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Retinal pigment epithelial detachments in the elderly: a controlled trial of argon laser photocoagulation

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SUMMARY A prospective randomised trial of argon laser photocoagulation of retinal pigment epithelial detachments in the elderly is presented. The results based on 18 months' follow-up show that, in terms of visual acuity, photocoagulation is not beneficial as carried out in this study. The morphological outcome of the treated and untreated eyes is discussed. Stricter entry criteria would not have affected the conclusions. Tearing of the pigment epithelium occurred earlier in the treated than in the untreated eyes.

1. VISUAL OUTCOME

Retinal pigment epithelial detachments occurring in the presence of diffuse, age-related, Bruch's membrane changes and drusen, but without detectable subretinal neovascularisation, form part of the spectrum of senile macular degeneration.[1] They present a typical appearance of discrete, round or oval, dome shaped lesions which, on fluorescein angiography, fill early and evenly with dye and continue to fluoresce after the background has faded.[2,3] Pigment epithelial detachments may progress to vascular disciform lesions, and it has been thought that this development is consistently associated with deterioration of the visual acuity.[4,5] It is recognised that the presence of subretinal new vessels cannot be excluded by clinical criteria alone.[6] However, the behaviour of apparently avascular lesions differs significantly from those with identifiable subretinal neovascularisation, and therefore their separate consideration is justified.

Treatment of pigment epithelial detachments by photocoagulation was first reported in 1968.[7] In the early reports either xenon arc photocoagulation was applied in a horseshoe shaped pattern[8] or, alternatively, pulsed ruby laser burns were scattered over the lesion.[9] Later reports described argon laser grid photocoagulation of the detachment avoiding the foveola.[10–12]

In one of the earlier studies 47 out of 53 detachments flattened following treatment and remained flat during the follow-up period without loss of visual acuity.[13] More recent evidence suggested that patients under the age of 56 had a good visual prognosis without treatment.[14,15] By contrast older patients and those with detachments larger than one disc diameter appeared to have a much higher risk of vascular complications and visual loss.[15] Although the initial photocoagulation studies had implied a possible benefit from treatment, a more recent study has suggested that this may not be the case.[16] Furthermore, a significant number of young patients who have a good visual prognosis were included in the earlier studies.[11,14,15] No controlled trial of treatment has yet been reported.

The purpose of this paper is to present the results of a prospective, randomised, controlled trial of argon laser photocoagulation in the treatment of pigment epithelial detachments in the elderly. The study has been carried out over a 4-year period, and the conclusions are based on a follow-up period of 18 months.

Material and methods

STRUCTURE OF THE STUDY

The purpose of the study was to determine whether argon laser photocoagulation altered the visual prognosis of pigment epithelial detachments in the

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elderly and whether the age of the patient, the location of the detachment, or the presenting visual acuity influenced the final outcome.

Entry criteria. Patients were considered suitable for entry according to the following criteria: (1) evidence of a pigment epithelial detachment extending to within 1500 μm of the centre of the fovea and which could underlie the foveola; (2) absence of detectable subretinal new vessels on angiography; (3) age limits of 50 to 80 years; (4) presence of drusen in both eyes; (5) consensus of opinion from the medical workers concerning the patient's suitability for the trial.

Exclusion criteria. Patients were excluded for the following reasons: (1) subretinal exudates and/or haemorrhages which implied the presence of subretinal vessels and which precluded adequate view of subretinal structures; (2) diseases which precluded adequate fundus examination and laser photocoagulation; (3) other disease associated with visual loss; (4) myopia of greater than 3 dioptres; (5) previous photocoagulation in the eye under consideration; (6) inability or unwillingness to give informed consent.

PATIENT MANAGEMENT

Initial visit. Clinical assessment, colour photography and fluorescein angiography were carried out on this occasion. Guttae phenylephrine 10%, and cyclopentolate 1% were used for mydriasis prior to fundus examination and photography. Fundi were examined by indirect ophthalmoscopy and biomicroscopy with the Zeiss (Oberkochen) slit-lamp with a Hruby lens attachment. Stereoscopic colour photographs were taken with the Zeiss Retinophot fundus camera using Ektachrome film. Stereo fluorescein angiography was carried out with the Zeiss (Oberkochen) fundus camera, Ilford FP4 film, and Spectrotec filters following an intravenous injection of 5 ml 20% fluorescein sodium *BP*. If on the basis of the clinical findings it was believed that the criteria for entry were satisfied, with no cause for exclusion, the patient was asked to return on the next available day for further evaluation.

Entry study visit. The entry visit was carried out within 4 days of the initial angiogram. The photographs were examined, and, if the entry criteria were satisfied, the nature of the study was explained to the patient, who was invited to enter the treatment trial. Informed consent was obtained prior to entry. Evaluation of the visual acuity and visual field assessment were carried out prior to stratification and randomisation.

Visual function before mydriasis was assessed by an ophthalmic optician at the entry study visit. The best corrected Snellen distance acuity and near vision acuity with a +4 dioptre reading addition were measured with the Faculty of Ophthalmologists reading test type for near vision. When the acuity was worse than N5 with a +4 dioptre addition, the best reading acuity with low vision aids was recorded; the type and power of the aids needed was noted. The data were converted to a numerical value for analysis (Table 1).

Table 1 *Visual acuity data conversion*

6/5 = 1	N5 = 1
6/6 = 2	N6 = 2
6/9 = 3	N8 = 3
6/12 = 4	N10 = 4
6/18 = 5	N12 = 5
6/24 = 6	N14 = 6
6/36 = 7	N18 = 7
5–6/60 = 8	N24 = 8
4–3/60 = 9	N36 = 9
2–1/60 = 10	N48 = 10
Less than 1/60 = 11	Less than N48 = 11

Visual fields were assessed with a Friedmann Mk 1 field analyser. The macular threshold level was identified for the affected eye and static field recordings started 0·2 log units brighter than threshold. Errors were plotted on the standard chart and a note made of the error score in the central 9 and 33 points (8 or 32 plus fixation). The number of absolute defects and the error score for both the central 9 and 33 points were used for analysis.

The patients were then stratified according to age (50–60, 61–80), visual acuity (6/24 or better, or worse than 6/24) and distance of the nearest edge of the detachment from the foveola as measured by a grid[17] (less than 200 or 200–1500 μm). Random numbers arranged in cells of 4 within each stratum were used to allocate patients for treatment or observation, so that 2 patients from each cell received photocoagulation.

Treatment. At the end of the entry visit patients allocated to treatment were photocoagulated. Treatment was performed by the member of the medical team entering the patient into the trial, using the Coherent Radiation series 800 or 900 argon laser photocoagulator with a Zeiss delivery system. Topical anaesthesia and a Goldmann contact lens were used. Focal burns (usually 200 μm) were scattered in a grid pattern over the surface of the pigment epithelial detachment leaving a gap of approximately 200 μm between each. Care was taken to avoid the foveola and the major vessels. The power setting and duration of the burns (usually 0·2 s) were adjusted to produce definite whitening at the level of the pigment epithelium (Figs. 1a,b). Colour photographs were obtained immediately after the treatment, providing a permanent record.

Treatment visits. Subsequent visits were at 2-weekly intervals until no further photocoagulation

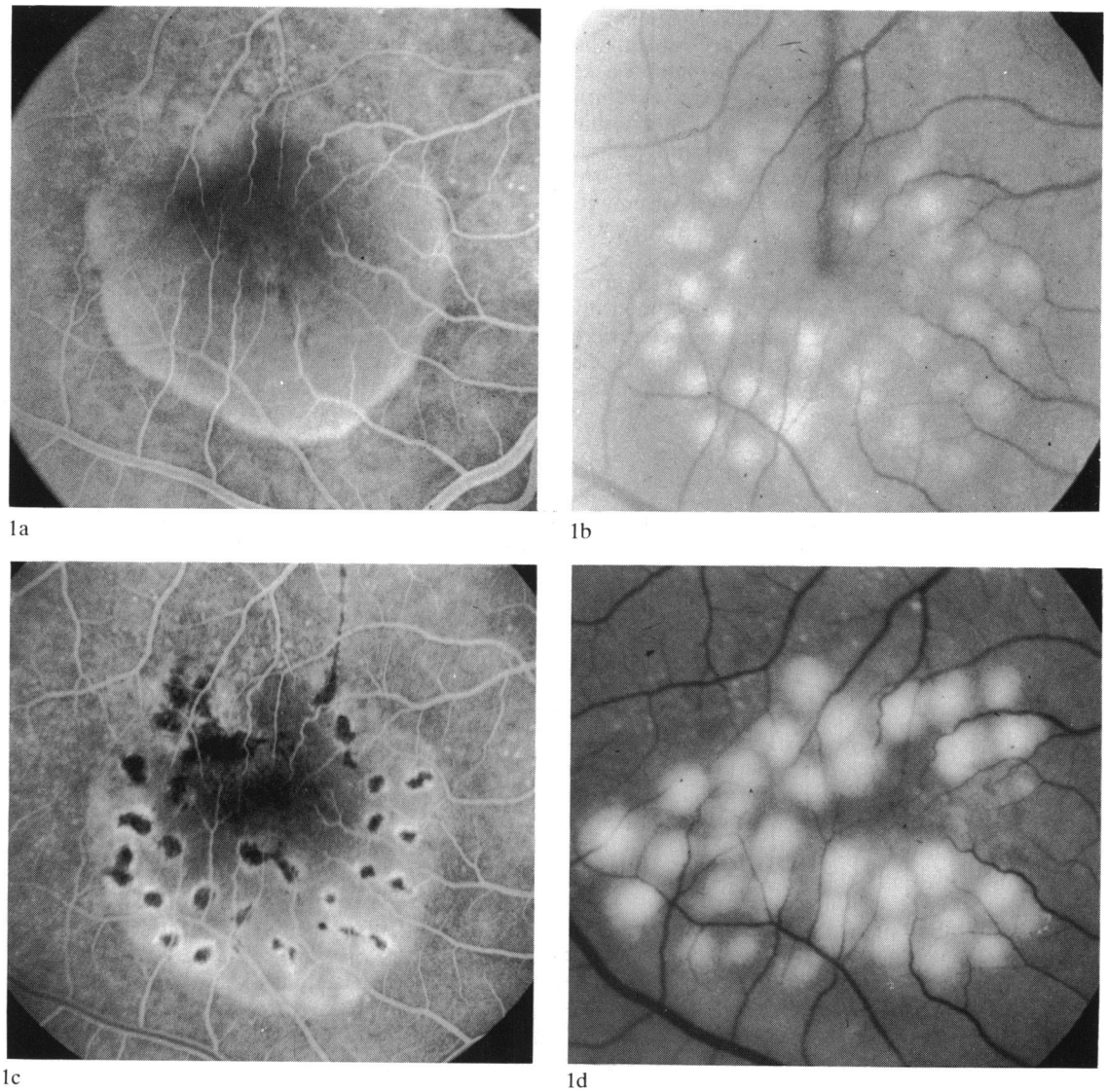


Fig. 1 *Treated pigment epithelial detachment:* (a) *before treatment;* (b) *immediately after treatment showing focal whitening over the surface of the detachment;* (c) *persistence of the detachment 2 weeks later despite photocoagulation;* (d) *retreatment of the persistent detachment.*

was indicated. Photocoagulation was repeated if there was persistence of the pigment epithelial detachment or neovascular tissue was detected under the retina (Figs. 1c,d). Neovascular lesions were treated with heavy confluent photocoagulation. The presence of subfoveolar neovascular tissue was a contraindication to additional treatment. Clinical examination, fluorescein angiography, and colour photography were repeated at each of these visits.

Study visits. Study visits were at 3-monthly intervals in the first year and 6-monthly thereafter for both treated and untreated patients (3, 6, 9, 12, 18 months). Visual acuity and field assessments were carried out by an ophthalmic optician on each visit, followed by further clinical examination, fundus photography, and fluorescein angiography.

Records were kept of intended visits, so that a missed appointment for a treatment or a study visit

was rapidly recognised. In this event the patient was recalled so as to obtain data as close as possible to the date of the planned visit and not later than 6 weeks after a study visit. The patient was instructed to return for further assessment if at any time after the initial treatment visits there was a deterioration of vision. The photographs of treated patients were reviewed at 2-weekly intervals as part of an audit of management. If recurrent disease was identified, the patient was recalled for reassessment.

The visual acuity data, together with the field error scores, were analysed statistically at 3-monthly intervals. Both the optician and the statistician were masked from the treatment status of the patient. The statistical findings were passed to the Data Monitoring Committee at regular intervals.

STATISTICAL METHODS

Qualitative analysis

The purpose of this analysis was to compare the changes of visual acuity within the 2 management groups, a movement of 1 line (1 unit) and 2 lines (2 units) being used as a definition of change. The visual acuity at each study visit was compared with the initial findings and categorised as improved, unchanged, or worse.

To compare the proportion of eyes with deterioration in vision in the 2 groups standard deviate z was computed.[18] Significance values can be obtained from z values with tables of the normal distribution. As the accumulating data were subjected to analysis every 3 months, caution was exercised when deciding upon the p value which was to be considered 'significant'. At the start of the trial an overall p value for this qualitative analysis of 0·05 was designated as indicating a significant difference between the 2 groups; because the data could have been analysed a maximum of 10 times, the p value required for 'significance' at any one analysis, was taken to be 0·01[19] (p. 420), giving an approximate overall value of 0·05 for the qualitative analysis. The proportion of patients with improved vision was analysed similarly.

As stratification had been used in allocating the patients, Cochran's test statistic[20] was also calculated. However, as the randomisation procedure ensured that approximately equal numbers of patients from each stratum were allocated to the 2 groups, the z value is given in the tables. A chi-squared test for trend[19] (p. 363) was also performed on the proportions that showed improvement, no change, and deterioration in the 2 groups.

Quantitative analysis

The size of visual change between the 2 groups was compared, movement of one line of the Snellen chart being used as a unit of movement. Although the data were discrete, the normal approximation was used, and this enabled the data to be analysed by *t* tests. As in the qualitative analysis the overall significance level was set at 0·05 and the level of each analysis at 0·01.

Visual field analysis

To test for any difference in field scores a separate *t* test was used on the mean field changes for each of the 4 field readings.

End-point analysis

If the main objective of any treatment is to prevent deterioration of the patient's central vision below a certain level, regardless of initial visual acuity, it is useful to consider the patient's visual acuity at the time of entry into the study and at the time of examination.

For each patient at each visit it was recorded whether visual acuity had been worse than the end-point at least once, twice, or 3 times consecutively.

A separate analysis was undertaken with an end-point of 6/24, 6/36, and 6/60. The proportion of patients having a particular event recorded in the 2 management groups was compared by means of the z value; an approximate overall p value of 0·01 was considered significant. As stratification was used, Cochran's test statistic was evaluated.[20] However, the z value and Cochran's statistic were similar in all analyses, and only the z value is given in the tables.

Results of the main study

SIZE OF STUDY AND FOLLOW-UP

Of the 22 patients in the treatment group 18 attended every follow-up visit for 18 months. One patient died between the 3 and 6 months' visits. Visits were missed at 6 and 9 months by one patient, at 6 months by another, and the last was not seen between 6 months and 2 years (Table 2).

Of the 27 control patients complete follow-up information was recorded for 23. One left the study after the initial visit to be treated elsewhere. One

Table 2 *Number of patients who had completed the indicated visit by 30 September 1980*

Visit	*Group*	
	Treated	*Untreated*
Initial	22	27
3 months	22	26
6 months	19	25
9 months	19	24
12 months	20	25
18 months	20	24

Table 3 *The change in visual acuity from the initial visit to the visit indicated*

Visit months	*Group*								
	Treated			*Untreated*					
	Improved	*Same*	*Worse*	*Improved*	*Same*	*Worse*	*Zi*	*Zw*	$\chi^2 t$
A. Taking a move of one or more lines as a change									
3	1	8	13	4	17	5	−1·25	2·82*	7·55*
6	1	4	14	5	10	10	−1·46	2·24	4·92
9	1	5	13	4	10	10	−1·19	1·75	3·24
12	1	5	14	4	10	11	−1·20	1·75	3·24
18	1	4	15	4	6	14	−1·24	1·17	1·84
B. Taking a move of two or more lines as a change									
3	0	14	8	1	23	2	−0·97	2·39	6·50
6	0	11	8	1	22	2	−0·97	2·59*	7·53*
9	0	11	8	0	20	4		1·82	
12	0	9	11	0	19	6		2·11	
18	0	6	14	0	14	10		1·89	

Zi: the Z value comparing the proportion of patients with improved acuity in each group.
Zw: the corresponding value for deterioration of visual acuity.
$\chi^2 t$: the value of the χ^2 variate testing for trend.
*: $p<0·01$.

patient died after having been seen at 3 months. Of the remaining 2 patients, one was lost to the study after 12 months and one missed the 9-month visit.

It was initially envisaged that, given the results of the preliminary study, approximately 150 patients would be required for the trial to be statistically valid. However, the study was designed to permit early termination if the Data Monitoring Committee thought that there was sufficient evidence to stop recruitment in the light of the results of any of the interim analyses. After approximately 40 patients had been followed up for at least one year, recruitment to the trial was stopped.

QUALITATIVE ANALYSIS

The percentage of patients showing any improvement in visual acuity was low in both groups, even when a move of one unit was taken as the criterion for change (Table 3A). The percentage that improved by at least one unit in the untreated group might have been greater than that in the treated group, but a much larger study would be required to show this. However, it is unlikely that treatment is beneficial if qualitative improvement in visual acuity is the basis for comparison.

There was strong evidence to suggest that the proportion of patients whose visual acuity deteriorated after photocoagulation was greater than that in the untreated group. This was particularly marked 3 months after treatment when a move of one or more units was taken as a change. At this time 61% of the treated patients had deteriorated, compared with 16% of the untreated ($z=2·82$, $p<0·01$). Between 9 and 18 months the percentage who deteriorated in the treated group remained fairly stable, whereas in the untreated group the percentage was steadily rising, but still some way from reaching the level in the treated group.

With a movement of 2 lines on the Snellen chart being taken as the criterion for change both groups showed steady increase in the proportion of patients who had deteriorated; the treated group consistently had the higher percentage (Table 3B). Although none of the z values obtained was significant at the 1% level, with more patients it is likely that the appropriate level of significance would have been obtained at each visit.

QUANTITATIVE ANALYSIS

The results (Table 4) showed that treated patients were prone to a large deterioration in visual acuity shortly after treatment, and it was this analysis that was the primary reason for termination of recruitment. The *t* values at the 3, 6, and 9 months visits were calculated with separate variance estimates, since the variance of the change in visual acuity was far greater in the treated group ($p<0·001$) at each of the first 3 visits. However, large and sudden deteriorations can also take place in the untreated group, albeit at a later stage. This is reflected in the standard deviation of the change in visual acuity in the untreated group, which increased at each visit.

Table 4 *Number of lines moved on Snellen chart since initial visit*

Number of lines	*Visit*									
	3 months		*6 months*		*9 months*		*12 months*		*18 months*	
	T	*U*	*T*	*U*	*T*	*U*	*T*	*U*	*T*	*U*
Worse −8	1	0	2	0	2	0	1	0	0	1
−7	0	0	1	0	0	0	1	1	2	1
−6	1	0	1	0	2	0	2	0	2	1
−5	3	0	3	0	3	0	4	0	4	1
−4	0	0	0	0	0	1	0	1	0	0
−3	2	0	1	0	0	1	2	2	2	2
−2	1	2	0	2	1	3	1	2	4	4
−1	5	3	6	8	5	6	3	5	1	4
Same 0	8	17	4	10	5	10	5	10	4	6
Better 1	1	3	1	4	1	4	1	4	1	4
2	0	1	0	1	0	0	0	0	0	0
Mean	−1·86	−0·77	−2·73	−0·24	−2·63	−0·50	−2·85	−0·88	−3·0	−1·67
SD	2·46	0·85	3·00	0·97	2·97	1·18	2·80	1·83	2·58	2·55
t	−3·25*		−3·50*		−2·95*		−2·84		−1·72	
P	0·003		0·002		0·007		0·007		0·09	

T=treated group; U=untreated group; SD=standard deviation; *indicates that separate variance estimates were used to calculate *t*.

END-POINT ANALYSIS

As would be expected from the results of the qualitative and quantitative analyses, the proportion of patients reaching a specified end-point was greater in the treated group for all 3 end-points used at each visit after entry into the trial (Table 5). The difference reached a maximum at 6 months (2·59 for 6/36) and decreased steadily thereafter. All treated patients who reached the lower end-points—i.e., 6/36 and 6/60—had done so by 6 months, but in the untreated group the number reaching these end-points appeared to be increasing at each subsequent visit.

VISUAL FIELDS

The field scores in both groups of patients generally showed a steady deterioration during the first 18 months (Table 6). It was only in the first 6 months after entry into the trial that any differences between the 2 groups were large enough to be detected and then only for the 'missed central' scores ($p<0·01$ at both 3 and 6 months). Other differences might have existed, but the standard deviations of the change in field scores were such that a far larger trial would have been required to detect them.

Baseline Variables

The variables used for the purposes of stratification were distance from the foveola, age, and visual acuity. However, except for age, any comparison of subgroups was either impossible or redundant, since the results would be merely a reflection of the trial results as a whole.

All analyses previously mentioned were carried out separately for patients aged 60 or less at the time of entry and for patients aged over 60. The results did not indicate that there was any interaction between age and the effect of treatment or that age influenced the outcome, although small differences could not have been discounted.

Table 5 *Number and percentage of patients who had visual acuity less than the specified end-point at one or more visits and had completed the visit indicated or a subsequent visit*

A=6/36					
Visit	*Group*				*Z*
	Treated		*Untreated*		
	Number	*%*	*Number*	*%*	
Initial	0	0	1	3·7	−0·96
3 months	6	27·3	2	7·7	1·78
6 months	8	42·1	2	8·0	2·59*
9 months	8	42·1	3	12·5	2·16
12 months	9	45·0	4	16·0	2·10
18 months	9	45·0	6	25·0	1·39
B=6/60					
Initial	0	0	0	0	0
3 months	3	13·6	0	0	1·87
6 months	5	26·3	0	0	2·56
9 months	5	26·3	0	0	2·54
12 months	5	25·0	2	8·0	1·53
18 months	5	25·0	4	16·7	0·68

*$p<0·01$.

Table 6 *The change in field scores from the initial visit to the visit indicated*

Visit	*Group*				*t*	*p*
	Treated		*Untreated*			
	Mean	*SD*	*Mean*	*SD*		
A: Error total						
3 months	−18·2	63·4	−18·1	39·5	−0·01	0·99
6 months	−19·2	101·9	−23·9	83·9	0·16	0·87
9 months	−10·6	82·6	−43·2	96·7	1·13	0·27
12 months	−26·4	81·6	−52·7	98·2	0·90	0·37
18 months	−27·8	88·0	−40·4	91·3	0·44	0·66
B: Error central						
3 months	−20·6	27·3	−5·3	18·7	−2·22	0·03
6 months	−18·7	33·4	−9·7	30·5	−0·90	0·37
9 months	−16·8	29·4	−23·5	36·7	0·62	0·54
12 months	−22·0	28·5	−25·7	40·2	0·34	0·74
18 months	−24·5	26·7	−27·9	37·2	0·33	0·75
C: Missed total						
3 months	2·90	7·0	1·00	5·7	1·01	0·32
6 months	1·56	6·4	1·87	5·9	−0·16	0·87
9 months	0·72	5·4	2·82	7·6	−0·99	0·33
12 months	1·00	5·4	3·74	6·6	−1·45	0·15
18 months	2·58	5·5	4·95	6·5	−1·24	0·22
D: Missed central						
3 months	2·14	2·6	0·38	1·3	2·85	0·008
6 months	2·61	3·0	0·26	1·1	3·18	0·009
9 months	2·50	2·7	1·32	2·8	1·33	0·19
12 months	2·89	2·7	1·65	3·3	1·32	0·19
18 months	2·84	2·3	2·24	3·3	0·67	0·51

Discussion

The study was carried out at a single centre, which ensured good control of both the patient visits and the standard of assessment and treatment. A limited number of workers was involved, and close co-operation was readily achieved. The decision about admissibility of a particular patient was made at the time of the second visit with all the medical workers present agreeing to entry. The records of the treated patients were audited following each visit, which ensured a uniformity of management.

The recruitment rate was lower than had been anticipated, but those patients who were admitted co-operated well. There was a low failure rate, and data were collected at 18 months on all but 5 patients, 2 of whom had died during the course of the study.

After 49 patients had been entered into the trial it was evident that the change in visual acuity was significantly worse in the treated group, and the Data Monitoring Committee decided that recruitment should be discontinued. A large deterioration of vision occurred in a significant number of treated patients soon after photocoagulation; such a deterioration was not seen in patients in the observation group during the early period after entry into the trial. It is clearly shown that with photocoagulation, as used in this study, there is no short-term visual benefit to elderly patients with pigment epithelial detachments.

The trial also shows that in the observation group rapid loss of vision could occur at any time. This contrasted with the treated patients, in whom additional visual loss was unusual after the initial period. However, at the 18-month visit the convergence between the 2 groups was insufficient to cancel out the early differences, and there is a little evidence to date to imply that a cross-over might occur later.

In designing the study it was thought that stratification into the groups described might show that a particular group would benefit from photocoagulation whereas another might not. The majority of patients were in the group with better acuity and had detachments within 200 μm of fixation. These patients were almost evenly divided between those from 50–60 years old and those over 60; comparison of these subgroups showed that photocoagulation conferred no benefit to either. Pigment epithelial detachments outside the central 200 μm or those associated with poor visual acuity rarely presented for assessment, which is consistent with clinical experience. There is no indication that any subgroup benefited from photocoagulation, although in some groups the numbers were so small that only gross differences would have been revealed.

2. MORPHOLOGICAL OUTCOME

Introduction

It has been assumed that the major threat to vision in patients with detachment of the retinal pigment epithelium is invasion of the subpigment epithelial space by blood vessels derived from the choroid,[5 14–16] and that this complication can be prevented if photocoagulation causes flattening of the detachment.[11]

The evolution of the lesions is correlated with the visual outcome in patients admitted to this trial.

Results

TREATED PATIENTS

Of 21 patients at the end of the review period the pigment epithelium and retina were flattened in 13,

there was persistence of the detachment in 2, and a vascular disciform lesion in 4 (Fig. 2). In the remaining 2 patients a tear in the pigment epithelium occurred immediately after photocoagulation, causing poor acuity, and was followed by submacular fibrosis (Fig. 3). In both cases incorrect identification of the lesion led to further treatment.

Of those patients with flattening of the retinal pigment epithelium 4 had one, 8 had 2, and 1 had 3 sessions of photocoagulation. The flattening occurred within 2 weeks of the final treatment. In none did the visual acuity improve, in 7 the acuity remained within one line of the pretreatment level, and in the remainder a drop of 2 lines or more occurred; only 5 had a final acuity of 6/12 or better. The drop of visual acuity coincided with flattening without any intervening event such as haemorrhage. In patients with visual loss the central retinal pigment epithelium appeared relatively normal (Fig. 4), but stereoangiography, when available, showed thinning of the central neuroretina. The fovea was not photocoagulated in any patient and the smallest distance between the foveola and a photocoagulation lesion was 150 μm.

Of the 4 with a vascular disciform lesion at the end of the period of observation, subretinal new vessels were evident within 2 weeks of initial photocoagulation in 2 cases; further treatment failed to destroy these vessels. In the other 2 cases the retinal pigment epithelium flattened rapidly after initial photocoagulation; in one a new disciform lesion occurred elsewhere in the posterior pole after 4 months and in the other subretinal new vessels grew from the edge of the previous detachment at 6 months. All 4 had poor acuity at the end of the study.

Both patients with persistent detachment of the retinal pigment epithelium had small subfoveal lesions, and it was thought that further photocoagulation might prejudice foveal function; one retained good visual acuity and in one there was deterioration from 6/18 to 6/36.

UNTREATED PATIENTS

Of the 24 untreated patients seen at 18 months 12 had persistent detachment of the retinal pigment epithelium, 3 had spontaneous flattening of the pigment epithelium, and 6 had a disciform lesion. In the remaining 3 a tear of the pigment epithelium developed during the first year after entry into the trial.

Two of the patients with subretinal neovascularisation had severe loss of visual acuity, and one had poor acuity on entry to the trial. The remaining 3 retained good vision (6/18 or better); in these, new vessels could be seen beneath an apparently intact retinal pigment epithelium (Fig. 5).

Of the 12 with persistent detachment of the retinal pigment epithelium 11 retained good visual acuity, and in only 3 did the acuity become worse that 6/18.

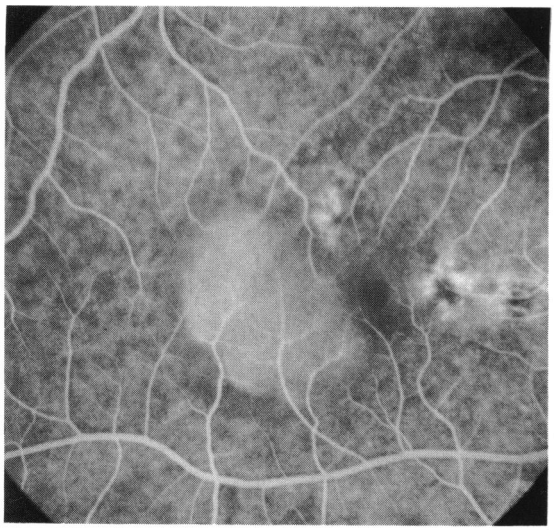
Flattening of the pigment epithelium was associated with good visual acuity. In each patient with a tear in the pigment epithelium severe loss of vision occurred soon after the tear.

Discussion

Three aspects of clinical behaviour during the trial were unexpected. It was disappointing that the high success rate in achieving pigment epithelial and retinal flattening was not accompanied by improvement of vision and maintenance of the initial visual acuity. The reason for the loss of vision is not clear, although the evidence suggests that poor vision was due to loss of foveal neuroretina. The central retinal atrophy was not due to direct coagulation of the foveola, but it is possible that photoxic damage might have occurred at the foveola due to scattered irradiation from the parafoveal burns. Alternatively, if there was significant absorption of argon laser energy by the luteal pigment in the neuroretina, the functional loss may have been caused by destruction of parafoveal neurones subserving foveal function[21]; this effect should be avoided by using the krypton laser.[22]

The retention of good acuity in half the untreated patients with subretinal neovascularisation is in marked contrast to the reported behaviour of disciform macular disease in the elderly and treated patients in this trial. Clinical observations during this period of the trial suggest that, in those who maintained good vision, the subretinal blood vessels proliferated on the inner surface of Bruch's membrane without destroying the integrity of the pigment epithelium. However, when there is rapid growth of vascular tissue within a disciform lesion in the absence of prior pigment epithelial detachment, it appears that the pigment epithelium becomes incorporated within the fibrovascular tissue in the early stages. In the first case the metabolic relationship between the pigment epithelium and retinal receptors would be relatively unaltered, whereas in the second it would be disrupted. The original assumption was that the main complication of pigment epithelial detachment was subretinal neovascularisation, which was inevitably followed by loss of visual acuity; clearly this assumption should be reconsidered.

The phenomenon of tearing of detached pigment epithelium was described only recently and was unrecognised at the start of the trial.[23] The results suggest that the incidence of tearing was not increased by photocoagulation but that treatment causes it to



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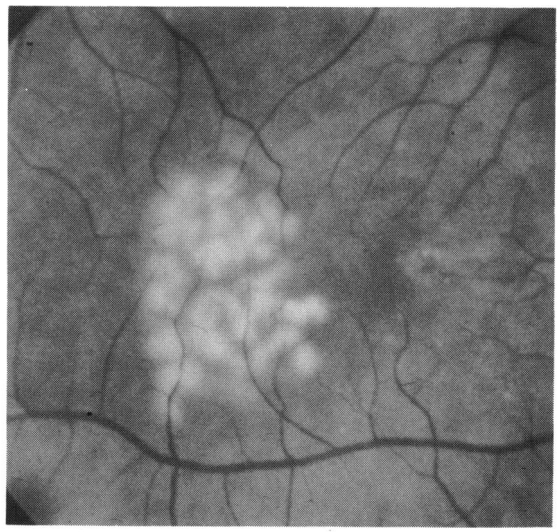

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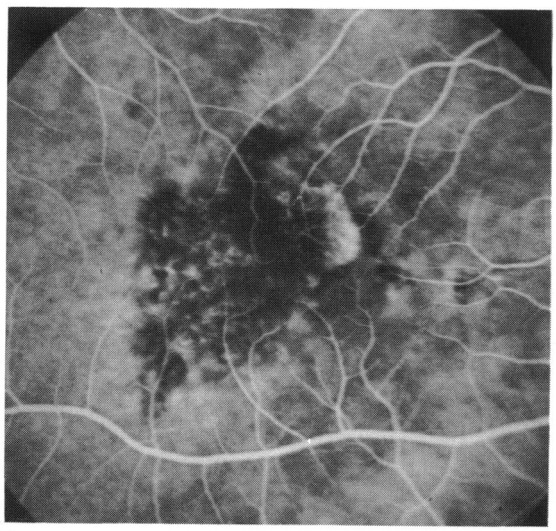


2c

Fig. 2 (a) *Pigment epithelial detachment with hyperfluorescence, but no leakage, upper nasal to, and remote from, the lesion;* (b) *treatment;* (c) *development of a vascular disciform lesion remote from the treated and flattened detachment.*

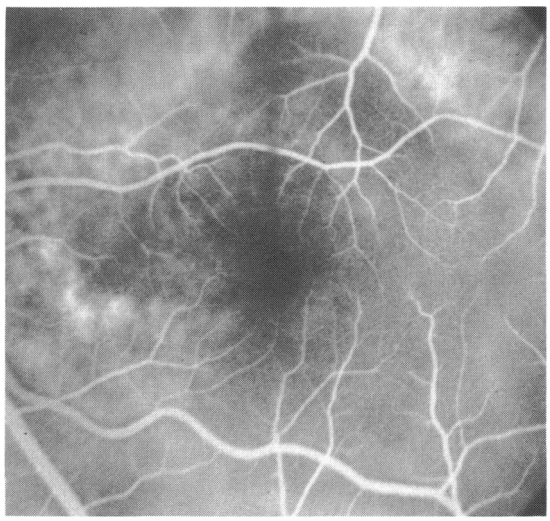
occur earlier than it might otherwise have done. The visual morbidity of pigment epithelium tearing was greater than subretinal neovascularisation in the individual patient. The number of patients losing vision from each of these complications was similar in the treated and untreated groups.

It is also evident that persistent detachment of the pigment epithelium in the elderly is compatible with retention of good visual acuity.

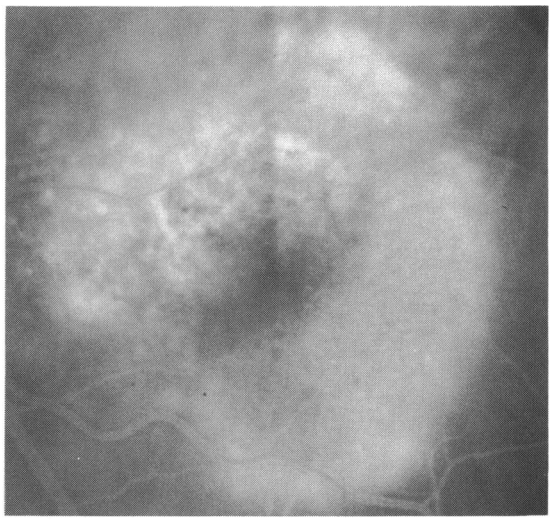
Various factors contribute to render the trial negative with respect to photocoagulation during the first 18 months after entry. The most important were the loss of vision in the treated patients with retinal pigment epithelial flattening and pigment epithelial tearing, and the retention of acuity in most untreated patients with persistent detachment and in some with subretinal neovascularisation. These factors combined to render the trial negative with respect to photocoagulation.

3. REVIEW OF ENTRY CRITERIA

In this study regular reviews of photocoagulation records ensured uniformity of treatment. However



3a



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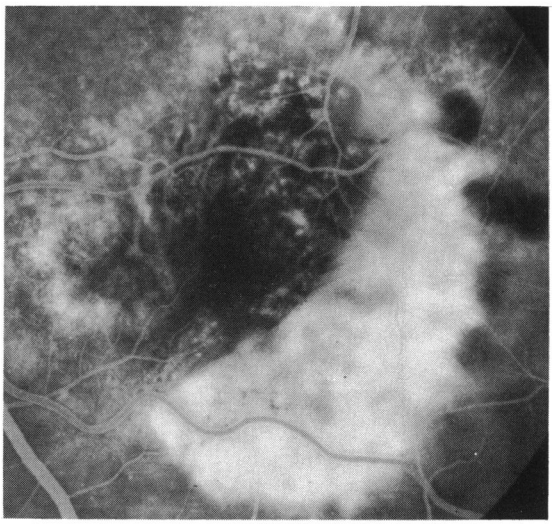


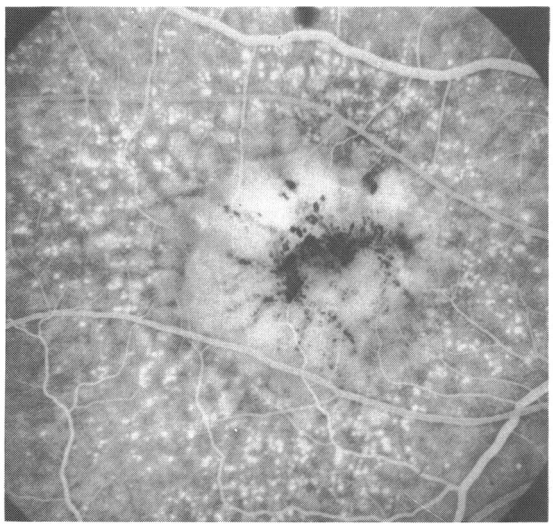
3c

Fig. 3 (a) *Pigment epithelial detachment with slow filling early in the angiogram;* (b) *in the late pictures there is even fluorescence temporally in contrast to the irregular transmission nasally;* (c) *tearing of the pigment epithelium seen 1 month following photocoagulation.*

the validity of any trial of therapy may also be questioned on the basis of patient selection or treatment technique. Every effort was made to prevent inclusion of lesions with subretinal neovascularisation, but there was sometimes doubt as to the nature of lesions at the time of entry.[6]

The original criteria for entry into the trial specifically excluded those lesions in which there was evidence of haemorrhage or exudate beneath the neurosensory retina or pigment epithelium, and those containing localised and increasing subretinal hyperfluorescence. Delayed but even hyperfluorescence of the detachment and uneven hyperfluorescence may indicate masking by debris under the pigment epithelium, and such cases were interpreted with care. They were not specifically excluded, since these variations do not inevitably imply the presence of subretinal new blood vessels.

Recently it has been suggested that the clinical appearance of a pigment epithelial detachment may be determined by the plane of cleavage between the retinal pigment epithelium and Bruch's membrane.[23] Detachment of the pigment epithelium with its basement membrane and associated debris gives rise to



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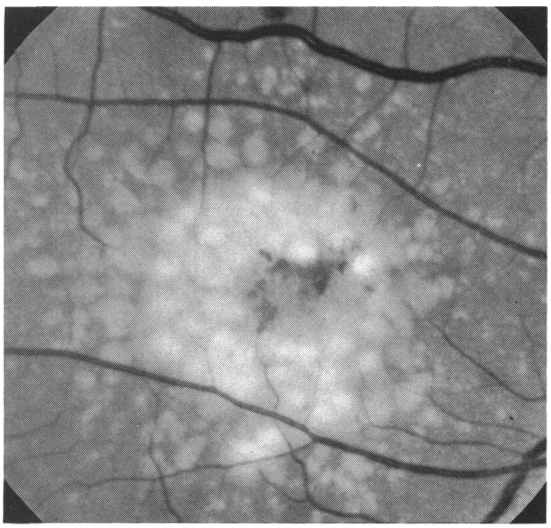

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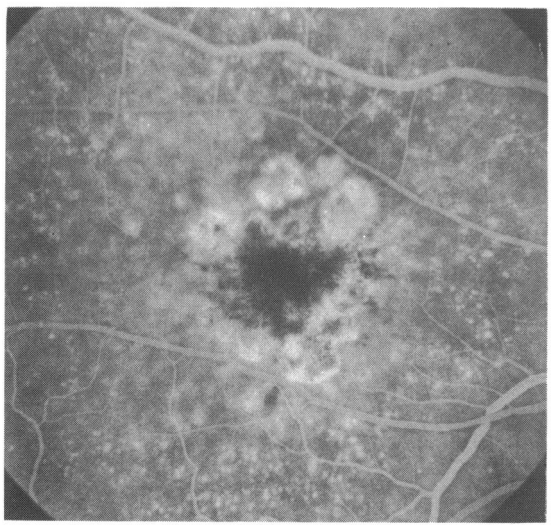


4c

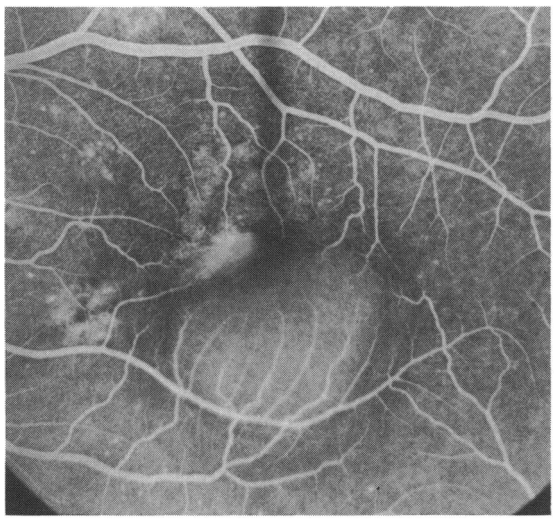
Fig. 4 (a) *Detachment with pigment figures on its surface;* (b) *grid photocoagulation sparing fixation;* (c) *flattened detachment with 1·5/60 visual acuity. The central pigment epithelium appears relatively normal, but is seen to be thin on stereoangiography.*

irregular hyperfluorescence due to uneven transmission of light by the detached tissues. By contrast in detachment of the pigment epithelium alone the fluorescein accumulates slowly and evenly. These observations may explain the variable appearance of pigment epithelial detachments.

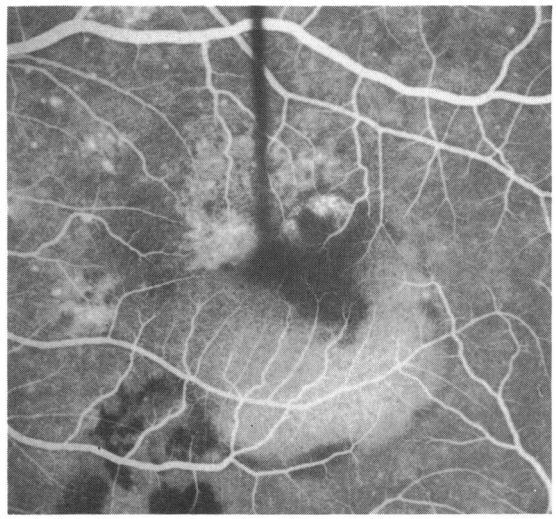
At the end of the study the initial angiograms were reviewed, and the results of the study were reanalysed to establish whether they would have been affected by revision of the entry criteria. The new criteria were designed to distinguish between irregular transmission of fluorescence by the pigment epithelium and focal hyperfluorescence within the subpigment epithelial space, and to assess the effect of excluding the patients with slow but even filling of the detachment.

Materials and methods

The entry films were studied retrospectively by 4 of the workers in the study who were masked from knowledge of the outcome. The films were assessed according to the original and to revised exclusion criteria which were (Fig. 6): (1) local progressive



5a



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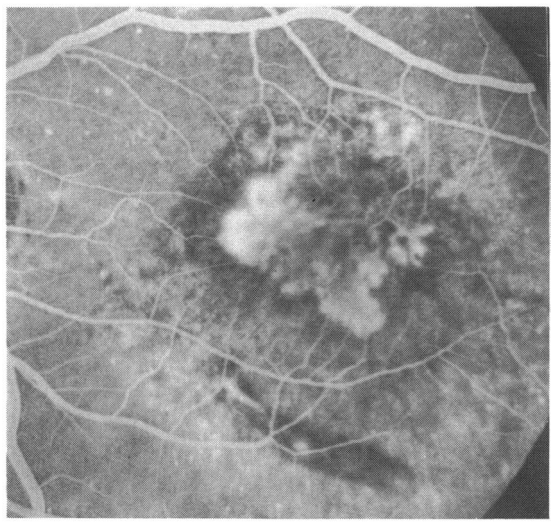

5c

Fig. 5 (a) *Untreated pigment epithelial detachment with hyperfluorescence superiorly;* (b) *9 months later there are subretinal and subpigment epithelial haemorrhages, with further hyperfluorescence above and enlargement of the detachment;* (c) *spontaneous flattening of the detachment with evidence of a vascular disciform lesion.*

hyperfluorescence beneath the pigment epithelium, as distinct from a transmission defect or dye accumulation within detached drusen; (2) regional masking not explained by irregular transmission at the level of the pigment epithelium due to hyperpigmentation; (3) late but even filling of the detachment after the arteriovenous phase.

The conclusions were pooled, and in those in which there was not agreement, a consensus was achieved following open discussion. The statistical results were re-examined to establish whether revision of the entry criteria might have influenced the conclusions.

Results

Twenty-two patients had been entered into the treatment group of the trial. The fluorescein angiograms of 2 of these patients were not available for retrospective study. Of the remaining 20, 1 was not considered to have satisfied the original entry criteria because of an area of hyperfluorescence within the pigment epithelial detachment. On analysis of the angiograms 10 (50%) were considered to have satisfied the revised criteria and 10 were not. (In 10 there was uniformity of opinion on masked assessment as to

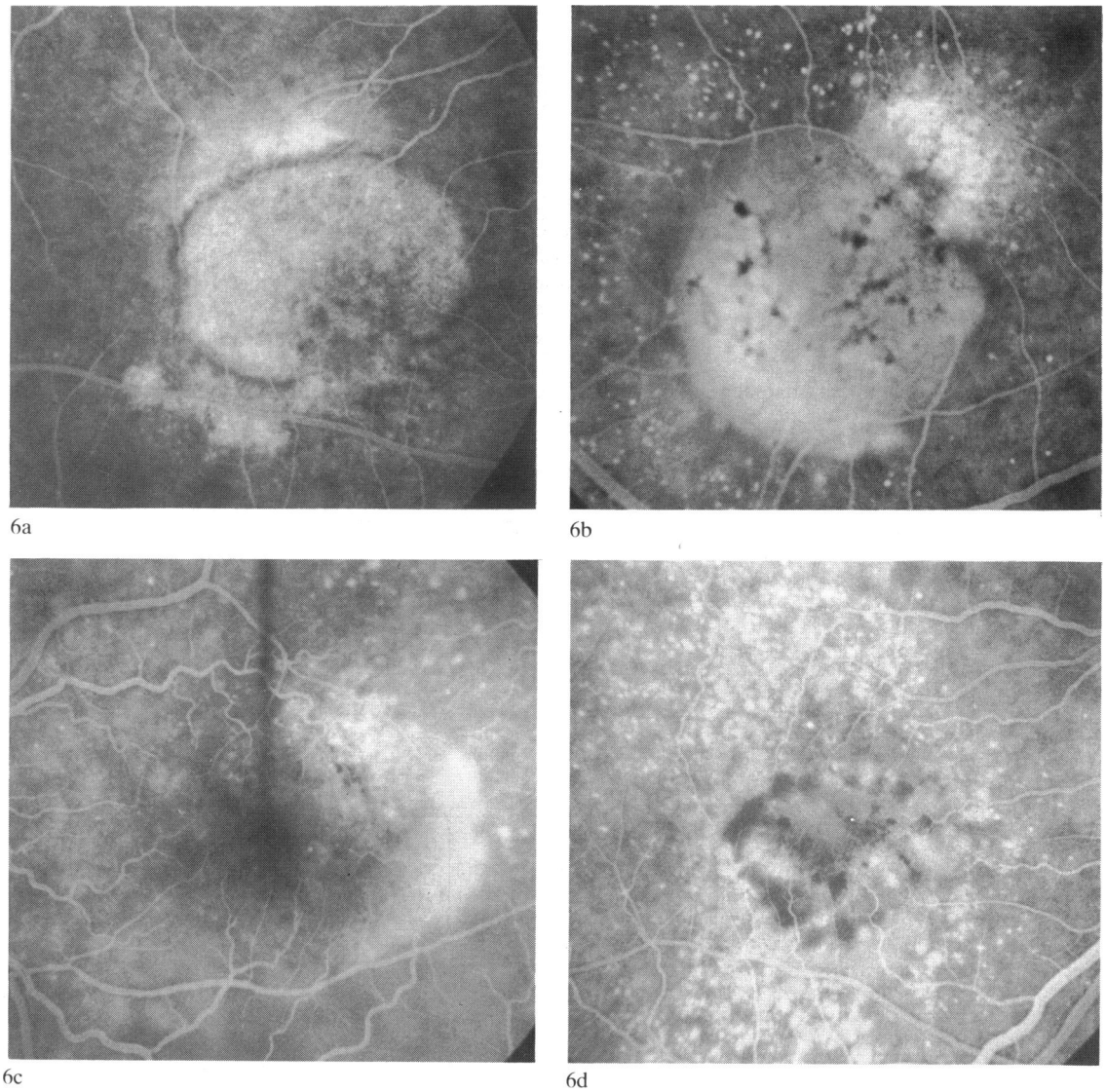

Fig. 6 (a) *Detachment showing hyperfluorescence in detached drusen on its posterior surface, without deep focal fluorescence on stereoangiography;* (b) *detachment showing regional masking due to hyperpigmentation on its surface;* (c) *detachment with delayed filling after the arteriovenous phase;* (d) *detachment with late filling after the arteriovenous phase, some deep masking in addition to surface pigment, and deep progressive hyperfluorescence seen on stereoangiography.*

their classification status, and in the remaining cases reclassification was made after open discussion.)

Of the 27 patients admitted to the untreated group 1 was considered not to have fulfilled the original entry criteria. Sixteen (61·5%) eyes were thought to have satisfied the revised criteria and 10 were not. (There was initial agreement about the classification status of 9 eyes and reclassification in the remainder was achieved after discussion.)

Nine patients developed vascular disciform lesions within the pigment epithelial detachment; only 3 of these would have been excluded by the revised criteria.

None of the 5 eyes that sustained tears of the pigment epithelium satisfied the revised criteria. Four

had delayed but even filling of the detachment, and the fifth had regional masking within the subpigment epithelial space. With the exception of pigment epithelial tears there was no correlation between the morphological outcome and the classification according to the revised criteria (Tables 7–11).

It is evident that the visual outcome in the 2 groups is similar to that in the main trial; in both, the treated patients fared worse than the untreated in terms of visual function.

Discussion

The revised criteria attempted to exclude any pigment epithelial detachment that demonstrated late filling after the arteriovenous phase on fluorescein angiography. Delayed filling may be due to opacity or turbidity of the subpigment epithelial fluid masking neovascular tissue present deep to that fluid. Alternatively, if the pigment epithelium detaches without its basement membrane, this structure, which remains attached to Bruch's membrane, may act as a barrier to diffusion of the fluorescein, and so delay the entry of dye into the subpigment epithelial space. It is reported that this type of pigment epithelial detachment may sustain a tear of the pigment epithelium[23] and it is notable that in 4 out of 5 of those cases in which this occurred slow filling of the detachment was demonstrated. However, retinal pigment epithelial tearing accounted for only 2 of the 8 treated patients

Table 7 *Number of patients who had completed the indicated visit by 30 September 1980, broken down by suitability for study*

Visit	*Group*			
	Treated		*Untreated*	
	Suitable	*Doubtful*	*Suitable*	*Doubtful*
Initial	10	9	16	9
3 months	10	9	16	9
6 months	9	7	16	9
9 months	8	8	16	8
12 months	8	9	16	9
18 months	8	9	15	9

Table 8 *Number and percentage of patients whose visual acuity deteriorated between the initial visit and the visit indicated, broken down by suitability for study*

A: Taking a move of one or more lines as a change

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
3 months	5	56	9	90	3	20	1	14
6 months	7	88	6	75	6	43	2	29
9 months	6	75	7	78	6	43	3	50
12 months	6	75	8	80	6	43	4	57
18 months	6	75	8	80	7	50	6	86

B: Taking a move of two or more lines as a change

3 months	3	33	4	40	2	13	0	0
6 months	4	50	4	50	1	7	1	14
9 months	4	50	4	44	2	14	1	17
12 months	5	63	6	60	3	21	1	29
18 months	6	75	8	80	6	43	3	43

Table 9 *Number of lines moved on Snellen chart since initial visit, broken down by suitability for study*

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
3 months	−2·2	3·1	−2·1	1·8	−0·1	1·0	0	0·6
6 months	−3·6	3·0	−2·3	3·0	−0·2	1·1	−0·3	0·9
9 months	−3·0	3·0	−2·8	3·1	−0·4	0·9	−0·8	1·7
12 months	−3·3	2·9	−3·0	2·7	−0·6	1·4	−1·4	2·4
18 months	−3·1	2·8	−3·2	2·6	−1·4	2·5	−2·1	2·7

Table 10 *Number and percentage of patients who had visual acuity less than the specified end-point at one or more visits and had completed the visit indicated, broken down by suitability for study*

A: 6/36

Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
3 months	4	40	2	22	2	13	0	0
6 months	5	56	2	29	2	13	0	0
9 months	4	50	3	38	2	13	1	13
12 months	4	50	4	44	2	13	2	22
18 months	4	50	4	44	4	27	2	22

B: 6/60

3 months	2	20	1	11	0	0	0	0
6 months	3	33	2	29	0	0	0	0
9 months	2	25	3	38	0	0	0	0
12 months	2	25	3	33	1	6	1	11
18 months	2	25	3	33	2	13	2	22

Table 11 *The change in field scores from the initial visit to the visit indicated, broken down by suitability for study*

A: Error total								
Visit	*Group*							
	Treated				*Untreated*			
	Suitable		*Doubtful*		*Suitable*		*Doubtful*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
3 months	−12·8	42·9	−24·8	65·2	−17·2	45·0	−19·1	32·4
6 months	9·4	48·4	−35·0	124·1	−9·2	74·9	−44·0	112·1
9 months	29·1	50·9	−50·2	97·1	−28·8	91·1	−81·7	128·7
12 months	7·4	65·4	−58·2	90·2	−44·8	110·3	−85·3	93·4
18 months	−3·7	51·7	−62·2	99·4	−21·3	69·2	−73·4	130·0
B: Error Central								
3 months	−21·5	20·4	−19·2	25·5	−5·7	24·5	−4·3	8·0
6 months	−11·7	27·1	−16·8	37·7	−8·5	30·7	−13·4	36·3
9 months	−5·9	24·7	−27·4	31·0	−17·1	31·8	−47·0	47·0
12 months	−13·7	31·0	−32·4	25·7	−25·8	47·3	−34·3	33·6
18 months	−26·0	15·7	−34·8	24·2	−23·7	33·0	−37·4	49·3
C: Missed total								
3 months	3·1	4·4	1·1	4·1	−0·6	5·7	2·9	6·5
6 months	3·6	4·1	−2·6	9·1	0·1	6·5	5·0	4·8
9 months	0·7	5·1	0·7	5·9	2·0	6·9	5·2	10·6
12 months	1·0	7·3	1·7	4·9	2·3	6·8	7·6	6·1
18 months	3·3	4·9	3·0	7·2	2·7	5·9	7·7	7·0
D: Missed central								
3 months	1·6	0·7	2·8	2·9	0·7	1·5	0·1	0·4
6 months	2·1	1·6	2·1	3·0	0·5	1·4	0·0	0·0
9 months	1·7	1·3	2·7	3·7	0·5	1·1	3·8	4·4
12 months	2·1	2·0	3·6	3·3	1·3	3·1	3·0	4·0
18 months	3·0	1·6	3·4	2·5	1·3	2·6	4·1	4·1

with visual loss, so that exclusion of these 2 patients would not have affected the findings of the trial.

Regional masking within a detachment was frequently a difficult sign to interpret. Importance was attached to the difference between masking caused by haemorrhage or exudate within the subretinal space, indicating possible neovascularisation, and that associated with local hyperpigmentation over the surface of the detachment. This distinction required high-quality stereoscopic angiograms, which may be hard to obtain in the elderly patient, and their comparison with colour photographs.

There was similar difficulty in making the distinction between the hyperfluorescence caused by detached drusen or pigment epithelial defects, and that of neovascular tissue beneath the pigment epithelium. In lesions in which the pigment epithelium detaches with its basement membrane and drusen, there may be focal and increasing hyperfluorescence, which is not always easy to differentiate from hyperfluorescence due to subpigment epithelial new vessels.

The problems of interpretation are reflected in the fact that an initial consensus of opinion as to whether a particular lesion fulfilled the revised entry criteria was achieved in only 40% of the cases. Nevertheless, it is clear that revision of the entry criteria would not have influenced the results or the conclusions drawn from this trial.

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