Expedited Publication

Photocoagulation for Diabetic Macular Edema

Early Treatment Diabetic Retinopathy Study Report Number 1

Early Treatment Diabetic Retinopathy Study Research Group

• Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) show that focal photocoagulation of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. In this randomized clinical trial, which was supported by the National Eye Institute, 754 eyes that had macular edema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation, while 1,490 such eyes were randomly assigned to deferral of photocoagulation. The beneficial effects of treatment demonstrated in this trial suggest that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation. Clinically significant macular edema is defined as retinal thickening that involves or threatens the center of the macula (even if visual acuity is not yet reduced) and is assessed by stereo contact lens biomicroscopy or stereo photography. Follow-up of all ETDRS patients continues without other modifications in the study protocol.

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For editorial comment see
"Photocoagulation Therapy for Diabetic Eye Disease"
JAMA, Dec 6, 1985.

The Early Treatment Diabetic Retinopathy Study (ETDRS) is a National Eye Institute–supported, multicenter, randomized clinical trial designed to evaluate photocoagulation and aspirin treatment in the management of patients with nonproliferative or early proliferative diabetic retinopathy. The ETDRS was designed to address the following three major questions:

1. When in the course of diabetic retinopathy is it most effective to initiate panretinal photocoagulation?
2. Is photocoagulation effective in the treatment of diabetic macular edema?
3. Is aspirin treatment effective in altering the course of diabetic retinopathy?

This first report deals only with question number 2.

Previous studies have suggested that photocoagulation may be beneficial in the treatment of diabetic macular edema.[1-17] These studies did not provide conclusive evidence because of one or more of the following reasons: (1) Patients were not randomized. (2) Visual acuity was measured without prior refraction and/or was not measured by a "masked" observer. (3) There were confounding effects of advanced proliferative diabetic retinopathy and/or panretinal photocoagulation. (4) The number of patients was small. (5) Treatment techniques were incompletely described. (6) Evaluation of possible photocoagulation effects on visual function other than visual acuity was not reported. Because of these limitations, clinical guidelines for the treatment of macular edema were difficult to formulate.[18,19]

In the ETDRS, the effects of *focal* photocoagulation for macular edema are being evaluated in a prospective, large-scale, randomized clinical trial involving 29 centers (including 23 clinical centers). This first ETDRS report presents the data that support the conclusion that focal photocoagulation for macular edema is beneficial.

PATIENTS AND METHODS

From April 1980 to August 1985, the ETDRS research group enrolled 3,928 diabetic patients with early proliferative retinopathy, moderate to severe nonproliferative retinopathy, and/or diabetic macular edema in each eye. Patients with "high-risk" proliferative retinopathy[20] (moderate or severe optic nerve neovascularization or any neovascularization with hemorrhage) were not eligible for the study, because immediate panretinal photocoagulation already has been recommended for such patients.[21] Patients with other significant ocular disease or visual acuity worse than 20/200 were also ineligible. Prior to

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A complete listing of the participants in this research study appears at the end of this article.

Reprint requests to the Biometry & Epidemiology Program, National Eye Institutes, Bldg 31, Room 6A24, 9000 Rockville Pike, Bethesda, MD 20892.

entry into the ETDRS, patients were asked to give written informed consent after receiving written and verbal information concerning their disease and the study.

Study Design

The complete design of the ETDRS has been summarized previously and is described in detail in the 848-page Manual of Operations (available from the US Department of Commerce, National Technical Information Service, 5285 Port Royal Rd, Springfield, VA 22161; Accession No. PB85 223006/AS).[22,23] The present report is limited to the subgroup of eyes in the ETDRS that were identified as having mild to moderate nonproliferative diabetic retinopathy and macular edema, as determined by the initial grading of baseline fundus photographs and fluorescein angiograms of the ETDRS Fundus Photograph Reading Center, Madison, Wis.

The treatment assignment scheme for these eyes is detailed in Fig 1. First, they were randomly assigned to immediate photocoagulation or deferral of photocoagulation until high-risk proliferative retinopathy developed. The eyes assigned to immediate photocoagulation were then randomly divided into two photocoagulation regimens. One half (754) of the eyes assigned to immediate photocoagulation received only focal treatment for macular edema initially. This report compares these focally treated eyes with those randomized to deferral of photocoagulation (1,490 eyes).

Excluded from this report are the results for the eyes with mild to moderate retinopathy and macular edema that were randomly assigned to an initial treatment of panretinal photocoagulation and follow-up focal photocoagulation if macular edema persisted (Fig 1), the eyes with moderate nonproliferative retinopathy that did not have macular edema at the time of entry into the ETDRS, and all eyes initially graded as having severe nonproliferative or early proliferative retinopathy at the time of entry into the ETDRS. Follow-up continues for these groups of eyes.

Treatment

In the ETDRS, an eye is classified by the Fundus Photograph Reading Center as having macular edema when there is retinal thickening at or within 1 disc diameter of the center of the macula or definite hard exudates in this region. Macular edema is designated as being "clinically significant" if at least one of the characteristics listed in Table 1 is present.

An example of an eye with clinically significant macular edema and mild to moderate nonproliferative diabetic retinopathy is illustrated in Fig 2. Figure 2, middle left, shows the appearance of the retina immediately after focal treatment for macular edema, as performed in the ETDRS. A pretreatment fluorescein angiogram is used during photocoagulation to identify "treatable lesions" (Table 2). Treatment is prescribed for all such lesions located within 2 disc diameters of the center of the macula but at least 500 microns from the center.

Microaneurysms and other focal leakage sites receive 50- to 100-micron argon blue-green or green-only burns of 0.1-s duration or less, with adequate power to obtain definite whitening around the microaneurysm or leakage site. For all microaneurysms greater than 40 microns in diameter, an attempt is made to obtain actual whitening or darkening of the microaneurysm itself, which is generally accomplished utilizing a 50-micron spot size. Repeated burns are sometimes needed. Care is taken to avoid rupturing Bruch's membrane.

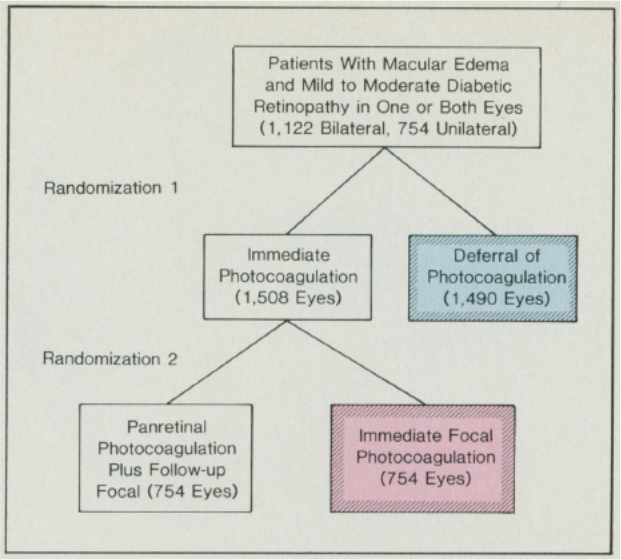

Fig 1.—Early Treatment Diabetic Retinopathy Study treatment assignment schedule for patients with macular edema and mild to moderate diabetic retinopathy in one or both eyes. Randomization 1: All study patients had one eye randomly assigned to immediate photocoagulation and other eye to deferral of photocoagulation until "high-risk" proliferative retinopathy (as described by the Diabetic Retinopathy Study[20]) developed. Macular edema and mild to moderate retinopathy were present in both eyes of 1,122 patients (2,244 eyes), and one eye was randomly assigned to immediate photocoagulation or deferral. Seven hundred fifty-four patients had macular edema and mild to moderate retinopathy in only one eye; these eyes are about equally divided between immediate and deferral groups. Randomization 2: Eyes with macular edema and mild to moderate retinopathy assigned to immediate photocoagulation were randomized to either a combination of initial panretinal photocoagulation and follow-up focal macular photocoagulation if macular edema persisted or only focal macular photocoagulation at initial treatment with panretinal photocoagulation if retinopathy progressed to severe nonproliferative stage or beyond. Hatched boxes indicate those groups compared in this report.

Table 1.—Clinically Significant Macular Edema (Any of the Following Characteristics)

Thickening of the retina at or within 500 microns of the center of the macula
Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening)
A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

Treatment of lesions closer than 500 microns to the macula is not required initially. However, if vision is less than 20/40, and the retinal edema and leakage persist, treatment of lesions up to 300 microns from the center is recommended, unless there is perifoveal capillary dropout, which might be worsened by this treatment.

Areas of diffuse leakage or nonperfusion within 2 disc diameters of the center of the macula are treated in a grid

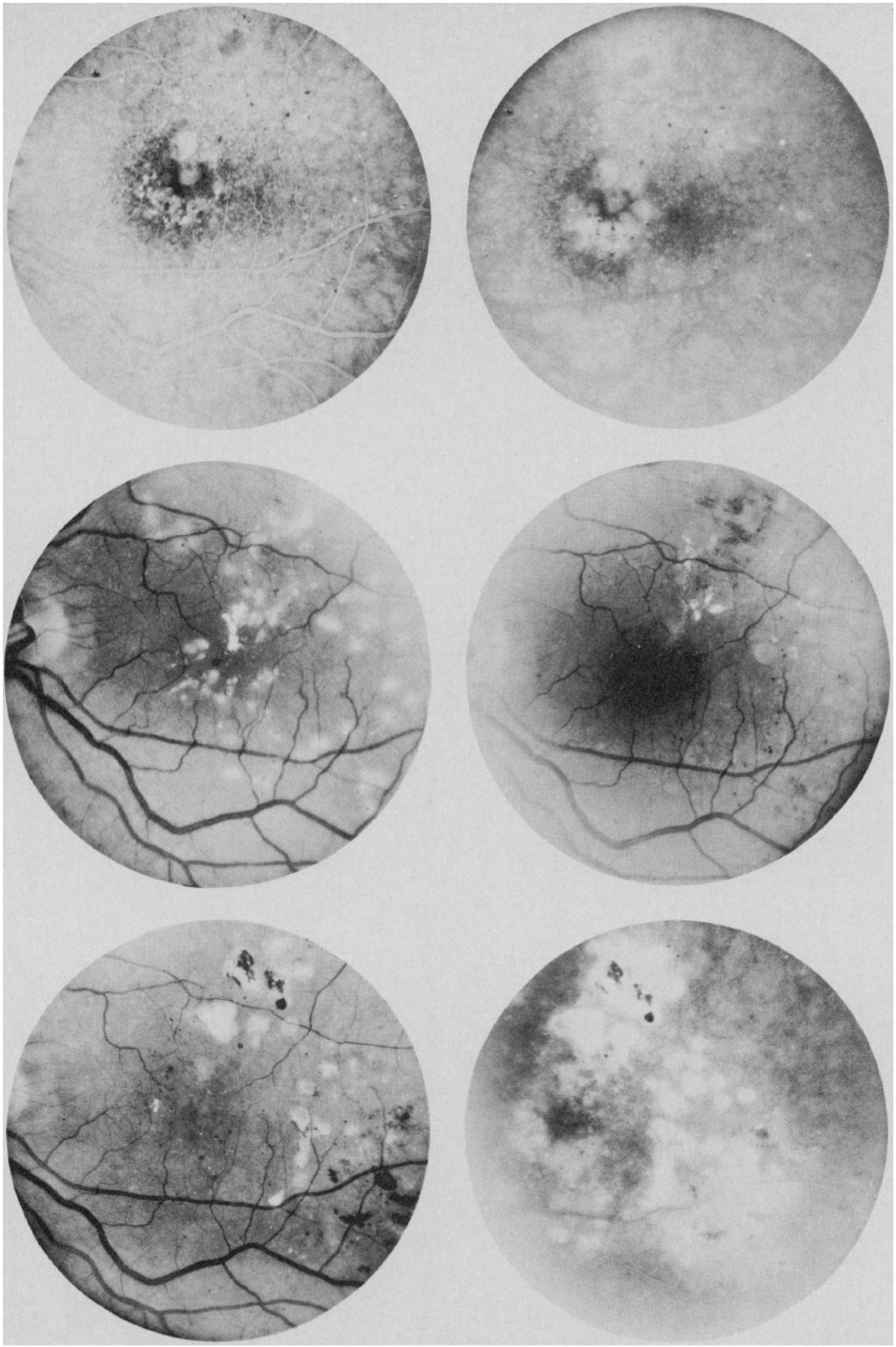

Fig 2.—Left eye with retinal thickening involving center of macula, small amount of hard exudate, and focal fluorescein leakage. Top left, Pretreatment fluorescein angiogram, mid-phase. Some microaneurysms have filled, others have not. Top right, Pretreatment angiogram, late phase (at seven to ten minutes). Fluorescein leakage in macular area is extensive and involves center. Middle left, Immediately following initial treatment, essentially all microaneurysms have been treated focally and many have lost original red color. Small hemorrhage just nasal to center of macula has been avoided. Middle right, At one-year follow-up visit, area of retinal thickening with adjacent hard exudate is present superotemporally, extending to within 500 to 1,000 microns of center of macula. Additional focal treatment was carried out. Bottom left, At three-year follow-up visit, note scars of additional focal treatment. Microaneurysms are present below and nasal to center of macula and there is small amount of hard exudate, but no retinal thickening was detected on contact lens examination or in stereo photographs. Additional focal treatment was therefore not required by protocol but was allowed. Bottom right, At three-year follow-up visit, late-phase fluorescein angiogram shows that some of microaneurysms below and nasal to center of macula do not fill with fluorescein, as was also case at baseline. Retinal thickening and fluorescein leakage no longer involves center of macula.

pattern. The goal of treatment in such cases is to produce a burn of light to moderate intensity, not more than 200 microns in diameter. To accomplish this, a 50- to 200-micron spot size is utilized. A space one burn wide is left between each lesion. The burns can be placed in the papillomacular bundle but not closer than 500 microns from the center of the macula.

A comparison of the results of focal photocoagulation for eyes with macular edema in patients who were randomly assigned to treatment with aspirin (650 mg/day) with the results of focal photocoagulation for eyes with macular edema in patients who were assigned to treatment with placebo shows that aspirin usage did not modify the effect of focal photocoagulation. Therefore, results are presented without regard to the aspirin treatment assignment.

Outcome Assessment

Visual acuity, the primary means of gauging treatment effects in this study, was measured at each visit by an examiner who did not know the treatment assignment (masked) and who followed a detailed protocol using a specially developed visual acuity chart (Fig 3).[24] The test results are used to calculate a visual acuity score by totaling the number of letters correctly read.[24] Changes in visual acuity are calculated by subtracting the visual acuity score measured during a follow-up visit from the baseline visual acuity score (taken not more than 72 hours before the initial treatment). A loss of 15 letters is equivalent to a three-line visual acuity decrease on this chart or a doubling of the initial visual angle (eg, 20/20 to 20/40 or 20/100 to 20/200). Changes in visual acuity, such as a doubling of the visual angle, are used to assess treatment effects. If visual acuity scores were missing for up to two consecutive follow-up visits, but scores were available from the visits immediately preceding and following the missing scores, then the arithmetic mean of the two bracketing scores replaced the missing score. This interpolation was done for less than 3% of the scores; more than 98% of patients have been seen within the last year.

Other visual function tests include the Farnsworth-Munsell 100-hue test scored in standard fashion[25] and Goldmann perimetry with the I-2 and I-4 test objects from which visual field scores are calculated by summing the peripheral extent of the field in 12 meridians, excluding areas of scotomas.

Table 2.—Characteristics of Treatable Lesions

Discrete points of retinal hyperfluorescence or leakage (most of these are microaneurysms)
Areas of diffuse leakage within the retina
Microaneurysms
Intraretinal microvascular abnormalities
Diffusely leaking retinal capillary bed
Retinal avascular zones

Each patient was scheduled for a follow-up visit six weeks after initial treatment and at four-month intervals. Follow-up focal photocoagulation is required for all eyes assigned to immediate treatment that have persistent clinically significant macular edema and treatable lesions.

Fundus photographs and fluorescein angiograms are taken at prescribed intervals and as needed for follow-up treatment. These photographs and angiograms are graded in a masked and standard fashion at the Fundus Photograph Reading Center. These assessments of the presence and extent of macular edema and retinopathy level are used in this report.

The effects of focal photocoagulation were assessed by comparing eyes in the immediate focal treatment group with eyes in the deferral of treatment group, using the two-sample test of proportions with unequal variances.[26] The usual critical Z value of ± 1.96 corresponding to a .05 level of significance for a two-sided test of one comparison of one end point was not appropriate because multiple end points in several subgroups were compared at frequent intervals during the course of the study. For monitoring purposes, an observed Z value of ± 1.96 to ± 2.57 was considered suggestive of a treatment difference, and an observed Z value of ± 2.58 or greater (corresponding to a .01 level for a single test of significance) was considered a statistically significant difference. Observed Z values of ± 3.29 or greater (corresponding to .001 level) are also identified below.

RESULTS

This report is based on data available at the Coordinating Center, Baltimore, as of June 14, 1985. At the time of this analysis, 12 months had elapsed since the time of initial treatment for 80% of the enrolled patients, and 36 months had elapsed since initial treatment for 35% of the patients. In the following sections, analyses are presented according to the outcome variable used to assess treatment effect (visual acuity, retinal thickening, or visual function tests that measure factors other than visual acuity).

Visual Acuity Results

Visual Acuity Results in All Eyes.—Eyes assigned to immediate focal photocoagulation were about half as likely to lose 15 or more letters on the ETDRS eye chart compared with eyes assigned to deferral of photocoagulation: 5% vs 8% at one year, 7% vs 16% at two years, and 12% vs 24% at three years (Fig 4).

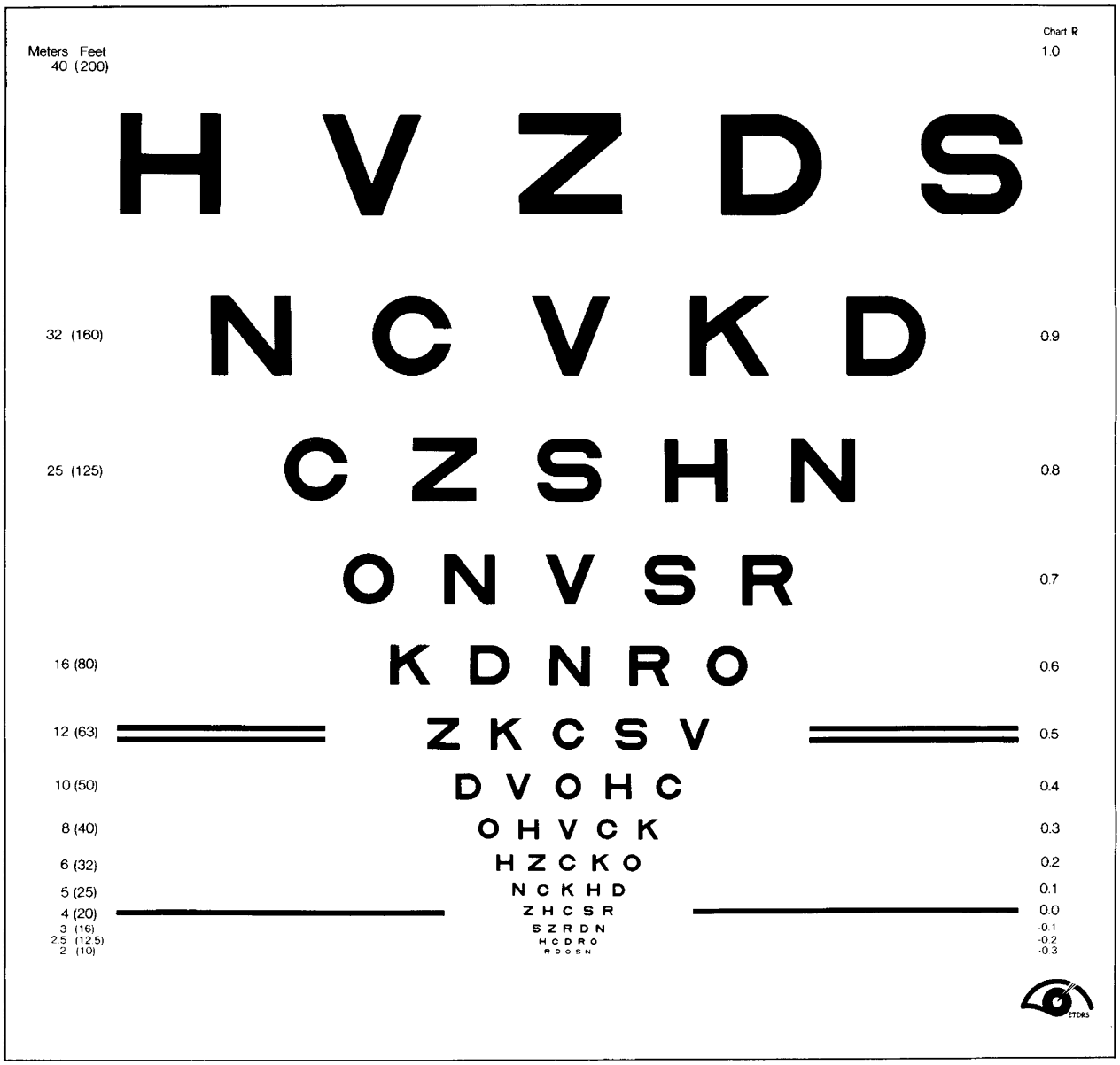

Fig 3.—One of three Early Treatment Diabetic Retinopathy Study visual acuity charts. Four-meter testing distance with this chart yields the following Snellen equivalent lines: 20/10, 20/12.5, 20/16, 20/20, 20/25, 20/31.5, 20/40, 20/50, 20/63, 20/80, 20/100, 20/125, 20/160, and 20/200. At 1 m, the following additional Snellen equivalent lines of visual acuity could be measured: 20/250, 20/315, 20/400, 20/500, 20/630, and 20/800. Note that every three lines is a doubling of the visual angle and that there are five letters on each line.

The comparison of the two groups yielded Z values of 2.58 or more from the end of the first year of follow-up through the third year of follow-up. This analysis includes all eyes with macular edema and nonproliferative retinopathy, as determined in the initial evaluation by the Fundus Photograph Reading Center. Of the 754 eyes assigned to immediate focal photocoagulation, 574 were from patients with bilateral macular edema and nonproliferative retinopathy. A separate analysis based on these paired eyes showed similar results.

Figure 5 shows the percentages of eyes with visual acuity scores less than 50 (equivalent to visual acuity worse than 20/100) at each visit, including baseline. The pattern of differences between the immediate photocoagulation group and the deferral of photocoagulation group is similar to that seen for a loss of 15 letters (Fig 4).

Visual Acuity Results in Eyes Classified by Baseline Visual Acuity Score.—Figure 6 shows the results when eyes are categorized according to baseline visual acuity score (see also Table 3). In each of the

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