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# Treatment of senile disciform macular degeneration: a single-blind randomised trial by argon laser photocoagulation

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SUMMARY A prospective randomised trial of argon laser photocoagulation of vascular disciform lesions in the elderly is presented. The results based on 2 years' follow-up show that patients within the treatment group fared better than those in the nontreatment group, although the difference between the 2 groups was not significant at a level of $p=0{\cdot}01$ in any single analysis. It is clear that in a large majority of vascular disciform lesions the neovascular tissue can be obliterated by photocoagulation, but recurrence of new vessel formation soon after treatment represents a risk to such patients after successful treatment.

Recent interest in senile disciform macular degeneration is due to recognition that this is now the most common cause of registrable blindness in England and Wales[1] and the United States,[2] to fluorescein angiography, which allows accurate analysis of the lesion during life,[3] and to photocoagulation, which provides a means of treating the lesion. The lesion is characterised by detachment of the retina and pigment epithelium from the underlying choroid by serous fluid, and proliferation in the subretinal space of blood vessels derived from the choroid. The disciform lesion represents a response of the tissues of the posterior fundus to pre-existing disease affecting the subretinal structures. In the elderly these changes are recognised clinically as drusen and pigmentary changes in the retinal pigment epithelium, and histologically as accumulation of phagosomal debris and basement membrane material on the inner aspect of Bruch's membrane.[4–7]

The fate of the disciform lesion is determined by the behaviour of the subretinal blood vessels. Early in the disease the blood vessels grow, causing the lesion to enlarge, while in old lesions capillary closure may allow the retina to flatten.[8,9] Successful treatment of the disciform process depends upon destruction of the subretinal neovascular system. The results in early reports were disappointing but in later studies appeared to be better due to improved selection of cases for treatment and the development of laser photocoagulators with slit-lamp delivery systems.[10–15] Until recently the possible benefits of laser photocoagulation had not been proved by controlled clinical trial. Within the last few months 2 trials have shown that treatment improves the visual prognosis during the early period following therapy.[16,17]

The purpose of this paper is to present the results of a prospective randomised control trial of argon laser photocoagulation in the treatment of neovascular disciform macular degeneration in the elderly. The study has been carried out over a 5-year period, and the conclusions are based on a follow-up period of 2 years.

## Materials and methods

### STRUCTURE OF THE STUDY

The purpose of the study was to determine whether argon laser photocoagulation altered the visual prognosis of neovascular disciform lesions in the macula of the elderly and whether the age of the patient, the location of the new vessel membrane, or the presenting visual acuity influenced the final outcome.

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*Entry criteria.* Patients were considered suitable for entry if they met the following criteria: (1) fluorescein angiographic evidence of a vascular disciform lesion with a well defined neovascular membrane; the closest edge of the membrane should be not less than 100 or more than 1500 μm from the centre of the foveola; (2) detachment of the sensory retina with associated visual symptoms; (3) presence of drusen in the affected and fellow eye; (4) age limits of 50 to 80 years; (5) a consensus of opinion from the medical workers concerning the patients' suitability for entry to the trial.

*Exclusion criteria.* Patients were excluded for the following reasons: (1) the presence of subretinal exudates or haemorrhages precluding an adequate view of the subretinal structures and new vessel membrane; (2) diseases preventing adequate fundus examination and laser photocoagulation; (3) other diseases associated with visual loss; (4) previous photocoagulation in the eye under consideration; (5) myopia of greater than 3 dioptres; (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. Phenylephrine 10% and cyclopentolate 1% drops 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 and 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 threshold 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 note was 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 neovascular tissue from the foveola as measured by a grid[18] (100 to 200 μm, 200–400 μm, 400–1500 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, by means of the Coherent Radiation series 800 or 900 argon laser photocoagulator with a Zeiss delivery system. Topical anaesthesia and a Goldmann contact lens were used. Heavy confluent treatment was applied over the whole of the lesion and at least 100 μm beyond the edge of the definable neovascular membrane, except in the direction of fixation, where care was taken not to coagulate the foveola. Major blood vessels were avoided. Comparison with the negatives obtained on angiography ensured complete cover of the lesion and in some circumstances fluoroscopy was used at the time of treatment. The lesion produced was intensely white and usually the result of a 200 μm spot size burn of 0·2–0·5 second duration. The power used to achieve this was adjusted according to the circumstances and transparency of the media. Colour photographs were obtained immediately after the treatment, providing a permanent record.

*Treatment visits.* Subsequent visits were at 2-weekly intervals until no further treatment was needed or possible because of progressive and subfoveal disease. Photocoagulation was repeated if there was persistence, or extension, of the neovascular tissue under the retina on the side of the lesion nearest the foveal pit. Leakage on the side away from the foveal pit or within the lesion did not necessarily require retreatment, as the aim was to ablate the neovascular tissue threatening central vision. The edge of an adequately treated lesion sometimes showed local hyperfluorescence and staining but no true leakage, and this was not retreated. The greater risk of intraretinal uptake of energy was a factor considered in the decision to retreat a neovascular complex.

*Study visits.* Study visits were at 3-monthly intervals in the first year and 6-monthly intervals thereafter for both treated and untreated patients (3, 6, 9, 12, 18, 24 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 in order 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, using both a movement of 1 line (1 unit) and a movement of 2 lines (2 units) 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 the standard normal deviate z was computed.[19] Significant values can be obtained from z values by using 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[20] (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 has been used in allocating the patients, Cochran's test statistic[21] 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 value of Cochran's test statistic was similar to the z value in all analyses. Only the z values are given in the tables.

A chi-squared tests for trend[20] (p. 363) was also performed on the proportions that showed improvement, no change, and deterioration in the 2 groups.

*Quantitative analysis.* Comparison of the size of visual change between the 2 groups was undertaken, with movement of one line of the Snellen chart 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.* In order 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 each study visit. For each patient at each visit it was recorded whether visual acuity had been worse than the end point at least once.

Separate analysis was undertaken with end points 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 the z value; an approximate overall p value of 0·01 was considered significant. As stratification was used, Cochran's test

Table 2 *Number of patients who had completed the indicated visit by 30 April 1982*

| *Visit* | *Group* | |
|---|---|---|
| | *Treated* | *Untreated* |
| Initial | 63 | 65 |
| 3 months | 61 | 62 |
| 6 months | 60 | 60 |
| 9 months | 58 | 60 |
| 12 months | 58 | 55 |
| 18 months | 54 | 51 |
| 24 months | 51 | 50 |

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

*A: taking a move of 1 or more lines as a change*

| *Visit* | *Treated group* | | | *Untreated group* | | | $Z_i$ | $Z_w$ | $\chi_t^2$ |
|---|---|---|---|---|---|---|---|---|---|
| | *Improved* | *Same* | *Worse* | *Improved* | *Same* | *Worse* | | | |
| 3 months | 12 | 11 | 38 | 6 | 22 | 34 | 1·57 | 0·84 | 0·04 |
| 6 months | 11 | 10 | 39 | 4 | 18 | 38 | 1·93 | 0·19 | 0·60 |
| 9 months | 12 | 9 | 37 | 6 | 7 | 47 | 1·61 | −1·74 | 3·40 |
| 12 months | 13 | 6 | 39 | 6 | 6 | 43 | 1·64 | −1·31 | 2·44 |
| 18 months | 11 | 4 | 39 | 5 | 4 | 42 | 1·51 | −1·24 | 2·08 |
| 24 months | 12 | 2 | 37 | 4 | 3 | 43 | 2·14 | −1·67 | 3·86 |

*B: taking a move of 2 or more lines as a change*

| *Visit* | *Treated group* | | | *Untreated group* | | | $Z_i$ | $Z_w$ | $\chi_t^2$ |
|---|---|---|---|---|---|---|---|---|---|
| | *Improved* | *Same* | *Worse* | *Improved* | *Same* | *Worse* | | | |
| 3 months | 3 | 35 | 23 | 1 | 39 | 22 | 1·03 | 0·26 | 0·01 |
| 6 months | 2 | 26 | 32 | 0 | 26 | 34 | 1·43 | −0·37 | 0·47 |
| 9 months | 3 | 23 | 32 | 1 | 21 | 38 | 1·05 | −0·90 | 1·28 |
| 12 months | 4 | 21 | 33 | 0 | 16 | 39 | 2·01 | −1·55 | 3·98 |
| 18 months | 4 | 15 | 35 | 1 | 13 | 37 | 1·32 | −0·85 | 1·40 |
| 24 months | 5 | 12 | 34 | 2 | 8 | 40 | 1·15 | −1·52 | 2·56 |

$Z_i$ is the Z value comparing the proportion of patients with improved visual acuity in the 2 management groups.
$Z_w$ is the corresponding value comparing the proportion of patients whose visual acuity had deteriorated.
$\chi_t^2$ is the value of the $\chi^2$ variate testing for trend.

statistic was evaluated.[21] However, the z value and Cochran's test-statistics were similar in all analyses, and only the z value is given in the tables.

## Results

### VISUAL OUTCOME

One hundred and twenty-eight patients were entered into the trial and data were collected up to 2 years on 101 (Table 2). Incomplete data were obtained on 27: 2 withdrew by 3 months (1 emigrated and 1 was withdrawn having been treated elsewhere); 6 patients died (2 by 6 months, 2 by 12 months, and 2 by 24 months); 11 patients missed a single visit and none more than one visit (2 at 3 months, 1 at 6 months, 5 at 9 months, 1 at 12 months and 2 at 18 months). Eight patients had not been entered long enough to have recorded a 2-year visit.

*Qualitative analysis.* The proportion of patients showing an improvement in visual acuity was consistently greater in the treated than in the untreated group, both when a 1 or 2 line shift was taken as the criterion for change. However, the difference was never significant at the required level of p=0·01 (Table 3).

The proportion of patients showing a deterioration of visual acuity was consistently smaller in the treated group after 9 months, but the difference was less marked than that for improvement.

The chi-squared test for trend also showed no significant difference at the required level.

*Quantitative analysis.* The results (Table 4) show that untreated patients suffered greater deterioration in visual acuity than treated patients throughout the study. Although the difference was never significant at the required level (p=0·01), the general trend appeared to be moving towards this level (at 24 months p=0·02).

When the 2 groups were compared with respect to a visual loss of 4 or more lines, it was found that the treated group consistently fared better. A larger number of the treated patients showed change of the visual acuity at the 3-month datum point when compared with the untreated group. This change was both in improvement and in reduction of the visual acuity. As the acuity of the untreated patients declined the treated group emerged as having a consistently better visual function.

*End-point analysis.* If the end point of 6/60 is considered (Table 5), it can be seen that the percentage of patients whose visual acuity fell below this level was greater for the untreated patients than the treated. Although the difference, as measured by the z statistic, was never once significant at the p=0·01 level, at 9 months the difference became significant at the p=0·05 level and remained at this level thereafter.

The difference between the 2 groups was less marked for the 6/24 and 6/36 end points, but still in

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

| *Months* | | *3* | | *6* | | *9* | | *12* | | *18* | | *24* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lines* | *T* | *U* | *T* | *U* | *T* | *U* | *T* | *U* | *T* | *U* | *T* | *U* |
| Worse | −9 | – | – | – | – | – | 1 | – | 1 | – | – | – | – |
| | −8 | – | 1 | – | 4 | 1 | 2 | 1 | 2 | 1 | 2 | – | 3 |
| | −7 | 1 | – | 2 | – | 2 | 3 | 1 | 4 | 1 | 3 | 2 | 3 |
| | −6 | 2 | – | 1 | 3 | 4 | 7 | 6 | 3 | 5 | 9 | 7 | 8 |
| | −5 | 4 | 3 | 4 | 4 | 7 | 5 | 8 | 8 | 12 | 9 | 8 | 12 |
| | −4 | 2 | 5 | 3 | 8 | 1 | 7 | 2 | 9 | 3 | 5 | 6 | 4 |
| | −3 | 4 | 4 | 12 | 8 | 11 | 8 | 9 | 6 | 7 | 7 | 2 | 6 |
| | −2 | 10 | 9 | 10 | 7 | 6 | 5 | 6 | 6 | 6 | 2 | 9 | 4 |
| | −1 | 15 | 12 | 7 | 4 | 5 | 9 | 6 | 4 | 4 | 5 | 3 | 3 |
| Same | 0 | 11 | 22 | 10 | 18 | 9 | 7 | 6 | 6 | 4 | 4 | 2 | 3 |
| Improved | 1 | 9 | 5 | 9 | 4 | 9 | 5 | 9 | 6 | 7 | 4 | 7 | 2 |
| | 2 | 3 | 1 | 2 | – | 3 | 1 | 4 | 0 | 4 | 1 | 5 | 2 |
| Mean | | −1·30 | −1·26 | −1·70 | −2·33 | −2·07 | −2·95 | −2·19 | −3·18 | −2·57 | −3·53 | −2·55 | −3·84 |
| SD | | 2·09 | 1·87 | 2·18 | 2·52 | 2·64 | 2·71 | 2·71 | 2·68 | 2·74 | 2·66 | 2·82 | 2·62 |
| *t* | | −0·10 | | 1·47 | | 1·79 | | 1·95 · | | 1·81 | | 2·38 | |
| p | | 0·918 | | 0·143 | | 0·076 | | 0·053 | | 0·073 | | 0·019 | |

T = treated group. U = untreated group. SD = standard deviation.

favour of treatment. It is apparent that some treated patients lose acuity from an early stage but also that the untreated group subsequently deteriorates to a lower level.

*Visual fields.* No greater difference could be found between the treated and untreated groups in respect of visual fields (Table 6).

*Base-line variables.* The variables used for the purpose of stratification were distance of the neovascular complex from the centre of the foveola, age, and

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

| *Visit* | | *Treated group* | | *Untreated group* | | |
|---|---|---|---|---|---|---|
| | | *Number* | *%* | *Number* | *%* | *Z* |
| *A:* | *6/24* | | | | | |
| | Initial | 5 | 7·9 | 6 | 9·2 | −0·26 |
| | 3 months | 24 | 39·3 | 22 | 35·5 | 0·44 |
| | 6 months | 32 | 53·3 | 36 | 60·0 | −0·74 |
| | 9 months | 35 | 60·3 | 43 | 71·7 | −1·30 |
| | 12 months | 37 | 63·8 | 42 | 76·4 | −1·46 |
| | 18 months | 38 | 70·4 | 41 | 80·4 | −1·19 |
| | 24 months | 36 | 70·6 | 43 | 86·0 | −1·88 |
| *B:* | *6/36* | | | | | |
| | Initial | 1 | 1·6 | 2 | 3·1 | −0·56 |
| | 3 months | 12 | 19·7 | 13 | 21·0 | −0·18 |
| | 6 months | 19 | 31·7 | 24 | 40·0 | −0·95 |
| | 9 months | 26 | 44·8 | 33 | 55·0 | −1·11 |
| | 12 months | 29 | 50·0 | 36 | 65·5 | −1·66 |
| | 18 months | 30 | 55·6 | 33 | 64·7 | −0·96 |
| | 24 months | 31 | 60·8 | 37 | 74·0 | −1·42 |
| *C:* | *6/60* | | | | | |
| | Initial | 1 | 1·6 | 0 | 0·0 | 1·01 |
| | 3 months | 5 | 8·2 | 5 | 8·1 | 0·03 |
| | 6 months | 7 | 11·7 | 14 | 23·3 | −1·68 |
| | 9 months | 10 | 17·2 | 22 | 36·7 | −2·38 |
| | 12 months | 14 | 24·1 | 24 | 43·6 | −2·19 |
| | 18 months | 15 | 27·8 | 26 | 51·0 | −2·43 |
| | 24 months | 18 | 35·3 | 29 | 58·0 | −2·29 |

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

| *Visit* | | *Treated group* | | *Untreated group* | | *t* | *p* |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | | |
| *A:* | *Error total* | | | | | | |
| | 3 months | −34·6 | 82·0 | −40·2 | 101·8 | 0·32 | 0·750 |
| | 6 months | −46·9 | 94·3 | −64·5 | 106·7 | 0·94 | 0·351 |
| | 9 months | −58·1 | 94·4 | −89·4 | 111·0 | 1·60 | 0·113 |
| | 12 months | −65·5 | 108·8 | −89·4 | 121·8 | 1·06 | 0·290 |
| | 18 months | −78·9 | 126·8 | −109·5 | 136·9 | 1·13 | 0·262 |
| | 24 months | −82·1 | 125·3 | −115·7 | 121·6 | 1·27 | 0·209 |
| *B:* | *Error central* | | | | | | |
| | 3 months | −35·6 | 35·9 | −38·7 | 40·1 | 0·44 | 0·660 |
| | 6 months | −37·8 | 34·6 | −46·6 | 37·2 | 1·31 | 0·193 |
| | 9 months | −42·3 | 36·7 | −55·8 | 40·8 | 1·83 | 0·070 |
| | 12 months | −44·7 | 37·9 | −54·0 | 44·2 | 1·16 | 0·250 |
| | 18 months | −47·5 | 44·1 | −59·3 | 45·5 | 1·27 | 0·206 |
| | 24 months | −46·5 | 44·9 | −60·7 | 42·0 | 1·52 | 0·132 |
| *C:* | *Missed total* | | | | | | |
| | 3 months | 11·3 | 6·4 | 12·7 | 6·6 | −1·15 | 0·253 |
| | 6 months | 12·2 | 5·6 | 15·1 | 7·4 | −2·32 | 0·022 |
| | 9 months | 13·0 | 6·7 | 15·1 | 6·5 | −1·68 | 0·096 |
| | 12 months | 13·4 | 6·9 | 15·8 | 7·4 | −1·74 | 0·084 |
| | 18 months | 14·1 | 7·4 | 16·3 | 6·4 | −1·51 | 0·134 |
| | 24 months | 13·8 | 8·0 | 16·0 | 6·7 | −1·36 | 0·178 |
| *D:* | *Missed central* | | | | | | |
| | 3 months | 2·2 | 2·4 | 2·3 | 2·8 | −0·16 | 0·876 |
| | 6 months | 2·5 | 2·3 | 2·5 | 2·8 | −0·01 | 0·992 |
| | 9 months | 2·8 | 2·5 | 3·7 | 3·1 | −1·71 | 0·091 |
| | 12 months | 3·1 | 2·8 | 3·9 | 3·1 | −1·31 | 0·192 |
| | 18 months | 3·5 | 2·8 | 4·2 | 3·4 | −1·12 | 0·265 |
| | 24 months | 3·7 | 2·9 | 4·4 | 3·2 | −1·00 | 0·321 |

visual acuity. The number of people in the groups 'age 50 to 60', 'initial visual acuity worse than 6/24', '100 to 200 $\mu$m' are so small that it is not possible to show any significant difference between the treated and untreated groups. For the patients in their complimentary subgroups, that is, 'aged 61 to 75', 'initial visual acuity 6/24 or better', '200 $\mu$m plus', the statistics show only minor differences from those for the total group of patients. When the patients are split into groups of '100 to 400 $\mu$m' and '400 $\mu$m plus' there does not appear to be so much difference between the treated and untreated group of patients. This suggests that, although the treated and untreated groups may have behaved differently, the difference is not great enough, nor are the number of patients large enough for the statistics to show this difference.

*Summary.* In all the analyses the difference between the groups was consistently in favour of treatment. In both the qualitative analysis and the end-point analysis for 6/60 the difference was regularly significant at the $p=0·05$ level but never at the $p=0·01$ level. No other analyses showed a significant difference at the $p=0·05$ level.

From these results it was considered that the treatment did result in reducing loss of visual acuity, and that the main reason for the differences between the treated and untreated groups not reaching the designated level of statistical significance was the small number of patients involved.

MORPHOLOGICAL OUTCOME (Table 7)

*Treated patients.* Within 3 months of entry into trial 36 of the 60 patients had no detectable subretinal new vessels, and in a further 3 photocoagulation undertaken at this time caused flattening of the retina. By 2 years 11 of these 39 patients had disciform lesions due to recurrence of neovascularisation beneath the retina, and an additional 2 had subfoveal new vessels but have not yet completed 2 years' review. A further 2 have not yet attended the 2-year study visit, but the retina was flat at the time of the last study visit. In summary, about half the number seen at 2 years had no detectable subretinal new vessels at that time.

During the period 3 to 12 months recurrence of subretinal neovascularisation was seen in 8 patients, which represents just under one-quarter of the total flat at 3 months. Of these, 4 were treatable at the time that they were identified, and in all the treatment was successful in causing the vessels to close. Of the 31 followed up during the second year of the study recur-

Table 7 *Morphological outcome of treated and untreated patients*

| *Visits* | *Treated* | | | | *Untreated* | | |
|---|---|---|---|---|---|---|---|
| | *Flat* | *Disciform* | *Recurrences* | *Retreated* | *Disciform* | *Subfoveal* | *Flat* |
| 3 months | 36 | 20 | 4 | 4 (3 successfully) | 47 | 21 | 2* |
| 6 months | 33 | 20 | 4 | 2 (2 successfully) | 46 | 30 | 1 |
| 9 months | 32 | 22 | 3 | 2 (2 successfully) | 46 | 35 | 1 |
| 12 months | 31 | 23 | 1 | 0 | 44 | 34 | 1 |
| 18 months | 25 | 21 | 5 | 2 | 41 | 33 | 2† |
| 24 months | 25 | 24 | 0 | — | 39 | 34 | 4 |

*One of these was subsequently lost to follow-up.
†One of these subsequently developed a new subfoveal disciform lesion.

rence was seen in 5 of which 2 were treated but without success. All recurrences occurred from the edge of the scar nearest the fovea. The success of treatment did not appear to be related to the distance between the fovea and the new vessels, since obliteration of the new vessels occurred as commonly in those whose lesions approached to within 200 μm as in those where the distance was over 400 μm.

*Untreated patients.* The growth or involution of the new vessel complexes and the position of the subretinal new vessels with respect to the fovea were studied in the untreated patients. In just over half the vessels were subfoveal by 3 months due to growth, and by 6 months there were only a small number in whom this was not the case. Complete involution of the subretinal vessels occurred in 6 patients within the 2-year period; of these 1 died after the 3-month visit, one developed a new disciform lesion and lost vision, leaving 4 who completed the 2 years without recurrence of symptoms. Of the 5 patients without subfoveal blood vessels at 2 years only 2 had a visual acuity of worse than 6/12. Spontaneous closure of the subretinal vascular system occurred only in those patients with a distance of greater than 400 μm between the foveola and the nearest edge of lesion.

## Discussion

The study was carried out at a single centre, which ensured good control of both 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 to admit a particular patient was made at the time of the second visit with all the medical workers present agreeing to the entry. The patients were treated and the records were audited following each visit, which ensured a uniformity of management. There was a low failure rate, and only 20 data points were missed that might have been recorded.

The data show a consistent trend towards benefit from photocoagulation, and, in view of this observation and the reports relating to a multicentre study carried out in the United States[16] and to a single centre trial in France,[17] the Data Monitoring Committee thought that recruitment to the study should be terminated.

The results of this study show that argon laser photocoagulation is beneficial in the treatment of patients conforming to the entry criteria used. While it had been hoped to show a greater benefit, the results are consistently in favour of treatment. No results beyond the 2-year datum point are presented, but at that time the lesions appear to be stable.

The results of this study support the conclusions of the Macular Photocoagulation Study Group in the United States[16] and of Coscas and Soubrane in France[17] from similar studies. The American study reports highly significant differences between treated and untreated patients at six months or later ($p=0{\cdot}001$). The difference in significance between the 2 trials may be explained by variations in the characteristics of the patients entered. Compared with the study reported here there were more patients of an older age group (75+ yr), more with good initial visual acuity (6/9 or better), and more with the neovascular complex located far from fixation (up to 2500 μm). The treatment techniques employed were not identical in the 2 trials: in the American study retrobulbar injection was used and treatment was more intense. We believe that the former is more important than the latter.

In designing this study it was thought that stratification in the groups described might show that a particular group would benefit from photocoagulation more than another. The majority of patients were in the groups with better acuity and with neovascular lesions situated either 200 or 400 μm or more than 400 μm from fixation. There did not appear to be a significant difference in the response to treatment

between these 2 groups. Other groups were too small for individual analysis to be made. It is clear from the results of the study that obliteration of the disciform lesion was achieved in the majority of the cases, but in many of them growth of the subretinal vessels continued towards the foveola so that the lesions became untreatable.

Recurrences were common particularly during the early period after photocoagulation; the incidence in this study is somewhat higher than previously reported,[15] but the difference is not great. The occurrence of renewed subretinal proliferation is not surprising, since this represents a reaction to age-related changes at the level of Bruch's membrane, and photocoagulation would have no effect on this process. If vascular proliferation is due to alterations of Bruch's membrane and to the presence of macrophages, it might be predicted that renewed neovascularisation might follow treatment. Some authors have used this theoretical argument to cast doubt on the potential efficacy of photocoagulation. In all patients the recurrence was derived from the edge of the treated area, which would support the contention that, while treatment is beneficial to visual prognosis, it may also sow the seed for recurrence.

The high incidence of recurrence has important implications for clinical management of the disease and may limit the time during which photocoagulation confers an improved visual prognosis. It is clear that initial success should be followed by vigilance on the part of the patient and the ophthalmologist, since recurrence may be treatable if seen early enough.

Finally recurrence may limit the time during which photocoagulation gives an improvement in visual prognosis. There is little doubt that a better visual outlook for a limited period is worth the time and effort expended, but a different or better form of management should be sought if the benefit is only for a limited period.

The behaviour of the untreated patients conformed with that implied by previous publications, though the number who retained good vision due to involution or cessation of growth of the subretinal vessels was rather higher than expected. It was predictable that the patients with a larger distance between the foveola and the edge of the vessels were those who did well without treatment.

The trial concerns solely the potential benefit of argon laser photocoagulation, the limitations of which have been discussed at some length in the ophthalmic literature.[22,23] The use of light with most of its energy in the blue wavelength is thought unsuitable for lesions near the fovea; distances of 50–200 $\mu$m have been quoted as being the inner limit of its effectiveness. This underlines the need for early identification of the disease before it grows to within these distances and there is some indication that the majority of lesions start outside this zone.[24] It also implies that argon laser energy could be used for most lesions. Nevertheless, if more than one session of treatment is required or there is recurrent disease, the only options available would be to photocoagulate close to the foveola or to abandon therapy where only argon energy is available. The use of the longer wavelengths of the krypton laser or the green line of argon may resolve this problem, but the efficacy of these alternatives have yet to be tested.

Not all patients with neovascular senile macular degeneration are suitable for laser treatment, and only a small proportion of those seen in this hospital was considered treatable. This was accounted for by delay in the referral system. Early identification of the lesion is important and treatment must be offered sooner than is currently achieved. Those responsible for eye care should be aware of this need and patients at high risk should be able to identify the onset of the process. If the patient is alerted to the relevant symptoms, it is more likely that the second eye may be treatable at the time of presentation than the first. Informed use of the Amsler grid will help to identify early distortion of central vision. This form of self-monitoring would probably be more effective than regular review and angiography. Similar considerations should apply to successfully treated patients. The little information available suggests that, with an effective system for delivering treatment to those at risk, up to 50% would benefit from laser photocoagulation.

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