more progressive loss of macular vessels visual function eventually becomes abnormal, as tested by currently available techniques.

Most of these posterior pole abnormalities may be attributable to acute vascular occlusions and their sequelae. For example, case 1 showed vascular changes both in the initial acute episode of vascular occlusion and in the more chronic state when some capillaries still were not perfused. The initial pathogenetic event is arteriolar vaso-occlusion. Although primary venous occlusions may occasionally occur, most occlusions in sickling patients occur on the arterial side of the retinal vasculature. Evidence has accumulated recently to show that deoxygenation of blood may occur in the small arteries to a level that is capable of inducing sickling and causing arteriolar occlusions (before the circulating erythrocytes reach the level of the capillaries and the venules) (Harris, Brewster, Ham, and

Castle, 1956; Duling and Berne, 1971). Retinal occlusions may occur in the small arterioles themselves or may be the result of 'log-jamming' in capillaries and 'back stasis' from the sickled cells. Arterial occlusions are not unique to the retinal vasculature as they have occurred in large cerebral arteries (Stockman, Nigro, Mishkin, and Oski, 1972), including the common carotid artery, though larger arteries probably occlude by a different mechanism.

With sudden arteriolar occlusion, when immediate restoration of flow does not occur, a localized area of retinal ischaemia results which is sometimes seen ophthalmoscopically as a cotton-wool patch. Several cotton-wool patches, each corresponding to arteriolar occlusions, were noted in case 1 and were clearly defined by fluorescein angiography. Fluorescein staining of the vessel wall at this stage may denote endothelial damage due to the intraluminal plugs of sickled erythrocytes. To our knowledge, this is the first report of acute arteriolar occlusion resulting in cotton-wool patches in a patient with sickling haemoglobinopathy. These patches represent localized areas of ischaemic necrosis of the inner retinal layers, predominantly the nerve fibre layer. That these lesions occur from occlusion of the precapillary arterioles and adjacent capillaries has been documented in patients with hypertensive and diabetic retinopathy (Esmann, Lundbaek, and Madsen, 1963; Kohner, Dollery,

(I4a)

(I4b)

FIG. 14 Case 3. Fluorescein angiograms of right posterior pole. (a) Dark segment seen ophthalmoscopically is not perfusing (arrow). (b) One year later : reperfusion of same segment (arrow). (c, opposite) One month later : reocclusion of same segment (arrow). Retrograde filling is evident (R). A indicates arteriole

(14c)

and Bulpitt, 1969; Wise, Dollery, and Henkind, 1971).

Although ischaemia is the major factor responsible for cotton-wool patches, some of these lesions may occasionally be the result of generalized endothelial damage and vascular leakage (Hodge and Dollery, 1964). In our patient, however, the lesions clearly resulted from acute arteriolar occlusions, since each localized patch corresponded precisely to the dependent capillary bed of an occluded arteriole. Angiography showed no leakage at these sites.

Although cotton-wool patches, if large enough, are associated with local scotomas, our patient did not complain of any visual impairment and her visual acuity, fields, and colour perception were all normal. Possibly the posterior pole abnormalities of many sickle-cell patients start with similar acute episodes and yet, because of lack of visual symptoms, are not seen by the ophthalmologist.

Subsequent to the occlusions the capillary bed dependent on this occluded arteriole is not completely perfused. This non-perfusion does not necessarily mean complete and permanent closure of the capillary bed, and many capillaries may remain patent. Indeed, in pathological specimens they may appear patent although unfilled with erythrocytes. Non-perfusion during ischaemia may be secondary to several factors, including total vaso-occlusion, low perfusion pressure, high tissue

pressure with capillary closure secondary to swelling of retinal tissue, capillary contraction or collapse, and endothelial swelling. Depending on the combination and course of these factors, the occluded capillaries reopen or remain non-perfused. In the latter state the areas represent finally the pathological avascular zones that are apparent angiographically. Eventually the cotton-wool spots disappear with return of normal retinal transparency, although their locations sometimes can be identified as localized dimples or facets.

Follow-up examination after the initial acute attack shows multiple vascular changes. The initial area of occlusion may remain non-perfused. Distal to this occlusion a low pressure area may develop. Blood from neighbouring capillaries may flow into this low pressure zone, and fluorescein angiography shows retrograde dye filling (Figs 5, 14c). The occluded vessel may reperfuse completely. The dependent capillary bed may re-establish circulation or remain non-perfused. The failure of the capillary bed to reperfuse after establishment of flow in an occluded arteriole and the return of retinal transparency probably indicate postnecrotic atrophy of the inner retinal layers, including the capillary bed, as has been shown by trypsin-digestion and other histopathological techniques (Kornzweig, Eliasoph, and Feldstein, 1964; Kuwabara and Cogan, 1965).

Interesting vascular changes, especially on the

(15a)

(15b)

(15c)

FIG. 15 Case 4. Fluorescein angiograms of right posterior pole. (a) Generalized vascular tortuosity is evident. FAZ is irregular with loss of nasal vascular arcade (arrow). (b) Enlarged view of FAZ. Loss of the nasal arcade of FAZ is due to arteriolar occlusions at 2 and 3 o'clock positions (arrows). (c) FAZ four months later shows reopening of previously occluded vessel re-establishing nasal arcade of FAZ (arrow)

venular side, occur adjacent to retinal areas where the capillary bed remains non-perfused. Venular loops develop and are almost always directed into areas of avascular retina. The significance of these loops is not currently understood. Similar venular hairpin-loop configurations have also been noted in diabetes mellitus. Haemodynamic, chemotactic, or even mechanical factors may play a role

in the initiation of these vascular loops. It is possible that the intraluminal pressure pushes the vessel into this necrotic, atrophic zone where low tissue pressure may prevail. It may be that the ischaemic area produces a chemotactic factor that induces the growth of vessels into it, the first step in neovascularization. It is also possible that change is induced in the internal limiting membrane or

(16a)

FIG. 16 Case 5. Fluorescein angiograms of right macular area and area temporal to it. (a) Shorter arrow indicates venular loop directed into area with sparse capillaries. Longer arrows indicate reference vessels that occluded five months later and are seen in (b)

(16b)

(17a)

FIG. 17 Case 6. Fluorescein angiograms of right posterior pole. (a) Beads of fluorescein are apparent in the capillaries surrounding the FAZ. Temporal to the FAZ is a PAZ. (b) Enlarged view of the FAZ. The spaces of the surrounding capillary meshwork are more variable in size than normal. Arrow shows area where further capillary loss occurred (see (c)). (c) One year later, further loss of capillaries surrounding FAZ (arrow)

(17b)

(17c)

other tissues which may mechanically pull the vessel in. All these are theoretical possibilities and more than one factor may be operative.

The maculopathy that starts with acute occlusions usually follows a chronic progressive course with larger and more numerous areas of the retina gradually becoming involved. Fluorescein angiography repeated at intervals of several months shows a continuous remodelling of the retinal vasculature

of the posterior pole. Occlusions may extend posteriorly or completely reopen (Fig. 13). Pathological avascular zones become larger and foveal avascular zones may change size and shape. Occasionally a reverse process may ensue, an avascular zone may become revascularized and an abnormal foveal avascular zone may revert to normal size and configuration (Fig. 15b, c). It is important to observe the patients regularly to recognize this

FIG. 18 Case 6. Fluorescein angiograms of left posterior pole. (a) Irregularly shaped FAZ with loss of capillaries accentuated at its temporal border. Beads of fluorescein are evident. Arrows indicate sites of future occlusions. (b) At follow-up six months later: further occlusions at the 5 and 7 o'clock areas (arrows) have enlarged FAZ. (c) 15 months later: single capillary reopened at 6 o'clock meridian (arrow)

continuous remodelling in the vasculature of the retina. The arterioles may plug and unplug and the dependent microvasculature may change accordingly. This phenomenon of continuous opening and closing of the affected vessels supports the view that there is a mechanical type of obstruction caused by aggregates of impacted sickle cells rather than a real thrombosis, but recanalization of a true thrombosis may also occur.

Such complex remodelling of the retinal vascular bed as the result of vascular occlusion is not unique to the posterior pole. We have recently reported similar vascular remodelling in the peripheral vasculature of patients with different sickling haemoglobinopathies (Galinos and others, 1975). Harnish and Pearce (1973) also reported retinal vascular remodelling in non-sicklers with hypertensive retinal vascular disease. Their observations were similar to ours in that vascular occlusions were followed by a complex remodelling of the retinal vasculature, a process which continued over a period of years.

The clinical implications of the posterior pole abnormalities are manifold. Although some of the vascular abnormalities do not cause any detectable

visual disturbances in some patients they may cause minimal to profound visual loss in others, even with normal-looking fundi. Thus careful screening of the maculae by ophthalmoscopy and fluorescein angiography becomes mandatory, especially in patients with unexplained central visual loss or colour vision abnormalities. Sickle maculopathy can occur even in children with no peripheral retinopathy, and therefore the absence of peripheral lesions does not preclude the need for careful assessment of the macula. Finally, these changes may in the future serve as indicators in the evaluation of systemic therapeutic regimens to minimize the sickling process and improve blood flow.

(19a)

(19b)

FIG. 19 Case 7. Fluorescein angiograms of right posterior pole. (a) Abnormally shaped FAZ with loss of vascular arcades at 9 to 10 o'clock meridian (arrow). L denotes venular loop directed into avascular zone. (b) Further changes in character of venular loop one year later

Summary

The posterior pole vasculature of 100 patients with different sickling haemoglobinopathies was studied prospectively over a period of three years. Various abnormalities of the posterior pole vasculature were seen in 29 per cent of the patients. Continuous remodelling of the macular and perimacular vasculature occurred. Visual acuity was variably affected and sometimes remained intact.

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FIG. 20 Case 7. Fluorescein angiogram of left posterior pole with abnormally shaped FAZ. Loss of vascular arcade of 7 o'clock meridian (arrow). Island of PAZ present at 2 o'clock meridian

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