Eye (1987) **1**, 136–145

Bilateral Coats' Disease in an Infant (A clinical, angiographic, light and electron microscopic study)

P. M. McGETTRICK and K. U. LOEFFLER
Glasgow

Summary
The clinical, angiographic, ultrastructural and immunohistochemical features of a bilateral and asymmetrical case of Coats' disease in a three year old girl are described. The left eye showed advanced disease and was enucleated. Pathological examination revealed an exudative vasculopathy with ultrastructural evidence of interendothelial cell separation and formation of fenestrations. An isolated vascular malformation was discovered in the right eye. This was successfully treated with Argon laser under general anaesthesia.

The typical clinical and histological features of Coats' disease are well known,[1,2,3] but the nature of the primary vascular disorder is poorly understood. We present a bilateral, asymmetrical case of Coats' disease in a three year old female. The severely affected eye was enucleated and examined by light and electronmicroscopy in an attempt to detect features which might explain early breakdown of the blood retinal barrier. An isolated vascular anomaly was found in the fellow eye by ophthalmoscopy, but fluorescein angiography revealed a wider area of vascular abnormality than was suspected clinically. This area was successfully treated by Argon laser.

Case Report
A three year old female referred with left leukocoria was found to have a painful blind eye. There was ectropion uveae and a fixed yellow retinal detachment. Two tufts of telangiectatic vessels were visible on the temporal surface of the detachment. The right eye appeared normal and vision was 6/6. The child had been delivered at 38 weeks gestation because of intra-uterine growth retardation. Birth weight was 2.2 kgs, and there was no post-natal respiratory distress. On admission to our unit she was healthy and had reached her developmental milestones.

At examination under anaesthesia a total retinal detachment with surface telangiectasia was confirmed in the left eye and a provisional diagnosis of Coats' disease was made. Because the eye was blind and painful it was enucleated. Simultaneously, examination of the right eye revealed a normal anterior segment, disc and macula. A large tortuous arteriovenous shunt vessel with aneurysmal dilatations was noted in the superior periphery. The adjacent capillaries were dilated and irregular in calibre, and some microaneurysms were visible along their course (Fig. 1). The retinal vessels were otherwise normal and there were no retinal exudates or haemorrhages. Four weeks later fluorescein angiography following the intravenous injection of 1 ml of 20 per cent sodium fluorescein was carried out under general anaesthesia. The angiogram outlined the full extent of the vascular changes, including a widespread coarse capillary

Correspondence to: Dr P. M. McGettrick, Tennent Institute of Ophthalmology Western Infirmary, Glasgow G11 6NT from Tennent Institute of Ophthalmology, Glasgow.

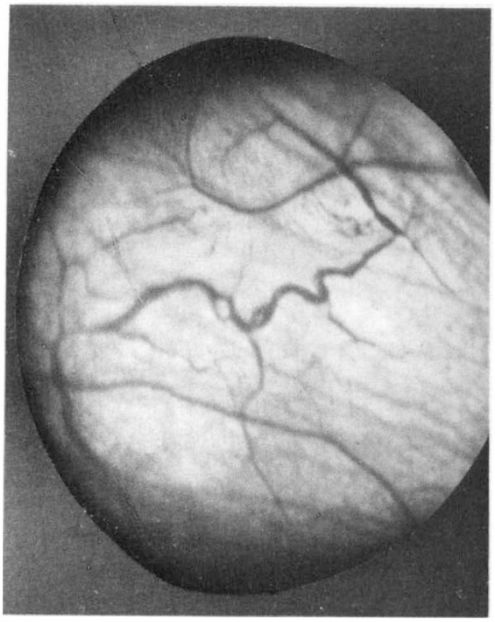

Fig. 1. *Dilated tortuous arteriovenous communication. Coarse capillary bed with some microaneurysms.*

meshwork in the region of the arteriovenous communication, with some areas of capillary fallout, and numerous microaneurysms, which did not leak. Beading of the pre-shunt retinal artery was a prominent feature. There was extravascular fluorescence from the shunt, but also from an apparently normal vein (Fig. 2). Immediately after assessment of the angiogram, and under the same anaesthetic, Argon-Green laser (514 nm) was applied via the operating microscope (Biophysics Médical). Fifty burns (500 μ×0.5 watt×0.2 secs) were necessary to cause visible blanching of the shunt vessel. One hundred burns (500 μ×0.35 watt ×0.2 secs) were applied to the abnormal capillary meshwork and adjacent peripheral retina. Two weeks later the shunt vessel was still present but its proximal and distal connections had been severed. Six weeks after treatment the shunt vessel was obliterated, and the irregular dilated capillaries destroyed (Fig. 3). At a recent examination six months after treatment the appearance of the treated area remained unchanged, and there was no progression of the vasculopathy. Visual acuity remained at 6/6.

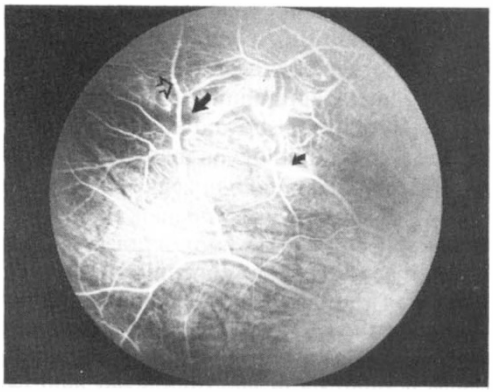

Fig. 2. *Fluorescein angiogram. A-V shunt with staining of the aneurysm walls; extensive coarse capillary meshwork with islets of capillary non-perfusion (◠). Arterial beading (◡). Staining of vein (◖).*

Material and Methods

The left enucleated globe was fixed in Cacodylate buffered glutaraldehyde (2 per cent). The lesions noted clinically were observed by direct examination through the cornea and seen as shadows on transillumination. The eye was opened across one shadow which was due to a localised disc-like yellow thickening at the periphery of the detached retina with prominent dilated vessels. A pupil-optic nerve-block including this lesion was processed for paraffin histology and serial sections were stained with Haematoxylin-Eosin. Special stains (PAS, Iron, Von Kossa, Alizarin Red, Bodian, Loyez, Reticulin, MSB) were used on selected levels. Immunohistochemistry using antibodies against fibronectin, immunoglobulins (A, G, M) and macrophages (α-1-antichymotrypsin, α-1-antitrypsin, muramidase) was also performed. A second block across a brownish nodule projecting from the choroid into the subretinal exudate was serial-sectioned for light microsopy. Tissue for ultrastructural investigation was taken from the second retinal lesion which was morphologically similar to the lesion in the paraffin block. Blocks from a subretinal nodule were also taken for electron microscopy. The osmicated tissue was embedded in araldite, sectioned with an LKB ultratome III, stained with uranyl acetate and lead citrate and examined with a Philips 301 transmission electron microscope.

Results

Pathological Findings

The macroscopic and microscopic appearances confirmed the clinical diagnosis of Coats' disease. The chamber angle was closed by a neovascular membrane which also caused an ectropion of the iris, and the trabecular meshwork was degenerate with obliteration of Schlemm's canal. The vitreous showed per-

ipheral condensation. The choroid contained a low-grade non-specific inflammatory cell infiltrate, and the optic nerve showed early atrophy. The localised vascular abnormalities of the detached retina were confirmed (Fig. 4): the changes comprised aneurysmal and telangiectatic vascular dilatations, thickening and hyalinisation of some vessel walls, thrombosis, organisation and recanalisation of thrombosed vessels and occasional perivasculitis. There was also glial cell proliferation and microcystic degeneration within the inner retina, deposition of fibrin within the outer retina and atrophy of the photoreceptor layer. Occasional intraretinal haemorrhages were seen, but neovascularisation was not detected. The subretinal space contained residual gelatinous exudate with cholesterol clefts and clusters of foamy melanin-containing cells forming the macroscopically visible brownish nodules of different sizes. Histologically, some of these cells were in continuity with and appeared to arise from the retinal pigment epithelium (Fig. 5). Immunohistochemistry revealed the presence of immunoglobulins within lumina of retinal vessels and their leakage into the vessel wall in the affected area of vascular abnormality. Fibronectin was demonstrated around some vessels and also within the exudate in the outer retina.

None of the macrophage markers reacted with *in-situ* RPE. However, pigment-laden cells within the subretinal exudate and non-pigmented cells within the retina reacted strongly with α-1-antichymotrypsin. No such positive reacting cells were seen in the choroid.

Electron microscopy

Ultrastructural examination of the retina confirmed the abnormalities previously reported by Tripathi and Ashton.[4] The vessel walls were thickened by plasma transudation and deposition of collagenous and multilayered basement membrane-like material. Many vessel walls contained exogenous macrophages, and sometimes red blood cells were seen outside the endothelium. A deficiency of mural cells was prominent in several dilated telangiectatic vessels. Cellular debris, however, as evidence of previously present myocytes was not significant. Some vessels showed advanced hyalinisation, occasionally up to complete acellularity. The two most striking features were the presence of intercellular gaps between otherwise morphologically normal endothelial cells (Fig. 6) and fenestrations in the endothelium of a hyalinised retinal vessel (Fig. 7). Lipid-containing macrophages were identified between neural cells and fibrin was demonstrated in the outer retina as well as within the lumen of a thrombosed vessel. The retinal pigment epithelium at the base of a "nodule-formation" showed an altered macrophage-like morphology in many of the cells (Fig. 8).

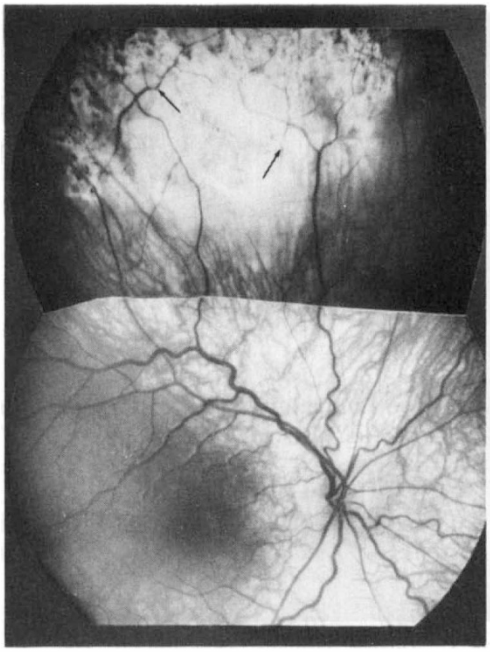

Fig. 3. *Post-treatment; obliteration of abnormal vascular complex; commencement and termination of shunt indicated (➧).*

Discussion

Coats' disease[5,6] is a congenital vascular anomaly of retinal vessels which is generally detected in the first decade of life.[3] The average age of presentation is 10.1 years,[7] and the disease is bilateral in less than 5 per cent of cases.[8] The predilection for males has been reported as between 69 per cent and 84 per cent.[3,8,9] Spontaneous regression is rare,[10] and

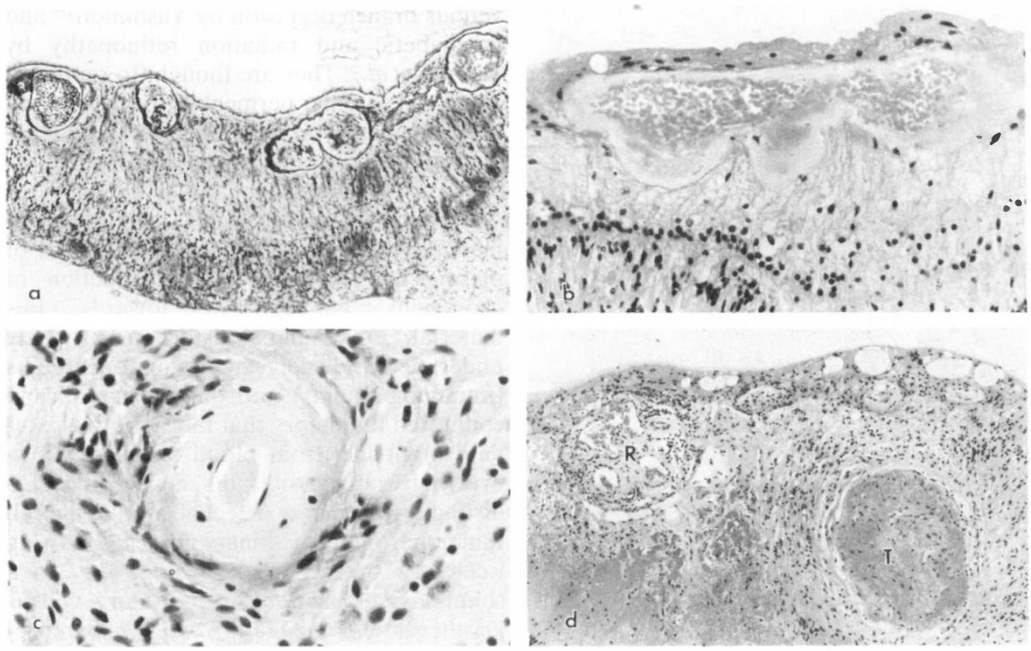

Fig. 4. *Light microscopic appearance of retinal vessels*
(a) telangiectasia (Reticulin ×25)
(b) aneurysmal dilatation (H and E ×60)
(c) hyalinisation (H and E ×96)
(d) thrombosis (T) and recanalisation (R) (H and E ×24).

in the absence of treatment the disease progresses towards visual loss and frequently enucleation.

Many authors[2,11,12,13] suggest that the initial insult is to the arterial side of the vascular tree, and we found changes of calibre with arterial beading to be a prominent angiographic feature in the less affected eye. The majority of microaneurysms appeared to be arterial in origin. However, there was extravascular fluorescence from a retinal vein, which indicates that both arteries and veins were abnormal. The capillaries, although dilated, did not leak fluorescein suggesting an intact endothelium.

The natural history of Coats' disease is that of progression to total retinal detachment.[14,15] Cryotherapy is more effective than photocoagulation in advanced cases with exudative retinal detachment.[2] Xenon and Argon laser photocoagulation are effective in treating flat vascular lesions although Xenon has been associated with vitreoretinal traction and subsequent macular pucker and the polychromaticity of the Xenon arc beam does not allow selective retinal coagulation.[16] Since the aim of treatment is the preservation of vision and the prevention of complications of the disease itself and the treatment modalities used, Argon laser may be more beneficial in early cases with isolated vascular abnormalities, since smaller amounts of total energy are necessary to affect vascular obliteration.

It has been suggested that younger patients have a more aggressive form of the disease and require repeated treatment with photocoagulation or cryotherapy.[7] Clinical assessment of the extent of vascular anomalies in young children can be difficult and we suggest that fluorescein angiography can be performed under general anaesthesia to outline the full extent of the vasculopathy, so that initial photocoagulation can be applied more effectively. This may then modify the progression of the disease and reduce the need for further treatment. Abnormal vascular permeability is fundamental to the pathogenesis of Coats' exudative vasculopathy, and in this case we were able to locate areas of structural

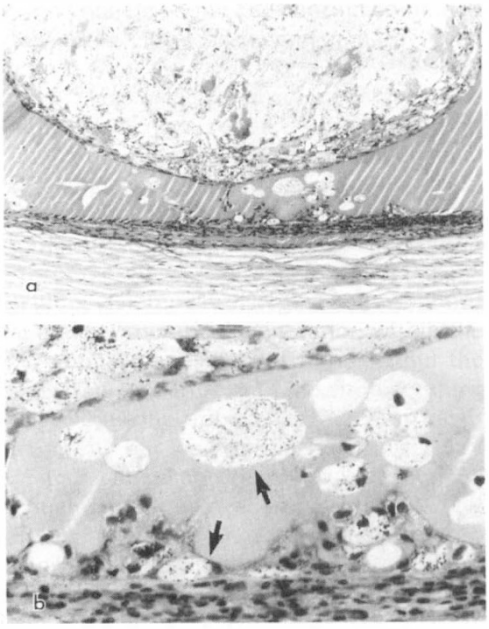

Fig. 5. *Subretinal nodule formation, showing proliferation of RPE. Note similarity in cytoplasmic appearance between some RPE cells and the subretinal 'ghost cells' (➧)*
(a) H and E ×24
(b) H and E ×96.

breakdown of the blood retinal barrier, although unable to localise the changes principally to either the arterial or venous side because of the already advanced stage of the disease.

Well-established features of longstanding vascular disease in Coats' disease[4,14,18] such as thickening and hyalinisation of vessel walls and degeneration of endothelial and mural cells could be confirmed in this study. In addition we were able to demonstrate two features of structural breakdown of the blood-retinal barrier, not previously described in the English literature, on retinal vessels in Coats' disease. Intercellular gaps between endothelial cells were seen, associated with lakes of plasma within the adjacent vessel wall. Fenestrations of individual endothelial cells represent the second important finding. Endothelial fenestrations in retinal vessels—normally present only in the choriocapillaries—have been described in Coats' disease only by Hada,[18] in retinal haemorrhage after venous branch occlusion by Yashimoto[19] and in diabetic and radiation retinopathy by Kimura *et al.*[20] They are thought to represent abnormal vascular permeability due to raised intracanalicular pressure, subsequently leading to thickening of the vessel wall.[20] The presence of intercellular gaps is an obvious morphological correlate for increased permeability and would explain the leakage of plasma and the subsequent attraction of exogenous macrophages towards this material. Our immunohistochemical study underlined the leakage of plasma constituents (immunoglobulins) into the vessel wall and confirmed the theory that the subretinal exudate originates from blood plasma.[21] However, it is not possible on these grounds to distinguish a primary defect of endothelial cell function from a reactionary process following ischaemia or increased pressure due to a shunt-vessel. The deficiency of mural cells is another interesting feature which may represent a primary defect, since so little cellular debris was found at their supposed location. This would support the hypothesis of congenital localised telangiectasia.[1,12]

The origin of the 'ghost cell' in the retina and the subretinal exudate remains controversial and has been questioned and investigated by many authors.[22,23,24] In this case, the morphological similarity of some *in situ* RPE cells and these ghost-cells favours a reactionary transformation of the RPE into macrophages. The final acquisition of macrophage characteristics appears to take place as soon as the RPE cell is disconnected from Bruch's membrane as could be demonstrated by one (α-1-ACT) of the macrophage markers. It seems unlikely that so many melanin-containing cells in such close proximity to the RPE could be exogenous macrophages entering the tissue via the retinal vessels. However, it is of interest that there was a prominent infiltration of positively labelled macrophages within the retina itself.

This study demonstrates the presence of structural breakdown of the blood retinal barrier in Coats' disease. It emphasises the presence of asymmetrical bilateral disease and the need for careful clinical and angiographic assessment of all fellow eyes in suspected Coats' disease, so that early vascular changes

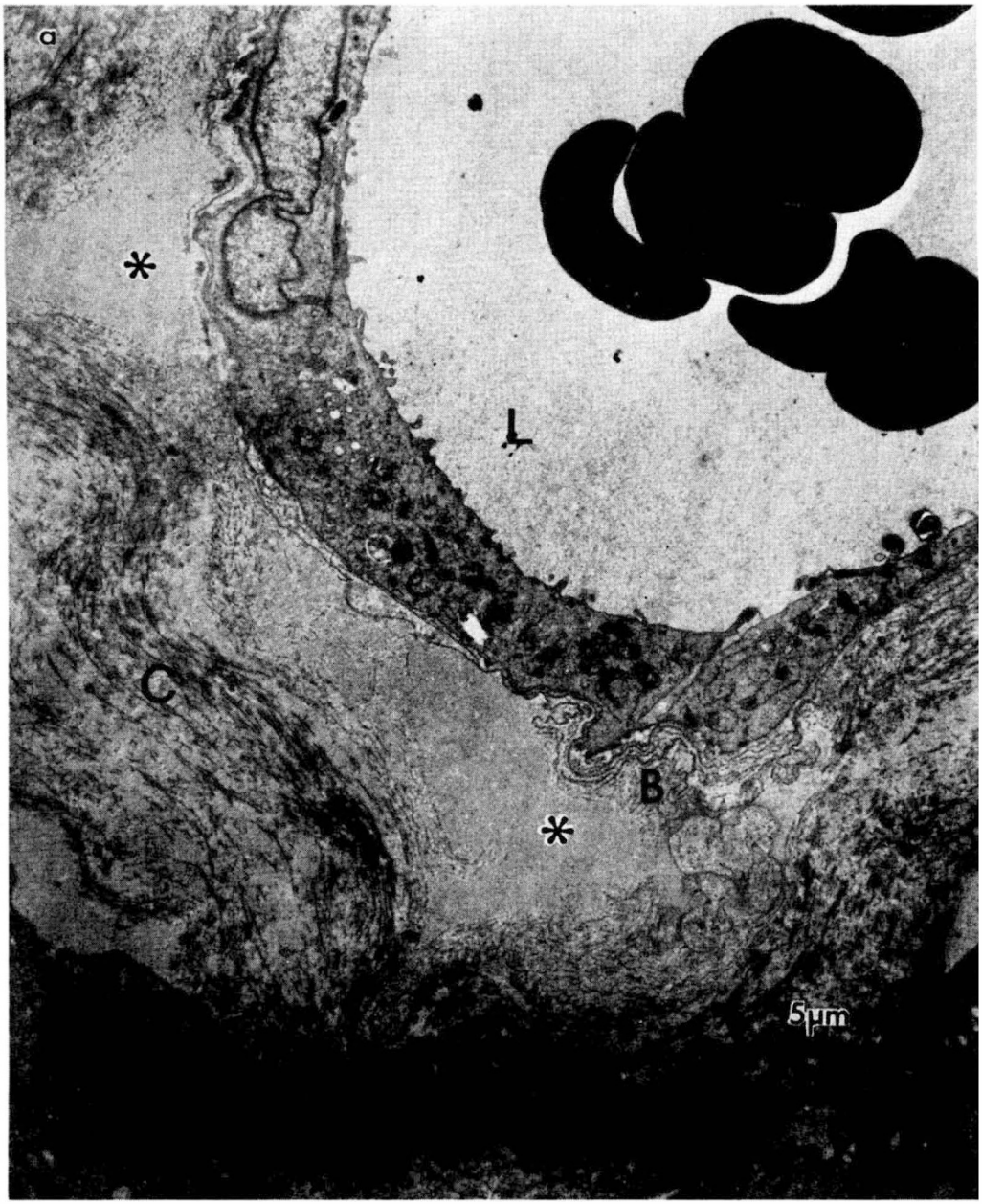

Fig. 6a. *Plasma-leakage into vessel wall*
(a) retinal vessel (★ plasma, L = lumen, B = basement membrane material, C = collagen)

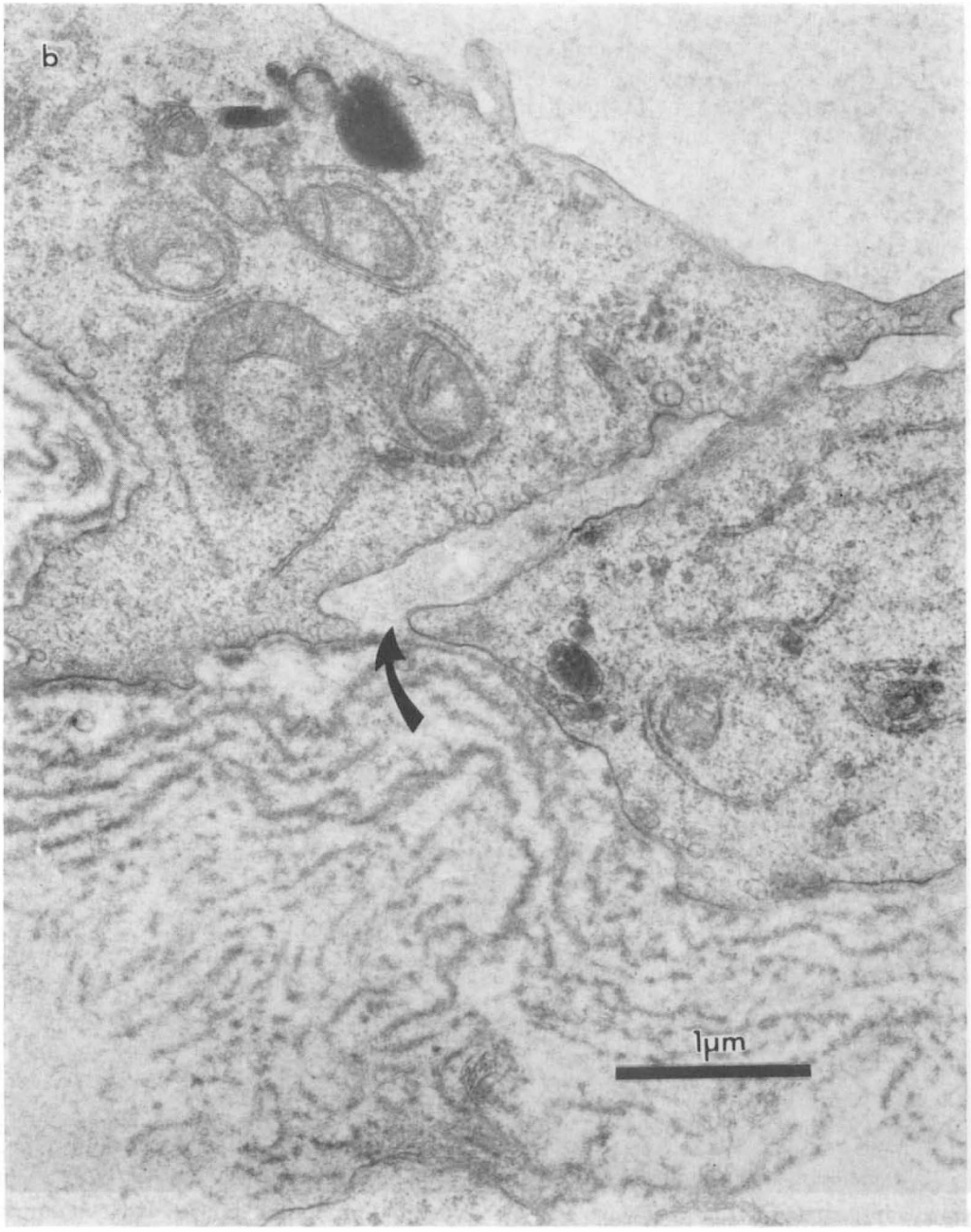

Fig. 6b. *Plasma-leakage into vessel wall*
(b) detail of (a) showing intercellular gap (◂).

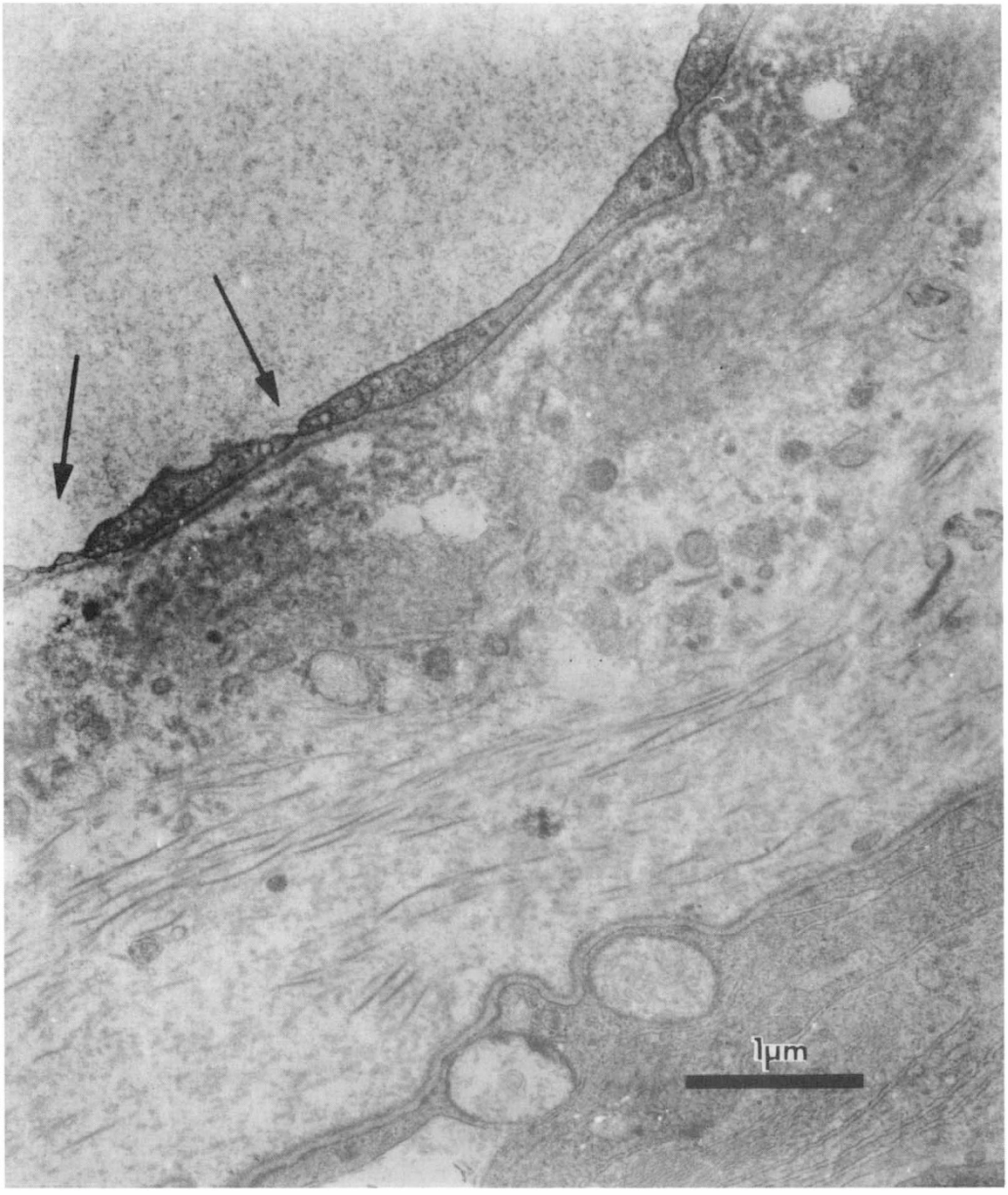

Fig. 7. *Retinal endothelial cell showing fenestrations (▲).*

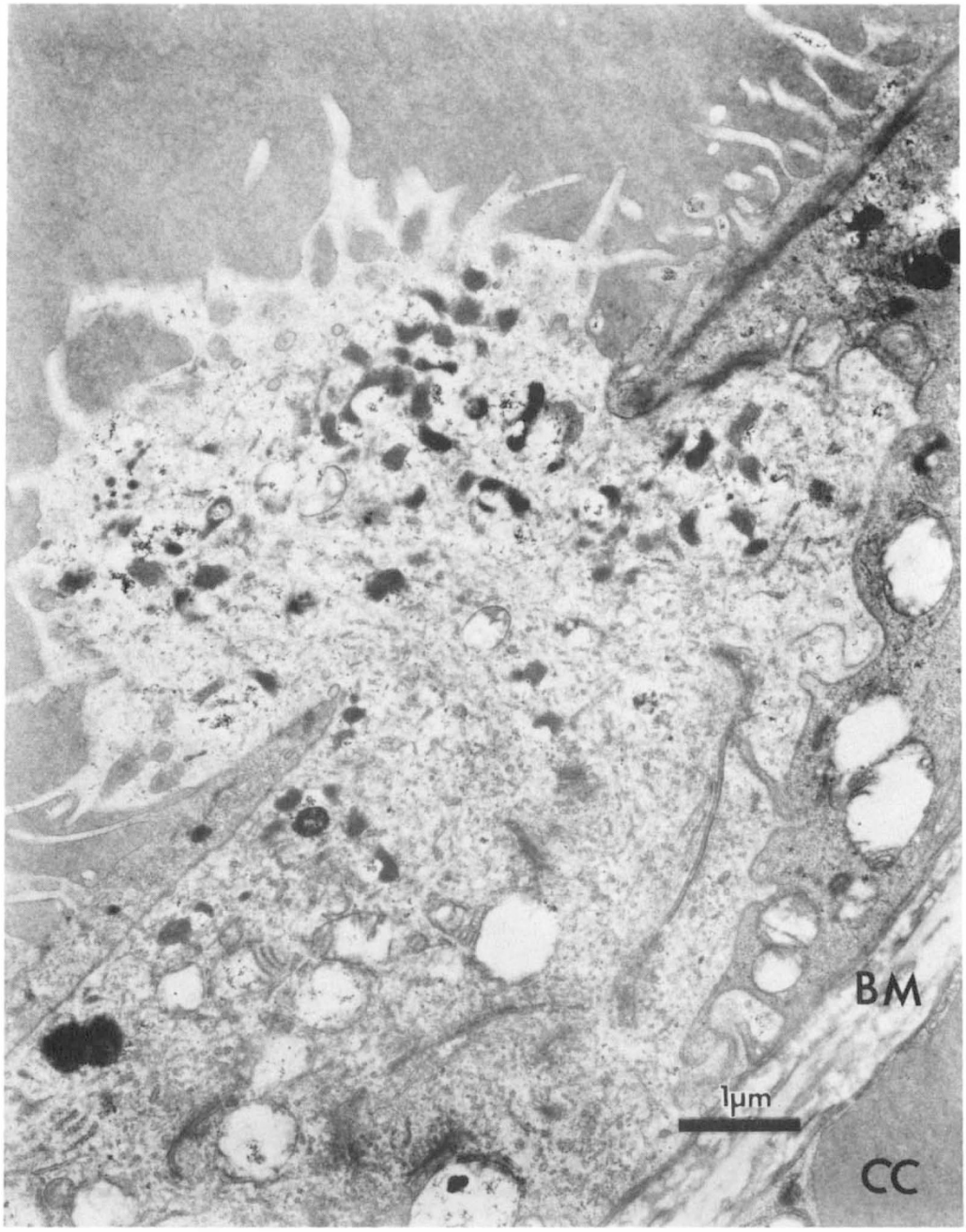

Fig. 8. *Atypical cell within retinal pigment epithelium adjacent to a focus of cellular proliferation. Note difference in cytoplasmic density compared to neighbouring cell. (BM = Bruch's membrane, CC = choriocapillaris).*

can be detected and promptly and effectively treated.

We are grateful to the medical secretaries and the staff of the Pathology and Photographic Departments for their help in preparing this manuscript. We would also like to thank Professor W. R. Lee and Professor W. S. Foulds for their guidance and Dr. E. I. McNaught for referring the patient.

References

[1] Manschot WA and de Bruijn WC: Coats' disease: definition and pathogenesis. *Br. J. Ophthalmol.* 1967, **51:** 145–57.

[2] Tarkkanen A and Laatikainen L: Coats' disease: clinical angiographic, histopathological findings and clinical management. *Br. J. Ophthalmol.* 1983, **67:** 766–76.

[3] Change M, McLean IW and Merritt JC: Coats' disease: a study of 62 histologically confirmed cases. *J. Pediatric Ophthal. and Strab.* 1984, **21:** (5) 163–8.

[4] Tripathi R and Ashton N: Electron microscopical study of Coats' disease. *Brit. J. Ophthalmol.* 1971, **55:** 289–301.

[5] Coats G: Forms of retinal disease with massive exudation. *R. Lond. Ophthal. Hosp.* 1907–1908, **17:** 440–525.

[6] Coats G: Ueber Retinitis exudativa (Retinitis haemorrhagica externa). *Graefe's Arch. Ophthalmol.* 1912, **81:** 275–327.

[7] Ridley ME, Shields JA, Brown GC and Tasman W: Coats' disease. Evaluation of management. *Ophthalmol.* 1982, **89:** 12, 1381–7.

[8] Woods AC and Duke JR: Coats' disease: review of literature diagnostic criteria, clinical findings and plasma lipid studies. *Br. J. Ophthalmol.* 1963, **47:** 385–410.

[9] Egerer I, Tasman W and Tomer TL: Coats disease. *Arch. Ophthalmol.* 1974, **82:** 109–112.

[10] Deutsch TA, Rabb MF and Jampol LM: Spontaneous regression of retinal lesions in Coats' disease. *Can. J. Ophthalmol.* 1982, **17:** 169–72.

[11] Chisholm IA, Foulds WS and Christison D: Investigation and therapy of Coats' disease. *Trans. Ophthalmol. Soc. UK* 1974, **94:** 335–41.

[12] Theodossiadis GP: Some clinical, fluorescein angiographic and therapeutic aspects of Coats' disease. *J. Pediat. Ophthalmol. and Strab.* 1979, **16:** 257–62.

[13] Leber Th: Ueber eine durch Vorkommen multipler Miliar-aneurysmen charakterisierte Form von Retinal-degeneration. *Graefe's Arch. Ophthalmol.* 1912, **81:** 1–14.

[14] Reese ASB: Telangiectasis of the retina and Coats' disease. *Am. J. Ophthalmol.* 1956, **42:** 1–8.

[15] Morales GA: Coats' disease: natural history and result of treatment. *Am. J. Ophthalmol.* 1965, **60:** 855–65.

[16] L'Esperance FA: Coats' disease: In ophthalmic lasers; photocoagulation, photoradiation and surgery, 2nd edn, Mosby 1983, 210–216.

[17] Ikui H, Kumano S and Inomata H: Histopathology of Coats' disease (report of a case). *Folia. Ophthalmol. Jap.* 1971, **22:** 832–9.

[18] Hada K: Clinical and pathological studies on Coats' disease. II. Clinical and histopathological observations. *Acta Soc. Ophthalmol. Jap.* 1973, **775:** 438–59.

[19] Yashimoto H: Ultrastructure of vessels in haemorrhagic area of human retina. *Jap. J. Ophthalmol.* 1976, **20:** 233–42.

[20] Kimura T, Matsuhashi H and Ishii A: Ultrastructural changes of pathological human retinal vessels showing abnormal permeability—endothelial fenestrations and atheromatous degeneration. *Nippon Gonka. Gakkas. Zasshi.* 1983, **87**(II): 119–211.

[21] Farkas T, Potts A and Boone, C: Some pathological and biochemical aspects of Coats' disease. *Am. J. Ophthalmol.* 1973, **75:** 289–301.

[22] Ishikawa T: Fine structure of subretinal fibrous tissue in Coats' disease. *Jap. J. Ophthalmol.* 1976, **20:** 63–74.

[23] Takei J: Origin of ghost cell in Coats' disease. *Invest. Ophthalmol. Vis. Sci.* 1976, **15:** 677–81.

[24] Ohba S, Yamada I, Miki T and Matsuyama M: A case of Coats' disease—Histopathological study. *Folia. Ophthalmol. Jap.* 1977, **28:** 1013–7.