Placoid pigment epitheliopathy and Harada's disease

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SUMMARY Twenty-six patients are described who suffered from acute bilateral multifocal pigment epithelial disease. In 7 the pattern of disease was indistinguishable from acute posterior multifocal placoid pigment epitheliopathy, while in 8 it was indistinguishable from Harada's disease. In a further 9 cases the pigment epithelial disease was associated with serous detachment of the retina simulating Harada's disease but without systemic symptoms; spontaneous resolution occurred within a few days, and there was no recurrence. One additional case had short-lived disease with detachment initially, but this was followed by severe recurrence, and the last patient had serous detachment in 1 eye but not the other. When seen as a whole these patients appeared to represent a continuous spectrum of disease making it difficult to define boundaries between one condition and another. The difficulties in distinguishing diseases according to morphology alone are emphasised.

During the last 5 years 26 patients have been seen at Moorfields Eye Hospital with acute multifocal disease affecting the retinal pigment epithelium bilaterally; all but 1 have been observed for at least 1 year. In some the characteristics of the disease were typical of Harada's disease (Harada, 1925; Shimizu, 1973) and in others were similar to those of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) (Gass, 1968; van Buskirk et al., 1971; Kirkham et al., 1972). In the remaining patients the retinal morphology and course of the illness were similar in certain respects to Harada's disease and in others to APMPPE (Bird and Hamilton,1972). The attributes of these diseases will be described.

Results

Seven patients had acute bilateral pigment epithelial disease without serous retinal detachment which conformed to the description by Gass (1968) of APMPPE (Table 1). These patients presented with the acute onset of bilateral visual loss associated with multifocal, grey-white lesions in the posterior pole at the level of the retinal pigment epithelium. During the initial transit of fluorescein angiography these placoid lesions were darker than the normal background choroidal fluorescence (Fig. 1a), but in

some large choroidal vessels were visible in the areas of hypofluorescence (Figs. 2a, b). Later in the study these lesions became hyperfluorescent (Figs. 1b, 2c). The swelling resolved spontaneously within 2 to 4 weeks without treatment in 6 patients, and in the same length of time in the 1 patient who received systemic corticosteroids. Visual recovery tended to take longer (2 to 12 weeks) and even then was incomplete in some cases. Only scattered areas of depigmentation or pigment clumping remained at the sites of the previous placoid lesions. The only systemic associations were genetically determined angioedema in 1 patient and myotonic dystrophy in another.

Seven patients (Cases 8 to 14) had severe acute bilateral disease affecting the retinal pigment epithelium, extensive serous retinal detachment, and other abnormalities associated with Harada's disease, including uveitis, papillitis, tinnitus, headache, and alopecia (Table 1). The appearance during the initial transit of fluorescein angiography was identical to that in APMPPE (Figs. 3a, b), but during the subsequent 5 minutes there was progressive accumulation of dye in the subretinal space (Fig. 3c). The pattern of choroidal filling when it could be seen was suggestive of slow perfusion of the choriocapillaris. Within 1 week there were no signs of spontaneous resolution of the detachment. All 7 patients were treated with systemic corticosteroids, and flattening of the retina occurred within 2 to 6 weeks. Five of these patients were Caucasians and
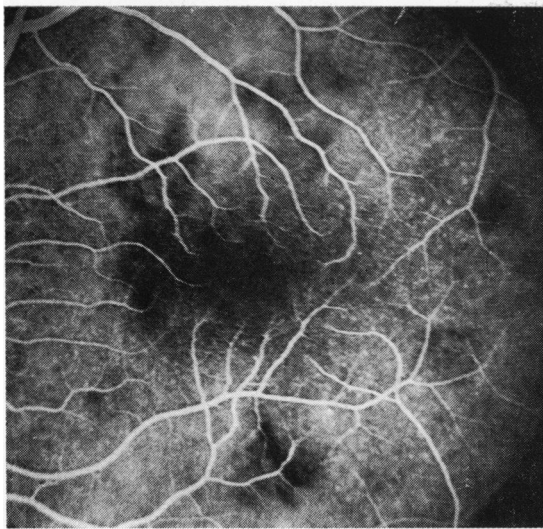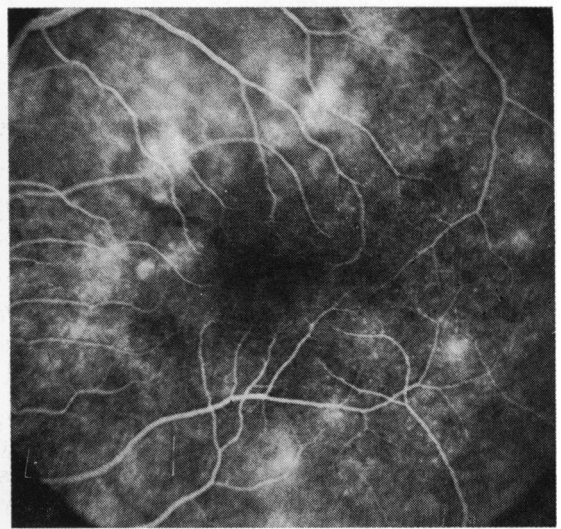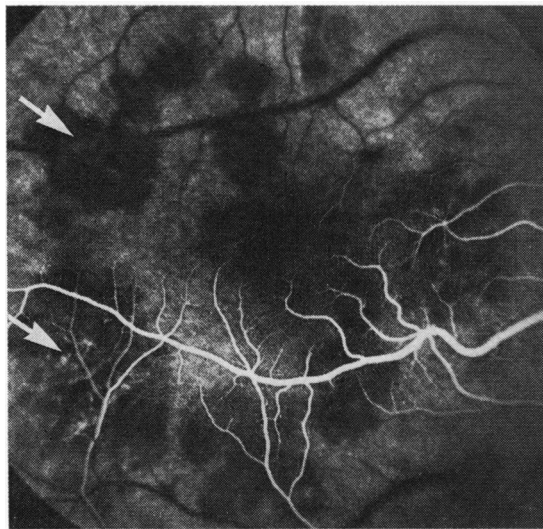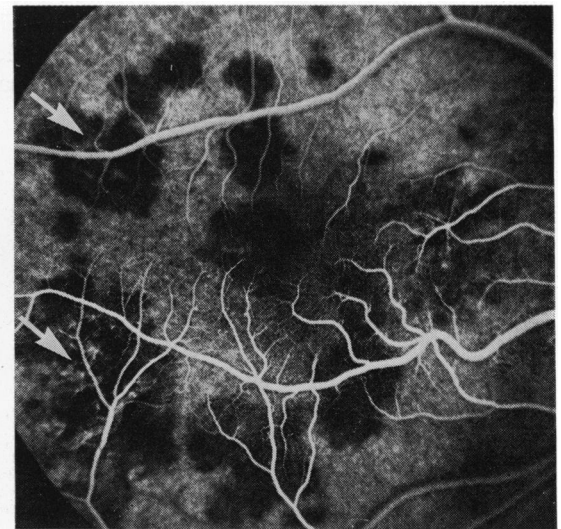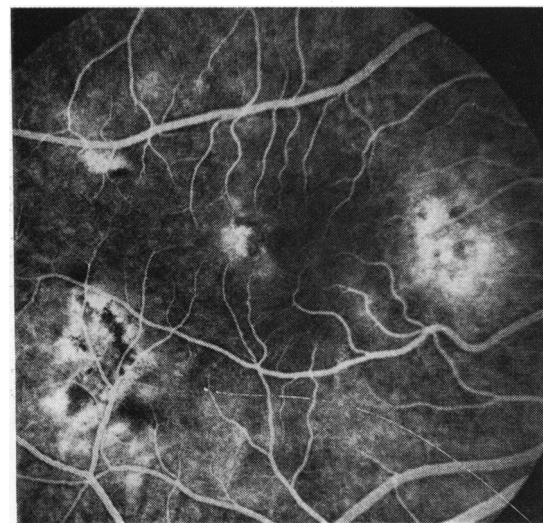
Fig. 1 *Case 5. Fluorescein angiography 6 days after initial visual loss showing dark patches during the initial transit of dye (Fig. 1a) with progressive accumulation of fluorescein in these areas during the subsequent 5 minutes (Fig. 1b)*


Fig. 2 *Case 3. Twelve days after initial visual loss.] Fluorescein angiography shows dark patches in the choroid during the initial transit, but all choroidal vessels can be seen within these areas (Fig. 2a, b). During the subsequent 5 minutes these areas became hyperfluorescent (Fig. 2c)*

2 Mongolians. Of the 6 patients available for follow-up all suffered later recurrences which also required corticosteroid therapy. One additional Mongolian patient seen with this syndrome did not receive systemic corticosteroids because of medical contraindications, and the ocular changes took 6 weeks to resolve; this patient has not yet suffered a recurrence.
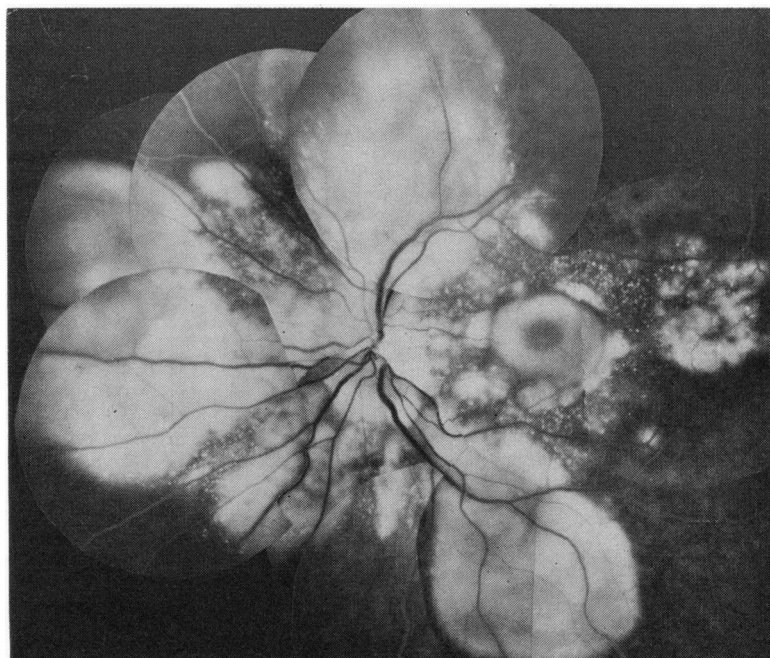
Nine further patients presented with the acute onset of bilateral visual loss associated with multifocal placoid, grey-white lesions in the posterior pole at the level of the retinal pigment epithelium
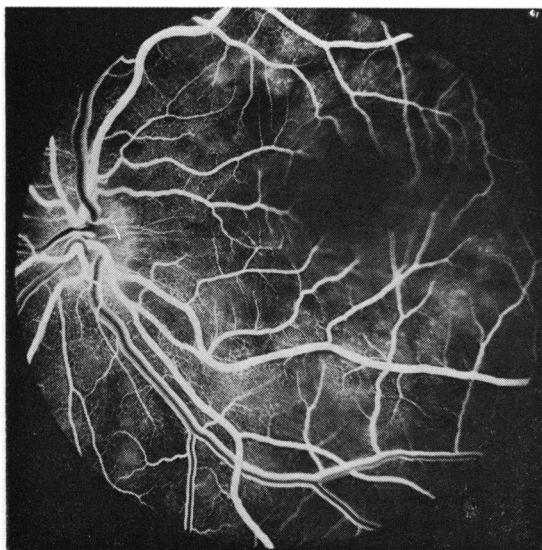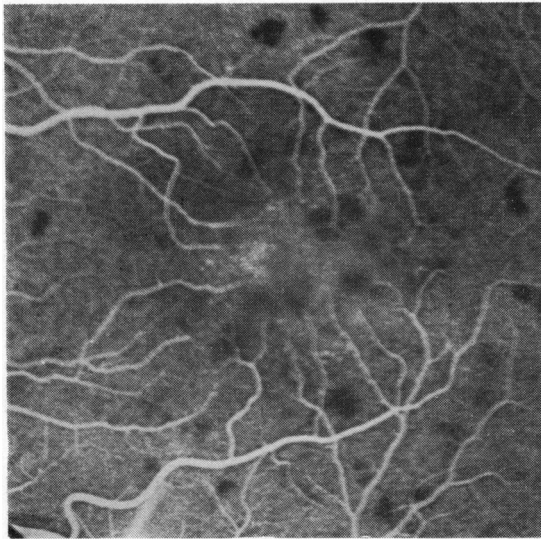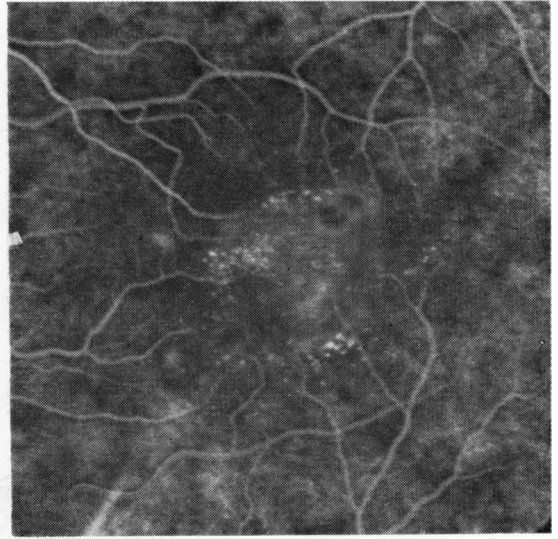

3a

3b

3c

Fig. 3 *Case 12. Three days following initial visual loss. Fluorescein angiography shows dark patches in the choriocapillaris during the initial transit of dye and subsequent progressive accumulation of dye within the pigment epithelium and subretinal space during the subsequent 5 minutes*

and overlying serous retinal detachment. The fluorescein angiograms were indistinguishable from those seen in Harada's disease, though the serous retinal detachment was usually less extensive (Figs. 4a, b, c; 5a, b; 6a, b; 7). The disease differed from classical Harada's disease in that partial or complete spontaneous retinal reattachment occurred within 1 week (Figs. 5c; 6c–g; 7); despite this 3 patients subsequently received systemic corticosteroids. The serous retinal detachment resolved within 2 weeks in all patients, leaving pigment epithelial lesions

beneath flat retina. At this stage the fundus appearance was indistinguishable from APMPPE during the recovery phase. In 1 case slow perfusion of the choriocapillaris was demonstrated during the recovery phase on fluorescein angiography (Figs. 6c–g) (Bird and Hamilton, 1972). Visual recovery was complete within another 4 weeks. Signs of inflammation were identified in most, but other features, namely, tinnitus, dysacousis, alopecia, poliosis, and vitiligo, were absent (Table 1). In none of these cases has the disease recurred.

4a

4b
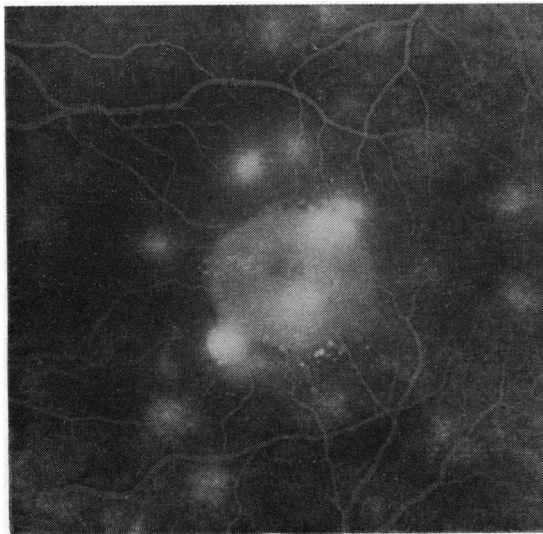
4c

Fig. 4   *Case 19. Three days following initial visual loss. Fluorescein angiography showing dark areas in the choroid during the initial transit of dye (Fig. 4a) with subsequent accumulation of dye in the pigment epithelium and subretinal space (Fig. 4a, b, c)*

One further case (25) was seen with acute pigment epithelial lesions and limited serous retinal detachment, which resolved spontaneously within 2 weeks. However, this patient suffered several recurrences of much more severe disease necessitating the use of systemic corticosteroids.

The last case (26) had typical placoid pigment epitheliitis in her left eye when first seen, but the posterior retina was detached in the right. Spontaneous retinal flattening occurred within 1 week of presentation.

Discussion

The acute bilateral disease of the retinal pigment epithelium without serous retinal detachment followed by spontaneous resolution within 2 to 4 weeks, and the lack of recurrence in the first 7 patients, clearly conform to Gass's description of acute posterior multifocal placoid pigment epitheliopathy (1968).

Patients 8 to 15 (Table 1), who had widespread serous retinal detachment accompanying the acute
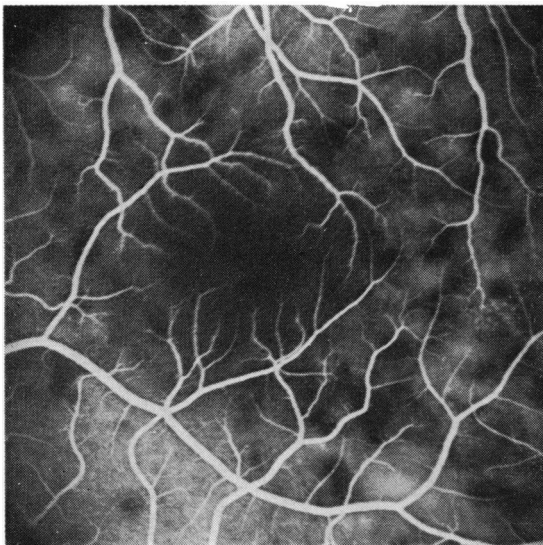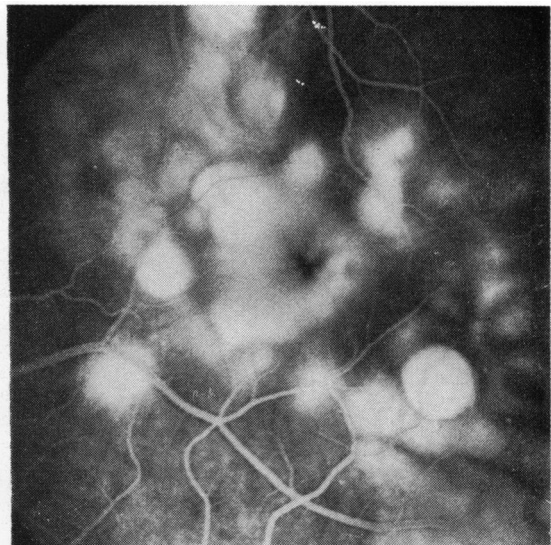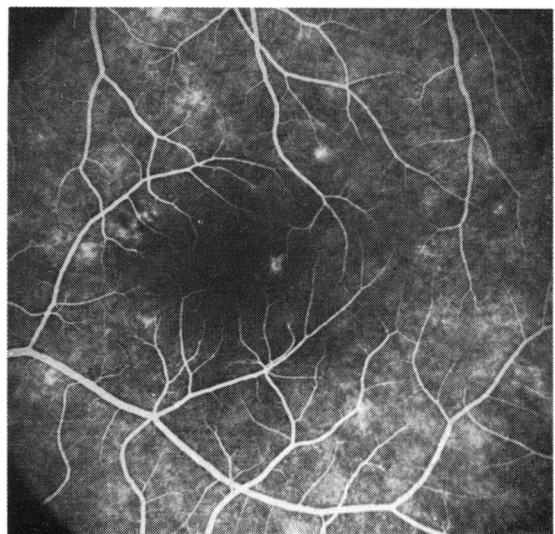
Fig. 5 *Case 21. Fluorescein angiography showing dark patches in the choriocapillaris during the initial transit of dye (Fig. 5a) and subsequent accumulation of dye in the pigment epithelium and subretinal spaces (Fig. 5b). Ten days later the retina had settled spontaneously leaving pigment epithelial changes only (Fig. 5c)*

6a

6b

6c   6d

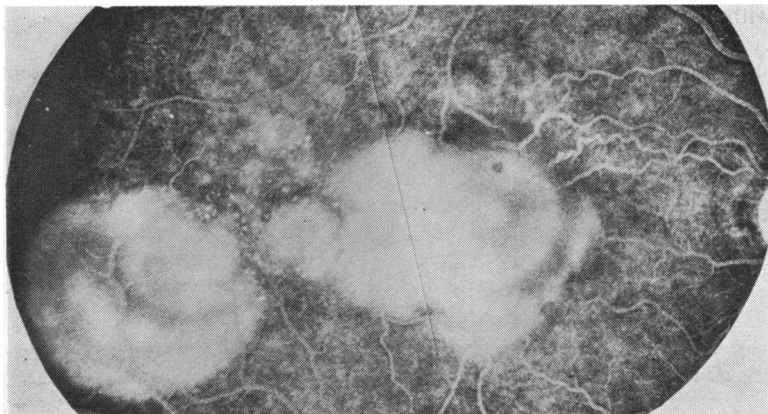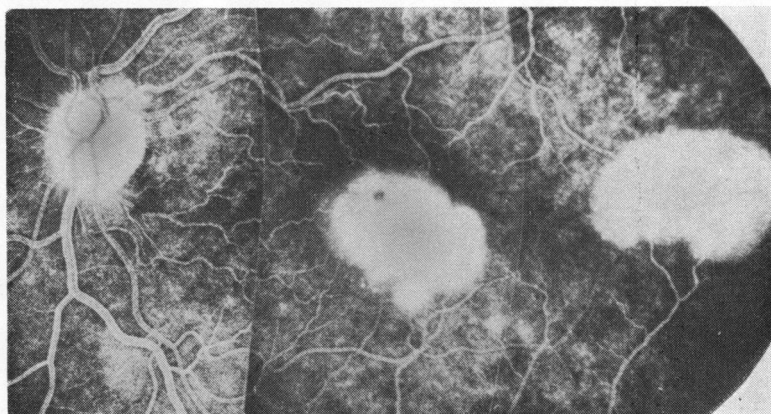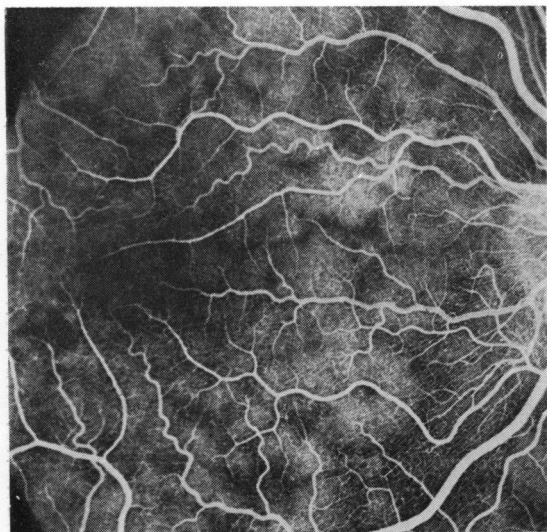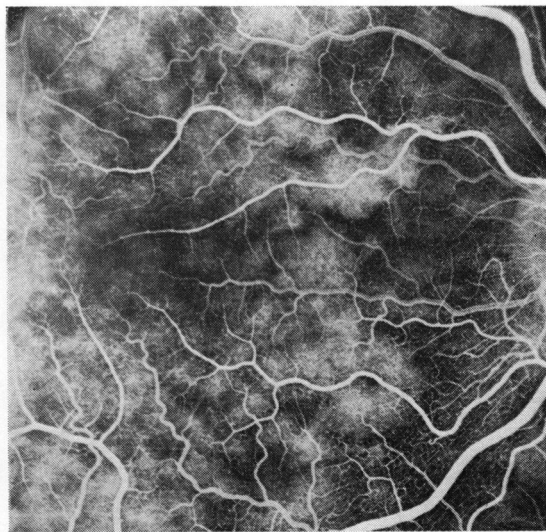multifocal pigment epithelial lesions and associated with uveitis, papillitis, tinnitus, headache, and alopecia, had disease similar to that described by Harada (1925), although 5 of our 8 cases occurred in Caucasians. No signs of recovery were identified within the first week, and all patients but one were given systemic corticosteroids. The disease in these patients was characterised by multiple recurrences, each requiring treatment.

As described, Harada's disease and APMPPE appear to be clearly different one from another in respect of their morphology and the subsequent behaviour of the disease. Nevertheless both present with acute multifocal pigment epithelial disease, and the changes identified during the initial fluorescein transit are indistinguishable; optic disc swelling is characteristic of Harada's disease and occurs in some patients with APMPPE. After recovery both show retinal pigment epithelial change; in APMPPE the changes are multifocal, with profound atrophy of the retina and choroid in some, whereas in Harada's disease they are diffuse.
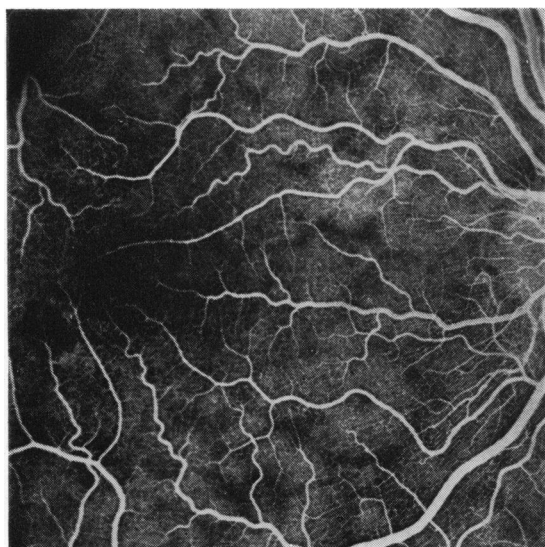
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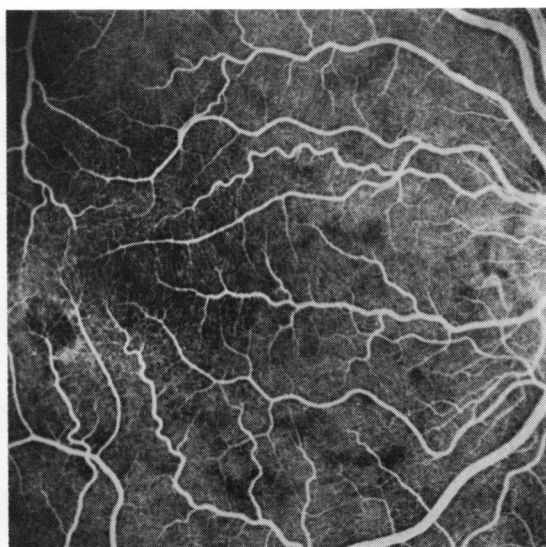
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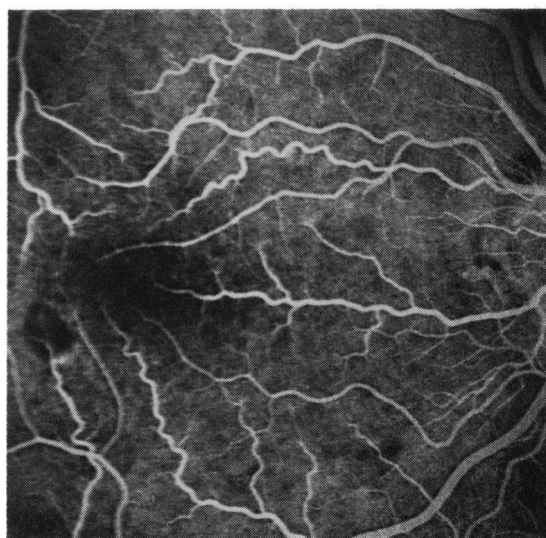
6g

Fig. 6   *Case 20. Four days after initial visual loss. Fluorescein angiography outlining limited retinal detachment at the posterior pole of each eye 5 minutes after initial dye entry (Fig. 6a, b). Within 18 days vision had recovered and the retina was flat. Fluorescein angiography showed slow filling of the choriocapillaris (Fig. 6c–g)*

The pathogenesis of neither disease is known, and no specific test is available to distinguish one from the other. No histopathological material is available on APMPPE, but the association of this disease with erythema nodosum (van Buskirk *et al.,* 1971) suggests that the disease may be caused by a vasculitis affecting the choroidal arteries or arterioles and that the focal pigment epithelial lesions may represent infarcts, a view supported by Deutman *et al.* (1972). The appearance of the large choroidal vessels in the areas of hypofluorescence during the initial transit of dye on fluorescein angiography in some patients (Figs. 2a, b) indicates that obstruction of choroidal fluorescence by swollen pigment epithelium cannot entirely explain hypofluorescence and that focal non-perfusion of the choriocapillaris occurs during the acute stage of the disease. Deutman and Lion (1976) have made similar observations. While the aetiology is unknown, viral disease has been implicated (Azur *et al.,* 1975), and many observers have reported an antecedent viral illness, either upper respiratory or gastrointestinal (Ryan

Table 1

| APMPPE	Age	Interval to visual improvement to 6/9	Treatment with systemic corticosteroids	Recurrence	Associated findings
1	52	2 weeks	+	−	Uveitis
2	38	2 weeks	−	−	Myotonic dystrophy
3	17	2 weeks	−	−	Genetically determined angioedema
4	15	3 weeks	−	−	−
5	32	3 weeks	−	−	—
6	31	2 weeks	−	−	—
7	24	2 weeks	−	−	—
Harada's					
8	31	6 weeks	+	+	Uveitis, headache, poliosis, viteligo, alopecia
9	38	3 weeks	+	+	Uveitis, headache, dysacousis, meningitis
10	45	3 weeks	+	+	Uveitis, headache, dysacousis, alopecia
11	36	2 weeks	+	+	Uveitis, papillitis, dysacousis
12	38	3 weeks	+	+	Uveitis, alopecia, viteligo
13	31	2 weeks	+	+	Uveitis, tinnitus, headache
14	48	6 weeks	Med. contraindications	−	Uveitis, headache, alopecia
15	26	6 weeks	+	+	Uveitis, headache, dysacousis
Intermediate					
16	24	1 week	+	−	Uveitis, papillitis, headache
17	34	6 days	−	−	—
18	34	2 weeks	+	−	Uveitis, papillitis, episcleritis, headache
19	21	1 week	−	−	—
20	26	2 weeks	+	−	Uveitis, headache
21	23	1 week	−	−	—
22	29	1 week	−	−	Uveitis
23	39	2 weeks	−	−	Uveitis
24	21	1½ weeks	−	−	Uveitis
25	28	5 days	−	+	Uveitis, headache, viteligo
26	20	2 weeks	−	−	Uveitis

and Maumenee, 1972; Annesley *et al.*, 1973; Fitzpatrick and Robertson, 1973; Savino *et al.*, 1974; Holt *et al.*, 1976).

In Harada's disease there is extensive lymphocytic and plasma cell infiltration of the choroid and proliferation of epithelioid cells with the formation of granulomatous nodular lesions (Woods, 1961; Hogan and Zimmerman, 1962). Involvement of the leptomeninges of the optic nerve by such an infiltration has also been reported (Perry and Font, 1977).

This severe inflammatory reaction in the uveal tract results in profound disturbance of the retinal pigment epithelium and the accumulation of large amounts of subretinal fluid. The mechanisms by which the choroidal inflammation affects the retinal pigment epithelium have not been identified. The aetiology is unknown, although viral disease (Sugiura *et al.*, 1953; Morris and Schlaegal, 1964) and a disturbed immunological state (Hammer, 1971; Hammer, 1974) have been suggested.

Patients 16 to 24 when first seen had disease morphologically indistinguishable from Harada's disease, but unlike our concept of Harada's disease the course of the disease was brief, the patients did not have associated generalised disturbance, and the disease did not recur. Furthermore, the only feature which distinguished these patients from those with APMPPE was the presence of serous retinal detachment. The serous detachment resolved spontaneously and rapidly, leaving a fundus appearance similar to APMPPE in some. Fluorescein angiography during recovery in 1 patient (Figs. 6c–g) was identical to that seen in some cases of APMPPE (van Buskirk *et al.*, 1971) and indicates strongly that decreased perfusion of the choroid existed, at least in this patient.
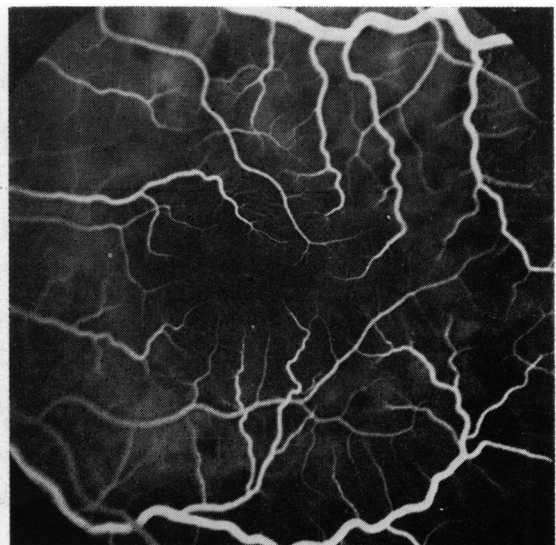
When viewed as a whole, these patients appear to present a continuum of disease rather than separate disease entities. This impression is strengthened by patient 25, who when first seen had a brief episode of disease which resolved spontaneously, followed 3 months later by a severe recurrence
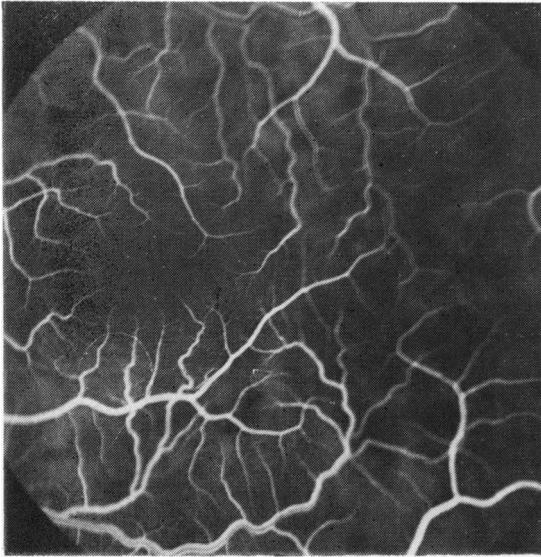

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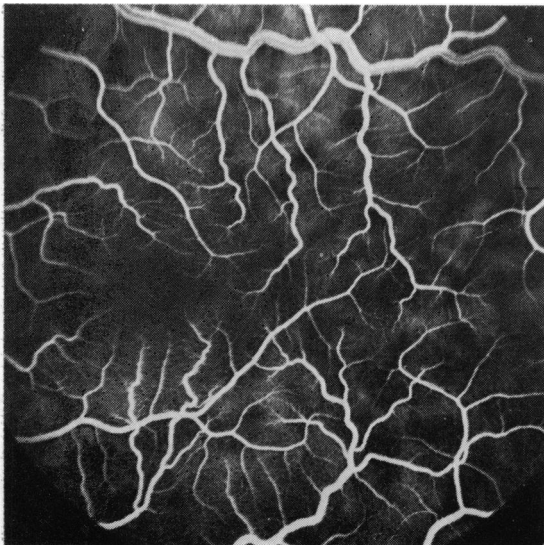
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typical of Harada's disease which required treatment with systemic corticosteroids. Patient 26 further confuses the differentiation of one disease from another since she had serous detachment in 1 eye but not the other.

Nevertheless, some of the patients described in this paper differ from others in many important respects, suggesting that more than one disease process might be involved. It is conceivable that those patients with serous retinal detachment (8 to 26) all fall within the spectrum of Harada's disease and that many had a more benign course than we

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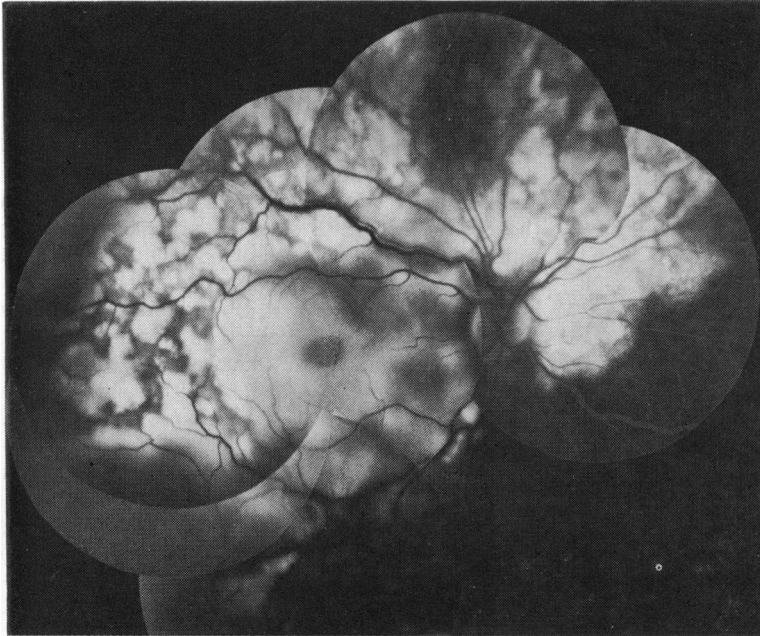
Fig. 7   Case 23. Four days after onset of visual loss. Fluorescein angiography demonstrating apparent slow filling of the choriocapillaris (Fig. 7a–c) and progressive accumulation of dye in the subretinal space (Fig. 7d, e). Five days later the retinal detachment largely resolved with visual recovery and within a further week the retina was quite flat (Fig. 7g–i)

would have expected. The relatively benign nature of the disease in some patients has been emphasised by previous authors (Salus, 1932; Woods, 1961; Ohno *et al.,* 1977). If the disease behaves differently in different races (Ohno *et al.,* 1977), the presence of the 3 non-Caucasians in the severely affected group is significant. Alternatively, the intermediate group may be part of the spectrum of APMPPE in which serous retinal detachment occurs, as was implied by Bird and Hamilton (1972) and Holt *et al.* (1976). It is also possible that 3 or more separate disease entities could have caused the disorders in these patients. The apparent similarities in dissimilar diseases would be understandable if the clinical manifestations were due to a mechanism common to all, possibly poor choroidal perfusion and focal retinal pigment epithelial infarction. Finally, all may fall within the spectrum of a single
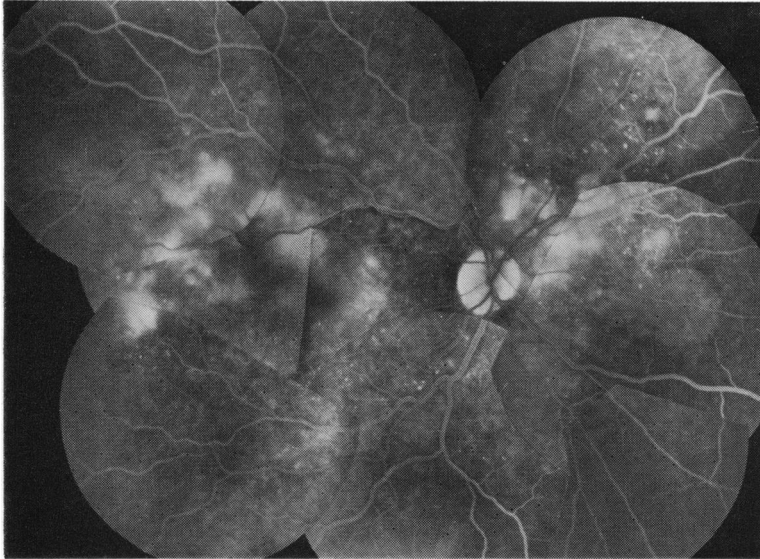
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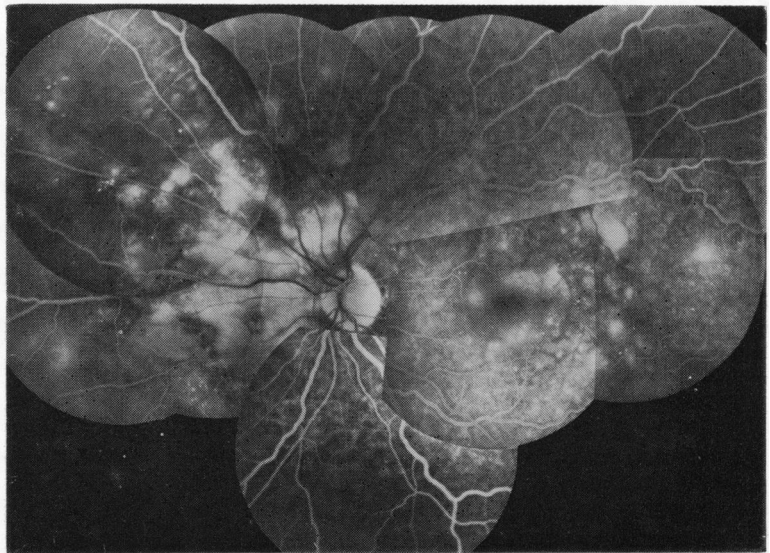
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disease entity, a possibility alluded to by Ohno and co-workers (1977).

There is no doubt that the identification of a specific disease is helpful in determining a patient's visual prognosis, and that the definition of single disease entities within a group of disorders is important for research. However, it is apparent that a single disease can produce a variety of manifestations, as shown by onchocerciasis (Bird *et al.,* 1976), and equally that different diseases may present similar appearances. Harada's disease may be mimicked by sympathetic ophthalmia (Shimizu, 1973) and by scleritis (Cleary *et al.,* 1975), and the changes in pigment epitheliitis are similar to a single lesion in APMPPE (Krill and Deutman, 1972). Until the specific cause of a disease is determined and becomes identifiable in each patient, the classification of disease can be based only on its morphology, but the limitations of this basis for classification cannot be ignored.

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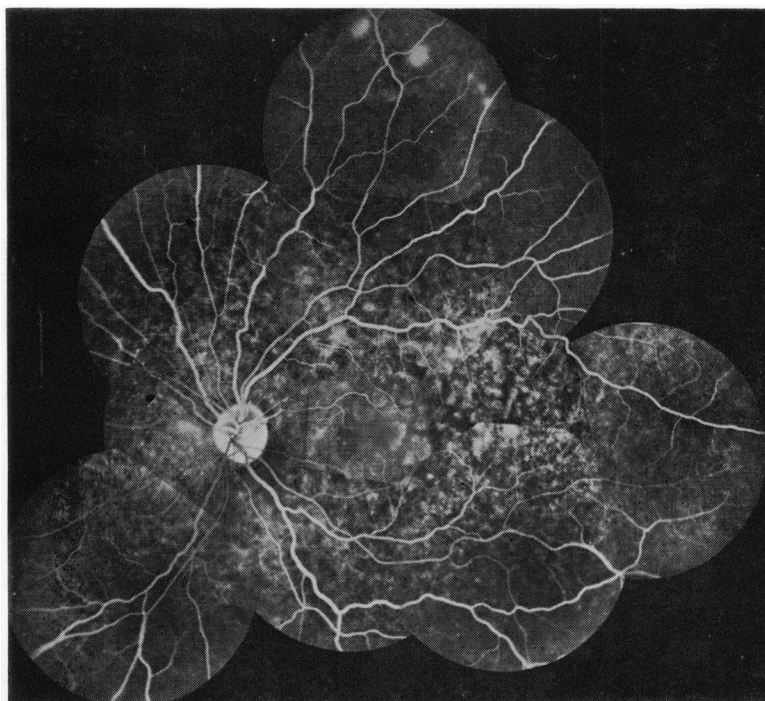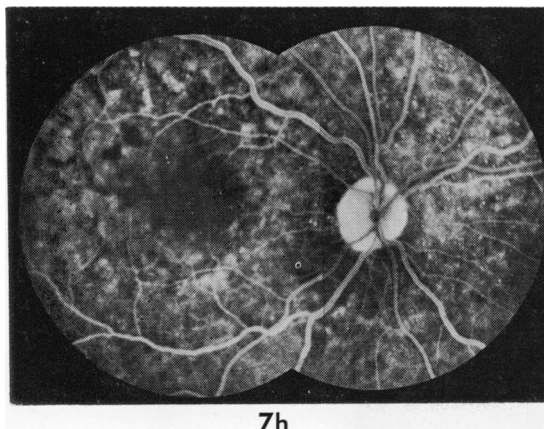
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