

THE USE OF THE SCANNING LASER OPHTHALMOSCOPE IN THE EVALUATION OF AMBLYOPIA (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

BY David A. Johnson MD PhD

ABSTRACT

Purpose: The purpose of this study was to evaluate amblyopic patients with scanning laser ophthalmoscope microperimetry to determine whether the scanning laser ophthalmoscope data provide useful information in our understanding of amblyopia and assess its utility in the evaluation of amblyopic patients.

Methods: In this retrospective case-series, clinical data of 46 patients with amblyopia were examined after treatment for anisometropic or strabismic amblyopia. Ten normal patients served as controls. All patients were tested with the scanning laser ophthalmoscope, evaluating for the presence of macular scotomata. Scanning laser ophthalmoscope findings were assessed within each group and between groups.

Results: A macular scotoma was found in the amblyopic eye of 25 of 26 anisometropic amblyopic patients and all 20 strabismic amblyopia patients. Twenty of 26 patients with anisometropic amblyopia had a relative scotoma in the nonamblyopic eye. All 20 patients with strabismic amblyopia had a nonamblyopic eye scotoma. None of the control patients had a scotoma in either eye. Several clinical features were correlated to scotoma findings within and between groups.

Conclusions: The scanning laser ophthalmoscope proved to be a useful tool for the assessment of some features of amblyopia. A scotoma was identified in not only the amblyopic eye of all but one of the amblyopic patients, but also in almost all of the nonamblyopic, presumably "normal" eyes. Thus, ocular effects of amblyopia may not be strictly limited to the amblyopic eye.

Trans Am Ophthalmol Soc 2006;104:414-436

INTRODUCTION

Amblyopia remains a common cause of visual loss, despite increasing understanding of its causes and mechanisms. It is defined by von Noorden¹ as a "unilateral or bilateral decrease of visual acuity caused by form vision deprivation and/or abnormal binocular interaction for which no organic causes can be detected by the physical examination of the eye and which, in appropriate cases is reversible by therapeutic measures." It is estimated to affect 1% to 4% of children^{2,3} and approximately 2.9 % of adults.⁴ It stems from early abnormal binocular interactions (usually from strabismus) or formed visual deprivation in one eye (from uncorrected anisometropia) or, less commonly, both eyes (uncorrected high hyperopia). Not infrequently, both factors are involved in the same patient.

Numerous approaches have been employed in the clinical assessment and research study of amblyopia. Methods of visual acuity measurement in the clinical setting usually are by age-appropriate subjective testing, such as Snellen acuity, Allen cards, Tumbling E game, and others. Preverbal children require testing methods such as forced choice preferential looking (Teller cards), fixation preference when strabismus is present, or induced tropia testing when eyes are aligned. Further evaluation may include measurement of contrast sensitivity and subjective tests of binocular interactions, such as Worth 4-dot test and stereopsis measurement. More recently, research methods have employed newer techniques, such as functional magnetic resonance imaging (fMRI) in the investigation of the cortical neurophysiologic mechanisms underlying amblyopia.⁵ Other approaches, such as positron emission tomography (PET) scanning, have also been used as a tool to evaluate central nervous system activity in amblyopic patients.⁶ Histological evaluation of visual neuronal pathways in visually deprived animals and humans has been studied as well.⁷⁻¹¹

The advent of the scanning laser ophthalmoscope (SLO) has brought another tool into the armamentarium of the clinician. The SLO has been used to evaluate many features of the visual system, including optic disc analysis in glaucoma, in which the SLO provides objective, quantitative, three-dimensional analysis of the disc surface.^{12,13} Other uses of the SLO include microperimetry, where it has been used to evaluate point of fixation and fixation stability in conditions such as macular dystrophies,¹⁴ idiopathic macular holes,¹⁵ age-related macular degeneration,^{16,17} and evaluation of preoperative and postoperative visual function after retinal surgery.¹⁸ Another area in which the SLO has been particularly valuable is in low vision rehabilitation, where microperimetry not only aids in the localization of a patient's preferred retinal locus of fixation, but also assists in rehabilitation of low vision patients in fixation stability and visual function optimization.¹⁹⁻²¹

The purpose of this study was to use the SLO as a microperimetry device to assess macular stimulation threshold and the presence and patterns of scotomata in the eyes of amblyopic and control patients. Further analysis attempts to find distinctions between different etiologies of amblyopia and to seek identifiable characteristics of patients that correlate with their clinical response, or lack thereof.

METHODS

PATIENTS

Forty-six patients with amblyopia were studied. Patients included those with strabismic or anisometropic amblyopia. Ten patients

From the Eye Associates of Wilmington, Wilmington, North Carolina. The author discloses no financial interests in this article.

served as controls. Human studies committee and institutional review board approval was obtained and informed consent was granted by each subject's parents.

Amblyopia was defined as meeting one of three criteria: (1) in preverbal children, a strong fixation preference for one eye over the other by either induced tropia testing if the child was orthophoric or fixation preference if strabismus was present; (2) an interocular visual acuity difference of ≥ 2 lines using projected pictures in age-appropriate children on a B-VAT instrument (Mentor O & O, Norwell, Massachusetts) at 20 feet testing distance; or (3) an interocular difference of ≥ 2 LogMAR lines at distance visual acuity testing with the B-VAT, using either Snellen letters or HOTV chart with surround bars at 20 feet testing distance. Children who were preverbal at the onset of treatment were included only if follow-up was sufficiently long that a final visual acuity could be determined by method (3) above.

Strabismus was defined as ocular misalignment of 10 prism diopters or greater measured at distance and/or near. Anisometropia was defined as an interocular spherical refractive error difference of 1.0 diopter or greater or an astigmatic difference of 1.50 diopters or greater. For purposes of data reporting, the refractive error difference between eyes is expressed as the spherical equivalent.

In all cases, a patient was not diagnosed as having amblyopia, nor was treatment started, unless the defined difference in interocular visual acuity persisted after at least 4 weeks of spectacle correction, when appropriate. Need for spectacles was based upon cycloplegic retinoscopy and, when age-appropriate, a cycloplegic refraction.

All patients needed to be free of confounding coexisting ocular disorders that may be responsible for decreased visual acuity or coexisting medical problems that might limit reliability of visual acuity measurements and any testing measures.

Control patients, in the same age range as the amblyopic patients, demonstrated 20/20 best-corrected visual acuity in each eye, normal ocular alignment, 40 seconds of arc stereoacuity, and normal ocular anatomy.

Amblyopia was treated either by occlusion or atropine penalization. Atropine penalization was instituted only in patients whose Snellen visual acuity in the amblyopic eye was 20/100 or better.

Some patients may have begun amblyopia treatment while still preverbal and, therefore, initial acuity was assessed by fixation preference, if strabismic, or induced tropia testing, if orthophoric. However, interim and final visual acuity was measured in all patients at 20 feet using age-appropriate testing, including projected pictures, HOTV optotypes (with surround bars) or Snellen letters. All stimuli were presented on a calibrated B-VAT. All Snellen visual acuities were converted to LogMAR format for proper statistical analysis.²²

Patients were excluded if they had undergone amblyopia therapy prior to initial evaluation by the author. Patients were included only after having completed a course of amblyopia therapy by the author and were felt to have reached either equal visual acuity or a still somewhat reduced but stable acuity that had remained stable after treatment had been discontinued for at least 3 months.

Because performance of SLO testing involves considerable cooperation, patients were excluded if they could not cooperate and follow instructions while maintaining steady fixation on a target at the slit-lamp biomicroscope, which simulated the cooperation necessary to perform the SLO measurements.

Measurements obtained included visual acuity, ocular alignment, stereopsis using the Titmus stereoacuity test, 4-diopter base-out prism test, Worth 4-dot test, slit-lamp examination, dilated fundoscopic examination and cycloplegic refraction. Amblyopia data included best-corrected visual acuity at beginning of treatment and end of treatment, age at onset of treatment, method of amblyopia treatment, treatment duration, need for retreatment, age at SLO testing, and total follow-up from onset of treatment to last follow-up.

MICROPERIMETRY

Microperimetry was performed with a SLO (Rodenstock Instruments GmbH, Model 101, Ottobrun-Riemerling, Germany). The SLO is a Class 1 Laser appliance and complies with laser protection regulations DIN VDE 0837 and IEC 825. This lowest laser classification is achieved because the laser beam is constantly scanning the retina and does not remain static on the same spot. Safety shutdown security is in place for failure of the scanning mechanism or excessive duration of examination.

Micoperimetry is similar to conventional perimetry in that it is a psychophysical test. That is, a stimulus is presented and the patient responds if the stimulus is recognized. Except for control patients, all patients tested had clinically defined amblyopia. All test points were applied in the macular region. The testing strategy is described below.

Definitions

Threshold was defined as the least intense stimulus which elicited a reliable recognition response. The threshold for a given eye may or may not be in the foveal area. During testing, threshold was defined as the stimulus level at which the patient recognized approximately 50% of the presented stimuli. Testing was begun at a level determined empirically to be recognized by most patients. The intensity was reduced until the patient could no longer recognize a stimulus and then the stimulus intensity was increased until approximately 50% of delivered stimuli were recognized. The location of greatest sensitivity and the threshold level in any given eye may be quite different in an individual patient from that point in the fellow eye, which may be centered on the fovea. For example, the point of greatest retinal sensitivity in a patient with a relative scotoma may be more distal from the fovea than the most sensitive point in the fellow eye. It follows that the entire macular area of an eye may have a higher threshold than that of the fellow eye and itself contain an absolute or relative scotoma.

An **absolute scotoma** was defined as a group of contiguous points in the macular area where the brightest of stimuli failed to elicit a recognition response. This corresponded to stimuli at 0 dB, which was the brightest stimulus deliverable.

A *relative scotoma* was defined as tested points in a definable contiguous area in the macula where a brighter stimulus was required to elicit recognition than the intensity required for recognition in areas bordering it on all sides. That is, points outside the scotomatous area more distal to the fovea were more sensitive (required a less bright stimulus) than were points closer to the fovea.

Relative scotomata differ in “density,” that is, the level of stimulus intensity (dB) required for recognition. In most patients with a relative scotoma, the sensitivity to recognition was uniform throughout the scotomatous region and a second relative scotoma was not identified. However, there were patients who demonstrated both an absolute scotoma and a surrounding relative scotoma. In those few patients, scotoma area was considered as that encompassed by the relative scotoma.

Testing

In SLO microperimetry, the retina is viewed at all times during the testing by way of an infrared laser (780 nm), at a background intensity of 10 candela/m² that is hardly perceptible by the patient. The examiner monitors the patient’s macula as a gray-scale image in real time on a computer monitor (Figure 1).



FIGURE 1

Scanning laser ophthalmoscope (SLO) testing. In a dimly lit room, the patient’s chin and forehead are positioned to allow the subject to view the SLO screen (left). The examiner views the macula, in real time, to monitor fixation, deliver stimuli, and map scotomata (right).

The patient is instructed to fixate on an illuminated cross 1.0-degree in size presented in the center of the field. The fixation cross is also visible to the examiner on the monitor. It is assumed that the localization of the fixation cross represents the patient’s preferred retinal locus of fixation. The examiner can also visualize whether this coincides with the anatomic foveal area. A reference point on the retina (for example, the intersection of two prominent blood vessels) is set to allow compensation for patient eye movements. If fixation changes, accurate centration of the macular image can be maintained and stimulus test points accurately registered.²³ Thus, the examiner can assess, by direct and continuous real-time observation, the patient’s stability and locus of fixation. As a result, a stimulus was not presented unless the patient was fixating properly. Hence, the concept of “fixation loss,” as is used as a measure of reliability in automated perimetry, does not apply in that stimuli were not presented if the patient was not properly fixating.

The stimulus was presented directly on the retina by a Helium-Neon (HeNe) laser (545 nm). A stimulus of 10 minutes of arc (50 μ m) was used. The stimulus could be graded in intensity and was presented for 100 ms, thus generating a static, rather than kinetic, perimetry assessment. The instrument’s stimulus intensity range is from a brightest possible intensity of 0 dB to the dimmest stimulus of 40 dB and is adjustable in steps of 1 dB. Patients were allowed 2.0 seconds to respond. When the stimulus was recognized, the patient pressed a toggle switch to register fixation.

When a positive response was made, or 2.0 seconds had transpired, the retinal image was frozen and the data point registered on the macular image in the precise location where it was delivered. The previously designated anatomical reference point then allowed each stimulus to be marked on the overlay in its exact location relative to other stimuli.

Stimuli presented are shown on the retinal image in true size and are color-coded for intensity. Stimuli are also shape-coded to represent whether or not the stimulus was detected. Filled circles represent positively recognized test points. An open triangle marked a missed test point.

Initial testing was begun with a 19 dB stimulus, which was an intensity empirically determined to be detectable by most subjects. The right eye was always tested first. The stimulus was first presented in close proximity to the fixation cross. Several points in this area were tested to determine whether the patient responded positively or failed to respond. If the patient failed to respond, the test area was expanded centrifugally to determine if there was a macular area in which the stimulus was detected. That is, testing addressed whether the patient responded to a 19-dB stimulus in a macular area more distal from the central macula. If no areas of greater sensitivity were identified, the stimulus intensity was increased and the above strategy repeated.

If positive responses were noted in an area not at the point of fixation, the stimulus intensity was reduced to determine threshold at that location (see definition above). This, then, represented a scotoma border. Numerous points were then tested in and out of the presumed scotoma to define its borders and size. This process was continued until a scotoma could be mapped and outlined as accurately as possible, much like scotoma mapping is performed with Goldmann kinetic perimetry.

If a definable scotomatous region could be identified, the stimulus intensity was increased within the scotoma borders until recognition to determine the "depth" of the scotoma. That is, the intensity of a stimulus necessary to evoke a response within the scotoma was determined. This stimulus intensity was then used to "re-map" the scotoma borders. Although uncommon, it was possible that a relative scotoma of greater "depth" might lie within a relative scotoma of lesser "depth" or an absolute scotoma might lie within a relative scotoma.

If there was a positive response to a 19-dB stimulus centrally, several points were tested more distally to determine if this level of sensitivity was uniform throughout the macula. Then stimulus intensity was decreased and the localization method described above was repeated. Such testing performed as the stimulus intensity was reduced might reveal a relative scotoma, but one requiring a less intense stimulus to discover and map than those that might be uncovered with the original 19-dB stimulus. This testing pattern was performed until the subject failed to recognize any stimuli presented. The stimulus intensity was then gradually increased until approximately 50% positive response rate was reached. This was the subject's threshold, as defined above. This method was used to examine each quadrant unless scotoma mapping already encompassed each quadrant.

Using the above strategy, the number of points necessary to thoroughly test a patient varied widely among patients, depending on the presence or absence of a scotoma, its borders, and depth. For example, a subject in which a scotoma was not found could be tested for threshold and the macula scanned for sensitivity in a much shorter time than a patient with a complex scotoma shape and size. Measurements in each patient typically took 5 to 10 minutes per eye.

Retesting of missed points was performed to determine reliability. If retesting confirmed the initial finding, the examination continued. If not, further testing at that point was performed for accuracy in terms of scotoma size and stimulus intensity required for recognition. Because the test points are applied while viewing a real-time image of the macula, precision of retest points was very high. However, such a high magnification view demonstrated that "steady" fixation does not mean "motionless" fixation when viewed at the microscopic level. Using anatomical landmarks, reapplication of a stimulus was typically very precise and within the range of no more than one-half stimulus width.

The mapping of scotomata thresholds, size, and depth could be done with stimulus variations of 1.0 dB. However, the final instrument printout only presents color-coded data points that span 5.0 dB; two same color points on the printout could be up to 5.0 dB different in intensity. Hence, scotoma boundaries were mapped and recorded as to stimulus intensity as the SLO was being performed, and not strictly from printed data, so as to allow as accurate a mapping as possible (see legend, Figure 2).

The retinal images, with scotomata mapped, were digitally scanned and converted to bit-map form. The area was measured using AutoDesk Architectural Desktop 3.3 software (Autodesk, Inc, San Rafael, California). Data were expressed as arc-min² based on a projected calibration image from the SLO.

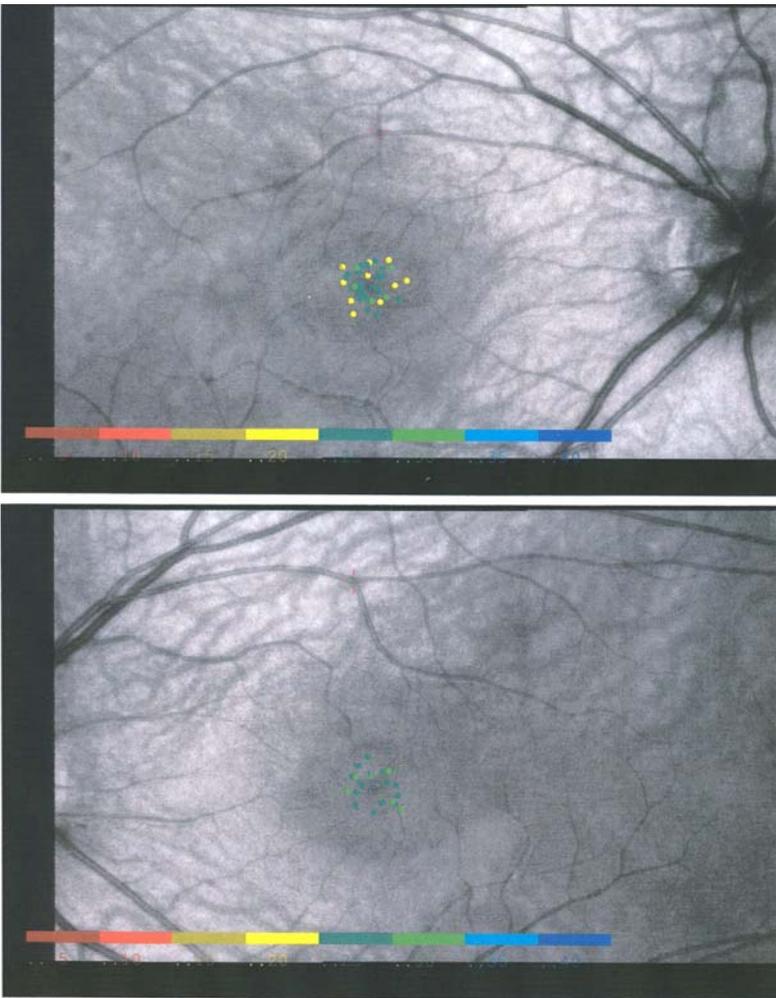
STATISTICAL METHODS

Data is presented as mean \pm standard deviation. Data analysis was performed using Minitab Release 14 statistical software (Minitab, Inc, State College, Pennsylvania). Comparisons between eyes of individual patients and comparisons in the same eye pretreatment and posttreatment were made using the paired *t* test. Comparisons between groups were analyzed with the two-sample *t* test. Correlations between variables were assessed with the Pearson correlation coefficient test. A probability of less than 5% ($P < .05$) was considered statistically significant.

RESULTS

DEMOGRAPHICS

A total of 56 patients were included (Table 1). Ten were control patients. The other 46 patients comprised two groups, based upon diagnosis: anisometric amblyopia ($n = 26$) and strabismic amblyopia ($n = 20$) (Table 1.) Twenty-five were male; 31 were female. Ages at time of SLO testing ranged from 66 to 146 months with a mean of 104.1 ± 20.2 months.

**FIGURE 2**

SLO record of a control patient. The patient was instructed to fixate on an illuminated central cross. A reference marker (red cross) was marked at a prominent vessel crossing to allow all test points to be recorded in precise register on the image. After determining threshold sensitivity, the macula was scanned for scotomatous areas. Scanning of the right eye (top) was started at 19 dB (yellow). When no scotoma was identified more peripherally, stimulus intensity was lowered to determine threshold and testing for scotomatous areas repeated. Based upon the threshold determined for the right eye, scanning of the left eye (bottom) was started at lower stimulus intensity (dark green). Stimulus intensity is greater at lower numerical values (red) and lessens in intensity as numerical values increase (brown, yellow, green, blue). Each colored bar represents a 5-dB range but stimuli could be increased in 1.0-dB steps.

TABLE 1. DEMOGRAPHIC AND TREATMENT CHARACTERISTICS OF ANISOMETROPIC OR STRABISMIC AMBLYOPIA PATIENTS AND CONTROL PATIENTS*

VARIABLE	ANISOMETROPIA	STRABISMUS	CONTROL
N	26	20	10
Male:Female	9:17	9:11	7:3
Age start (months)	66.5 ± 22.2	62.7 ± 29.6	NA
Follow-up (months)	47.8 ± 26.4	49.4 ± 25.1	NA
Age SLO (months)	104.0 ± 19.1	101.3 ± 19.3	110.0 ± 25.1
Amblyopic eye OD:OS	10:16	8:12	NA
Treatment duration (months)	20.5 ± 12.6	20.4 ± 12.2	NA

NA = not applicable; SLO = scanning laser ophthalmoscope.

*Values expressed as mean ± standard deviation.

CONTROL PATIENTS

Ten patients (seven male, three female) served as control patients who underwent SLO testing (Table 1). Each patient had normal best-corrected visual acuity, ocular alignment, binocularity, stereopsis, and normal anatomy. None had any prior ophthalmologic intervention other than spectacle wear for myopia in three patients. All were healthy with no confounding medical problems that might affect performance of the clinical or SLO examination.

The mean age of the control group at time of SLO testing was 110.0 ± 25.1 months, which was not statistically significantly

different from the 26 anisometropic amblyopia patients tested ($P = .51$, two-sample t test) or the 20 strabismic amblyopia patients ($P = .35$, two-sample t test).

Using the SLO, threshold was determined and the central macular area studied for scotomatous regions. Threshold sensitivity at the SLO was 26.0 ± 3.9 dB, with a range of 18 to 31 dB. No scotomatous areas were found in either eye of any of the 10 control patients.

The SLO images of a control patient are seen in Figure 2.

ANISOMETROPIC AMBLYOPIA PATIENTS

Twenty-six patients (nine male, 17 female) with anisometropic amblyopia were treated for amblyopia and tested with the SLO (Table 1). The mean age at which amblyopia was diagnosed and treatment begun was 66.5 ± 22.2 months, with a range of 24.0 to 113.0 months. Follow-up averaged 47.8 ± 26.4 months (range, 8 to 98 months). Mean age at SLO testing was 104.0 ± 19.1 months with a range of 66 to 142 months. The right eye was the amblyopic eye in 10 patients and the left eye in 16 patients. The mean difference in the refractive error between the amblyopic eye and the fellow eye, expressed as spherical equivalent, was 2.68 ± 1.76 diopters.

The mean visual acuity in the amblyopic eye at the start of treatment was LogMAR 0.65 ± 0.27 (approximate Snellen equivalent, 20/90) with a range of 0.30 to 1.30 (Table 2). The mean acuity in the fellow, nonamblyopic eye was LogMAR 0.10 ± 0.12 (Snellen equivalent, 20/25). The mean pretreatment acuity difference between the amblyopic eye and the fellow eye was 5.53 ± 2.41 LogMAR lines (range, 2.0 to 11.0 lines). The mean acuity in the amblyopic eye after treatment was LogMAR 0.30 ± 0.23 (Snellen equivalent, 20/40), reflecting an improvement of 3.51 ± 2.29 LogMAR lines, on average (range, 0 to 9 lines; $P = .000$, paired t test, Figure 3). Acuity in the nonamblyopic eye posttreatment was LogMAR 0.02 ± 0.04 (Snellen equivalent, 20/21), with a change of 0.84 ± 1.35 lines from pre-treatment (range 0.0 – 4.77 lines). This was also a statistically significant improvement ($P = .002$, paired t -test), although the average improvement in visual acuity was less than one LogMAR line.

TABLE 2. VISUAL ACUITY DATA AND SCANNING LASER OPHTHALMOSCOPE CHARACTERISTICS OF ANISOMETROPIC AND STRABISMIC AMBLYOPIA PATIENTS*

VARIABLE	ANISOMETROPIA	STRABISMUS
Number of patients	26	20
Visual acuity (LogMAR) (Snellen equivalent)		
Amblyopic eye pretreatment	0.65 ± 0.27 (20/90)	0.48 ± 0.15 (20/60)
Amblyopic eye posttreatment	0.30 ± 0.23 (20/40)	0.25 ± 0.13 (20/36)
Nonamblyopic eye pretreatment	0.10 ± 0.12 (20/25)	0.10 ± 0.08 (20/25)
Nonamblyopic eye posttreatment	0.02 ± 0.04 (20/21)	0.06 ± 0.05 (20/23)
Interocular acuity difference (LogMAR lines)		
Pretreatment	5.53 ± 2.41	3.81 ± 1.47
Posttreatment	2.86 ± 2.26	1.97 ± 1.24
LogMAR lines improved		
Amblyopic eye	3.51 ± 2.29	2.35 ± 1.81
Nonamblyopic eye	0.84 ± 1.35	0.50 ± 0.70
Threshold (dB)		
Amblyopic eye	17.8 ± 3.9	17.3 ± 5.8
Nonamblyopic eye	22.5 ± 2.8	21.6 ± 3.3
Scotoma area (arc-min ²)		
Amblyopic eye	162.5 ± 178.7	157.4 ± 171.6
Nonamblyopic eye	42.2 ± 46.2	70.3 ± 77.0

*Values expressed as mean \pm standard deviation.

The mean posttreatment visual acuity difference between the amblyopic and the nonamblyopic eye was 2.86 ± 2.26 lines (range, 0.0 to 9.0 lines). This is significantly different from the pretreatment interocular visual acuity difference ($P = .000$, paired t test), reflecting an average improvement of interocular visual acuity difference of 2.71 ± 2.06 LogMAR lines (Figure 4).

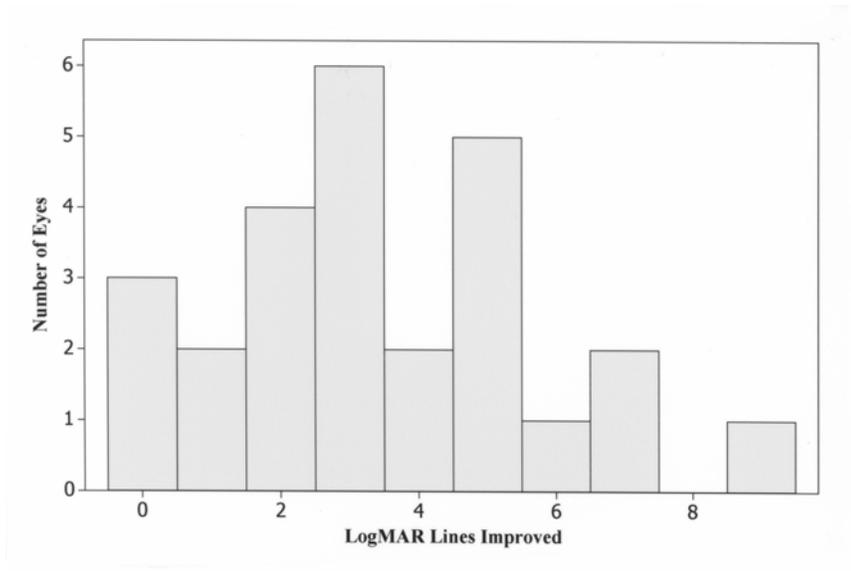


FIGURE 3

Histogram of LogMAR lines improved after amblyopia treatment in anisometric patients.

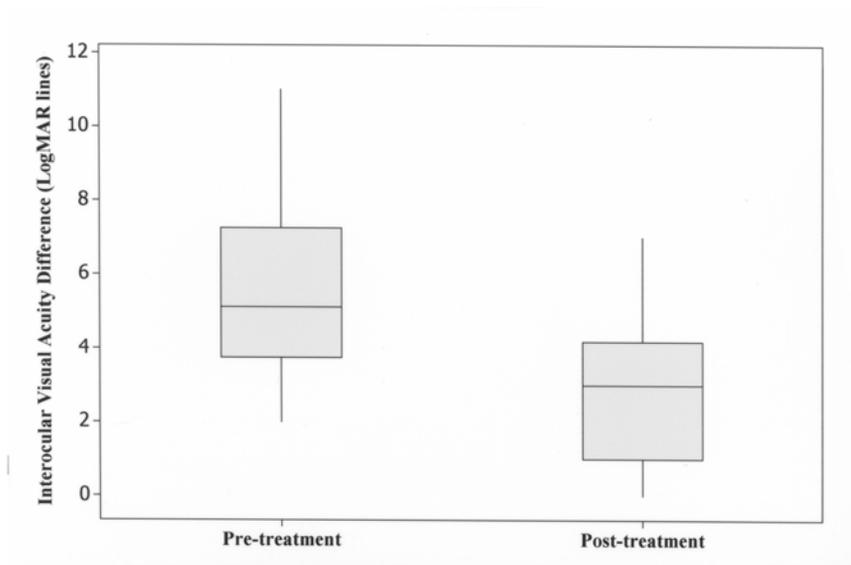


FIGURE 4

Boxplot of interocular visual acuity difference between the amblyopic and nonamblyopic eyes pretreatment (left) and posttreatment (right) in patients with anisometric amblyopia. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

Treatment duration averaged 20.5 ± 12.6 months (range, 6.0 to 51.0 months, Table 1). Not all treatment was continuous; total treatment duration includes the sum of treatment periods in cases where treatment was discontinued but then restarted. Thirteen of the 26 patients required retreatment. Eighteen patients had measurable stereopsis. Six of these patients had stereopsis of 50 seconds of arc or better.

Threshold sensitivity averaged 17.8 ± 3.9 dB (range, 9 to 24 dB) in the amblyopic eye and 22.5 ± 2.8 dB (range, 17 to 27 dB) in the nonamblyopic eye of these anisometric patients. (Table 2, Figure 5). (Recall that a lower threshold value corresponds to a light stimulus of greater intensity). Threshold for the nonamblyopic eye was significantly different from the control patients ($P = .002$, two-sample t test). Threshold sensitivity in the amblyopic eyes was significantly different from the matched nonamblyopic eye ($P = .000$, paired t test) and from control threshold levels ($P = .000$, two-sample t test). However, a correlation between the threshold in the amblyopic eye and that in the nonamblyopic eye did not reach a statistically significant level ($P = .094$, Pearson correlation). That is, eyes with reduced sensitivity in the amblyopic eye did not all have a commensurately reduced sensitivity in the nonamblyopic eye.

In 25 of 26 patients, a scotoma was measured in the amblyopic eye. The mean scotoma area was 162.5 ± 178.7 arc-min² with a range of 0.0 to 512.5 arc-min² (Table 2). Interestingly, 20 of the 26 patients had a scotoma in the fellow, nonamblyopic eye. Six patients did not show a scotoma in the fellow eye. The mean scotoma size, including the six patients not showing a scotoma, was 42.2

$\pm 46.2 \text{ arc-min}^2$ (range, 0 to 150.2 arc-min^2). Average scotoma size, eliminating the six patients who did not have a scotoma, was $54.8 \pm 45.5 \text{ arcmin}^2$ (range, 4.95 to 150.2 arc-min^2). The SLO images of two patients with anisometropic amblyopia with scotomata areas delineated are shown in Figures 6 and 7.

As a group, the area of the scotoma in the amblyopic eye was, on average, 3.9 times larger than the scotoma, if any, in the fellow eye ($P = .001$, paired t test, Figure 8).

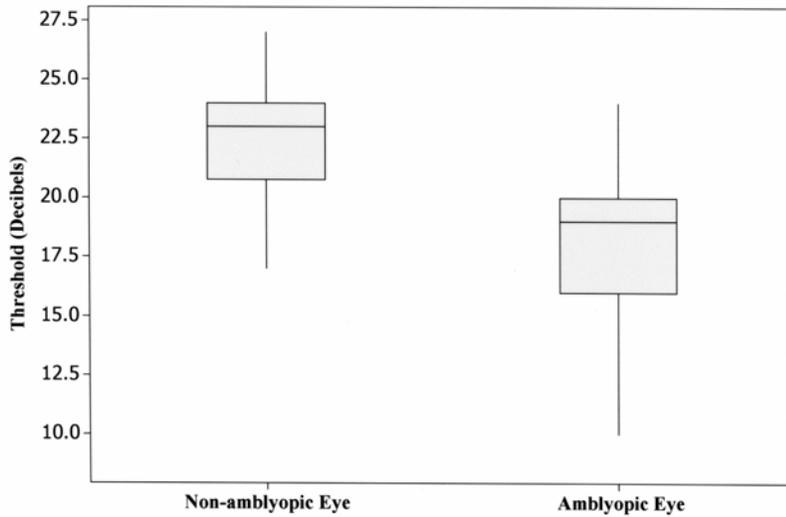


FIGURE 5

Boxplot of threshold sensitivity in nonamblyopic (left) and amblyopic (right) eyes of patients with anisometropic amblyopia. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

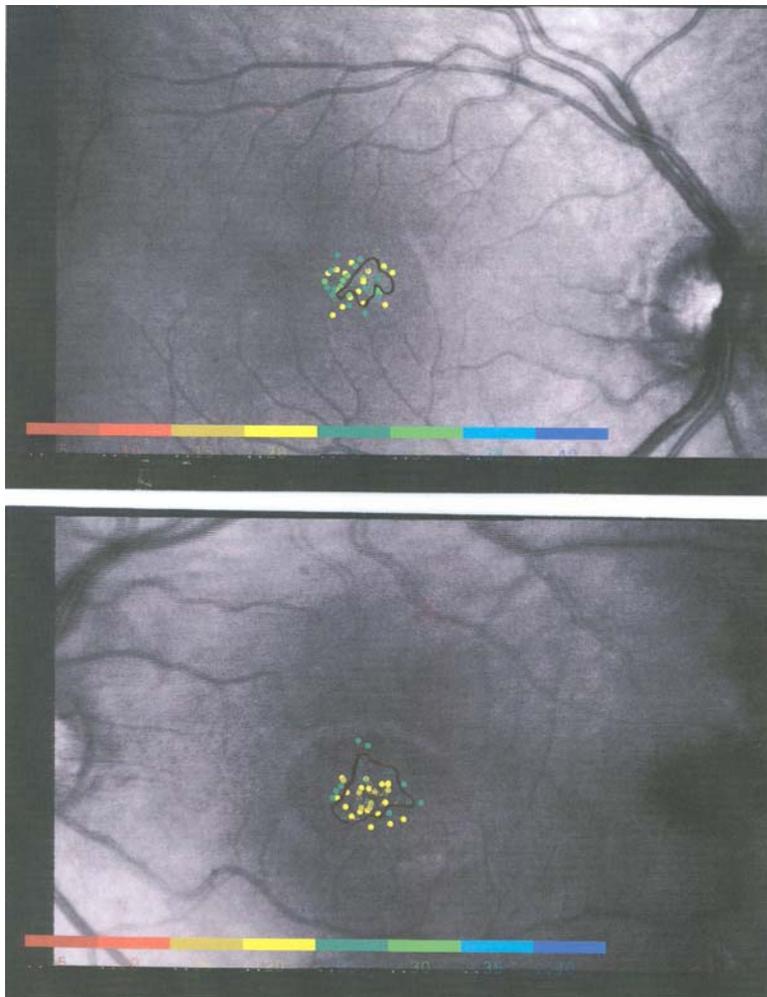


FIGURE 6

SLO image of a patient with anisometropic amblyopia. Testing was started in the right eye (top) with a 19-dB stimulus (yellow). Once threshold was obtained (see “Methods” section), the macula was tested for presence of a scotoma. If a scotoma was identified, its borders were determined. Missed points (open triangles) surrounded by recognized points (filled circles) localized scotoma borders. In the left eye (bottom), a larger scotoma was identified and mapped at a brighter stimulus intensity than that needed in the right eye. Stimulus intensity could be varied in 1.0-dB steps, but a single color code encompassed a 5.0-dB range. Hence, two points of the same color on the final printout could vary up to 5.0 dB. Scotoma borders are delimited as the test progresses. This patient had 20/20 visual acuity in the right, nonamblyopic eye before and after treatment. The left, amblyopic eye had a pretreatment visual acuity of 20/60 and improved, with treatment, to 20/20. This patient demonstrated 40 seconds of arc stereopsis.

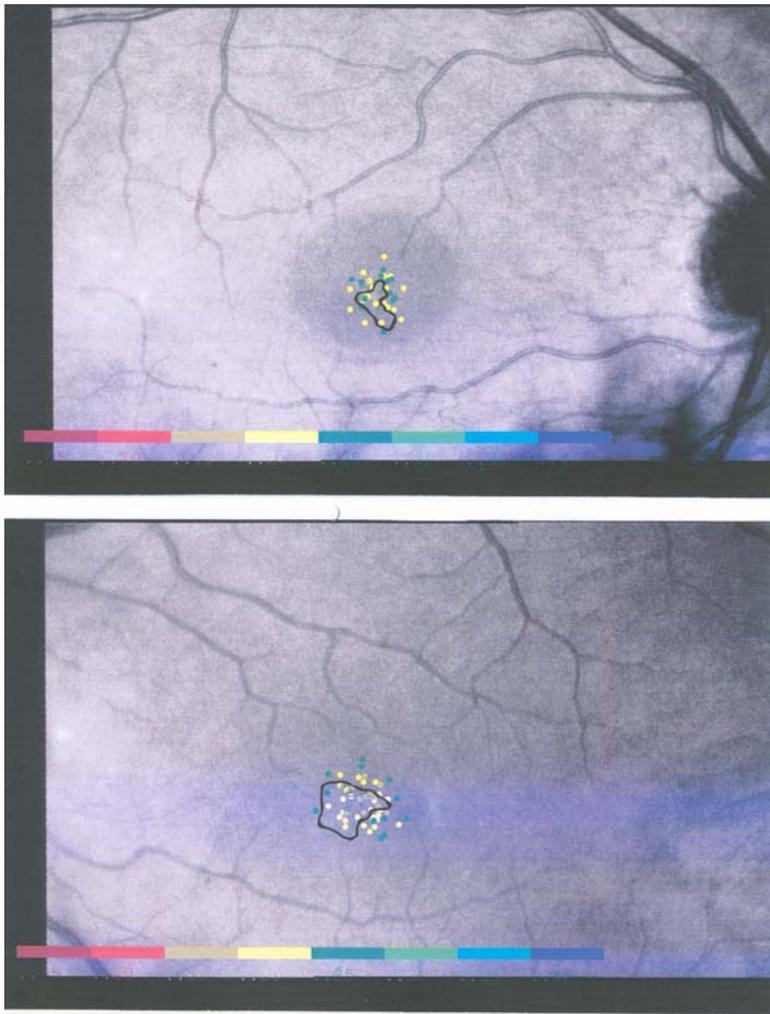


FIGURE 7

SLO image of a patient with anisometropic amblyopia. The right (top) nonamblyopic eye had a pretreatment visual acuity of 20/30, which, by treatment end, had improved to 20/20. The left (bottom) amblyopic eye visual acuity improved from 20/60 to 20/20 with treatment. This patient demonstrated 40 seconds of arc stereopsis.

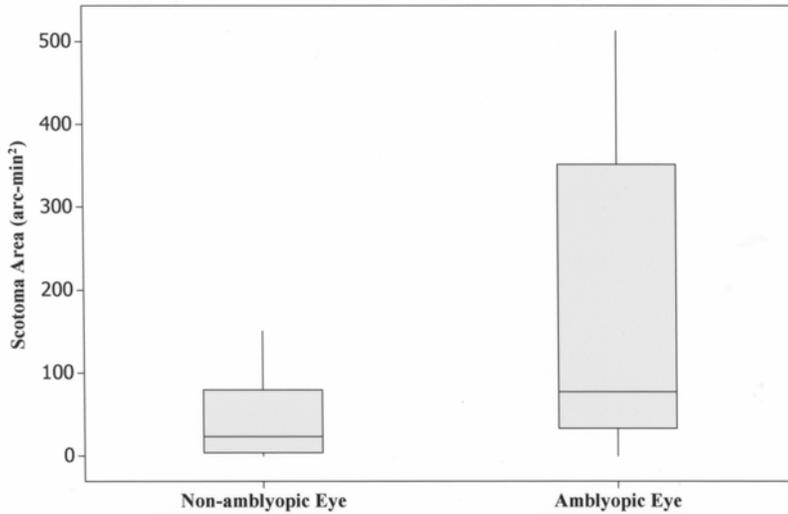


FIGURE 8

Boxplot of the scotoma areas of the nonamblyopic (left) and amblyopic (right) eyes of anisometropic patients. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

Of only those patients with a scotoma in the fellow eye (20/26), the scotoma in the amblyopic eye was, on average, 3.7 times larger than the scotoma in the fellow eye ($P = .002$). This includes five patients where the scotoma in the fellow eye measured larger than that in the amblyopic eye, but was mapped at a lower stimulus intensity than that necessary to evoke a response in the amblyopic eye (ie, the stimulus to elicit a response in the fellow eye was much dimmer than that necessary in the amblyopic eye). There was a

correlation between the scotoma size in the amblyopic eye and that in its fellow eye ($P = .048$, Pearson correlation). That is, patients with larger scotomata in the amblyopic eye had, on average, a larger scotoma in the fellow eye.

One patient did not have an identifiable scotoma in either the amblyopic or the nonamblyopic eye. There were no distinct clinical features of this patient that differed from the group as a whole. Visual acuity was 20/20 in the nonamblyopic eye, and in the amblyopic eye acuity improved from 20/40 to 20/20. Stereopsis was 50 seconds of arc.

Several other factors were correlated in a statistically significant relationship. There was a significant correlation between the visual acuity of the amblyopic eye prior to treatment and the acuity in that eye at the end of treatment ($P = .002$, Pearson correlation; Figure 9). Similarly, there was a significant correlation between the difference in visual acuity between the eyes in a patient prior to treatment (expressed as LogMAR lines), and the difference between the eyes at the end of treatment ($P = .001$, Pearson correlation), as well as the number of LogMAR lines of improvement ($P = .047$, Pearson correlation). However, although those eyes with denser amblyopia prior to treatment may have shown a greater overall improvement in LogMAR lines after treatment, eyes with poorer visual acuity at the start of treatment persisted with lesser acuities at the cessation of treatment.

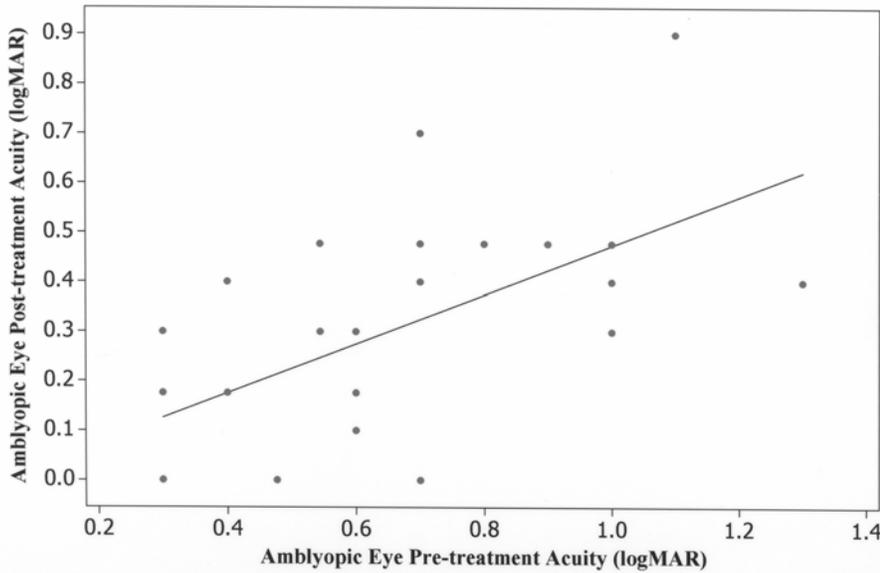


FIGURE 9

Scatterplot of visual acuity pretreatment and posttreatment in anisometric amblyopia patients. Eyes with poorer pretreatment visual acuities had poorer posttreatment visual acuities ($P = .002$, Pearson correlation). A best-fit regression line is shown.

Data was analyzed to determine if there were any features of the SLO findings that correlated with amblyopia patient clinical outcomes. There was a correlation between amblyopic eye scotoma area and the interocular visual acuity difference before treatment ($P = .034$) and after treatment ($P = .000$, Pearson correlation). This correlation also existed in the nonamblyopic eye before ($P = .048$) and after treatment ($P = .003$, Pearson correlation). That is, scotomata areas in the amblyopic and nonamblyopic eyes were larger in patients with greater interocular visual acuity differences before treatment and after treatment.

There were significant correlations between the scotoma size in the nonamblyopic eye and the visual acuity of the amblyopic eye. Scotoma size in the nonamblyopic eye was larger in those patients whose amblyopic eye visual acuity was poorer before treatment ($P = .035$) and after treatment ($P = .003$, Pearson correlation).

As a group, patients with larger amblyopic eye scotomata had a poorer LogMAR visual acuity at the start ($P = .034$) and end of amblyopia treatment ($P = .001$, Pearson correlation). Such a correlation did not exist in the nonamblyopic eye, where scotoma size was not correlated with pretreatment ($P = .490$) or posttreatment visual acuity ($P = .285$).

To further evaluate whether SLO findings correlated with amblyopia clinical features, two subgroups of patients were assessed. One subgroup comprised the seven patients who had the best final visual acuity in the amblyopic eye, and the other subgroup comprised the seven patients who showed the poorest final amblyopic eye visual acuity. (Seven patients were chosen because five patients had the “third poorest” final visual acuity in the amblyopic eye.)

In the two subgroups of patients with anisometric amblyopia, those who showed the poorest final visual acuity in the amblyopic eye (LogMAR 0.57 ± 0.17 lines, $n = 7$; Snellen equivalent 20/74) had significantly larger macular scotomata in both the amblyopic and nonamblyopic eye than those found in the patients whose amblyopic eye final visual acuity was among the best (0.03 ± 0.05 , $n = 7$; Snellen equivalent 20/21). Scotoma area in the amblyopic eye measured 325 ± 192.4 arc-min² in the poorer outcome patients vs 60.0 ± 67.1 arc-min² in the better outcome patients ($P = .011$). Similarly, scotoma area in the nonamblyopic eye of the poorer outcome patients (68.2 ± 57.8 arc-min²) was greater than that measured in the nonamblyopic eye of patients with better outcomes (12.56 ± 11.86 arc-min², $P = .047$).

No such relationship existed between SLO threshold and clinical outcomes in the two subgroups. Threshold in the amblyopic eye of the better outcome patients (17.4 ± 2.8 dB) was not significantly different from that found in patients with poorer amblyopic eye

final visual acuity (17.0 ± 5.5 dB, $P = .859$). Threshold was also not significantly different between the nonamblyopic eye of the better outcome (22.0 ± 1.8 dB) vs the poorer outcome patients (23.6 ± 3.0 dB, $P = .266$).

Data was similarly analyzed for the subgroups of patients who showed the greatest number of lines of visual acuity improvement in the amblyopic eye (6.85 ± 1.42 LogMAR lines, $n = 5$) vs the subgroup with the fewest lines of improvement (0.16 ± 0.29 LogMAR lines, $n = 5$). There did not appear to be any features of the SLO data that correlated with visual acuity outcome in terms of number of LogMAR lines improved. Between the two subgroups, there was no difference in threshold in the amblyopic eye ($P = .952$) or nonamblyopic eye ($P = .363$). Nor was there any difference between patients who improved the greatest or fewest number of lines visual acuity in terms of the scotoma size of the amblyopic eye ($P = .847$) or nonamblyopic eye ($P = .754$).

As a group, scotoma area in the amblyopic or nonamblyopic eye was not correlated with level of stereopsis. Patients who had high levels of stereopsis (50 seconds of arc or better) were compared to those who showed no stereopsis. Six patients had excellent stereopsis (5 at 40 seconds of arc; 1 at 50 seconds of arc). Eight anisometropic patients had no stereopsis. Scotomata in both the amblyopic and nonamblyopic eyes were larger in those patients who had no stereopsis, although statistical significance did not reach the level of $P = .05$. Scotoma area in those patients with good stereopsis averaged 37.4 ± 33.4 arc-min² in the amblyopic eye and 10.9 ± 12.1 arc-min² in the nonamblyopic eye, whereas the scotoma areas in the amblyopic and nonamblyopic eyes of patients with no stereopsis averaged 209 ± 207 arc-min² ($P = .055$) and 58.2 ± 60.5 arc-min² ($P = .068$), respectively.

Patient age was not a factor in this study in terms of either response to amblyopia treatment or performance on SLO testing. There was no correlation between age and pretreatment or posttreatment visual acuity, number of LogMAR lines improved, or interocular visual acuity difference. This was true of both the amblyopic and the nonamblyopic eye. Similarly, there was no correlation between age and SLO results (threshold or scotoma area) in either the amblyopic or the nonamblyopic eye.

In summary, there was a correlation between the size of the amblyopic eye scotoma and the amblyopic eye visual acuity prior to initiation of amblyopia treatment and at the end of treatment. There was also a positive correlation between scotoma size and number of lines difference between the amblyopic eye and the fellow eye at the start and end of treatment. Eyes with larger amblyopic eye scotomata areas had commensurately larger scotomata in the fellow, nonamblyopic eye. Those patients whose amblyopic eye had better final visual acuities had smaller macular scotomata in the amblyopic and nonamblyopic eyes than did those patients whose final visual acuity was poorer.

STRABISMIC AMBLYOPIA PATIENTS

Twenty patients (nine male, 11 female) with strabismic amblyopia were treated clinically and evaluated with the SLO (Table 1). The mean age at which amblyopia was diagnosed and treatment begun was 62.7 ± 29.6 months (range, 15.0 to 129.0 months). Follow-up averaged 49.4 ± 25.1 months (range, 12.0 to 91.0 months). Mean age at SLO testing was 101.3 ± 19.3 months (range, 71.0 to 142.0 months). In eight patients the right eye was the amblyopic eye; in 12 patients the left eye.

Seven patients had accommodative esotropia, which was well controlled with spectacle correction, and surgery was unnecessary. Thirteen patients had either a nonaccommodative deviation or a mixed accommodative and nonaccommodative deviation for which surgery had been performed. In this latter group, only one patient was exotropic. The others were all esotropic. The preoperative deviation averaged 31.3 ± 9.5 prism diopters (range, 20.0 to 45.0 prism diopters). All patients in the strabismus group had a deviation of 10 prism diopters or less on alternate prism cover testing at final follow-up.

The visual acuity in the amblyopic eye at the start of treatment was LogMAR 0.48 ± 0.15 (Snellen equivalent approximately 20/60) with a range of LogMAR 0.18 to 0.70 (Table 2). The mean fellow eye pretreatment visual acuity was LogMAR 0.10 ± 0.08 (Snellen equivalent approximately 20/25), with a range of 0.0 to 0.3 LogMAR. The pretreatment visual acuity difference between eyes averaged 3.81 ± 1.47 LogMAR lines (range, 1.76 to 7.00 lines). After treatment, the visual acuity in the amblyopic eye had improved, on average, 2.35 ± 1.81 LogMAR lines (range, 0.00 to 6.00 lines; $P = .000$; Figure 10), yielding a posttreatment visual acuity of LogMAR 0.25 ± 0.13 (range, 0.10 to 0.48; approximate mean Snellen equivalent 20/36; Table 2). Fellow eye acuity posttreatment was LogMAR 0.06 ± 0.05 (range, 0.0 to 0.1; Snellen equivalent 20/23), reflecting a change of 0.50 ± 0.70 logMAR lines (range, 0.0 to 2.0 LogMAR lines; $P = .009$).

There was a significant difference between the interocular difference in visual acuity before treatment and after treatment. Prior to amblyopia therapy, the mean interocular difference was 3.81 ± 1.47 LogMAR lines. After therapy, this difference was 1.97 ± 1.23 LogMAR lines ($P = .000$, paired t test), reflecting an average improvement of interocular visual acuity difference of 1.85 ± 1.74 lines (range, 0.0 to 6.0 lines; Figure 11).

Treatment duration averaged 20.4 ± 12.2 months (range, 4.0 to 40.0 months), although not all treatment duration was continuous. In eleven patients amblyopia therapy needed to be repeated. Stereopsis was measurable in 10 patients, but all but two were poorer than 100 seconds of arc. One of the two patients achieved 40 seconds of arc stereopsis after strabismus surgery. The other measured 100 seconds of arc stereopsis.

Threshold sensitivity averaged 17.3 ± 5.8 dB (range, 0 to 24 dB) in the amblyopic eye and 21.6 ± 3.3 dB (range, 15 to 27 dB) in the nonamblyopic eye of these strabismic patients (Table 2). Threshold sensitivity was reduced compared to control patients in both the amblyopic eye ($P = .000$, two-sample t test) and the nonamblyopic eye ($P = .000$, paired t test). As was seen in anisometropic amblyopia patients, there was a significant difference in threshold sensitivities between the amblyopic and nonamblyopic eyes of the same patient ($P = .008$, paired t test, Figure 12). Also, there was a significant correlation between the two eyes, in that a lower

threshold level in the amblyopic eye correlated with a lower threshold level in the nonamblyopic eye ($P = .022$, Pearson correlation; Figure 13).

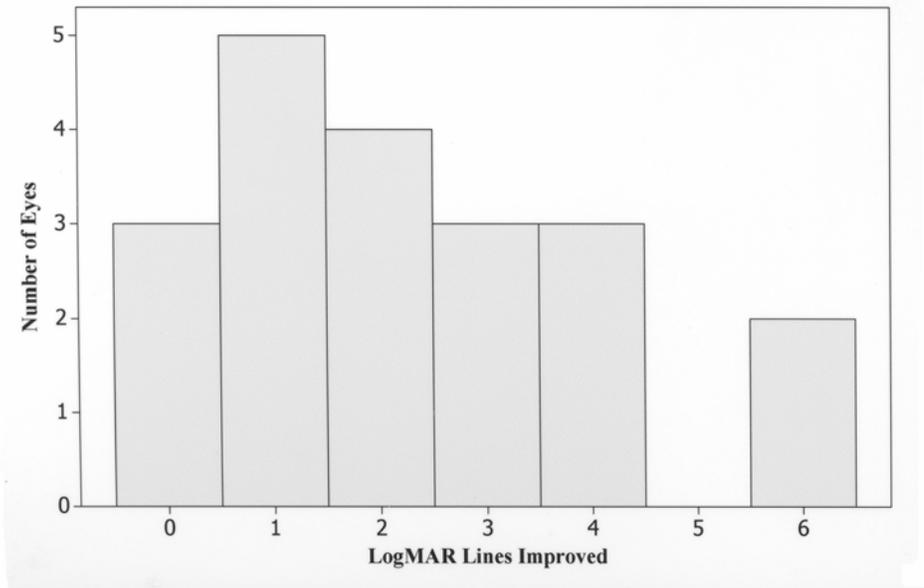


FIGURE 10
Histogram of LogMAR lines improved after amblyopia treatment in strabismic patients.

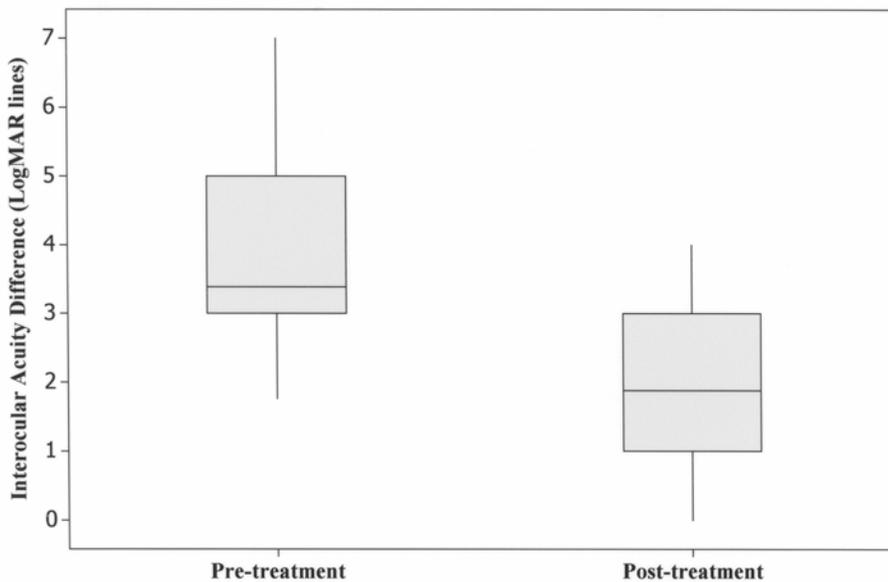


FIGURE 11
Boxplot of interocular visual acuity difference between the amblyopic and nonamblyopic eyes pretreatment (left) and posttreatment (right) in patients with strabismic amblyopia. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

In all 20 patients, a scotoma was found in the amblyopic eye, averaging 157.4 ± 171.6 arc-min² with a range of 23.3 to 699.6 arc-min² (Table 2). All 20 patients were also found to have a scotoma in the fellow eye, averaging 70.3 ± 77.0 arc-min² (range, 9.75 to 274.9 arc-min²). The SLO images of a patient with strabismic amblyopia are shown in Figure 14.

As a group, the area of the scotoma in the amblyopic eye was 2.23 times larger than that in the fellow eye ($P = .038$, paired t test; Figure 15). In three patients, the scotoma in the fellow eye was larger than that in the amblyopic eye, but in each case, the amblyopic eye required a greater stimulus intensity to evoke a response. There was not a correlation between scotoma size in the amblyopic and nonamblyopic eyes ($P = .426$, Pearson correlation).

Although there was not a significant correlation between the visual acuity in each amblyopic eye at the start of amblyopia treatment and the acuity in that eye after treatment ($P = .535$, Pearson correlation), there was a correlation between the visual acuity of the amblyopic eye before treatment and the number of lines of acuity improved by therapy ($P = .003$, Pearson correlation). This is not surprising in that it might be expected that those eyes with poorer initial visual acuity will show greater improvement, in terms of lines of acuity improved, than those eyes with better pretreatment acuity. Also, there was a correlation between the difference in the number of LogMAR lines between the amblyopic and fellow eyes and the number of LogMAR lines improvement with treatment ($P = .006$, Pearson correlation). That is, the greater the interocular acuity difference, the greater the improvement in LogMAR lines of visual acuity.

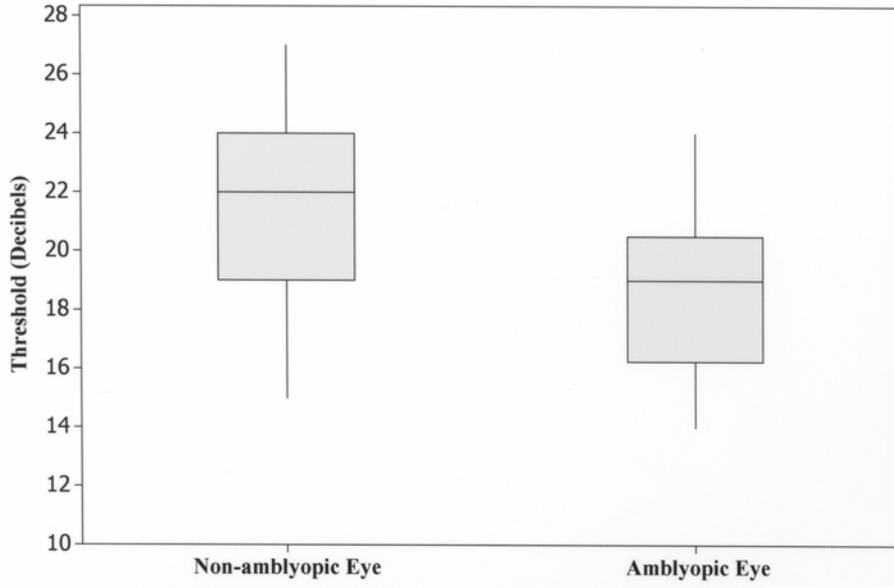


FIGURE 12

Boxplot of threshold sensitivity in nonamblyopic (left) and amblyopic (right) eyes of patients with strabismic amblyopia. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

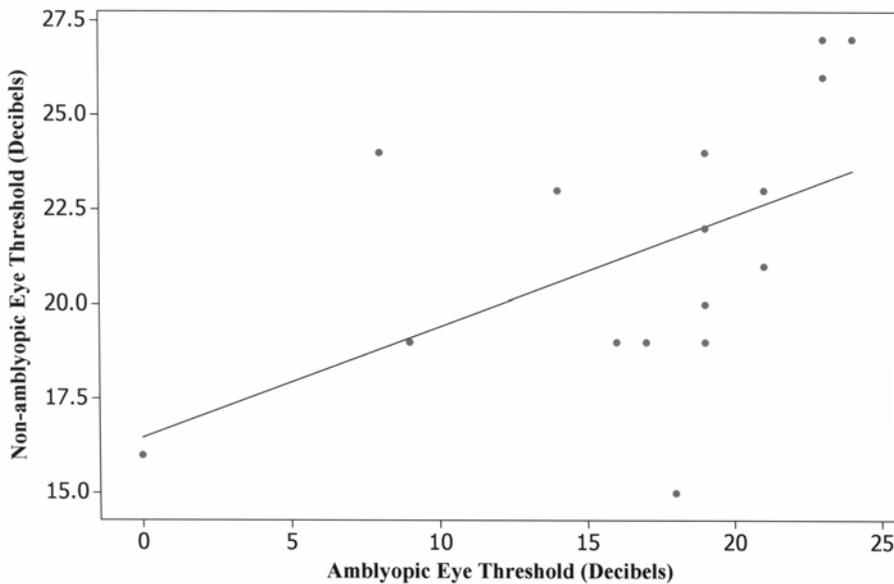


FIGURE 13

Scatterplot of the amblyopic eye and nonamblyopic eye thresholds. A best-fit regression line is shown ($P = .022$, Pearson correlation).

The amblyopic eye scotoma size was larger than that of the fellow eye, but there was no linear correlation between the two. That is, a larger scotoma in the amblyopic eye was not predictive of a larger scotoma in the fellow eye or vice versa ($P = .426$, Pearson correlation).

In the amblyopic eye, threshold level and scotoma size were not linearly related ($P = .720$, Pearson correlation). However, there was a statistical correlation between threshold sensitivity and scotoma area in the nonamblyopic eye. Patients who required a more intense stimulus for threshold detection were found to have larger scotoma areas ($P = .008$).

Data was analyzed to determine if there were any features of the SLO findings that correlated with the clinical findings of the patients with strabismic amblyopia. There was a significant correlation between the LogMAR line difference between the eyes at the start of treatment and the size of the amblyopic eye scotoma ($P = .002$, Pearson correlation) but not between scotoma size and interocular visual acuity difference after treatment ($P = .129$, Pearson correlation). There were no correlations between the scotoma area in the nonamblyopic eye and any visual acuity features of the amblyopic eye, including amblyopic eye pretreatment visual acuity ($P = .809$), posttreatment visual acuity ($P = .660$), or lines of acuity improved ($P = .915$, Pearson correlation).

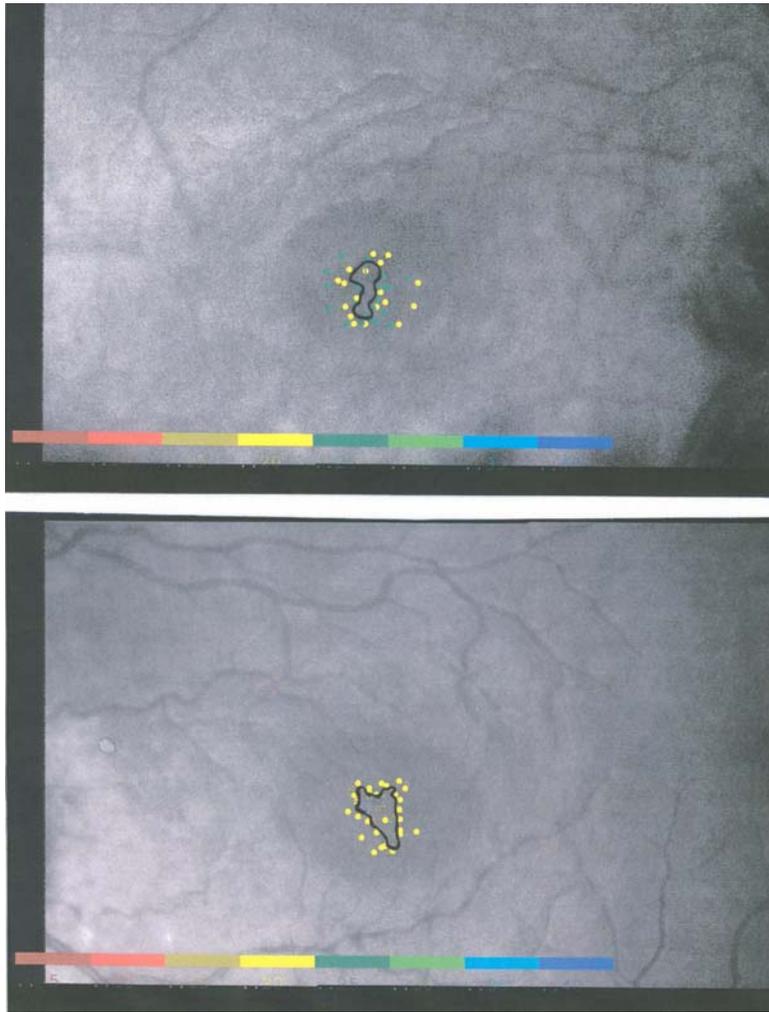


FIGURE 14

SLO images of a patient with strabismic amblyopia. After determining threshold, scotomata were delineated in the right, nonamblyopic eye (top) and left, amblyopic eye (bottom). This patient's visual acuity in the nonamblyopic eye was 20/25. The amblyopic eye visual acuity was 20/60 and did not improve with amblyopia treatment. The patient demonstrated no stereopsis.

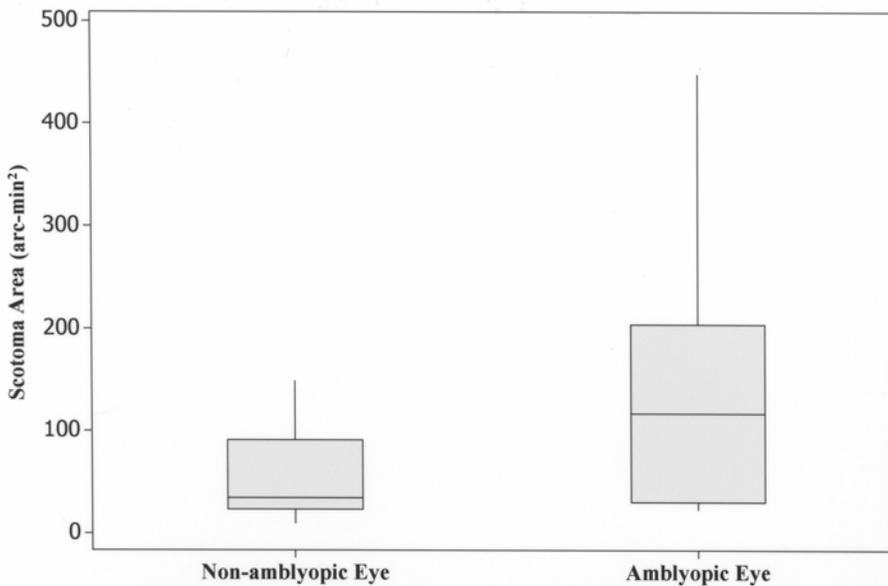


FIGURE 15

Boxplot of the scotoma areas of the nonamblyopic (left) and amblyopic (right) eyes of strabismic patients. The shaded box represents the middle 50% of observations, and the line in the shaded area indicates the median data value. The lines extending from the box indicate the lowest and highest values among the data.

The subgroup of the five patients with the best final visual acuity in the amblyopic eye (LogMAR 0.10 ± 0.0 , Snellen equivalent 20/25) was compared to the five patients whose amblyopic eye showed the poorest final visual acuity (LogMAR 0.41 ± 0.07 , Snellen equivalent 20/51). There was no significant difference in threshold sensitivity of the amblyopic eye of the patients with the best final acuity when compared to those whose final acuity was the poorest ($P = .50$, two-sample t test). Similarly, there was no difference between these subgroups when threshold sensitivity in the nonamblyopic eye was considered ($P = .085$, two-sample t test).

There was a greater difference in threshold sensitivity between the amblyopic and nonamblyopic eyes of patients with poorer final amblyopic eye acuity ($P = .004$, paired t test) as opposed to that difference in patients with better final acuity ($P = .178$, paired t test). That is, patients whose final visual acuity in the amblyopic eye was poorest after treatment had a greater difference in threshold sensitivity between the amblyopic and nonamblyopic eyes. No features of SLO scotoma sizes were found to correlate with final visual acuity outcome in the amblyopic eye for either the best or worst final acuity subgroup. Nor were any SLO findings correlated with stereopsis.

When the patients were subdivided into those five patients whose amblyopic visual acuity increased the greatest number of lines (4.84 ± 1.08 LogMAR lines) and those who had the fewest number of lines improvement (0.4 ± 0.55 LogMAR lines), no correlations were found among SLO results.

Otherwise, there were no significant correlations between the scotoma size in either the amblyopic eye or the fellow eye and the following: amblyopic eye acuity at start or end of treatment, fellow eye acuity at start or end of treatment, treatment duration, number of LogMAR lines improved with treatment, difference in acuity between the eyes at the end of treatment, age at which treatment was begun or ended, or age at which the SLO was performed.

Patient age did not appear to be an important factor in the response to amblyopia treatment. There was no correlation between age and pretreatment and posttreatment visual acuity, number of LogMAR lines acuity improved or interocular visual acuity. Age also did not appear to be a factor in SLO performance. No correlation was found between patient age and threshold in the amblyopic ($P = .532$) or nonamblyopic ($P = .088$) eye. Nor was age correlated to scotoma area in the amblyopic ($P = .291$) or nonamblyopic ($P = .605$) eyes.

COMPARISON OF ANISOMETROPIC TO STRABISMIC AMBLYOPIA

The findings of those patients with anisometropic amblyopia were compared and contrasted to those of strabismic amblyopia patients. Although the anisometropic patients were, on average, slightly older than the strabismic patients when diagnosis was made and treatment begun (66.5 months and 62.7 months, respectively), there were no significant differences between the two groups in terms of age at start of treatment ($P = .63$, two sample t test) or age at which treatment ended ($P = .72$, two sample t test, Table 2). The strabismic group had a longer average follow-up than the anisometropic group (49.4 months and 47.8 months, respectively), but this also was not significantly different ($P = .84$, two sample t test). Treatment duration was not significantly different between the two groups ($P = .98$). Nor was there a difference between the groups in terms of age at which the SLO was performed ($P = .64$, two sample t test).

More patients in the anisometropic group had some measure of stereopsis (69.2 %) than in the strabismic group (50%). However, only three strabismic patients reached a stereoacuity of 100 seconds of arc or better, whereas six of the anisometropic patients were 50 seconds of arc or better, five achieving 40 seconds of arc.

There was no difference between the groups in terms of the nonamblyopic eye visual acuity at the start of treatment ($P = .95$) and number of lines improved in the nonamblyopic eye ($P = .28$, two-sample t test). However, because the anisometropic group showed slightly greater improvement from treatment start to final follow-up, the difference between the groups reached statistical significance in terms of final visual acuity in the nonamblyopic eye ($P = .006$). Two qualifications are important. First, the difference in final visual acuities is quite small (anisometropic, LogMAR 0.015; strabismic, LogMAR 0.055; Snellen equivalents, 20/21 vs 20/23, respectively). Second, in some patients, the initial acuity was recorded using projected pictures. Not only might this acuity testing method be less precise than letter recognition, the patients were considerably younger at the entry point. Thus, the apparent statistically significant difference most likely has little or no clinical relevance.

In terms of the visual acuity in the amblyopic eye, there was a significant difference between the two groups at the start of treatment ($P = .009$), but not at final follow-up ($P = .314$, two-sample t test), although the mean acuity of the amblyopic eyes in the anisometropic group was poorer than the strabismic group at each time-point.

There was a significant difference between the two groups in terms of the number of LogMAR lines difference between the amblyopic and fellow eyes at the start of treatment ($P = .005$), but not at the end of follow-up ($P = .095$), with the anisometropic patients having a greater pretreatment LogMAR line visual acuity difference between the eyes (5.53 ± 2.41 LogMAR lines vs 3.81 ± 1.47 LogMAR lines, respectively). On average, the amblyopic eyes in the anisometropia group showed a greater LogMAR line improvement than those in the strabismic group (3.51 lines vs 2.35 lines), but this was not significantly different between the two groups ($P = .06$, two-sample t test).

Thus, although patients with anisometropic amblyopia had a lower visual acuity level in the amblyopic eye pretreatment and a greater interocular visual acuity difference between the amblyopic and the nonamblyopic eye, these eyes showed a significantly greater improvement with treatment such that amblyopic eye visual acuities of anisometropic and strabismic patients were not significantly different posttreatment.

There was no difference between the two groups for SLO threshold in the amblyopic eye ($P = .74$) or the fellow, nonamblyopic eye ($P = .31$). It is of note that in both anisometropic amblyopia and strabismic amblyopia patients, threshold stimulus intensity for recognition in both the amblyopic and nonamblyopic eyes was at greater light intensities than in control patients.

There was no difference between mean scotoma area in the nonamblyopic eye in anisometropic patients compared to strabismic patients (42.2 vs 70.3 arc-min², $P = .16$, two-sample t test), although the fellow eye scotoma in strabismic patients tended to be larger. Nor was there a difference between amblyopic eye scotoma areas in anisometropic patients (mean, 162.5 arc-min²) vs strabismic patients (mean, 157.4 arc-min²; $P = .92$). There was a difference between the two groups in terms of scotoma size related to stereopsis.

When anisometropic patients were subdivided based on stereopsis, those patients with better stereopsis has smaller macular scotomata in both the amblyopic and nonamblyopic eye than did those with no stereopsis. No such correlation existed among strabismic amblyopia patients.

In summary, among all features analyzed, the two groups were significantly different in only several areas: stereopsis (greater in the anisometropic group), visual acuity in the amblyopic eye pretreatment (poorer in the anisometropic group), posttreatment visual acuity in the nonamblyopic eye, and LogMAR lines different at start (greater difference in the anisometropic group) but not at final follow-up.

DISCUSSION

In this study, a group of patients that had been treated for anisometropic or strabismic amblyopia was evaluated with the SLO after reaching optimal visual acuity in the amblyopic eye. Forty-five of the 46 patients who were tested with the SLO showed a macular scotoma in the amblyopic eye. Forty of the 46 patients were found to have a relative scotoma in the fellow, presumably "normal," eye. In contrast, no scotoma was identified in either eye of any of 10 control patients.

SCANNING LASER OPHTHALMOSCOPY

Scanning laser ophthalmoscopy, developed in the late 1970s to 1980s, has shown increased clinical utility in the last 10 to 15 years. Its use has been shown to be of benefit in optic nerve analysis,^{12,13} retinal assessment of macular lesions,^{14,15} assessment of retinal foci that underlie metamorphopsia,¹⁶⁻¹⁸ and microperimetry,¹⁹⁻²¹ as was its use in this study.

The SLO uses a weak laser beam to scan the retina, generating a raster image of the retina that can be viewed on a monitor. Simultaneously, a HeNe laser (545 nm) can project a stimulus of variable size, intensity, and duration directly onto the retina. It is directed by the examiner, guided by a real-time view of the retina, including reference points set to control for eye or patient movement.²³ Pupillary dilatation is not required for macular viewing.

As a microperimetry tool, the SLO has been most extensively used in low-vision evaluation of patients with macular lesions, especially age-related macular degeneration.¹⁹⁻²¹ Affected patients may develop foveal scotomata, resulting in the development of an extrafoveal preferred retinal locus of fixation. The SLO allows the examiner to determine that portion of the retina the patient is using for fixation. If it is found that another retinal area provides greater sensitivity, the patient may be "trained" to refixate with this more sensitive retinal locus.

In this study, the SLO was used to assess for the presence, size and depth of scotomata in patients with amblyopia of various types and contrast these findings with a control group. This data, along with data acquired by typical examination assessment, was assessed overall and within groups based on amblyopia etiology, to evaluate whether any factors were associated with either amblyopia type or treatment outcome.

SCANNING LASER OPHTHALMOSCOPE EVALUATION OF AMBLYOPIA

Amblyopia was defined using generally accepted criteria; that is, in preverbal children, a strong fixation preference of one eye over the other or, in verbal children, the demonstration, using age-appropriate testing, of a two-line or greater visual acuity difference between the eyes. Patients were therapeutically addressed utilizing standard treatment modalities, including occlusion and/or atropine penalization. Eye muscle surgery was performed in those patients with a nonaccommodative strabismic deviation. Appropriate spectacle correction was instituted in patients with anisometropia or accommodative esotropia.

All Amblyopic Patients

Forty of the 46 patients evaluated showed an improvement in visual acuity in the amblyopic eye in response to treatment. In the other six patients, the visual acuity did not change from entry level: no amblyopic eyes showed a decrease in visual acuity. Twenty-four of 46 amblyopic patients required repeat treatment, in that, as amblyopia therapy was tapered or discontinued, the visual acuity worsened. In some patients for whom the diagnosis of amblyopia was based upon either fixation preference or initial visual acuity measurement using projected Allen pictures, once the patient had matured to the point of allowing more accurate visual acuity assessment, it was found that the amblyopia was not thoroughly treated and treatment was restarted.

As might be expected, a scotomatous defect was found in the amblyopic eye of almost all patients. Only one anisometropic patient did not have a recognizable scotoma in the amblyopic eye. While true physiologic mechanisms may underlie the variation in scotoma sizes, several factors may account for the range of values obtained. Primary among these is the fact that this is a psychophysical test being performed in children. Although children were selected based on their perceived ability to maintain steady fixation at the SLO, any such test in children is subject to some variability. Overall, the patients were felt to have performed the SLO very well. Mapping of the scotoma also lacks some precision, similar to that of Goldmann kinetic perimetry, in that this is a "best-fit" approach based upon patient response and examiner map of responses.

However, compared to other similar psychophysical tests, SLO microperimetry is extremely precise in terms of stimulus delivery location and centration of data on the final image. Because the macula is being viewed in real time while testing, a stimulus is not delivered unless the patient is seen to be fixating properly. Thus, there is no measure of "fixation loss" because a stimulus is not delivered if fixation is not central.

Interestingly, a scotoma was uncovered in the fellow "normal" eye of 40 of 46 patients. In the group as a whole, the scotoma size was, on average, more than 2.5 times greater in the amblyopic eye than the fellow eye. In the eight patients in whom the fellow eye

scotoma measured a greater area, however, the testing stimulus in the amblyopic eye was of greater intensity than that used in the fellow eye. Although this confounds the data somewhat, it was necessary to increase the stimulus threshold intensity for accurate measurement; this would only underestimate the mean difference between the two eyes.

Anisometropic Amblyopia Patients

Twenty-six of the study patients were diagnosed with anisometropic amblyopia. All but three of the patients with anisometropic amblyopia had improvement in visual acuity in the amblyopic eye with typical clinical treatment of amblyopia, averaging an increase of 3.51 LogMAR lines improvement. Although there may have been small variations in amblyopia treatment strategies employed among this group of patients, the level of improvement compares favorably to other studies.^{24,25} In the Pediatric Eye Disease Investigator Group (PEDIG) study comparing atropine penalization to occlusion,²⁵ visual acuity improved 3.16 LogMAR lines in the occlusion group and 2.84 LogMAR lines in the atropine group. This is similar to the overall improvement of 3.51 LogMAR lines in this study. It should be noted that the current study had broader initial amblyopic eye visual acuity inclusion criteria than the PEDIG study, which limited amblyopic eye acuity to no poorer than 20/100. Fifteen of the 26 anisometropic patients in this study achieved a final Snellen visual acuity of 20/40 or better in the amblyopic eye; only five, however, could read to the Snellen 20/20 level. One of these patients had no scotoma in the amblyopic or nonamblyopic eye. Three of these five patients had no scotoma in the nonamblyopic eye, and amblyopic eye scotomata tended to be smaller, but statistically significantly smaller, than the anisometropic group as a whole. Interestingly, these five patients were among the six anisometropic patients with the best stereopsis (40 seconds of arc in four patients, 50 seconds of arc in the other). Assessing all other measured clinical features of these five patients failed to reveal any significant differences from the anisometropia group.

While all but one of the 26 patients with anisometropic amblyopia had a scotomatous defect in the amblyopic eye, 20 were found to have a scotoma in the fellow, presumably normal, eye, despite an average visual acuity in the nonamblyopic eye of LogMAR 0.015 (Snellen equivalent, 20/20.7). This included three patients who had stereopsis of 40 seconds of arc or better.

The amblyopic eye scotoma was, on average, almost four times greater than that in the fellow eye, an amount that reached statistical significance. There was a direct correlation between the size of the amblyopic eye scotoma and that of the fellow eye; a larger scotoma in the amblyopic eye was predictive of a larger scotoma in the fellow eye. Scotomata areas in the amblyopic and nonamblyopic eyes were also larger in patients who had greater interocular visual acuity differences before and after treatment. Further, anisometropic patients who had poorer visual acuity outcomes in the amblyopic eye had larger amblyopic and nonamblyopic eye scotomata than those patients who had better visual acuity outcomes. There did not appear to be any correlation between scotoma size (in either the amblyopic or fellow eye) and age at treatment start, follow-up, treatment duration, LogMAR lines of acuity improvement in the amblyopic eye, age at SLO testing, or refractive error difference between the amblyopic and fellow eyes.

Five patients were found to have a larger scotoma in the fellow eye than the amblyopic eye. However, in each of these patients, it was necessary to test the amblyopic eye with a more intense stimulus to accurately map the scotoma area.

Strabismic Amblyopia Patients

Twenty of the amblyopic patients had strabismic amblyopia. All but three patients in this group had improvement in amblyopic eye visual acuity with treatment, averaging an increase of 2.35 LogMAR lines. The improvement in amblyopic eye acuity in this study also compares favorably to that of other amblyopia treatment studies.^{24,25} Although none of the patients in this group achieved final amblyopic eye acuity of Snellen 20/20, 14 of the 20 patients read 20/40 or better at final follow-up.

All of the patients in the strabismic amblyopia group had a measurable scotoma in the amblyopic eye. A scotoma was also measurable in all 20 of the fellow, nonamblyopic eyes. The amblyopic eye scotoma was, on average, more than twice as large as that in the fellow eye. Unlike that of the anisometropic amblyopia group, there was no linear correlation between the size of the scotoma in the amblyopic eye and the scotoma in the fellow eye. There was, however, a correlation between the number of LogMAR lines difference between the amblyopic and fellow eyes prior to treatment and the area of the amblyopic eye scotoma, but not at the end of treatment. That is, the larger the difference between the amblyopic eye and the fellow eye prior to treatment, the larger the size of the amblyopic eye scotoma. No correlation was found between either the amblyopic or fellow eye scotoma size and amblyopic eye acuity at start or end of treatment, interocular difference in acuity at the end of treatment, number of LogMAR lines improvement in visual acuity, age at entry or age at which the SLO was performed, or treatment duration. In this group, three patients were found to have a scotoma of greater size in the fellow eye than in the amblyopic eye. Similar to those cases in the anisometropic group, in each of the three cases different stimulus intensities in each eye were necessary to map the scotomata; a stimulus of greater intensity was necessary in the amblyopic eye.

Comparison of Anisometropic Amblyopia to Strabismic Amblyopia

One question of interest in this study was whether amblyopia treatment and outcome features or SLO characteristics were different between patients with anisometropic amblyopia as opposed to those with strabismic amblyopia.

There were no significant demographic differences between the two groups. Pretreatment and posttreatment visual acuities also were not significantly different between the two groups, in either the amblyopic eye or the fellow eye.

More anisometropic patients had measurable stereopsis at final follow-up and the level of stereopsis was greater. Only three strabismic patients had stereopsis that reached 100 seconds of arc, whereas 12 of 26 anisometropic patients had stereopsis of 100 seconds of arc or better. Five anisometropic amblyopia patients had 40 seconds of arc stereopsis and better stereopsis correlated with smaller scotomata in the amblyopic and nonamblyopic eyes. This difference may stem from one of the fundamental differences in the

underlying cause of the amblyopia. In those patients with anisometropia, the image, although degraded in the amblyopic eye, remains in alignment with, and, therefore potentially fusible with, the fellow eye, whereas in the strabismic patients, the visual axes are misaligned, and regardless of surgical alignment, establishment of fusion and stereopsis may be reduced or impossible.

There was a greater pretreatment interocular visual acuity difference in the anisometropic patients than in the strabismic patients, and the former group did not show a significantly greater LogMAR line improvement with treatment than the latter group. However, the finding that the anisometropic patients had better stereoacuity than the strabismic patients further supports the idea that potentially fusible, aligned eyes, despite relatively greater degraded image clarity in the amblyopic eye, have the potential for finer degrees of stereopsis, as was seen in the anisometropic patients.

Threshold levels for stimulus recognition were almost identical in the amblyopic and nonamblyopic eyes of the two groups. In terms of scotomata size measured in either the amblyopic eye or the fellow eye, there were no statistically significant differences between the groups. However, although it did not reach statistical significance, the interocular difference between amblyopic and fellow eye scotoma size was greater in the anisometropic patients than in the strabismic patients. One might postulate that this may stem from a greater interocular visual acuity difference in the anisometropic patients, and this was, in fact, the case, both prior to treatment and at final follow-up. Thus, although the potential for stereopsis may be greater in patients with a fusible, although degraded, image in the poorer-seeing eye, the data suggest that such a situation may not result from, or result in, a smaller interocular scotoma area difference.

SCOTOMA FEATURES IN THE AMBLYOPIC AND NONAMBLYOPIC EYE

A relative scotoma in an amblyopic eye is not unexpected. Electrophysiological examination of amblyopic patients shows findings indicative of a scotoma in the amblyopic eye. Fioretto and colleagues²⁶ evaluated eight patients with dense amblyopia in one eye using pattern electroretinogram (PERG), pattern visual evoked potential (VEP), and event-related potentials (ERPs), in association with computerized perimetry, to assess scotoma presence and features. PERG traces from the amblyopic eyes were irregular in morphology and of reduced amplitude relative to both the nonamblyopic eye and control patients. This finding suggests some inherent defect in amblyopic eyes at the level of the retina, specifically, the ganglion cell and amacrine cell layers. However, their study also showed similar response profiles when the nonamblyopic eye was blurred with filters to the acuity of the amblyopic eye. Thus, they concluded, if there is a functional defect at the level of the retina, it is likely minor in that form degradation produced similar results. VEP assessment of the amblyopic eyes found significant reductions in amplitude and latency relative to the controls. Such a test cannot differentiate a true conduction pathway deficit (which seems unlikely) from a more significant deficit at the level of the lateral geniculate nucleus (LGN), as has been previously felt to be one of the underlying abnormalities in amblyopia. The abnormal ERP findings suggest a cognitive component to the deficit in amblyopia. Thus, the fundamental defect in amblyopia may be multifactorial, but predominantly localizable to abnormal binocular interactions at the level of the lateral geniculate and ultimately reflected by abnormal binocular interactions at the level of the visual cortex. As a result, one might predict a scotomatous defect on psychophysical testing. Such was the case in this study, as a scotoma could be mapped in the amblyopic eye of 45 of the 46 patients.

The threshold for stimulus recognition was higher in the amblyopic than the nonamblyopic eye in this study. Similar findings were noted by Fioretto and colleagues²⁶ using automated perimetry. They found reduced sensitivity particularly in the central field. They attribute some of this to poor fixation. It should be noted that the patients in the Fioretto study, although older (aged 11 to 46 years) had denser amblyopia (approximately 20/100 to 20/250) than most of the patients in this study.

What was not anticipated was the presence of a scotoma in the fellow, presumably "normal," eye. This was present in 40 of the 46 patients. In the six patients who did not demonstrate a nonamblyopic eye scotoma, there were no apparent clinical features that distinguished them from other patients in the cohort other than that they had among the better stereoacuties and smaller amblyopic eye scotomata of patients tested. However, other patients, who did have nonamblyopic eye scotomata, showed similar clinical characteristics.

One might also expect there to be some correlation between amblyopic eye scotoma size and visual function and/or interocular interactions. For anisometropic patients, scotoma sizes were larger in the amblyopic eyes with poorer acuity and when there was a larger interocular visual acuity difference. Both of these correlations held at pretreatment and final follow-up. Such a correlation did not exist in the nonamblyopic eye, perhaps because of the relatively small range of pretreatment and posttreatment visual acuities. In strabismic amblyopia patients, there were no correlations, in the amblyopic or nonamblyopic eye, between scotoma size and pretreatment or posttreatment visual acuity or number of lines improvement. There was a direct correlation between scotoma areas in the amblyopic and the nonamblyopic eyes of anisometropic patients but not among strabismic amblyopia patients. Stereopsis, as an indicator of interocular interaction, was significantly different between the two groups, with better stereopsis among anisometropic patients. Further, anisometropic patients with better stereopsis had smaller amblyopic and nonamblyopic eye scotomata, suggesting that scotoma size was smaller when binocular interactions were greater. Thus, despite form degradation because of refractive differences, there are greater interocular relationships in anisometropic patients than in strabismic patients with image disparity.

VISUAL PATHWAY FEATURES IN AMBLYOPIA

The consensus of experimental work localizes the defects in amblyopia to the level of the lateral geniculate nucleus and its projection to the striate cortex, particularly, layer IV. That is, there is a reduction of binocularly driven cortical neurons and neurons driven by the amblyopic eye.

There have been some suggestions that there may be abnormalities at the level of the retina that play a role in decreased visual

acuity in the absence of an organic abnormality on clinical examination. Enoch,²⁷ for example, has suggested that one component of amblyopia may involve abnormalities in photoreceptor homogeneity across the retina. He is cautious to point out that such an anomaly of receptor alignment was not likely to be a central issue in amblyopia, but a possibility in some unusual cases. Counter to this, Delint and colleagues²⁸ attempted to address some of the issues raised by Enoch in earlier work. Their work utilizing the Stiles-Crawford effect and assessment of foveal pigment density using an SLO found no difference between the eyes of unilaterally amblyopic patients. As mentioned above, Fioretto and coworkers²⁶ found pattern ERG abnormalities in amblyopic eyes, but the effects were replicated with image blurring, suggesting that a true retinal abnormality was subtle, if existent at all. Using nerve fiber layer analysis, Colen and coworkers²⁹ found that the nerve fiber layer thickness was greater in the nonamblyopic eye than the amblyopic eye in 20 patients with strabismic amblyopia. However, the difference did not reach statistical significance. Despite suggestions of perhaps subtle retinal abnormalities in amblyopia, data supporting this premise are sparse.

A wealth of data localizes the abnormalities in amblyopia to the lateral geniculate and its projections to the visual cortex. Wiesel and Hubel,⁷ using a cat model, and Von Noorden and colleagues,^{9,30} using a primate model, found shrinkage of lateral geniculate neurons that receive input from the amblyopic eye in experimentally induced amblyopia in monkeys.

Further work of Wiesel and associates³¹ and others^{32, 33} has shown that the visual pathway representations in the striate cortex are segregated into columnar clusters of cells in alternating stripes. Each column is preferentially driven by one or the other eye in an alternate fashion, hence the term, ocular dominance columns. These early researchers found that monocular lid closure results in shrinkage of the ocular dominance columns from the affected eye, reflecting loss of geniculocortical neuronal connections.

Such a process is believed to underlie the mechanism of amblyopia, as we know it in humans. Hence, the geniculocorticate projections from the affected eye fail to "compete" effectively for neuronal connections in the striate cortex. As a result, neuronal units that, in normal development, would receive binocular input (and, hence, result in proper visual acuity development and binocularity), fail to develop properly, and binocularity is impaired. Such an effect was found in a human with anisometric amblyopia by von Noorden, Crawford, and Levacy.¹⁰

As is well known clinically and has subsequently been proven experimentally, reversal of the deficit of the affected eye alone is insufficient to restore good acuity and binocularity. However, penalization of the unaffected eye, if undertaken during the so-called critical period of early visual development, can result in improvement of visual function in the previously affected eye and restore a more normal anatomical and physiological character to the ocular dominance column organization.^{34,35}

Interestingly, damage to one eye after the critical period results in loss of cortical metabolic activity in columns driven by that eye (as would be expected), but no shrinkage in the corresponding ocular dominance column. Horton and coworkers³⁶ and Hendrickson and colleagues,³⁷ using cytochrome oxidase (CO) histochemical techniques as a marker of patterns of metabolic activity, found that in normal monkeys, levels of CO activity are homogeneous throughout layer IVc in the striate cortex, corresponding to equal ocular input to each column. However, after removal of one eye, they found a pattern of alternating pale and dark similarly sized columns, representing the normal and the affected eye.

Subsequently, Horton and Hedley-Whyte³⁸ noted similar findings in postmortem examinations of humans. In patients with a history of a loss of one eye, even if that loss occurred as much as 20 years or more before death, but after the critical period of early visual development, there was a mosaic of alternating dark and light CO-labeled columns. In 1993, Horton and Stryker¹¹ reported another case evaluating ocular dominance column appearance in humans. A 53-year-old man, with documented anisometric amblyopia first diagnosed at approximately 5 years of age, had an amblyopic eye visual acuity of 20/400 (refractive difference between the eyes was approximately 6 diopters). He subsequently became blind in his nonamblyopic eye from a metastatic lesion compressing the optic nerve. Postmortem histochemical analysis showed that the ocular dominance columns of the two eyes were essentially the same size. Cytochrome oxidase staining (indicative of metabolic activity) was absent in the columns corresponding to the previously normal, but subsequently blinded, eye and present but reduced in width and not occupying the full width of the column in the amblyopic eye. These findings suggest that, once established, ocular dominance columns may persist anatomically, if not functionally, even in the absence of retinal input.

These observations all were made in cases of severe insult to the visual system, that is, loss or total occlusion of one eye. Such may not be the case in situations such as anisometric or strabismic amblyopia, where the visual deficit is not total but either a degradation of form vision (anisometropia) or spatial localization (strabismus).

Horton, Hocking, and Kiorpes³⁶ studied a single monkey with naturally occurring anisometropia and a behaviorally assessed visual acuity of approximately 20/60. Using autoradiographic techniques, there was preservation of clusters of cortical cells arranged in columns corresponding to each eye. Although these columns were not shrunken, assessment of the same columns for CO activity (and, hence, commensurate physiologic activity), revealed a pattern of dark central bands of positive stain separated by a pale gap of cells. Superimposition of the CO images onto the autoradiographs showed the dark bands to occupy the center of the ocular dominance columns and the paler bands to represent a transitional zone, which most likely represents the electrophysiologically less active binocular cell zones.

Kiorpes and associates³⁹ measured cortical neuronal responses in monkeys that had been experimentally rendered either strabismic or anisometric. In all animals, cortical binocularity was reduced. As had previously been shown by Wiesel and colleagues,³¹ as well as others,³³ columnar clusters of cells were identified that were strongly dominated by one or the other eye. However, they also encountered transition zones between the columns where neuronal units were difficult to drive visually, suggesting that these cellular

regions represent binocular neuronal units, which in normal monkeys contain the most strongly driven binocular cells, but in this study were absent.

Although binocularly driven units were almost absent in the strabismic monkeys, the investigators also found significantly few binocularly driven cortical neurons in the anisometric animals. Quantitatively, there was not a significant difference in proportion of binocularly driven neuronal units between the anisometric and strabismic animals. However, differences in cortical neuronal unit response tended to follow a continuum related to severity of behaviorally measured depth of amblyopia. Although the reduction of cortical binocularly excited units was slightly greater in the strabismic animals, the overall physiological changes in cellular response were more directly correlated to the severity of the amblyopia, rather than the etiology of the visual loss.

Although some of the above results may suggest that there had been shrinkage in the size of the ocular dominance columns in response to the experimental alterations, a number of studies indicate that some forms of amblyopia might not result in shrinkage of the ocular dominance columns.^{11,36}

These results are not in fundamental disagreement with the pioneering studies of Hubel and Wiesel and others that found shrinkage of ocular dominance columns in experimental amblyopia. In those early experiments, visual deprivation was total, achieved by suturing one eyelid closed or enucleation. Hence, there is a significant difference between total deprivational visual deficits and amblyopia secondary to either form degradation or spatial dislocation.

Other approaches have been used to assess functional abnormalities in amblyopia. Imaging studies have used high-resolution MRI, blood-oxygen-level-dependent (BOLD) fMRI, PET, and brain single positron emission tomography (SPECT) to address brain function in amblyopia. Kabasakal and coworkers tested ten patients, aged 8 to 14 years, with known amblyopia (not specified as either strabismic or anisometric) using SPECT scans.⁴⁰ While visually stimulating one or the other eye, patients were injected with a Technetium-labeled marker and imaged 20 to 30 minutes later. In all cases, they found greater occipital cortex activity accumulation when the normal eye was stimulated, as compared to the amblyopic eye. Although obviously less anatomically precise than histochemical and autoradiographic analysis, this study supports the finding of reduced visual system activity from the amblyopic eye. Demer and coworkers,⁶ using PET imaging, found that cortical blood flow and glucose metabolism were reduced in the primary visual cortex when monocular stimulation was applied to the amblyopic eye relative to stimulation of the nonamblyopic eye in strabismic amblyopia. Comparing the above two studies, PET scanning has better spatial resolution than SPECT scanning, although the clinical utility may not be practical or cost-effective in either case.

Evaluating normal and amblyopic eye responses to different contrast sensitivity stimuli, Goodyear and colleagues,⁴¹ using BOLD fMRI, found a consistently reduced level of stimulus-evoked response in areas of visual cortex when the amblyopic eye was stimulated, as opposed to the response to fellow eye stimulation.

In an effort to improve the resolution of neuroimaging methods, Goodyear and coworkers⁴² used high-resolution fMRI to evaluate visual cortex response in human amblyopia. They found that in adult patients with a history of early-onset amblyopia, greater responses were found in areas corresponding to the unaffected eye vs the amblyopic eye. On the contrary, in two adult patients with later-onset amblyopia, a shift in ocular dominance columns was not noted, further supporting the studies above which suggest that, outside of the critical period of early visual development, ocular dominance columns are relatively static anatomically, despite reduced response to amblyopic eye stimulation. Choi and coworkers⁵ found similar results of reduced activity in response to amblyopic eye stimulation, using fMRI, in amblyopic patients ranging from 5 to 23 years of age.

DIFFERENCES BETWEEN ANISOMETROPIC AND STRABISMIC AMBLYOPIA VISUAL PATHWAYS

A number of studies have found features of visual system structure and function that differ based upon the etiology of the amblyopia.^{11,39,42} Some studies have suggested distinctly different underlying visual pathway mechanisms between strabismic amblyopia and anisometric amblyopia whereas others find more similar features. It follows that because anisometropia generates an interocular discrepancy in form vision and strabismus generates a discrepancy in spatial localization, different processing pathways may be affected or preserved. Further, studies that have induced visual loss by deprivation (eg, lid closure, corneal scarring) may identify totally different alterations in visual function.

In this study, there were some contrasts between anisometric amblyopia and strabismic amblyopia, such as stereopsis, pretreatment visual acuity in the amblyopic eye, final visual acuity in the nonamblyopic eye, and interocular LogMAR line visual acuity difference at the start but not at the end of treatment. However, for the most part, there were no significant differences between the groups, especially in terms of presence and size of SLO-mapped scotomata.

Although not found in the current study, one such difference may be that amblyopic scotomata are not as deep in anisometric amblyopia as they are in strabismic amblyopia. Abrahamsson and Sjostrand,⁴³ using contrast sensitivity measurements, found that, although all amblyopic patients had deficits in the contrast sensitivity function, the strabismic amblyopia patients had a greater visual acuity loss in relation to contrast sensitivity deficits than did the anisometric amblyopia patients.

Histological findings in the lateral geniculate nucleus also differ between strabismic and anisometric amblyopia in human and monkey. That is, both monocular and binocular cell regions were found to be shrunken in the LGN in anisometric amblyopia, whereas binocularly innervated cellular regions were exclusively affected in strabismic amblyopia.^{10,44}

Functional magnetic resonance imaging findings showed a difference among patients with anisometric amblyopia (interocular refractive error difference of 3.0 diopters or more) compared to those with strabismic amblyopia (deviation 15 prism diopters or more).⁵ Assessing calcarine activation in response to checkerboard visual stimulation, using stimuli of different checkerboard sizes and different temporal frequencies, Choi and colleagues⁵ found that calcarine activation was more suppressed in anisometric-

induced amblyopic eyes at higher spatial frequency whereas responses were more suppressed at lower spatial frequencies in strabismic amblyopia patients. These findings suggest that there may be differences in the spatial-temporal characteristics between anisometropic and strabismic amblyopia by the time the ocular information reaches the calcarine fissure. Thus, there may be fundamental differences in visual system pathways between anisometropic amblyopia and strabismic amblyopia.

SCOTOMA IN THE “NORMAL” EYE

Finding a relative scotoma in the nonamblyopic eye of 20 of 26 patients with anisometropic amblyopia and all 20 of the strabismic amblyopia patients was unexpected. Many studies of amblyopia routinely refer to the nonamblyopic eye as “normal,” “sound,” or “unaffected.” However, with the advent of tools to assess visual function beyond clinical visual acuity, studies have found abnormalities in the fellow eye of amblyopic patients.

Measuring contrast sensitivity in amblyopic children, Rogers and colleagues⁴⁵ found that the contrast sensitivity function (CSF) was reduced in the amblyopic eye even though that eye had achieved, with treatment, a visual acuity of 20/20. Thus, in “successfully” treated amblyopia, the amblyopic eye is still not normal.

In a subsequent study, this same group found losses in the CSF in the “normal” eye of amblyopic patients, despite 20/20 acuity.⁴⁶ Their findings of diminished CSF in the fellow “normal” eye of amblyopic patients were not seen in nonamblyopic control patients. The decreased CSF was not induced by amblyopia treatment by occlusion. In fact, as the amblyopic eye visual acuity improved with treatment, the CSF in the nonamblyopic eye improved also. Further, they found that over the course of the occlusion treatment (during which the interocular difference between amblyopic and fellow eye decreased from 45% to 25%), the nonamblyopic fellow eye not only improved in CSF, but also actually became better than the normal controls.

Leguire and colleagues⁴⁶ found that there was a correlation between CSF frequency response and binocularity. They found greater binocularity when there were smaller differences in CSF between the eyes and lesser binocularity when interocular CSF differences were greater. Thus, these factors may all interrelate in terms of necessary criteria for binocularity such that normal ocular alignment promotes lesser interocular CSF discrepancy and, hence, greater binocular interaction. This is supported by the greater degrees of binocularity noted in the anisometropic patients in this study also. Because so many visual cortical neuronal units are driven binocularly, it is reasonable to assume that the nonamblyopic eye might be affected by the amblyopic eye, as was proposed by Leguire and coworkers.⁴⁶ Disruption of binocularity by abnormal input from one eye would alter the function of binocularly driven cortical cells and thereby alter the measurable function of the fellow eye.

Other studies have also found abnormalities in the “normal” eye of an amblyopic patient. Rentschler and Hilz⁴⁷ reported that orientation sensitivity was abnormal in not only the amblyopic eye, but also the nonamblyopic eye of strabismic patients.

The current study provides further evidence that the “normal” eye may not be normal in amblyopia. Leguire and colleagues⁴⁶ followed CSF sensitivity before, during, and upon completion of occlusion therapy. The current study assessed patients retrospectively at most recent follow-up after completion of amblyopia treatment. Thus, it is not known whether there were changes in scotoma size in either eye during treatment.

STUDY LIMITATIONS

While helpful in exploring the nature of amblyopia of different etiologies, some of the clinical approaches mentioned above, including that of this study using the SLO, suffer from technical limitations, particularly in data precision and resolution. Foremost among these is the age range of the patients of greatest interest. While some aspects of visual function in amblyopia can be assessed in more mature children and adults, important information would be gained by using “adult” techniques to analyze visual functional abnormalities of the early, developing visual system. Also, some of the tests were psychophysical in nature and, thus, will have some limitation of accuracy, especially in children. Psychophysical studies do not lend themselves to precise localization of the defect responsible for features of amblyopia in that the stimulus response represents the summated responses of the entire visual system, including higher-order cognitive functions.

There are other limitations in this study, especially in the use of the SLO to evaluate features of amblyopia. The current study was retrospective, with data analysis at the end of follow-up after amblyopia treatment was felt to be clinically stable. As a result, whereas entry criteria were relatively uniform, amblyopia treatment approaches varied considerably among patients, being readily adapted to each individual child and/or family. As in any study of amblyopia, compliance cannot be accurately assessed. Although each child in this group of patients was felt to have good treatment compliance, this cannot be quantified. Indicative of less than perfect compliance is the fact that a number of patients had a change in treatment modality (occlusion to atropine or vice versa), usually based upon issues of comfort and compliance.

Depth of amblyopia was, in some patients, an underestimate. That is, there were four patients in whom the initial diagnosis of amblyopia was made while the child was preverbal. Treatment was initiated and numerical visual acuity data only registered when the child became verbally cooperative. Hence, a small number of patients may have had amblyopic eye visual acuity poorer than could be quantitatively recorded.

The patient selection process was not random. Although there were certain criteria for inclusion in the data analysis, patients were chosen to perform the SLO only if the child’s performance at the slit-lamp biomicroscope indicated that the child was sufficiently cooperative to perform the test. This obviously eliminated younger patients. Further, there might be some correlation between a child’s performance in the clinical setting and overall child and family compliance with treatment recommendations.

However, many aspects of the SLO testing, by virtue of the testing procedure itself, are very precise. Because microperimetry is

performed while monitoring a live image of the macula, stimulus location was extremely accurate. Also, rather than relying on a computerized paradigm to assess fixation reliability, as is done in automated perimetry, the real-time monitoring of the macula assured that stimuli were not delivered unless fixation was on target.

The SLO data collection is similar to that obtained with the Goldmann perimeter. That is, the examiner must identify levels of sensitivity and map the scotomatous area based upon a finite number of testing points. The legitimacy of the data generated was facilitated by the fact that the SLO was performed by an individual skilled in the testing and blinded to all clinical information about the patient except name and age. By far, the most accurate data were generated by the computer-assisted measurement of scotoma area. Such great precision capability far exceeded the precision of the scotoma mapping.

SUMMARY

This study evaluated patients with amblyopia using the SLO. All patients but one were found to have a scotoma in the amblyopic eye. Also, most patients had a relative scotoma in the fellow, nonamblyopic eye, adding further support to the contention that, in amblyopia, the "normal" eye is not normal. Further studies may address the features of scotomata prior to treatment and follow any changes during amblyopia management.

REFERENCES

1. Von Noorden GK. *Binocular Vision and Ocular Motility*. St Louis: Mosby; 1990: 208.
2. National Eye Institute Office of Biometry and Epidemiology. *Report on the National Eye Institute's Visual Acuity Impairment Survey Pilot Study*. Washington, DC: Department of Health and Human Services; 1984.
3. Simons K. Preschool vision screening: rationale, methodology and outcome. *Surv Ophthalmol* 1996;41:3-30.
4. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. *Ophthalmology* 1998;105:154-159.
5. Choi MY, Lee K-ML, Hwang J-M, et al. Comparison between anisometropic and strabismic amblyopia using functional magnetic resonance imaging. *Br J Ophthalmol* 2001;85:1052-1056.
6. Demer JL, von Noorden GK, Volkow ND, Gould KL. Imaging of cerebral blood flow and metabolism in amblyopia by positron emission tomography. *Am J Ophthalmol* 1988;105:337-347.
7. Wiesel TN, Hubel DH. Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J Neurophysiol* 1963;26:978-993.
8. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 1963;26:1003-1017.
9. Von Noorden GK, Middleditch PR. Histology of the monkey lateral geniculate nucleus after unilateral lid closure and experimental strabismus: further observations. *Invest Ophthalmol* 1975;14:674-683.
10. Von Noorden GK, Crawford MLJ, Levacy RA. The lateral geniculate nucleus in human anisometropic amblyopia. *Invest Ophthalmol Vis Sci* 1983;24:788-790.
11. Horton JC, Stryker MP. Amblyopia induced by anisometropia without shrinkage of ocular dominance columns in human striate cortex. *Proc Natl Acad Sci U S A* 1993;90:5494-5498.
12. Anton A, Yamagishi N, Zangwell L, et al. Mapping structural to functional damage in glaucoma with standard automated perimetry and confocal scanning laser ophthalmoscopy. *Am J Ophthalmol* 1998;125:436-446.
13. Ahn B-S, Kee C. Ability of a confocal scanning laser ophthalmoscope (TopSS) to detect early glaucomatous visual field defect. *Br J Ophthalmol* 2000;84:852-855.
14. Mori F, Ishiko S, Kitaya N, et al. Scotoma and fixation patterns using scanning laser ophthalmoscope microperimetry in patients with macular dystrophy. *Am J Ophthalmol* 2001;132:897-902.
15. Haritoglou C, Ehrt O, Gass CA, et al. Paracentral scotomata: a new finding after vitrectomy for idiopathic macular hole. *Br J Ophthalmol* 2001;85:231-233.
16. Sunness JS, Bressler NM, Maguire MG. Scanning laser ophthalmoscopic analysis of the pattern of visual loss in age-related geographic atrophy of the macula. *Am J Ophthalmol* 1995;119:143-151.
17. Fujii GY, De Juan E, Humayun MS, et al. Characteristics of visual loss by scanning laser ophthalmoscope microperimetry in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Am J Ophthalmol* 2003;136:1067-1078.
18. Sabates NR, Crane WG, Sabates FN, et al. Scanning laser ophthalmoscope macular perimetry in the evaluation of submacular surgery. *Retina* 1996;16:296-304.
19. Fletcher DC, Schuchard RA. Preferred retinal loci relationship to macular scotomas in a low-vision population. *Ophthalmology* 1997;104:632-638.
20. Schuchard RA, Naseer S, de Castro K. Characteristics of AMD patients with low vision receiving visual rehabilitation. *J Rehabil Res Dev* 1999;36:294-302.
21. Fletcher DC, Schuchard RA, Watson G. Relative locations of macular scotomas near the PRL: effect of low vision reading. *J Rehabil Res Dev* 1999;36:356-364.
22. Holladay JT, Prager TC. Mean visual acuity. *Am J Ophthalmol* 1991;111:372-374.

23. Sunness JS, Schuchard RA, Shen N, et al. Landmark-driven fundus perimetry using the scanning laser ophthalmoscope. *Invest Ophthalmol Vis Sci* 1995;36:1863-1874.
24. Simons K, Gotzler KC, Vitale S. Penalization versus part-time occlusion and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology* 1997;104:2156-2160.
25. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002;120:268-278.
26. Fioretto M, Gandolfo E, Burtolo C, et al. Evaluation of amblyopic scotoma by electrophysiological examinations and computerized perimetry. *Eur J Ophthalmol* 1996;6:201-207.
27. Enoch JM. A comment on "photoreceptor function in unilateral amblyopia." *Vision Res* 1999;39:2311-2312.
28. Delint PJ, Weissenbruch C, Berendschot TT, Norren DV. Photoreceptor function in unilateral amblyopia. *Vision Res* 1998;38:613-617.
29. Colen TP, de Faber JT, Lemij HG. Retinal nerve fiber layer thickness in human strabismic amblyopia. *Binocul Vis Strabismus Q* 2000;15:141-146.
30. Von Noorden GK. Histological studies of the visual system in monkeys with experimental amblyopia. *Invest Ophthalmol* 1973;12:727-738.
31. Wiesel TN, Hubel DH, Lam DNK. Autoradiographic demonstration of ocular dominance columns in the monkey striate cortex by means of transneuronal transport. *Brain Res* 1974;79:273-279.
32. LeVay S, Hubel DH, Wiesel TN. The pattern of ocular dominance columns in macaque visual cortex revealed by a reduced silver stain. *J Comp Neurol* 1975;159:559-576.
33. LeVay S, Connolly M, Houde J, Van Essen DC. The complete pattern of ocular dominance stripes in the striate cortex and visual field of the macaque monkey. *J Neurosci* 1985;5:486-501.
34. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eyelid closure in kittens. *J Physiol* 1970;206:419-436.
35. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in the monkey striate cortex. *Philos Trans R Soc Lond B Biol Sci* 1977;278:377-409.
36. Horton JC, Hocking DR, Kiorpes L. Pattern of ocular dominance columns and cytochrome oxidase activity in a macaque monkey with naturally occurring anisometropic amblyopia. *Vis Neurosci* 1997;14:681-689.
37. Hendrickson AE, Hunt SP, Wu J-Y. Immunocytochemical localization of glutamic acid decarboxylase in monkey striate cortex. *Nature* 1981;292:605-607.
38. Horton JC, Hedley-Whyte ET. Mapping of cytochrome oxidase patches and ocular dominance columns in human visual cortex. *Phil Trans Roy Soc Lond B Biol Sci* 1984;304:255-272.
39. Kiorpes L, Kiper DC, O'Keefe LP, et al. Neuronal correlates of amblyopia in the visual cortex of Macaque monkeys with experimental strabismus and anisometropia. *J Neurosci* 1998;18:6411-6424.
40. Kabasakal L, Devranoglu K, Arslan O, et al. Brain SPECT evaluation of the visual cortex in amblyopia. *J Nucl Med* 1995;36:1170-1174.
41. Goodyear BG, Nicolle DA, Humphrey GK, Menon RS. BOLD fMRI response of early visual areas to perceived contrast in human amblyopia. *J Neurophysiol* 2000;84:1907-1913.
42. Goodyear BG, Nicolle DA, Menon RS. High resolution fMRI of ocular dominance columns within the visual cortex of human amblyopes. *Strabismus* 2002;10:129-136.
43. Abrahamsson M, Sjostrand J. Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia. *Br J Ophthalmol* 1988;72:44-49.
44. Von Noorden GK, Crawford MLJ. Form deprivation without light deprivation produces the visual deprivation syndrome in *Macaca mulatta*. *Brain Res* 1977;129:37-44.
45. Rogers GL, Bremer DL, Leguire LE. The contrast sensitivity function and childhood amblyopia. *Am J Ophthalmol* 1987;104:64-68.
46. Leguire LE, Rogers GL, Bremer DL. Amblyopia: the normal eye is not normal. *J Pediatr Ophthalmol Strabismus* 1990;27:32-38.
47. Rentschler I, Hilz R. Abnormal orientation selectivity in both eyes of strabismic amblyopes. *Exp Brain Res* 1979;37:187-191.