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PRELIMINARY REPORT ON EFFECTS OF PHOTOCOAGULATION THERAPY

THE DIABETIC RETINOPATHY STUDY RESEARCH GROUP

Diabetic retinopathy, uncommon only a few decades ago, has in two generations become a leading cause of blindness and visual disability in the United States. The use of photocoagulation to treat proliferative diabetic retinopathy has gained widespread acceptance in ophthalmic practice since its introduction in 1959 by Meyer-Schwickerath.[1] However, only a few studies of photocoagulation have incorporated any of the basic principles of controlled clinical trials and these have involved only small numbers of patients. Consequently there has been inadequate evidence of the actual value of this procedure.[2]

Because of the clinical importance of diabetic retinopathy and the increasing use of photocoagulation in its management, the Diabetic Retinopathy Study (DRS) was begun in 1971 under the sponsorship of the National Eye Institute.[3] This randomized, controlled clinical trial involves more than 1,700 patients enrolled in 15 medical centers. Each DRS clinic follows standardized procedures and data are collected and analyzed centrally. Strong emphasis is placed on completeness of follow-up, and precautions are taken to minimize bias in the assessment of the major measures of treatment effects, visual acuity, visual fields, and appearance of the retina in stereoscopic fundus photographs. Analysis of accumulating data is performed at periodic intervals by a group of clinicians and biostatisticians, the Data Monitoring Committee. Reports of the ongoing monitoring of DRS results by this group are reviewed regularly by a Policy Advisory Group of senior clinicians, epidemiologists, and biostatisticians not involved in the study.

Recent findings of this study, based on analysis of two-year follow-up data, have necessitated some changes in the research protocol of this therapeutic trial. However, follow-up of all study patients continues and, in fact, is essential. The National Eye Institute and DRS investigators consider it important to convey this information as rapidly as possible to the medical community. For this reason, special arrangements have been made for immediate publication of this preliminary report. Because of the necessary stringent limitations of the length of this report, full discussion of study methods and findings will be deferred and only the most essential data presented. More complete and detailed discussion of study results and relevant issues will appear in subsequent publications.

While the manuscript has been in press, all DRS patients have been informed of

For a list of the participants in the Diabetic Retinopathy Study see page 396.

The Diabetic Retinopathy Study is continuing and is supported by contracts 1EY-32118, 1EY-32119, 1EY-32121, 1EY-32122, 1EY-32123, 1EY-32124, 1EY-32125, 1EY-32126, 1EY-32127, 1EY-32129, 1EY-32130, 1EY-42128, 1EY-42142, 1EY-42170, 1EY-42171, 1EY-42172, and 1EY-42173 from the National Eye Institute, National Institutes of Health, U.S. Department of Health, Education, and Welfare.

Reprint requests to DRS Coordinating Center, Department of Social and Preventive Medicine, University of Maryland, 600 Wyndhurst Ave., Baltimore, MD 21210.

these results and their implications. The National Eye Institute has written to ophthalmologists in the United States and physician members of the American Diabetes Association to inform them of the actions taken within the DRS.

METHODS

The primary eligibility criteria for this trial were (1) diabetic retinopathy in both eyes, either proliferative changes in at least one eye or severe nonproliferative changes in both eyes, and (2) visual acuity of 20/100 or better in both eyes. One eye of each patient was randomly selected for treatment and the other eye observed without treatment. One of two treatment modalities, xenon arc or argon laser, was also chosen randomly. Both treatment techniques included extensive "scatter" photocoagulation ("panretinal photocoagulation," "retinal ablation") and focal treatment of new vessels on the surface of the retina. Focal treatment of new vessels on the disk was required in argon-treated eyes.

Best-corrected visual acuity was measured in both eyes by "masked" techniques[4,5] before treatment and at four-month intervals after treatment. A detailed ophthalmic examination, including an abbreviated visual field examination and stereoscopic fundus photography, was carried out before treatment, four months later, and at annual intervals after treatment. Fundus photographs were graded according to a modified version of the Airlie classification of diabetic retinopathy,[4,6] in which new vessels on the disk or within 1-disk diameter of the disk margin, or located any distance anterior to this area, are designated NVD and new vessels in any other area are referred to as NVE (new vessels "elsewhere"). "Mild" NVD are less in severity than standard photograph No. 10A (Fig. 1) and "mild" NVE occupy less than 0.5-disk area in the photographic field being graded. More detailed information concerning the design and methods of this study is outlined in the DRS Manual of Operations.[4]

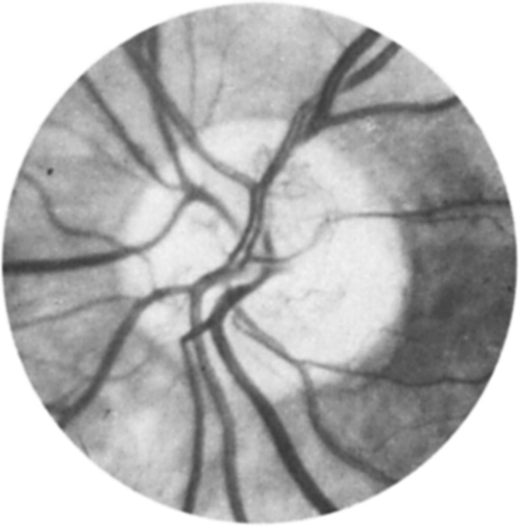

Fig. 1 (DRS Research Group). Standard photograph 10A modified Airlie classification of diabetic retinopathy.

GLOSSARY OF TERMS

Event—Any defined end point or response variable such as the occurrence of visual acuity less than 5/200, the occurrence of visual acuity less than or equal to 20/200, or death.

At risk—An eye is considered at risk of having a defined event in a given interval if the eye was examined for the event in that interval and did not have the defined event in a previous interval.

Cumulative event rate—Estimate of the relative frequency (expressed as a percentage, per 100 population, or per 100 eyes at risk) of the occurrence of an event over a defined time interval such as two years; the rates in this report were calculated by a life table method[7] which takes into account all follow-up information available for the specified follow-up interval, including that for patients observed for less than the full interval.

Severe visual loss—Occurrence of visual acuity less than 5/200 at two or more consecutively completed four-month follow-up visits.

Visual field score—The sum of twelve meridian scores: A meridian score (measured in degrees) is the peripheral extent of the field in a meridian minus the width of any scotomas on that meridian.

z value—Observed difference between the proportions of events observed in the untreated and treated groups divided by the standard error of the difference.

$$z = (p_1 - p_2) / \sqrt{\bar{p}\,(1 - \bar{p})\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

where p_1 and p_2 are the proportion of events in the untreated and treated groups respectively; and $\bar{p} = (n_1p_1 + n_2p_2) / (n_1 + n_2)$ is the proportion of events in the two groups combined. Similar computations using the cumulative event rates and standard errors obtained using the Littell life table method[7] were made to obtain z values for differences in event rates. A positive z value denotes an event rate in the treated group that is lower than the event rate in the untreated group. In some tables in this report the standard errors of the difference are not given because of space limitations, but they may be obtained by dividing the difference in event rates by the z value.

The classical statistical tests are not appropriate in this report because multiple response variables have been evaluated for multiple subgroups and because these multiple tests have been carried out repeatedly at three-month intervals. The multiplicity of statistical tests utilized to evaluate observed differences between untreated and treated eyes in the DRS makes it impossible to specify the exact P-value for a given comparison. P-values, or significance levels, are conventionally obtained from z values by the use of a table of the normal (Gaussian) distribution. A z value of 1.96 is usually associated with a P-value of .05 for a two-sided test, a z value of 2.58 with a P-value of .01, and a z value of 3.29 with a P-value of .001. As a consequence of multiple testing, a z value of 1.96 will be obtained more frequently than 5% of the time when there is no true difference between the two groups being compared, but how much more frequently is not readily determined. In this report the statistical evaluation of results is given in terms of z values since no satisfactory method for estimating the P-value is available.

In addition to z values, two other factors have been considered in the evaluation of the posttreatment findings for evidence of adverse or beneficial treatment effects. These factors are (1) the magnitude of the event rate in the untreated group, and (2) the magnitude of the difference in event rates between the untreated and treated groups. All three factors were considered important in evaluating treatment effects in subgroups.

Other approaches to evaluating the statistical significance of observed differences have been utilized in monitoring the results of this study and the results of these analyses, which attempted to cope with the problems of multiple testing, will be presented in subsequent reports. Other analyses took into account the correlation between the two eyes of each enrolled patient and these analyses will also be presented in future reports.

RESULTS

Amount of follow-up information—As of Sept. 30, 1975, based on data available in the Coordinating Center, a total of 1,732 patients had been enrolled (Table 1). Five patients who could not be treated according to study protocol have been excluded; therefore, the results are based on 1,727 patients, 858 treated with argon laser and 869 treated with xenon arc.

A total of 84 patients were reported to have died (46 in the argon-treated group and 38 in the xenon-treated group). The cumulative death rate per 100 population at risk for these 1,727 patients was 2.6 (standard error = 0.4) at the end of 12 months and 7.2 (standard error = 0.8) at the end of 24 months of follow-up.

Occurrence of visual acuity less than 5/200—The principal end point which was evaluated every three months by the Data Monitoring Committee was the occurrence of visual acuity less than 5/200 at one or more, at two or more, and at three or more consecutively completed four-month follow-up visits. Visual acuity less than 5/200 at two or more follow-up visits occurred in 129 untreated eyes (9.4%) and in 56 treated eyes (4.1%, Table 2). This difference amounts to a reduction

TABLE 1

NO. OF PATIENTS WHO HAD COMPLETED THE INDICATED VISIT AS OF SEPT. 30, 1975, BY TREATMENT GROUP*

Visit Completed	Argon Group	Xenon Group	Both Groups
Pretreatment visit† (Initial visit 2)	861	871	1732
Initial treatment session	858	869	1727
4 mos Posttreatment (Follow-up visit 2)	747	747	1494
1 yr Posttreatment (Follow-up visit 4)	532	545	1077
2 yrs Posttreatment (Follow-up visit 7)	176	174	350
3 yrs Posttreatment (Follow-up visit 10)	5	6	11
Mean months of follow-up	14.7	14.5	14.6

*Each of the follow-up visits listed was to be completed at four-month intervals after the initiation of treatment. The allowable time period for completing the visit was two months on either side of the expected appointment date.

†This visit is completed one to two days before the start of the initial treatment session which may consist of one or more separate sittings or "episodes" for the application of treatment usually during a seven-day period.

of 57% in the occurrence of severe visual loss in treated eyes ($z = 5.6$).

The findings for the occurrence of visual acuity less than or equal to 20/200 were similar as were other analyses of these low levels of visual acuity which took into account the status of the other eye. All of these analyses yielded similar results for the comparison of untreated vs. treated eyes.

Recovery from visual acuity less than 5/200—The percent of eyes with visual acuity less than 5/200 at one, two, or three consecutively completed four-month follow-up visits which showed improvement in visual acuity at a subsequent follow-up visit is given in Table 3. The longer the duration of visual acuity less than 5/200, the less frequently was recovery observed. However, regardless of the duration of this level of visual acuity, recovery was more frequent in treated than in untreated eyes.

As results were analyzed in this study, the occurrence of visual acuity less than 5/200 at two or more consecutively completed follow-up visits evolved as the principal end point or definition of severe visual loss. The use of an end point based on two consecutively completed follow-up visits rather than only one visit reduced the likelihood of recording a transient event, although it delayed the identification of the event by four months from the onset of visual acuity less than 5/200. An end point based on three consecutive visits would impose a delay of eight months.

Cumulative event rates of visual acuity less than 5/200—Cumulative event rates for visual acuity less than 5/200 at two or more consecutively completed follow-up visits are plotted for all patients in Figure 2 and for patients in each treatment group in Figure 3. More detailed information is given in Table 4. The first time an eye can have the event, visual acuity less than 5/200 at two or more visits, is eight months after the initiation of treatment and this can occur only if the eye had this low level of acuity at the first four-month follow-up visit. At the end of two years of follow-up the event rate was 16.3% in untreated eyes and 6.4% in treated eyes, a

TABLE 2

NO. AND PERCENT OF EYES WITH VISUAL ACUITY LESS THAN 5/200 BY TREATMENT GROUP

No. of Consecutively Completed Follow-up Visits With Low Visual Acuity		Argon Group	Xenon Group	Both Groups
	A. No. of Eyes with Visual Acuity Less than 5/200			
One or more	Untreated eyes	104	119	223
	Treated eyes	64	55	119
Two or more	Untreated eyes	63	66	129
	Treated eyes	29	27	56
Three or more	Untreated eyes	37	41	78
	Treated eyes	19	17	36
	B. Percent of Eyes with Visual Acuity Less than 5/200			
One or more	Untreated eyes	13.5	15.4	14.4
	Treated eyes	8.3	7.1	7.7
	z value	3.3	5.2	6.0
Two or more	Untreated eyes	9.2	9.5	9.4
	Treated eyes	4.3	3.9	4.1
	z value	3.7	4.2	5.6
Three or more	Untreated eyes	6.7	7.3	7.0
	Treated eyes	3.5	3.0	3.2
	z value	2.5	3.2	4.0
	C. No. of Patients Completing Specified Number of Follow-up Visits			
One or more		772	773	1545
Two or more		682	693	1375
Three or more		550	560	1110

TABLE 3

PERCENT OF EYES WITH SOME EVIDENCE OF RECOVERY* AFTER VISUAL ACUITY LESS THAN 5/200 AT ONE, TWO, OR THREE CONSECUTIVELY COMPLETED FOLLOW-UP VISITS

No. of Consecutively Completed Visits With Visual Acuity < 5/200	Percent of Eyes Showing Some Evidence of Recovery	
	Untreated Eyes†	Treated Eyes†
One	28.6 (161)	48.8 (82)
Two	12.2 (82)	28.6 (42)
Three	7.7 (52)	20.8 (24)

*"Some evidence of recovery" is defined as visual acuity greater than or equal to 5/200 at any subsequent follow-up visit.

†Denominators, that is, number of eyes with at least one follow-up visit after the defined event, given in parentheses.

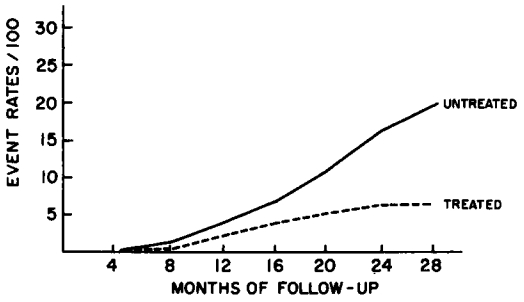

Fig. 2 (DRS Research Group). Cumulative event rates of visual acuity less than 5/200 at two or more visits for all patients.

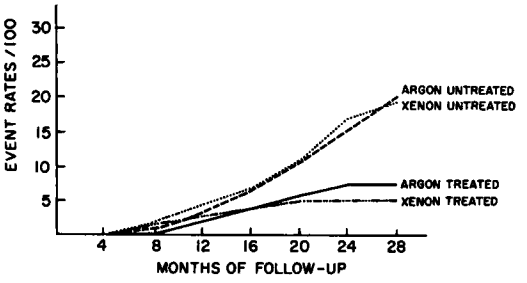

Fig. 3 (DRS Research Group). Cumulative event rates of visual acuity less than 5/200 at two or more visits for patients in each treatment group.

reduction of 61% in severe visual loss in treated eyes ($z = 5.5$). Similar reductions in the occurrence of severe visual loss were observed when the results for each treatment group were considered separately, 52% reduction in argon-treated eyes ($z = 3.0$) and 69% reduction in xenon-treated eyes ($z = 4.6$). Although it may appear that there was more reduction in xenon-treated eyes than in argon-treated eyes, comparing these two reductions yielded a z value of only 1.1.

Occurrences of small losses of visual acuity—Comparison of posttreatment visual acuity levels with the pretreatment level indicated losses of two to four lines of visual acuity were more frequent in treated eyes than in untreated eyes (Table 5). In argon-treated eyes, these changes were minimal four months after treatment (9.8% in treated eyes compared to 6.3% in untreated eyes, Table 5, A), and one year after treatment (10.2% in treated eyes compared to 8.9% in untreated eyes, Table 5, B), and were no longer present two years after treatment (Table 5, C). Losses of two to four lines in visual acuity occurred more frequently in xenon-treated eyes (17.8% in treated eyes and 8.1% in untreated eyes) at four months after treatment (Table 5, A) and persisted two years after treatment (Table 5, C).

Visual field changes—The distribution of visual field scores for argon-treated eyes was almost the same as the distributions observed for untreated eyes (Fig. 4). After one year of follow-up about 85% of eyes in all groups except xenon-treated eyes had visual field scores of 500 degrees or more, that is, an average of 42 degrees or more field in each meridian. The remaining eyes either had smaller visual field scores or the examination was not performed. About 44% of xenon-treated eyes had visual field scores in the range 240 to 500 degrees. Six percent of argon-treated eyes and 5% of untreated eyes had visual field scores in this range.

Subgroups determined by grading pretreatment fundus photographs—Eyes were classified according to severity of retinopathy by grading pretreatment fundus photographs. Subgroups were defined: no new vessels; presence of NVE without NVD; and presence of NVD, with or without NVE. Cumulative event rates of visual acuity less than 5/200 at two or more consecutively completed follow-up visits were calculated for each subgroup and these results are presented in Table 6.

The two-year event rates of visual acuity less than 5/200 in eyes with no new vessels before treatment were 2.4% in untreated eyes and 2.7% in treated eyes ($z = -0.2$; Table 6, Aa). The corresponding event rates in eyes with NVE, but without NVD, were 9.6% in untreated eyes and 4.5% in treated eyes ($z = 1.9$; Table 6, Ab).

After two years of follow-up the rate of

TABLE 4

CUMULATIVE EVENT RATES OF VISUAL ACUITY LESS THAN 5/200 AT TWO OR MORE CONSECUTIVELY COMPLETED FOLLOW-UP VISITS, STANDARD ERRORS, AND NUMBER OF EYES AT RISK IN EACH FOUR-MONTH INTERVAL BY MONTHS OF FOLLOW-UP AND TREATMENT GROUP

Follow-up, mos	Argon Group			Xenon Group			Both Groups		
	Untreated	Treated	z Value	Untreated	Treated	z Value	Untreated	Treated	z Value
				A. Cumulative Event Rates Per 100 Eyes at Risk					
8	0.9	0.1	2.0	1.7	1.2	0.8	1.3	0.7	1.5
12	3.2	2.0	1.3	4.5	2.7	1.6	3.9	2.4	2.1
16	6.5	3.7	2.0	6.9	3.8	2.2	6.7	3.8	2.9
20	10.6	5.8	2.5	11.0	4.8	3.4	10.8	5.3	4.2
24	15.3	7.4	3.0	17.3	5.3	4.6	16.3	6.4	5.5
28	20.3	7.4	3.8	19.6	5.3	4.8	20.0	6.4	5.9
				B. Standard Errors of Difference in Rates of Untreated and Treated Eyes					
8		0.4			0.6			0.4	
12		0.9			1.1			0.7	
16		1.4			1.4			1.0	
20		1.9			1.8			1.3	
24		2.6			2.6			1.8	
28		3.4			3.0			2.3	
				C. No. of Eyes at Risk in Each Four-Month Interval					
4-8	682	682		693	693		1375	1375	
8-12	629	632		650	651		1279	1283	
12-16	497	500		492	501		989	1001	
16-20	394	398		381	392		775	790	
20-24	227	237		230	240		457	477	
24-28	124	130		113	129		237	259	

TABLE 5

PERCENTAGE DISTRIBUTION OF CHANGE IN VISUAL ACUITY BETWEEN THE PRETREATMENT VISIT AND SELECTED FOLLOW-UP VISITS BY TREATMENT GROUP

Change in Visual Acuity	Argon Group		Xenon Group		Both Groups	
	Untreated	Treated	Untreated	Treated	Untreated	Treated
A. 4 mos Posttreatment (Follow-up visit 2)						
≤ 1 line decrease	88.8	85.1	84.8	73.8	86.8	79.5
2-4 line decrease	6.3	9.8	8.1	17.8	7.2	13.8
≥ 5 line decrease but ≥ 5/200	2.6	3.3	3.4	5.3	3.0	4.3
Visual acuity < 5/200	2.3	1.8	3.8	3.0	3.1	2.4
No. of eyes	766	766	768	768	1534	1534
B. 1 yr Posttreatment (Follow-up visit 4)						
≤ 1 line decrease	77.5	80.2	72.4	71.0	74.9	75.5
2-4 line decrease	8.9	10.2	11.4	18.1	10.2	14.2
≥ 5 line decrease but ≥ 5/200	5.6	3.6	7.7	7.1	6.7	5.4
Visual acuity < 5/200	8.0	6.0	8.6	3.7	8.3	4.9
No. of eyes	550	550	561	562	1111	1112
C. 2 yrs Posttreatment (Follow-up visit 7)						
≤ 1 line decrease	66.3	78.3	63.1	71.5	64.7	74.9
2-4 line decrease	11.4	10.3	9.5	15.6	10.5	13.0
≥ 5 line decrease but ≥ 5/200	7.4	5.7	10.1	8.4	8.8	7.1
Visual acuity < 5/200	14.9	5.7	17.3	4.5	16.1	5.1
No. of eyes	175	175	179	179	354	354

occurrence of visual acuity less than 5/200 at two or more visits in eyes with NVD with or without NVE was 24.5% in untreated eyes and 8.4% in treated eyes, a reduction of 66% ($z = 5.0$; Table 6, Ac).

The eyes with new vessels were further subdivided on the basis of severity of new vessels and the presence or absence of hemorrhage (vitreous or preretinal) in any photographic field before treatment. Cumulative event rates of the occurrence of visual acuity less than 5/200 at two or more consecutively completed follow-up visits were calculated for these subgroups (Table 7).

The two-year event rates in untreated eyes were greater than 35% in the two subgroups which had moderate or severe new vessels (either NVD, with or without NVE, or NVE without NVD) and hemorrhage. Event rates of about 25% in untreated eyes were observed in two additional NVD subgroups: (1) eyes with mild NVD (less than standard photograph 10A, Fig. 1) with hemorrhage, and (2) eyes with moderate or severe NVD (greater than or equal to standard photograph 10A, Fig. 1) without hemorrhage. In all four of these subgroups, a substantial reduction of event rates was observed in treated eyes (Table 7; Af, h, i, j).

In the remaining NVD subgroup, that is, eyes with mild NVD and without hemorrhage, the two-year event rate was 9.9% in untreated eyes and 3% in treated eyes, a reduction of 70% ($z = 1.5$; Table 7, Ag).

In the remaining subgroups the event rates were low and the differences between untreated and treated eyes were small. The comparisons between untreat-

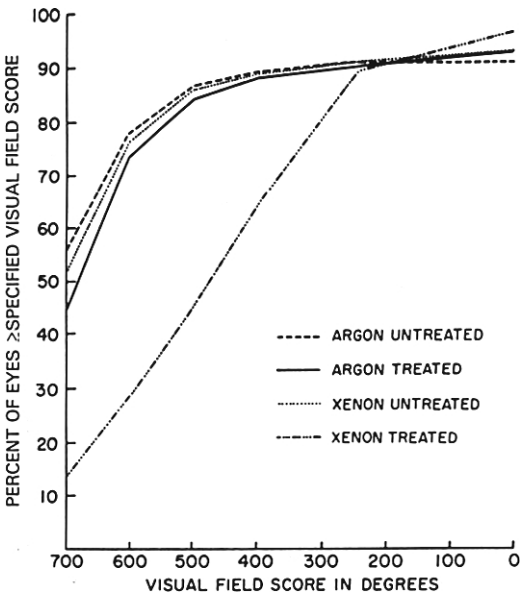

Fig. 4 (DRS Research Group). Cumulative percentage distribution of visual field scores 12 months after treatment.

ed and treated eyes within each treatment group were consistent with the findings for all patients, but the number of eyes in some subgroups was small.

Discussion

This study was designed to determine whether photocoagulation treatment would delay or prevent severe visual loss in patients with diabetic retinopathy. The two types of management to which eyes in the DRS were randomized were prompt treatment regardless of the stage of retinopathy at the time of the initial examination or no treatment regardless of the course followed. As already indicated, the definition of severe visual loss used in this report is visual acuity less than 5/200 at two consecutively completed four-month follow-up visits.

The purpose of this preliminary report

TABLE 6

CUMULATIVE EVENT RATES OF VISUAL ACUITY LESS THAN 5/200 AT TWO OR MORE CONSECUTIVELY COMPLETED FOLLOW-UP VISITS AND NUMBER OF EYES AT RISK BY PRESENCE OR ABSENCE OF NEW VESSELS BASED ON GRADING OF PRETREATMENT FUNDUS PHOTOGRAPHS

Follow-up, yrs	Argon Group			Xenon Group			Both Groups		
	Untreated	Treated	z Value	Untreated	Treated	z Value	Untreated	Treated	z Value
	A. Cumulative Event Rates Per 100 Eyes at Risk*								
	a. Eyes with no new vessels								
1	0.9	2.1	−0.7	0.0	0.9	−1.0	0.5	1.5	−1.0
2	0.9	3.5	−1.2	3.9	2.0	0.7	2.4	2.7	−0.2
	b. Eyes with NVE without NVD								
1	0.6	2.4	−1.4	2.2	2.3	−0.1	1.4	2.3	−0.9
2	7.9	5.4	0.7	11.2	3.4	2.0	9.6	4.5	1.9
	c. Eyes with NVD with or without NVE								
1	5.5	1.6	2.4	7.8	3.4	2.2	6.7	2.5	3.2
2	23.2	10.1	2.9	25.7	6.5	4.3	24.5	8.4	5.0
	B. No. of Eyes at Risk in Specified Four-Month Intervals†								
Follow-up, mos									
	a. Eyes with no new vessels								
8-12	114	105		124	130		238	235	
20-24	44	36		43	44		87	80	
	b. Eyes with NVE without NVD								
8-12	181	180		180	180		361	360	
20-24	66	69		80	71		146	140	
	c. Eyes with NVD with or without NVE								
8-12	262	279		277	270		539	549	
20-24	98	112		94	108		192	220	

*The yearly cumulative event rates were calculated using four-month interval rates.

†The number of eyes at risk are those for the last four-month interval of a given year of follow-up and represent the minimum number at risk for a given year. At the time of the analyses for this report, duplicate gradings of the pretreatment fundus photographs were not available for all enrolled patients: one grader's evaluation of the photographs for 1313 of the 1727 patients was utilized.

TABLE 7

CUMULATIVE EVENT RATES OF VISUAL ACUITY LESS THAN 5/200 AT TWO OR MORE CONSECUTIVELY COMPLETED FOLLOW-UP VISITS AND NUMBER OF EYES AT RISK BY SEVERITY OF NEW VESSELS AND PRESENCE OF HEMORRHAGE BEFORE TREATMENT

Follow-up, yrs	Argon Group			Xenon Group			Both Groups		
	Untreated	Treated	z Value	Untreated	Treated	z Value	Untreated	Treated	z Value
	A. Cumulative Event Rates Per 100 Eyes at Risk*								
	a. Eyes with no new vessels and without hemorrhage								
1	0.0	2.3	−1.4	0.0	1.0	−1.0	0.0	1.6	−1.8
2	0.0	3.8	−1.9	4.2	2.1	0.8	2.1	2.9	−0.4
	b. Eyes with no new vessels with hemorrhage								
1	10.6	0.0	1.0	0.0	0.0	—	5.6	0.0	0.9
2	10.6	0.0	1.0	0.0	0.0	—	5.6	0.0	0.9
	c. Eyes with mild NVE without NVD and without hemorrhage								
1	0.0	3.7	−1.6	0.0	1.6	−1.1	0.0	2.6	−1.9
2	8.1	3.7	0.8	2.9	1.6	0.4	5.4	2.6	0.9
	d. Eyes with mild NVE without NVD with hemorrhage								
1	0.0	0.0	—	0.0	0.0	—	0.0	0.0	—
2	0.0	0.0	—	0.0	0.0	—	0.0	0.0	—
	e. Eyes with moderate or severe NVE without NVD and without hemorrhage								
1	1.5	1.3	0.1	1.4	2.3	−0.4	1.5	1.9	−0.3
2	1.5	3.4	−0.7	7.4	4.4	0.6	4.4	4.0	0.1
	f. Eyes with moderate or severe NVE without NVD with hemorrhage								
1	0.0	4.0	−0.9	8.4	5.7	0.4	5.4	4.7	0.2
2	33.2	18.0	0.8	39.8	5.7	1.8	36.8	13.3	1.8
	g. Eyes with mild NVD with or without NVE without hemorrhage								
1	1.5	1.6	0.0	0.0	0.0	—	0.7	0.7	0.0
2	14.0	7.1	0.9	5.3	0.0	1.2	9.9	3.0	1.5
	h. Eyes with mild NVD with or without NVE with hemorrhage								
1	0.0	0.0	—	7.9	0.0	1.3	3.8	0.0	1.3
2	30.5	0.0	1.5	26.0	0.0	1.9	24.0	0.0	2.2
	i. Eyes with moderate or severe NVD with or without NVE without hemorrhage								
1	6.9	0.0	2.8	5.9	1.0	1.9	6.4	0.5	3.3
2	18.3	9.3	1.4	32.8	3.7	3.6	25.3	6.8	3.7
	j. Eyes with moderate or severe NVD with or without NVE with hemorrhage								
1	10.4	4.0	1.5	18.5	11.9	1.1	14.8	7.7	1.9
2	41.2	15.9	2.3	35.6	19.3	1.7	38.6	17.5	2.9

*The yearly cumulative event rates were calculated using four-month interval rates.

is to describe the recent protocol changes which have been made in the DRS and to summarize the data and rationale which led to this action. The clear evidence that, after two years of follow-up, there are treatment effects on visual function, in eyes with certain characteristics required (1) modification of the management of the previously untreated eyes of DRS patients, and (2) a report to the scientific community.

The assessment of treatment effects in this report is limited to visual acuity and visual field. Evaluation of the development and progression of new vessels or other retinopathy features based on grading of follow-up fundus photographs is underway and may lead to other important conclusions. Furthermore, no information has been presented in this report about treatment complications other than small losses of visual acuity or losses of visual field. The posttreatment fundus photographs are being reviewed to determine the extent of changes to be regarded as treatment complications, and the effect of these changes on visual outcome will be evaluated. Additional follow-up, as well as the results of analyses described above, is required for a complete assessment of photocoagulation, as used in the DRS, and the results of these analyses will be presented in future reports. Follow-up of all patients continues and monitoring of accumulating data is performed at three-month intervals. Significant new information will be acted on and reported promptly.

The results in this report provide evidence that photocoagulation treatment as

TABLE 7 *(Continued)*

CUMULATIVE EVENT RATES OF VISUAL ACUITY LESS THAN 5/200 AT TWO OR MORE CONSECUTIVELY COMPLETED FOLLOW-UP VISITS AND NUMBER OF EYES AT RISK BY SEVERITY OF NEW VESSELS AND PRESENCE OF HEMORRHAGE BEFORE TREATMENT

Follow-up, mos	Argon Group		Xenon Group		Both Groups	
	Untreated	Treated	Untreated	Treated	Untreated	Treated
	B. No. of Eyes at Risk in Specified Four-Month Intervals†					
	a. Eyes with no new vessels and without hemorrhage					
8-12	104	96	114	120	218	216
20-24	41	29	39	39	80	68
	b. Eyes with no new vessels with hemorrhage					
8-12	10	9	10	10	20	19
20-24	3	7	4	5	7	12
	c. Eyes with mild NVE without NVD and without hemorrhage					
8-12	74	58	69	62	143	120
20-24	20	21	31	20	51	41
	d. Eyes with mild NVE without NVD with hemorrhage					
8-12	14	15	8	12	22	27
20-24	2	3	4	4	6	7
	e. Eyes with moderate or severe NVE without NVD and without hemorrhage					
8-12	73	78	73	86	146	164
20-24	37	37	33	39	70	76
	f. Eyes with moderate or severe NVE without NVD with hemorrhage					
8-12	20	29	30	20	50	49
20-24	7	8	12	8	19	16
	g. Eyes with mild NVD with or without NVE without hemorrhage					
8-12	73	70	79	85	152	155
20-24	32	25	28	34	60	59
	h. Eyes with mild NVD with or without NVE with hemorrhage					
8-12	30	23	26	20	56	43
20-24	8	7	9	5	17	12
	i. Eyes with moderate or severe NVD with or without NVE without hemorrhage					
8-12	103	109	105	100	208	209
20-24	39	56	35	46	74	102
	j. Eyes with moderate or severe NVD with or without NVE with hemorrhage					
8-12	56	77	67	65	123	142
20-24	19	24	22	23	41	47

†The number of eyes at risk are those for the last four-month interval of a given year of follow-up and represent the minimum number at risk for a given year. At the time of the analyses for this report, duplicate gradings of the pretreatment fundus photographs were not available for all enrolled patients: one grader's evaluation of the photographs for 1313 of the 1727 patients was utilized.

carried out in the DRS (extensive scatter photocoagulation and focal treatment of new vessels) is of benefit in reducing, but not entirely eliminating, the occurrence of severe visual loss over a two-year period, at least for eyes with certain characteristics. The occurrence of visual acuity less than 5/200 for two consecutively completed four-month follow-up visits was reduced from 16.3% in all untreated eyes to 6.4% in all treated eyes, a change of 61% ($z = 5.5$, Table 4). There was some evidence that losses of two to four lines of visual acuity occurred more frequently in treated eyes (Table 5) and clear evidence of loss of peripheral visual field, at least in xenon-treated eyes (Fig. 4).

The patients enrolled in the DRS had a broad range of severity of diabetic retinopathy; therefore, it was essential to evaluate the results for different stages. As might be expected from clinical experience, location and severity of new vessels and presence of hemorrhage all appeared to be important prognostic factors. In general, low rates of severe visual loss in both untreated and treated eyes were observed in eyes with no new vessels or eyes with only NVE (Table 7, sections a-e). Only if hemorrhage was present, and NVE were moderate or severe in extent, was the rate of severe visual loss substantial (Table 7, section f). In all eyes with NVD, on the other hand, rates of severe visual loss were relatively high in untreated eyes and reduced in treated eyes (Table 7, sections g-j). In all of these eyes except those with mild NVD and without

hemorrhage, the z value for the difference between untreated and treated eyes was greater than 2.0 and the rate of occurrence of severe visual loss in the untreated group was 24% or greater.

On the basis of these results a decision has been made to consider photocoagulation treatment of the initially untreated eye when moderate to severe NVD (greater than or equal to standard photograph 10A, Fig. 1) are present. Treatment will also be considered for two other groups of eyes if fresh hemorrhage is present: those with mild NVD (less than standard photograph 10A, Fig. 1) and those with moderate or severe NVE (occupying 0.5 disk area or more in at least one photographic field). Continuing analyses of DRS data may lead to modification of these recommendations.

The decision to exclude eyes with mild NVD without hemorrhage from the recommendations above is based in part on the lower rate of severe visual loss observed in untreated eyes and in part on clinical grounds. Eyes with mild NVD without hemorrhage do not usually progress suddenly to severe hemorrhage. Clear-cut increase in the severity of the neovascularization or minor symptomatic vitreous hemorrhage which does not preclude photocoagulation usually precedes such a catastrophe and may provide a signal that could be used to initiate treatment. Data presented provide evidence that treatment of eyes in this subgroup resulted in a lower rate of severe visual loss than did indefinite withholding of treatment, but do not indicate the optimum time for treatment. Analysis of follow-up fundus photographs currently underway may provide some information on this question; however, additional controlled clinical trials comparing immediate treatment with deferred treatment may be necessary to resolve this issue.

It should be emphasized that the policy established is to consider treatment of initially untreated eyes which now or in the future fall into the groups defined above. Each case is to be evaluated on an individual basis to determine whether treatment is appropriate. For example, if a patient with moderate or severe NVD has been observed for a period of time and the new vessels have spontaneously regressed, some ophthalmologists may decide that treatment is not warranted unless the retinopathy appears to be reentering an active stage. However, the DRS has no evidence to support or refute such a decision.

The relative efficacy of the two treatment approaches used in the DRS in preventing or delaying severe visual loss for a period as long as three or more years remains undetermined. The harmful effects of treatment, moderate losses of visual acuity and peripheral field losses, were greater in the xenon-treated group, but these relatively minor disadvantages might be outweighed if, with further follow-up, xenon treatment is found to be more effective than argon treatment in reducing severe visual loss. Complete follow-up of treated eyes under the current protocol, both with regard to visual function and follow-up photographs, is essential to evaluate the long-term effects of these two treatments. Fortunately, this is entirely feasible and ethically acceptable since the risk of additional harmful effects from follow-up treatment is small and probably no greater with xenon than with argon.

It is important to emphasize that the scatter technique used in the xenon treatment group may be more extensive than that used by many advocates of xenon arc photocoagulation. Less extensive treatment might be accompanied by minimal loss of visual field and visual acuity, but the efficacy in reducing severe visual loss may be a result of extensive scatter treatment.

When the initially untreated eyes of DRS patients are to be treated, either of the two treatment techniques used in the study is recommended to the ophthalmologist caring for the patient. Since the data do not indicate that focal treatment of NVD or elevated NVE with argon led to better results, adherence to these technically difficult features of the argon treatment protocol will be optional in these eyes.

This preliminary report is based on two years of follow-up after treatment. Although the information beyond two years of follow-up was limited, there was a continued reduction in the occurrence of severe visual loss in treated eyes as compared to untreated eyes. There is, of course, the theoretical possibility that a late reversal of beneficial treatment effect could occur with development of catastrophic complications in the treated eyes, but this seems unlikely on the basis of past experience. Similarly, there is no information to suggest significant improvement in untreated eyes which had severe visual loss (Table 3) or to suggest a diminution of the rate of occurrence of severe visual loss in untreated eyes after two years of follow-up. Some estimates which took the life expectancy of these patients into account showed that the substantial gains in the first 24 months after treatment would not be outweighed by delayed harmful effects over the next 20 years, even if the latter were severe (according to a report from the Office of Biometry and Epidemiology, National Eye Institute: Average years of sight after treatment assuming a delayed deleterious effect of treatment, Dec. 24, 1975).

If a reversal of present trends does occur, it will be detected since follow-up of treated eyes will continue according to the original protocol. Although information on the comparable group of untreated eyes will not be available because of the protocol change described above, this is not essential for the interpretation of the results for treated eyes after longer periods of follow-up.

SUMMARY

Analyses of visual acuity and visual field results in the Diabetic Retinopathy Study provide evidence that photocoagulation treatment as carried out according to the study protocol (extensive "scatter" photocoagulation and focal treatment of new vessels) is of benefit in preventing severe visual loss, over a two-year follow-up period, in eyes with proliferative retinopathy. Location of new vessels relative to the disk, severity of new vessels, and the presence of hemorrhage (vitreous or preretinal) all proved to be important prognostic factors. On the basis of these findings, these steps have been taken: All patients in the study have been informed of results to date and given an explanation of their implications. Photocoagulation treatment will be considered for the initially untreated eyes which now or in the future fulfill any one of the following criteria: (a) moderate or severe new vessels on or within 1-disk diameter of the optic disk; (b) mild new vessels on or within 1-disk diameter of the optic disk if fresh hemorrhage is present; and (c) moderate or severe new vessels elsewhere, if fresh hemorrhage is present. Follow-up of all patients will continue to allow long-term comparison between the argon- and xenon-treatment techniques employed. Further analyses of accumulating data will be performed to evaluate more completely the efficacy of photocoagulation therapy.

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REFERENCES

1. Meyer-Schwickerath, G.: Light-coagulation. Buech. Augenarzt. 33:1, 1959.

2. Ederer, F., and Hiller, R.: Clinical trials, diabetic retinopathy and photocoagulation, a reanalysis of five studies. Survey Ophthalmol. 19:267, 1975.

3. Diabetic Retinopathy Study: Letter to Editor. Am. J. Ophthalmol. 76:403, 1973.

4. Diabetic Retinopathy Study: Manual of Operations. Baltimore, Diabetic Retinopathy Study Coordinating Center, 1972.

5. Davis, M. D.: Application of the principles of clinical trials. Am. J. Ophthalmol. 79:779, 1975.

6. Goldberg, M. F., and Fine, S. L. (eds.): Symposium on the Treatment of Diabetic Retinopathy, U.S.P.H.S. publication No. 1890. U.S. Government Printing Office, chapter 2, 1969.

7. Littell, A. S.: Estimation of the T-year survival rate from follow-up studies over a limited period of time. Hum. Biol. 24:87, 1952.