Photocoagulation for Diabetic Maculopathy

A Randomized Controlled Clinical Trial Using the Xenon Arc

BRITISH MULTICENTRE STUDY GROUP

SUMMARY

The final results of a randomized controlled clinical trial of photocoagulation for diabetic maculopathy are reported, when all patients have been followed for at least 5 yr and some for as long as 7 yr. Ninety-nine patients with two similarly affected eyes had one eye chosen by a random procedure, treated with the xenon-arc photocoagulator; the untreated eyes remained as control.

The mean visual acuity deteriorated by less than one line in treated eyes but by more than 2 lines in the controls ($P < 0.01$). The difference in deterioration was greatest in patients whose initial vision was 6/6–6/9, and was not significant in those whose visual acuity was 6/36 or worse. Thirteen patients became blind in both eyes (visual acuity of 6/60 or less for 2 consecutive yearly assessments), 6 in the treated eye only, and 26 in the control eye only ($P < 0.01$). Again the divergence between treated and control eyes was most marked in those whose initial vision was 6/6–6/9, (only one treated but 10 control eyes became blind). Hard exudates, microaneurysms, and hemorrhages improved more in the treated eyes ($0.05 < P < 0.001$) and more control eyes developed new vessels during the follow-up period.

Twenty-three patients died during follow-up and another 16 failed to complete the study. Though the blood pressure of those who died was higher than those who survived ($P < 0.05$ for both systolic and diastolic) no other medical abnormalities at entry had any clear effect on visual outcome or 5-yr survival.

It is concluded that photocoagulation is of benefit in maintaining vision in diabetic maculopathy if the disease is not too far advanced. **DIABETES *32*:1010–1016, November 1983.**

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Participating centers and ophthalmologists: Hammersmith/Moorfields: R. K. Blach, A. M. Hamilton, P. K. Leaver, and C. Townsend; Kent and Sussex Hospital: H. Cheng; Kings College: E. W. G. Davies; Newcastle: J. Richardson; St. Thomas': T. ffytche and J. Shilling; Bergen (Norway): M. Odland.

Medical Advisors: E. M. Kohner and H. Keen.

Statisticians: Prof. P. Armitage and E. Hoinville.

Address reprint requests to Dr. Eva M. Kohner, Department of Medicine, Hammersmith Hospital, Du Cane Road, London W12 OHS, England.

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There are several reports in the literature of randomized controlled clinical trials demonstrating the effectiveness of photocoagulation in the treatment of proliferative diabetic retinopathy.[1–4] There are also a few publications—usually smaller series and of shorter duration—on the effects of treatment of diabetic maculopathy.[5–8] The long-term effectiveness of photocoagulation in diabetic maculopathy has not yet been established.

The present communication is the final report of the British Multicentre Study of xenon-arc photocoagulation in diabetic maculopathy. The study has been completed and all patients have been followed for at least 5 yr.

PATIENTS AND METHODS

PATIENTS

Between January 1, 1970 and December 31, 1974, 102 patients in six centers (Hammersmith/Moorfields Hospital, Newcastle, St. Thomas', Kings College, Kent and Sussex Hospital and the Bergen, Norway) gave their informed consent and entered the study. Of these, three died before completion of the 1st year (one of renal failure, one of myocardial infarction, and one of cerebral tumor) and so were excluded from the analysis. The report deals therefore with the remaining 99 patients in the study. Key diabetes and clinical variables at entry are detailed in Tables 1, 2, and 3.

Definition of maculopathy. For the purposes of this study, maculopathy was defined as best corrected visual acuity of 6/12 or worse, where the visual loss was due to macular edema (as determined by slit lamp biomicroscopy) in the presence of microvascular abnormalities with or without hard exudates. Patients with visual acuity of 6/6 and 6/9 were also included if there was either documented visual loss or

TABLE 1
Age and duration of diabetes for subjects

Duration of known diabetes at entry (yr)	Age at diabetes diagnosis (yr)			Total
	0–29	30–59	60 and over	
0–5	0	18	22	40
6–10	1	10	3	14
11–15	1	14	1	16
16–20	3	10	0	13
Over 20	4	4	0	8
Total	9	56	26	91
Not known 8				

hard exudate rings were seen to encroach on the macula, whether macular edema was present or not.

Eligibility criteria for entry into the study. Patients with maculopathy were eligible to enter the study, irrespective of age, if: (1) The two eyes were affected similarly, i.e., the difference in visual acuity was within two lines of the Snellen Chart, at least one eye had 6/60 or better vision, and the retinopathy features were within two grades of the Hammersmith Grading System;[9] (2) there was no concomitant eye disease affecting the retina or lesions interfering with treatment, assessment, or prognosis of the eye condition. Thus patients were ineligible if they had congenital abnormalities including amblyopia, if the refraction was significantly different between the two eyes (over 2 dioptres). They were also excluded if they had previous eye operation of any sort, or photocoagulation, or were on local or systemic treatment for any nondiabetic eye condition. Patients with chronic simple glaucoma were also excluded as this may alter the prognosis; (3) the patient understood and consented to the procedure of having one eye treated and the other untreated as control; (4) the patients' general health offered a reasonable likelihood for a 5-yr follow-up. This excluded among others patients with history of stroke, myocardial infarction, amputations, and those with all but minimal renal impairment. The study was approved by the Ethical Committees at the different hospitals.

PROCEDURE

As each patient fulfilling these criteria was recruited to the trial, envelopes prepared by the coordinating center were opened in numerical order. The content indicated which eye should be treated. The patient then had photographs of the disc and macular field of both eyes. As soon as possible thereafter, the eye chosen for treatment had xenon-arc photocoagulation under local (retrobulbar) or general anesthesia.

Treatment. Exact instructions for number of burns were not given. However, guidelines for treatment were given as follows: The center of hard exudate rings should be treated (except when this was at the fovea), even when they were situated between the disc and macula. In the absence of full or partial hard exudate rings and/or if there were other microvascular lesions (microaneurysms, hemorrhages, and dilated capillaries now known as intraretinal microvascular abnormalities) between the inferior and superior temporal vessels (including the area lateral to the macula), these should be treated by focal treatment, leaving at least one disc diameter around the fovea clear from treatment. The setting of the coagulator was 1 s with a burn diameter of 1°. The power varied between setting 2 and 8, depending on the retinal and pigment epithelial uptake. The aim was to get a pale, greyish white lesion, just visible to the observer.

Focal or scatter treatment could be given to lesions outside the superior and inferior temporal vessels, including the nasal areas. Here the burn diameter was increased to 3°. Extent and details of the treatment as well as the decision whether to do it was left to the ophthalmologist. It was also left to the decision of the ophthalmologists whether they gave the treatment in one or more session.

Follow-up treatment in the treated eye was given if there were new lesions between the superior and inferior temporal vessels outside the foveal area as indicated above; or if new vessels developed in any area.

The reason for allowing such diversity was that, as there was no consensus on the treatment of maculopathy, it was hoped that one method developed during the study will show clear advantages; this could then be used in clinical practice in the future.

The control eye remained untreated. In 1977, when the results of the British Multicentre Group[3] study confirmed those obtained in the US[1] "control" eyes with disc new vessels could be treated. Only one such eye was treated during

TABLE 2
Diabetic maculopathy—patient details

Sex		Age		Duration of DM at entry mean (range)	Treatment				
		At entry mean + (range)	At DM diagnosis mean + (range)		Insulin	Oral agents	Diet only	Not known	Retinopathy present at DM diagnosis
Male	50	59.1	49.9	9.2	34	57	4	4	20
Female	49	(20–76)	(10–73)	(0–34)	(−11)				

(−) = patients treated with oral agents until diagnosis of retinopathy. DM = diabetes mellitus.

TABLE 3
Medical conditions at entry

	Blood pressure		
	Systolic	Diastolic	S. urea
Elevated	52	38	34
Normal	40	54	47
Not known	7	7	18
Upper limit of normal	159 mm Hg	89 mm Hg	39 mg%

	Proteinuria	Neuropathy	ECG changes/ angina	Claudication
Present	11	62	11	6
Absent	82	33	82	89
Not known	6	4	6	4

S = serum.

the 5th year of follow-up, and this patient was excluded from the 5-yr analysis. Five further eyes which developed disc new vessels were considered untreatable by the time the treatment decision was taken.

Follow-up. Both eyes were examined regularly by the ophthalmologists. Yearly corrected visual acuities of each eye were obtained by an optician not participating in the trial, who was unaware of identity of the treated eye. The standard back illuminated Snellen Chart was used for visual acuity determinations. Instructions were given to have all the lights in working order. No other effort for standardization was made (e.g., height of chart); however, in each center the same chart was used throughout the study and treated and control eyes were assessed similarly. Results of yearly eye examination and severity grading of photographs of the disc and macular field [performed independently at the coordinating center by a trained technician and one of the coordinators (HCh or EMK)] were recorded on forms designed for computer analysis. Grading of photographs was by the Hammersmith grading system.[9]

The yearly examinations, medical, eyes, and photography, were done in one "long" visit in centers where joint diabetic eye and medical clinics were established, Hammersmith/ Moorfields and Bergen. In other clinics, the medical exam was as near as possible to the yearly eye exam; the latter being usually within 3 mo (±6 wk) of the anniversary of the initial eye examination.

Results of standard clinical examination were also recorded and analyzed. Since the study was particularly one on photocoagulation only physical findings relevant to the study were recorded.

STATISTICAL ANALYSIS

The treated and control eyes were compared for their difference in deterioration between initial and yearly visits by use of the paired *t* test. To enable statistical analysis, the visual acuity obtained from the Snellen Chart was converted to numerical scale, 6/5 and 6/6 = 1, 6/9 = 2, 6/12 = 3, etc.[6] McNemar's test[10] was used to compare the eyes that improved, remained the same, or deteriorated. Improvement or deterioration was defined as a change of two lines or more in visual acuity. McNemar's test was also used to compare the blind and not blind eyes. For the purpose of this analysis, blindness was defined as a visual acuity of 6/60 or worse for two consecutive yearly assessments. The paired *t* test was also used for comparing grading of yearly retinal photographs. The Chi square test was used for the comparative analysis of clinical characteristics of patients dying or surviving and those deteriorating to blindness or retaining vision.

RESULTS

Follow-up. Of the 99 patients, 39 failed to complete the 5-yr follow-up. Twenty-three of these were known to have died, eight were blind or too ill to come, two had treatment for their control eye and refused further follow-up in the study, three moved away, and three defaulted for other reasons.

Age and duration of diabetes. As shown in Tables 1 and 2, diabetic maculopathy is primarily a disease of the middle aged and elderly; 90% of the patients were 30 yr or older at diabetes diagnosis, and 29% were over the age of 60. Diabetes duration as expected was longest at the time of maculopathy diagnosis in those whose diabetes was diagnosed early in life. Retinopathy was known to be present in 20 patients at diagnosis of their diabetes and in 59% the duration of diabetes at entry into the study was less than 10 yr. Neither the presence of diabetic retinopathy at diagnosis nor the age of onset of known prestudy duration of diabetes significantly influenced the visual outcome in either the treated or the control eyes.

Medical conditions. Of the coexistent medical abnormalities shown in Table 3, only blood pressure influenced life ex-

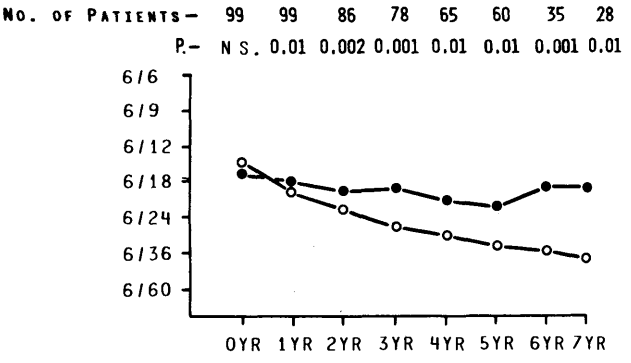

FIGURE 1. Mean initial and yearly visual acuity of treated (●—●) and control (○—○) eyes. NS = not significant.

TABLE 4
Difference in deterioration (initial visual acuity 6/6–6/9)

Year	No.	$\bar{d} \pm SE$	P
1	20	0.3 ± 0.4	NS
2	20	1.4 ± 0.6	<0.05
3	17	1.8 ± 0.8	<0.05
4	14	1.9 ± 0.9	NS
5	13	2.2 ± 1.0	<0.05
6	9	3.2 ± 1.0	<0.02

$\bar{d}$ = mean difference in deterioration between treated and untreated eye at 1-yr follow-up. $(VA_{u1}–VA_{u0}) – (VA_{t1}–VA_{t0})$ where VA = visual acuity, u and t untreated and treated eye, 0 and 1 initial and 1-yr visual acuity. SE = standard error. P = level of significance. NS = not significant (P > 0.05).

TABLE 5
Difference in deterioration (initial visual acuity 6/12–6/24)

Year	No.	$\bar{d} \pm SE$	P
1	60	0.6 ± 0.2	<0.01
2	52	0.6 ± 0.2	<0.02
3	48	1.1 ± 0.3	<0.01
4	39	1.0 ± 0.4	<0.05
5	36	0.8 ± 0.5	NS
6	20	1.4 ± 0.5	<0.02

$\bar{d}$ = mean difference in deterioration between treated and untreated eye at 1-yr follow-up. $(VA_{u1}–VA_{u0}) – (VA_{t1}–VA_{t0})$ where VA = visual acuity, u and t untreated and treated eye, 0 and 1 initial and 1-yr visual acuity. SE = standard error. P = level of significance. NS = not significant (P > 0.05).

pectancy significantly. The mean initial blood pressure of those who died was 175 ± 8 mm Hg systolic and 98 ± 7 mm Hg diastolic, compared with 160 ± 9 mm Hg and 89 ± 2 mm Hg in the survivors ($P < 0.05$ for both systolic and diastolic). The other baseline indices of cardiovascular status affected neither survival nor visual outcome significantly.

Visual outcome. The study was completed when all patients were followed for at least 5 yr (at least potentially). When a sufficient number of patients were available with 6 and 7 yr follow-up, to observe a significant outcome, these were included in the results of the eye assessment.

The mean visual acuity at entry and at the yearly intervals of follow-up is shown in Figure 1. The treated eyes deteriorated on average by less than one line while the control eyes deteriorated by more than 2, a divergence which increased with time and was more marked in those followed for over 5 yr. The deterioration of visual acuity from baseline was significantly less in treated than control eyes at each yearly assessment.

Tables 4, 5, and 6 show the difference in deterioration between treated and control eyes at each yearly interval grouped according to the initial visual acuity. These tables demonstrate that in those with initially good (6/6–6/9) or moderate (6/12–6/24) vision, treated eyes deteriorated significantly less than did control eyes. For those with initially poor vision, 6/36 or worse, the difference was small and failed to achieve significance.

Using McNemar's test to compare those who remained the same or improved with those who deteriorated by 2 lines or more there was a significantly increased deterioration in the control eyes at 2 ($P < 0.05$), 4 ($P < 0.05$), 5 ($P < 0.01$), 6 ($P < 0.005$) and 7 yr ($P < 0.05$) (Table 7).

Fewer treated than control eyes deteriorated to blindness (as defined). Thirteen patients became blind in both eyes, six in the treated eye when the control eye could still see, but 26 in the control eye alone. Table 8 shows the number of treated and control eyes deteriorating to blindness according to initial visual acuity. This demonstrates that those with the best visual acuity benefit most from treatment. In those with initial vision of 6/6–6/9 only one treated eye became blind, while 10 out of the 20 (50%) control eyes had visual acuity of 6/60 or less for 2 consecutive years. In those with an initial visual acuity of 6/36 or less the difference between blind treated and control eyes is not statistically significant.

The most common cause of blindness was worsening of the maculopathy with hard exudate plaques or increasing edema at the fovea (Table 9). Vitreous hemorrhage occurred in seven control eyes, but four of these had already advanced visual loss from maculopathy before the development of hemorrhage.

New vessels developed during the follow up period in nine treated eyes (five disc, three peripheral and one both). Sixteen control eyes also developed proliferative lesions (five disc, five peripheral, and six both). In the treated eyes, new vessels usually cleared after further treatment. In seven control eyes, they were the final cause of complete loss of vision.

Treatment effects. There were 58 patients who had one treatment session only, and 41 who had their treatment in several sessions, usually within the first 3 mo. The nine patients who developed new vessels in their treated eye during the follow-up period had a further total of 20 treatment sessions. Twenty-four other eyes had further treatment session (after the 1st year) for other lesions.

Thirty-one patients had focal treatment only in the macular area, 44 had focal treatment in the macular area and peripheral pattern bombing, and 24 had focal treatment in the macular area and also in the periphery.

There was a great variation in the number of burns given corresponding to the severity of the retinopathy. The mean number of burns applied to the retinae of those who developed new vessels—prior to their development—was 94.2 ± 12.5 (standard error SE) and they had a mean of 93.8 ± 26.1 (SE) burns after the development of new vessels. Those who did not develop new vessels had a mean number of

TABLE 6
Difference in deterioration (initial visual acuity 6/36 and worse)

Year	No.	$\bar{d} \pm SE$	P
1	19	0.37 ± 0.4	NS
2	14	0.07 ± 0.3	NS
3	13	0.00 ± 0.4	NS
4	12	0.25 ± 0.7	NS
5	11	0.36 ± 0.6	NS
6	6	1.40 ± 1.4	NS

$\bar{d}$ = mean difference in deterioration between treated and untreated eye at 1-yr follow-up. $(VA_{u1}–VA_{u0}) – (VA_{t1}–VA_{t0})$ where VA = visual acuity, u and t untreated and treated eye, 0 and 1 initial and 1-yr visual acuity. SE = standard error. P = level of significance. NS = not significant (P > 0.05).

TABLE 7
Change in visual acuity (McNemar's test)

			Control eye			
			impr./same	Worse	Total	
After 1 yr	Treated eye	impr./same	62	17	79	
		worse	7	13	20	
		Total	69	30	99	P = NS
After 2 yr	Treated eye	impr./same	43	20	63	
		worse	8	15	23	
		Total	51	35	86	P < 0.05
After 3 yr	Treated eye	impr./same	39	18	57	
		worse	8	13	21	
		Total	47	31	78	P = NS
After 4 yr	Treated eye	impr./same	30	18	48	
		worse	7	10	17	
		Total	37	28	65	P < 0.05
After 5 yr	Treated eye	impr./same	23	18	41	
		worse	4	15	19	
		Total	27	33	60	P < 0.01
After 6 yr	Treated eye	impr./same	15	10	25	
		worse	0	9	9	
		Total	15	19	34	P < 0.005
After 7 yr	Treated eye	impr./same	8	9	17	
		worse	1	7	8	
		Total	9	16	25	P < 0.05

McNemar's test Chi square $= \frac{[(b - 1) - 1]^2}{b - c}$

where b = number worse in control eye and improved or same in the treated and c = number improved or the same in the control eye and worse in the treated eye.
impr. = improved by 2 lines or more on the Snellen Chart. P refers to the test difference between treated and control eyes.
EG: at 2 yr: in 43 patients, both eyes stayed the same or improved; in 8 patients, the treated eye became worse, the control eye stayed the same or improved; in 20 patients, the treated eye stayed the same or improved when control eyes worsened; in 15 patients, both treated and control eye worse.

burns of 106.3 ± 12.8 (SE). These differences were not significant. The maximum number of burns was 498 in those with new vessels and 248 in those without.

Those who had focal treatment only had a mean number of burns of 68.1 ± 38.3 (SE) which was significantly less than the 148.2 ± 64.5 (SE) in those who had scatter treatment as well ($P < 0.001$). There was no difference in change in visual acuity between those who had focal treatment only and those who had both focal and scatter treatment.

Photographic grading. The severity of lesions was similar in the disc and macular fields at entry except for hard exudates, which were significantly worse in the treated group. For each yearly interval thereafter, control eyes had significantly worse hard exudates, hemorrhages, and microaneurysms than treated ones in both fields (Figures 2 and 3). After 6 yr, only the macular fields were significantly worse in control than treated eyes. Mean grading for new vessels remained below grade 1 at each yearly interval for both treated and control eyes. Only at 3 yr were the control eyes significantly worse for new vessels in the macular and disc field ($P < 0.002$ and < 0.05); the mean grading for new vessels in the macular field was 0.05 for treated and 0.37 for control eyes and in the disc fields, 0.17 in the treated and 0.47 in the control eyes. At 3 yr, fibrous tissue in the control eyes disc field was also worse ($P < 0.05$). The mean grading being 0 for treated and 0.25 for control eyes.

DISCUSSION

These results confirm previous reports[5-7] that treatment of diabetic maculopathy by photocoagulation confers significant advantage with respect to vision. The slowing in deterioration in treated compared with control eyes is significant, but not as dramatic as in patients with proliferative retinopathy.[1,2] This is not unexpected for two reasons. First,

TABLE 8
Diabetic maculopathy blind eyes by initial visual acuity

Initial visual acuity	No. of patients	Blind both eyes	Blind treated eye only	Blind control eye only	P
All eyes	99	13	6	26	<0.001
6/6–6/9	20	0	1	10	<0.025
6/12–6/24	60	9	2	11	<0.05
6/36–and worse	19	4	3	5	NS

P refers to the test for difference between treated and control eyes.

TABLE 9
Primary causes of visual loss

	Treated	Control
Hard exudate plaque at macula	5(2)	14(2)
Edema/ischemia at macula	5(2)	12(4)
Other macular	5	3
Vitreous hem.	1	3
Maculopathy + new vessels	0	4
Other	3	3

Numbers in parentheses represent eyes with 6/60 at entry.

photocoagulation is more useful in maintaining than in improving vision. Patients with maculopathy have some degree of visual loss at entry, and if macular edema is long-standing, the damage at the fovea is not reversible even when the edema disappears. Second, in this study, xenon-arc treatment was used. The xenon arc cannot be aimed accurately at small individual lesions near the fovea and the treatment itself can cause visual impairment by provoking preretinal fibrosis and pigment epithelial changes. These operational problems are reduced with laser treatment, but this equipment became available in Europe only after 1973, when most of the recruitment was complete. It was hoped that by giving ophthalmologists a free choice between treating the retinal periphery as well as the area between the superior and inferior temporal vessels would indicate a preferred form of treatment. This, however, did not emerge.

This study has been designed and completed when Whitelock et al.[8] published their further analysis of argon laser photocoagulation of both eyes for diabetic maculopathy. In that study, maculopathy was classified into subgroups. Of these subgroups, the ones with the circinate hard exudates away from the macula (in this study many of the 6/6–6/9 vision group) were shown to respond best while the edematous group and ischemic group fared less well. Certainly most of the patients with 6/36 and worse vision would fall into these groups. At the time of starting this study,

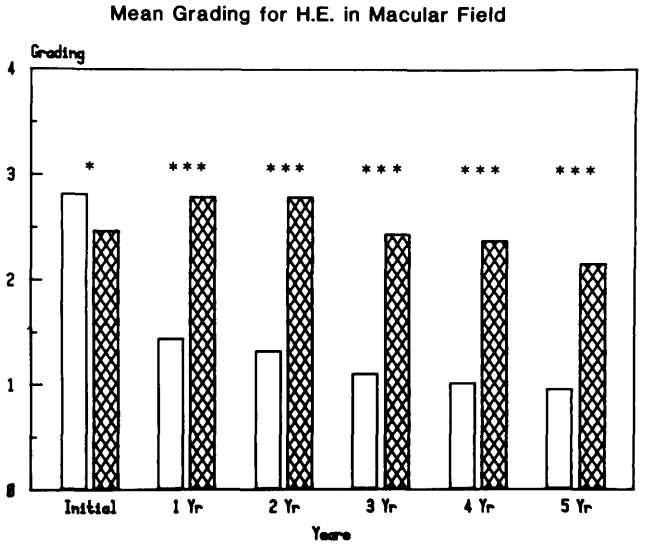

FIGURE 2. Photographic grading of macular field for hard exudates in treated (□) and control (⊠) eyes. *P < 0.05; **P < 0.01; ***P < 0.001.

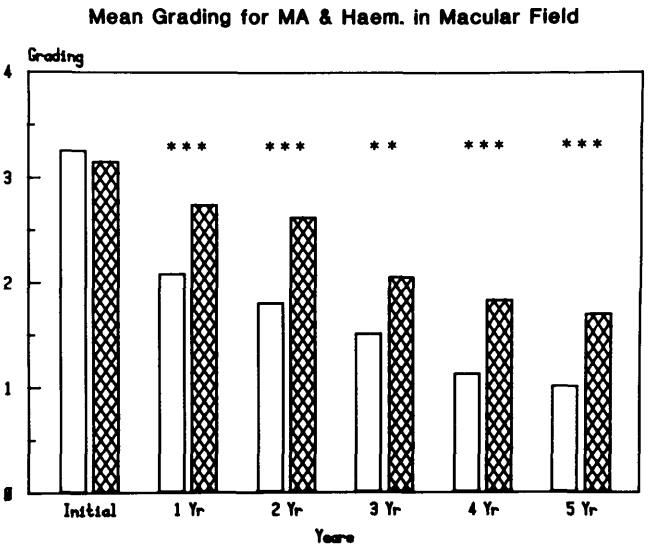

FIGURE 3. Photographic grading of macular field for microaneurysm and hemorrhages. Annotations as in Figure 2.

too little was known about the maculopathy for logical subdivision; indeed, the later classification into groups[8,11,12] resulted from the observations made on the patients in this study and patients seen since the recruitment was complete. Retrospective classification was not possible as only disc and macular pictures were required and fluorescein angiograms were not mandatory. The significant benefit from xenon-arc treatment is most evident when the initial visual acuity is good. It could be argued that patients with good initial visual acuity have a better prognosis because the visual deterioration in diabetic maculopathy is slow and therefore 5 yr is not enough for the deterioration to occur. This is not the case, because 50% of the untreated eyes did become blind during this period. By 5 yr, three treated eyes also deteriorated to 6/60; however, this was the first time such poor vision was recorded in these eyes.

The marked difference in treated and control eyes in deterioration to blindness is also impressive, but it must be stressed that there were 13 patients who became blind in both the treated and control eye.

This report emphasizes that diabetic maculopathy affects particularly the middle-aged and elderly and occurs after relatively short duration of known diabetes.[13] Previous studies indicate that proliferative retinopathy is primarily a disease of the insulin-dependent younger patients.[14,15] This report indicates that new vessels also develop in middle-aged and elderly and if untreated finally becomes the cause of complete loss of vision. In recent years, this has been well recognized,[15–17] but it was not fully appreciated at the time of initiating this study.

Contrary to clinical impressions of a particularly bad prognosis of patients with retinopathy at diabetes diagnosis, prognoses for vision and survival were not worse for the 20 patients in this study with retinopathy at presentation than for those without this diabetic complication.

In this study, 39 out of the 99 patients (i.e., 40%) did not complete the 5-yr follow-up. Both life expectancy and good health are limited in those with maculopathy, even if generally

fit, especially when their blood pressure is elevated. These results are not unlike those reported by Davis et al.,[18] although the two studies are not really comparable. In Davis' study, subdivision was according to retinopathy and only group B2 can be used for comparison with these patients. However, in the present report, the patients were nearly twice as old at the time of diagnosis of diabetes and at examination, but had only one-half the duration of the disease. In insulin-dependent diabetics—the large majority of Davis' patients—extensive hard exudates are frequently associated with renal impairment. There is no indication of how many of Davis' patients already had this complication or indeed any other complication after long-standing diabetes such as stroke, myocardial infarction and amputation, all suggesting a poor prognosis for life. In the present study patients were selected on the basis that they were *likely* to survive 5 yr.

That none of the concomitant medical conditions influenced visual outcome is not unexpected. The visual loss is due to macular edema or hard exudates already present. In the earlier stages, it is likely that blood pressure[19] and if present abnormal renal function and probably diabetic control[20] influence the appearance and progression of the retinopathy. Once a certain severity of disease is present change in blood pressure and diabetic control are unlikely to have much effect.

It is particularly in the older diabetic patient, liable to attribute slow deterioration of vision to aging or cataract, that it is important to carry out regular and systematic retinal examination. The results of this trial make it clear, that if detected sufficiently early and adequately treated, the progression of maculopathy may be arrested or slowed and the period of useful vision significantly prolonged.

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