

# Randomized Trial of Treatment of Amblyopia in Children Aged 7 to 17 Years

Pediatric Eye Disease Investigator Group\*

**Objective:** To evaluate the effectiveness of treatment of amblyopia in children aged 7 to 17 years.

**Methods:** At 49 clinical sites, 507 patients with amblyopic eye visual acuity ranging from 20/40 to 20/400 were provided with optimal optical correction and then randomized to a treatment group (2-6 hours per day of prescribed patching combined with near visual activities for all patients plus atropine sulfate for children aged 7 to 12 years) or an optical correction group (optical correction alone). Patients whose amblyopic eye acuity improved 10 or more letters ( $\geq 2$  lines) by 24 weeks were considered responders.

**Results:** In the 7- to 12-year-olds ( $n=404$ ), 53% of the treatment group were responders compared with 25% of the optical correction group ( $P<.001$ ). In the 13- to 17-year-olds ( $n=103$ ), the responder rates were 25% and 23%, respectively, overall (adjusted  $P=.22$ ) but 47% and 20%, respectively, among patients not previously treated with patching and/or atropine for amblyopia (adjusted  $P=.03$ ). Most patients, including responders, were left with a residual visual acuity deficit.

**Conclusions:** Amblyopia improves with optical correction alone in about one fourth of patients aged 7 to 17 years, although most patients who are initially treated with optical correction alone will require additional treatment for amblyopia. For patients aged 7 to 12 years, prescribing 2 to 6 hours per day of patching with near visual activities and atropine can improve visual acuity even if the amblyopia has been previously treated. For patients 13 to 17 years, prescribing patching 2 to 6 hours per day with near visual activities may improve visual acuity when amblyopia has not been previously treated but appears to be of little benefit if amblyopia was previously treated with patching. We do not yet know whether visual acuity improvement will be sustained once treatment is discontinued; therefore, conclusions regarding the long-term benefit of treatment and the development of treatment recommendations for amblyopia in children 7 years and older await the results of a follow-up study we are conducting on the patients who responded to treatment.

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**A**LTHOUGH THERE IS CONSENSUS that amblyopia can be treated effectively in young children,<sup>1-3</sup> many eye care professionals believe that treatment beyond a certain age is ineffective. Some eye care professionals believe that a treatment response is unlikely after the age of 6 or 7 years, while others consider age 9 or 10 years to be the upper age limit for successful treatment.<sup>4-8</sup> The American Academy of Ophthalmology Preferred Practice Pattern for amblyopia recommends treatment up to age 10 years.<sup>9</sup> The opinion that amblyopia treatment is ineffective in older children may have arisen because the age of 6 to 7 years is thought to be the end of the "critical period" for visual development in humans.<sup>10</sup> This belief, however, is not based on adequate prospectively collected data. In fact, there are numerous reports, primarily retrospective case series, of older

children and adults with amblyopia responding to treatment with patching.<sup>11-24</sup>

*For editorial comment  
see page 557*

In preparation for conducting a randomized trial, we performed a pilot study of 66 patients with amblyopia 10 to 17 years to estimate the response rate to treatment with part-time patching combined with near visual activities. We found improvement in visual acuity of 2 or more lines in 27% of patients.<sup>13</sup> We now report the results of a randomized clinical trial designed to assess the benefit of treating amblyopia in children aged 7 to 17 years.

## METHODS

The study, supported through a cooperative agreement with the National Eye Institute of

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**Group Information:** A list of the members of PEDIG appears on page 445.  
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the National Institutes of Health, Bethesda, Md, was conducted by the Pediatric Eye Disease Investigator Group at 49 clinical sites. The protocol and informed consent forms were approved by institutional review boards. The parent or guardian (referred to subsequently as "parent") of each study patient gave written informed consent and each patient gave assent to participation. Study oversight was provided by an independent data and safety monitoring committee. The major aspects of the protocol are summarized herein.

## PATIENT SELECTION

The major eligibility criteria for the trial included age 7 to 17 years, a diagnosis of unilateral amblyopia with a history of strabismus or the presence on examination of an amblyogenic factor meeting study-specified criteria for strabismus and/or anisometropia, no amblyopia treatment (other than spectacles) in the past month and no more than 1 month of amblyopia treatment in the last 6 months, best-corrected amblyopic eye visual acuity between 20/40 and 20/400 inclusive and best-corrected sound eye acuity of 20/25 or better, no ocular cause for reduced acuity, and no more than 6 diopters (D) of myopia in the amblyopic eye. For patients younger than 13 years, additional eligibility criteria included no more than 0.50 D of myopia in the sound eye (since this age group could be randomized to patching in combination with atropine sulfate penalization and myopia could negate the blurring effect at near of the atropine) and a bifocal not being used. Based on a postrandomization review, 5 patients did not have a study-defined amblyogenic factor (1 in the treatment group and 4 in the optical correction group); the data of these patients were included in the analyses.

## BASELINE EXAMINATION PROCEDURES

Visual acuity was measured in each eye with the patient wearing optimal optical correction by a study-certified vision tester using the electronic Early Treatment Diabetic Retinopathy Study testing procedure.<sup>25,26</sup> Acuity testing was repeated in the amblyopic eye. The better of the 2 visual acuity scores in the amblyopic eye was used to assess eligibility and to serve as the baseline for assessing improvement.

Additional baseline testing included: (1) assessment of binocularly with the Titmus test (fly only) and the Randot Preschool Stereoacuity Test (Stereo Optical Co, Chicago, Ill), (2) measurement of ocular alignment with a simultaneous prism and cover test at distance and near fixation (modified Krinsky test used if fixation poor), (3) cycloplegic refraction (using 1% cyclopentolate hydrochloride, performed according to the investigator's usual routine with retinoscopy, subjective refraction, or both), (4) ocular examination including pupillary dilation, and (5) assessment of eccentric fixation with a direct ophthalmoscope.

## OPTICAL CORRECTION

At a screening visit prior to randomization, a new pair of spectacles was provided for all patients regardless of whether a change was needed. Anisometropia, myopia, and astigmatism were fully corrected. Hyperopia was either fully corrected or symmetrically undercorrected by no more than 1.50 D. Since the study provided a pair of glasses to every patient, there were no minimums for amount of astigmatism or anisometropia corrected. Patients without refractive error were prescribed safety glasses. The protocol specified that the spectacles were not to be worn prior to the day of the baseline examination. Contact lens wear was only permitted if in use at the time of study entry.

For classification purposes for analysis, the amblyopic eye in patients with anisometropic or combined-mechanism amblyopia who were already wearing optical correction at the time of

enrollment were considered to be optimally corrected when anisometropia, myopia, and astigmatism were fully corrected and hyperopia was not undercorrected by more than 1.50 D or overcorrected. Patients with strabismic amblyopia currently wearing optical correction were considered to be optimally corrected when the difference between the cycloplegic refraction and the current optical correction in the amblyopic eye did not exceed 1.50 D of hyperopia, 0.25 D of myopia, or 0.50 D of cylinder and the difference in the cylinder axis did not exceed 5°. In patients with strabismus who were not wearing spectacles or contact lenses at the time of enrollment, optical correction was not considered to be optimal (and spectacles therefore were prescribed) when the amblyopic eye had residual refractive error of more than 1.50 D of hyperopia, 0.25 D of myopia, or 0.50 D of cylinder.

## RANDOMIZATION

Each patient was randomly assigned with equal probability to either optical correction plus amblyopia treatment (treatment group) or to optical correction only (optical correction group). Randomization was accomplished following data entry by the clinical center staff on the study's Web site using a permuted-blocks design of varying block sizes, with a separate sequence of computer-generated random numbers for each clinical site in 4 age strata.

## TREATMENT PROTOCOL FOR THE TREATMENT GROUP

In addition to protocol-guided optical correction, patients in the treatment group were prescribed 2 to 6 hours per day of patching of the sound eye (number of hours at investigator discretion). Patients were instructed to perform near visual activities for at least 1 hour a day while patching and were provided with a GameBoy (Nintendo, Redmond, Wash) that could be used for this purpose. Other suggested near activities included homework, reading, computer work, and the use of workbooks designed for the study with mazes, word finds, and other eye-hand activities. Patients in the younger age group (7-12 years) also were prescribed 1 drop daily of 1% atropine sulfate for the sound eye. In these patients, reading ability was assessed after cycloplegia of the sound eye, and glasses for near work were prescribed (to be used in school) for patients who were unable to read grade-appropriate print. Patients using atropine were advised to wear spectacles or sunglasses with UV protection and a brimmed hat when outdoors. As a compliance aid, calendars were provided to the patients to record the treatment used each day.

The treatment prescribed at baseline was continued for the duration of the randomized trial, with the 1 exception being that atropine use could be discontinued if it was not being tolerated. At each visit, the patient and parent were queried about the adverse effects of treatment.

## FOLLOW-UP SCHEDULE

During the randomized trial, follow-up visits occurred every 6 weeks until criteria were met to classify the patient as a responder or nonresponder (see "Primary Outcome" subsection). At each visit, visual acuity was measured in each eye using the electronic Early Treatment Diabetic Retinopathy Study procedure and then repeated in the amblyopic eye. When the amblyopic eye visual acuity testing (better of the 2 measurements) indicated that the patient met the criteria for responder or nonresponder (see "Primary Outcome" subsection), visual acuity in the amblyopic eye was remeasured by a masked examiner (who did not observe the patient prior to occluding the sound eye), either on the same day or within 2 weeks (at the 24-week visit, the masked acuity testing could have been the only acuity test performed). Prior to 24 weeks, when the

**Table 1. Demographic and Baseline Clinical Characteristics\***

	Patients Aged 7-12 Years		Patients Aged 13-17 Years	
	Treatment Group (n = 201)	Optical Correction Group (n = 203)	Treatment Group (n = 55)	Optical Correction Group (n = 48)
Age at randomization, mean (SD)	9.6 (1.6)	9.5 (1.7)	14.7 (1.4)	14.9 (1.2)
Female	89 (44)	87 (43)	31 (56)	25 (52)
Race/Ethnicity				
White	154 (77)	148 (73)	36 (65)	33 (69)
African American	16 (8)	16 (8)	10 (18)	6 (13)
Hispanic or Latino	29 (14)	34 (17)	6 (11)	6 (13)
Other	2 (1)	5 (2)	3 (5)	3 (6)
Prior treatment for amblyopia				
None	96 (48)	99 (49)	17 (31)	20 (42)
Patching	77 (38)	74 (36)	32 (58)	27 (56)
Atropine sulfate	6 (3)	2 (1)	0	0
Patching and atropine sulfate	22 (11)	28 (14)	6 (11)	1 (2)
Cause of amblyopia†				
Strabismus	52 (26)	52 (26)	11 (20)	14 (29)
Anisometropia	75 (38)	81 (41)	20 (36)	17 (35)
Strabismus and anisometropia	73 (37)	66 (33)	24 (44)	17 (35)
Distance visual acuity in amblyopic eye				
20/200-20/400 ( $\leq$ 37 letters)	16 (8)	18 (9)	2 (4)	3 (6)
20/100-20/160 (38-52 letters)	44 (22)	48 (24)	20 (36)	16 (33)
20/40-20/80 ( $\geq$ 53 letters)	141 (70)	137 (67)	33 (60)	29 (60)
Median (quartiles) logMAR	0.52 (0.40, 0.70)	0.54 (0.40, 0.72)	0.60 (0.40, 0.72)	0.59 (0.44, 0.71)
Distance visual acuity in sound eye‡				
Median (quartiles) logMAR	0.00 (-0.06, 0.06)	-0.02 (-0.06, 0.04)	-0.04 (-0.10, 0.02)	-0.05 (-0.11, 0.00)
Intereye acuity difference				
Median (quartiles) letters	28 (19, 36)	28 (21, 37)	30 (20, 38)	32 (24.5, 39)
Refractive error in amblyopic eye				
<0	9 (4)	9 (4)	4 (7)	8 (17)
0 to <1.00 D	15 (7)	18 (9)	7 (13)	6 (13)
1.00 to <2.00 D	18 (9)	16 (8)	4 (7)	6 (13)
2.00 to <3.00 D	20 (10)	16 (8)	4 (7)	3 (6)
3.00 to <4.00 D	28 (14)	24 (12)	11 (20)	6 (13)
$\geq$ 4.00 D	111 (55)	120 (59)	25 (45)	19 (40)
Median (quartiles) spherical equivalent	4.25 (2.38, 5.75)	4.50 (2.50, 5.75)	3.75 (1.25, 5.13)	3.13 (0.50, 4.63)
Refractive error in sound eye				
Median (quartiles) spherical equivalent	1.50 (0.50, 3.25)	1.50 (0.63, 3.00)	0.75 (0.00, 2.25)	0.50 (0.00, 1.00)
Optical correction§				
No correction worn/no correction needed	7 (3)	10 (5)	1 (2)	6 (13)
Correction worn optimal	32 (16)	30 (15)	5 (9)	7 (15)
Correction worn requires change	82 (41)	75 (37)	24 (44)	11 (23)
No correction worn/correction needed	77 (38)	83 (41)	25 (45)	24 (50)

Abbreviation: D, diopter.

\*Values are expressed as number (percentage) of patients unless otherwise indicated.

†One patient younger than 13 years in the treatment group and 4 patients younger than 13 years in the optical correction group had an indeterminate cause of amblyopia. These were not included in the denominators for cause of amblyopia.

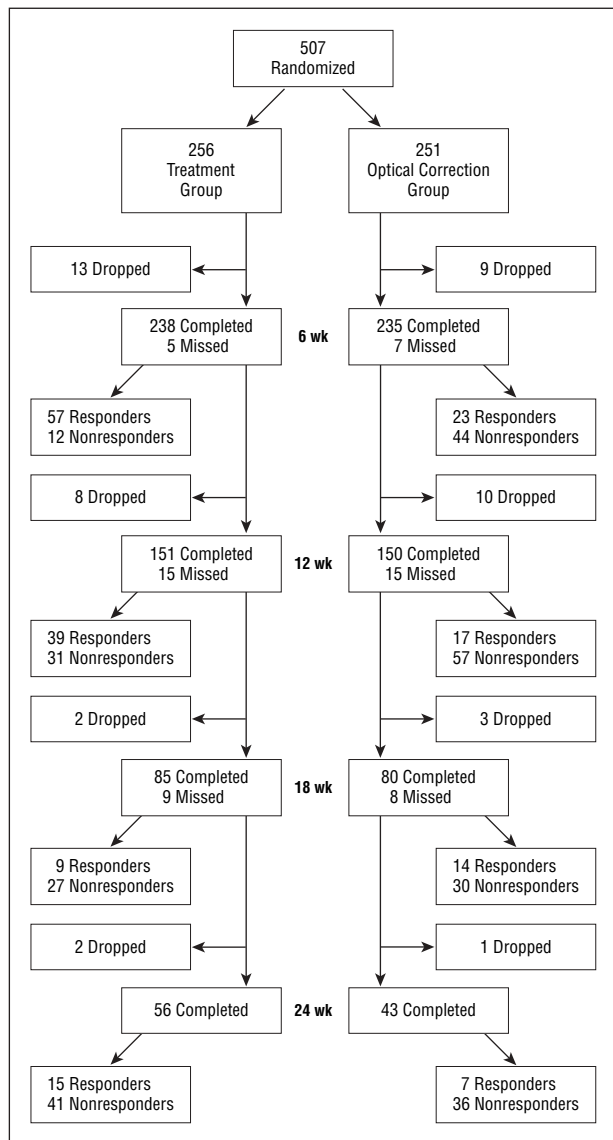
‡Two patients younger than 13 years in the treatment group and 1 patient younger than 13 years in the optical correction group had distance visual acuity in the sound eye worse than 20/25 (<80 letters).

§See "Methods" section for definitions of the classification. Current optical correction was with contact lenses for 6 patients: in the younger age group, 1 in the treatment group and 3 in the optical correction group, and in the older age group, 2 in the optical correction group. Eight patients were missing optical correction and were not included in the denominators: 5 were missing because cause of amblyopia was indeterminate and 3 because spectacle correction was unknown.

masked acuity testing did not confirm the classification of the patient as a responder or nonresponder, the patient continued in follow-up (and for patients in the treatment group, continued receiving treatment) and the masked examination was repeated when indicated at a subsequent visit.

Follow-up of nonresponders in both groups was discontinued at the visit at which nonresponder criteria were met (on the masked testing). Responders in both groups continued in follow-up with visits every 6 weeks until there was no further improvement (visual acuity score no more than 2 letters better than the score at the prior visit). During this time, responders in the treatment group could continue receiving the same

treatment regimen or could be prescribed additional treatment at the discretion of the investigator (additional treatment was almost exclusively an increase in patching hours). When there was no further improvement, follow-up of responders in the optical correction group was discontinued. Responders in the treatment group could continue for 1 additional 6-week period, during which time treatment could be tapered at investigator discretion, and then enter a 12-month observation phase during which time they were seen after 13, 26, and 52 weeks to monitor for a worsening of visual acuity. The observation phase of the trial is still in progress, and results will be reported on its completion.



**Figure 1.** Flowchart of the 507 randomized patients through the 24 weeks of the randomized trial phase of the study.

## PRIMARY OUTCOME

The primary outcome was the proportion of patients in each group classified as a responder. A patient was classified as a responder if the amblyopic eye acuity was 10 or more letters (2 lines) better than the baseline acuity on the testing conducted by the masked examiner at the 6-week, 12-week, 18-week, or 24-week visit. By the 24-week visit, if the amblyopic eye acuity had not improved 10 or more letters, then the patient was classified as a nonresponder. A patient could also be classified as a nonresponder at an earlier visit if there was no improvement (0 letters) from the prior follow-up visit or minimal improvement from baseline (defined at the 6-week visit as 0-letter improvement from baseline, at the 12-week visit as <3-letter improvement from baseline, and at the 18-week visit as <5-letter improvement from baseline). Patients who did not complete the randomized trial and patients in the optical correction group who received amblyopia treatment prior to being classified as a responder or nonresponder were considered to be nonresponders in the primary analysis.

## DIPLOPIA ASSESSMENT

At each visit, the patient and parent were queried about the occurrence and frequency of symptoms of diplopia. The patient was asked "Do you ever see 2 (double) of the same thing when you are looking directly at it?" and the parent was asked if the child ever complained of double vision. Frequency was recorded as 1 of the following: less than once a week, once a week, once a day, up to 10 times a day, more than 10 times a day, and all the time.

## STATISTICAL METHODS

The minimum sample size was computed to be 90 patients in each of 4 age strata (7-8 years, 9-10 years, 11-12 years, and 13-17 years) based on having a minimum of 80% power for each age stratum with a 5% 1-sided type 1 error rate to detect a difference in responder rates between an optical correction group rate of 5% and a treatment group rate of 25%. With these assumptions, statistical power for the primary analysis of the 404 patients in the younger age group (7-12 years) was 99% and for the 103 patients in the older age group (13-17 years), 86%.

Separate analyses were preplanned for the younger age group (7-12 years) and older age group (13-17 years) because of the expectation of statistical interaction between age group and randomization group (*P* value for the observed interaction in the trial between randomization group and age group = .03) and because the treatment regimens were not the same in the 2 age groups. The primary analysis compared the proportion of patients in each randomization group who were classified as a responder using a Fisher exact test. Unadjusted and adjusted odds ratios were computed in logistic regression models. Additional analyses compared the maximum improvement achieved (at any visit) between randomization groups and the interocular difference at the time of maximum improvement in analysis of covariance models adjusted for baseline amblyopic eye visual acuity and baseline interocular difference, respectively. Confounding and interaction between baseline factors and randomization group on the primary outcome were assessed by including covariates of interest and interaction terms in the models. Linearity of the relationship of continuous covariates with the outcome was verified. Visual acuity of 20/25 or better was considered a secondary outcome for moderate amblyopia (20/40-20/80) and visual acuity of 20/40 or better was considered a secondary outcome for severe amblyopia (20/100-20/400); proportions meeting these criteria were compared between randomization groups using the Fisher exact test. Similar results for all analyses were obtained in secondary analyses that excluded patients in both randomization groups who dropped out and patients in the optical correction group who received amblyopia treatment (other than spectacles) prior to being classified as a responder or nonresponder (data not shown).

All analyses followed the intention-to-treat principle. Reported *P* values are 1-tailed for between-randomization group comparisons and 2-tailed for within-randomization group comparisons. Analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

## RESULTS

Between October 2002 and March 2004, 507 patients entered the trial. There were 170 patients aged 7 to 8 years, 150 aged 9 to 10 years, 84 aged 11 to 12 years, and 103 aged 13 to 17 years. The number of patients randomized per site at the 49 sites ranged from 1 to 44 (median, 7). **Table 1** provides the baseline characteristics by randomization group for the younger (7-12 years) and older (13-17 years) age groups.



**Table 2. Randomization Group Comparisons for Younger Age Group (7-12 Years)\***

	Responder Rate†			Maximum Improvement			Interocular Difference‡		
	Treatment Group, No. (%) of Patients	Optical Correction Group, No. (%) of Patients	Unadjusted/Adjusted P Value§	Treatment Group, Mean Letters	Optical Correction Group, Mean Letters	Unadjusted/Adjusted P Value§	Treatment Group, Mean Letters	Optical Correction Group, Mean Letters	Unadjusted/Adjusted P Value§
All patients n = 201/203	106 (53)	50 (25)	<.001/<.001	13.3	7.3	<.001/<.001	12.6	23.2	<.001/<.001
Severity of amblyopia									
Moderate (20/40-20/80) n = 141/137	70 (50)	30 (22)	<.001/<.001	11.8	6.2	<.001/<.001	7.3	18.2	<.001/<.001
Severe (20/100-20/400) n = 60/66	36 (60)	20 (30)	<.001/<.001	17.0	9.6	<.001/<.001	25.4	34.0	<.001/<.001
Cause of amblyopia									
Strabismus n = 52/52	21 (40)	10 (19)	.01/.001	11.7	5.9	<.001/<.001	10.0	20.4	<.001/<.001
Anisometropia n = 75/81	47 (63)	24 (30)	<.001/<.001	15.6	8.8	<.001/<.001	9.8	24.0	<.001/<.001
Combined n = 73/66	37 (51)	15 (23)	<.001/<.001	12.3	7.1	<.001/<.001	17.3	24.4	<.001/<.001
Prior amblyopia treatment									
Yes									
n = 105/104	42 (40)	14 (13)	<.001/<.001	10.8	5.3	<.001/<.001	14.5	23.6	<.001/<.001
No									
n = 96/99	64 (67)	36 (36)	<.001/<.001	16.2	9.6	<.001/<.001	10.4	22.8	<.001/<.001

\*Maximum improvement and interocular difference columns exclude 16 patients who were randomized but dropped out with no follow-up visits.

†Responder has improved at least 10 letters. Among the 106 responders in the treatment group, the responder criterion was met at the 6-week visit by 51 (48%), at the 12-week visit by 35 (33%), at the 18-week visit by 6 (6%), and at the 24-week visit by 14 (13%). Among the 50 responders in the optical correction group, the number of patients meeting the criterion at each visit was 16 (32%), 16 (32%), 11 (22%), and 7 (14%), respectively.

‡At visit of maximum improvement.

§Adjusted P values adjusted for age (continuous), baseline amblyopic eye acuity (continuous), cause (strabismus/anisometropia/combined), prior treatment (yes/no), and current optical correction at enrollment (yes/no). P values under responder rate are from logistic regression models. P values under maximum improvement and interocular difference are from analysis of covariance models, adjusting for baseline acuity and baseline interocular difference, respectively.

## FOLLOW-UP

**Figure 1** provides a summary of patient follow-up during the randomized trial phase by randomization group. The completion rates of the randomized trial phase in the younger group were 91% in the treatment group and 90% in the optical correction group and in the older group, 87% and 94%, respectively. Among the patients classified as a responder in the randomized trial phase, follow-up continued until maximal improvement was reached in the younger group for 87 (82%) of the 106 responders in the treatment group and for 43 (86%) of the 50 responders in the optical correction group and in the older group for 13 (93%) of 14 and 9 (82%) of 11, respectively.

The visual acuity tester was masked to randomization group for 97% of the visual acuity measurements used to classify each patient as a responder or nonresponder.

## TREATMENT

Most patients met our criteria for not having optimal optical correction, with most having moderate to high degrees of hyperopia in the amblyopic eye. In the younger group, 79 patients (20%) were classified as having optimal optical correction at baseline, 157 (39%) were wearing optical correction meeting criteria for a change, and 160 (40%) needed optical correction that was newly prescribed at the time of enrollment (see "Methods" section for definitions of the classification). In the older

group, the number of patients and percentages were 19 (18%), 35 (34%), and 49 (48%), respectively.

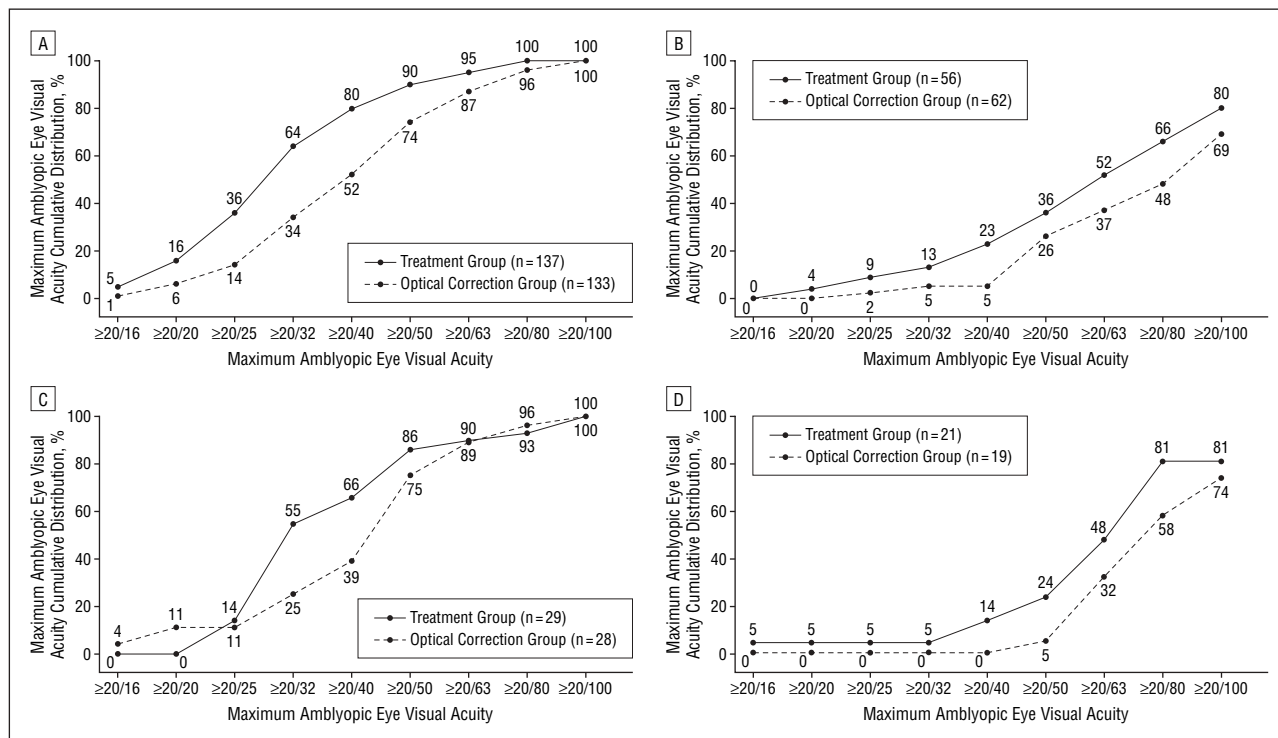
In the treatment group, among the 201 patients in the younger group, 2 hours of patching per day were prescribed for 101 patients (50%), 4 hours for 82 patients (41%), and 6 hours for 18 patients (9%) and atropine was prescribed for all but 1 patient. Glasses for near work were prescribed for 46 (23%) of these patients. Among the 55 patients in the older group assigned to the treatment group, 2 hours of patching per day were prescribed for 34 patients (62%), 4 hours for 19 patients (35%), and 6 hours for 2 patients (4%).

In the optical correction group, 3 patients (3 in the younger group and 0 in the older group) began patching and/or atropine treatment prior to being classified as a responder or nonresponder (violations of the protocol).

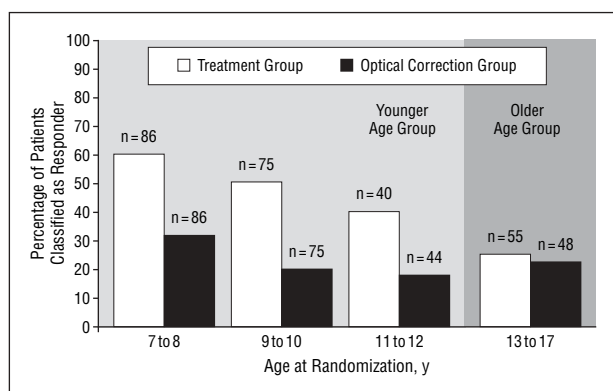
## PRIMARY OUTCOME: AMBLYOPIC EYE VISUAL ACUITY

### Younger Group (7-12 Years)

The responder criterion was met by 106 (53%) of the 201 patients in the treatment group and by 50 (25%) of the 203 patients in the optical correction group (Fisher exact test P value <.001; unadjusted odds ratio, 3.41 [95% confidence interval, 2.24-5.21]; P<.001; adjusted odds ratio [for age, baseline visual acuity, history of prior amblyopia treatment, current optical correction, cause], 4.19 [95% con-



**Figure 2.** Cumulative distribution of the best visual acuity achieved in the amblyopic eye during either the randomized trial phase or the postrandomized trial phase (excludes 22 patients who dropped out of the study with no follow-up). A, Patients aged 7 to 12 years with a baseline visual acuity of 20/40 to 20/80 (n=137 in the treatment group and 133 in the optical correction group). B, Patients aged 7 to 12 years with a baseline visual acuity of 20/100 to 20/400 (n=56 in the treatment group and 62 in the optical correction group). C, Patients aged 13 to 17 years with a baseline visual acuity of 20/40 to 20/80 (n=29 in the treatment group and 28 in the optical correction group). D, Patients aged 13 to 17 years with a baseline visual acuity of 20/100 to 20/400 (n=21 in the treatment group and 19 in the optical correction group).



**Figure 3.** Percentage of patients meeting responder criterion in each randomization group according to age.

fidence interval, 2.63-6.67];  $P < .001$ ). A benefit of treatment was seen for both moderate amblyopia (20/40-20/80) and severe amblyopia (20/100-20/400) in responder rates, maximal improvement, and interocular difference at the time of maximal improvement (**Table 2**). For moderate amblyopia, 36% of the treatment group compared with 14% of the optical correction group achieved 20/25 or better acuity ( $P < .001$ ) (**Figure 2A**), and for severe amblyopia, 23% of the treatment group compared with 5% of the optical correction group achieved 20/40 or better acuity ( $P = .004$ ) (**Figure 2B**).

Greater improvement occurred with the patching near activities/atropine regimen compared with optical correction alone throughout the age range of 7 to 12 years

(**Figure 3**). The relative treatment effect comparing the 2 randomization groups was similar across this age range ( $P$  value for interaction = .84). In both the treatment group and the optical correction group, younger age was associated with greater improvement (for responder rate,  $P = .01$  and  $.04$ , respectively; for maximum improvement,  $P = .002$  and  $.10$ , respectively) (**Figure 4**).

A treatment effect favoring the patching near activities/atropine regimen compared with optical correction alone was seen both for strabismic and anisometropic amblyopia (**Table 2**) and was seen regardless of whether the patient had received prior treatment for amblyopia (**Table 2**), but there was no interaction between either factor and randomization group ( $P$  value for interaction = .85 and  $.63$ , respectively). The response to patching near activities/atropine treatment was not related to whether eccentric fixation was present ( $P = .54$ ).

### Older Group (13-17 Years)

The responder criterion was met by 14 (25%) of the 55 patients in the treatment group and by 11 (23%) of the 48 patients in the optical correction group (Fisher exact test  $P$  value = .47; unadjusted odds ratio, 1.15 [95% confidence interval, 0.46-2.84];  $P = .38$ ; adjusted odds ratio [for age, baseline visual acuity, history of prior amblyopia treatment, current optical correction, cause], 1.47 [95% confidence interval, 0.55-3.89];  $P = .22$ ). The mean maximum improvement was slightly greater in the treatment group than in the optical correction group with a

similar difference between groups being present for moderate amblyopia and for severe amblyopia (**Table 3**). For moderate amblyopia, 20/25 or better was achieved by 14% of the treatment group and 11% of the optical correction group ( $P=.52$ ) (Figure 2C), and for severe amblyopia, 20/40 or better was achieved by 14% of the treatment group and none of the optical correction group ( $P=.13$ ) (Figure 2D). Among patients who had not been previously treated for amblyopia, those in the treatment group showed greater improvement than did those in the optical correction group (Table 3). The sample size was too small to evaluate this observation separately for moderate amblyopia and severe amblyopia.

## ADVERSE EFFECTS

### Diplopia

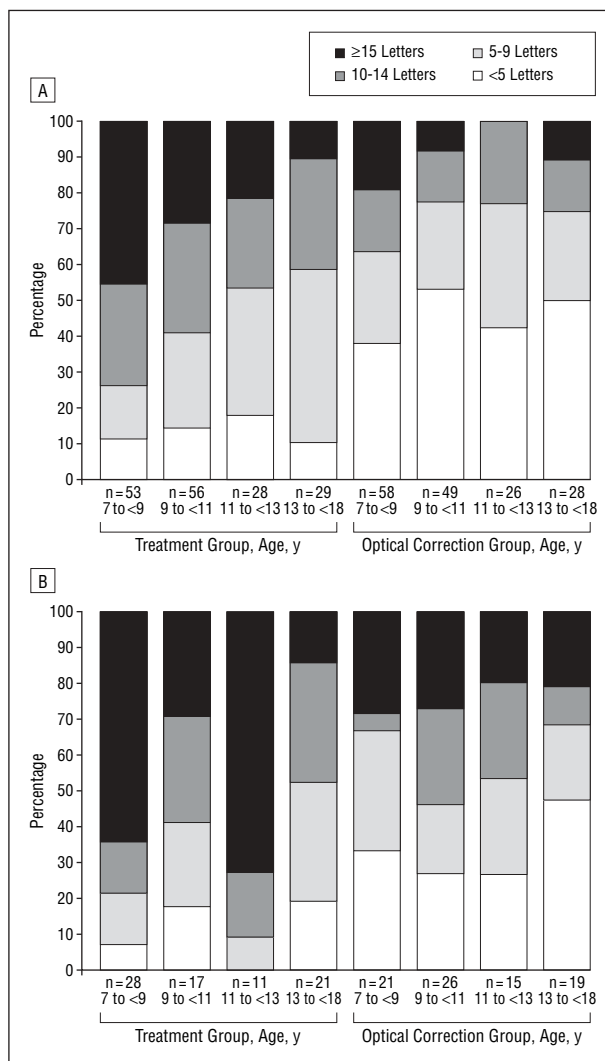
No patients developed constant diplopia during the randomized trial phase. In the younger age group, among patients not reporting diplopia at baseline, intermittent binocular diplopia occurring more than once a day was reported by 4 patients in the treatment group and by 1 patient in the optical correction group. For 3 of the 4 patients in the treatment group, diplopia was not reported at the last study visit; 1 patient at the last visit reported diplopia once a day, while the parent reported the diplopia once a week. While still receiving treatment after the end of the randomized trial phase, an 8-year-old in the treatment group, who had a history of a prior sixth nerve palsy and an esotropia at near at baseline, developed intermittent daily diplopia; at the last visit, the patient indicated diplopia was occurring several times a day but the parent indicated once a week. In the older age group, no patients reported binocular diplopia occurring more than once a day.

### Other Adverse Effects

Two patients were switched from atropine to homatropine methylbromide because of possible adverse effects, although the relationship to atropine was uncertain (vomiting in 1 patient, tachycardia in 1 patient). Atropine use was discontinued prior to the end of the randomized trial phase in 9 (4%) of the 201 patients in the younger age group (because of ocular symptoms or difficulty with near vision that was not satisfactorily treated with glasses for near work).

## COMMENT

The maximum age for attempting amblyopia treatment has been an unresolved question among pediatric eye care professionals. We found that throughout the age range of 7 to 17 years, optical correction alone improved visual acuity by 10 or more letters (which equates to 2 or more lines) in about one fourth of patients. In the patients aged 7 to 12 years, augmenting the optical correction with patching (combined with near activities during the patching) and atropine doubled the responder rate. This response to treatment was seen regardless of sever-



**Figure 4.** Maximum improvement in amblyopic eye acuity achieved during either the randomized trial phase or postrandomized trial phase in each randomization group according to age (excludes 22 patients who dropped out of the study with no follow-up). A, Patients with a baseline visual acuity of 20/40 to 20/80. B, Patients with a baseline visual acuity of 20/100 to 20/400.

ity of amblyopia, cause of amblyopia, and whether the amblyopia had been previously treated. In the patients 13-17 years, the primary analysis did not demonstrate a benefit to prescribing patching (with near activities) over optical correction alone, but there was a strong suggestion of improvement with this treatment among patients who had not been previously treated for amblyopia with patching and/or atropine, with the responder rate being 47% in patients not previously treated compared with 16% in those previously treated. Most patients in both age groups, including responders, were left with a residual visual acuity deficit.

The treatments generally were well tolerated. However, for atropine, this must be viewed in the context that we prescribed a separate pair of glasses for near work for the 23% of the patients treated with atropine who had difficulty reading owing to the cycloplegic effect on the sound eye. Intractable, constant diplopia, which has been reported to occur following amblyopia treatment in older children and adults,<sup>27,28</sup> did not occur in any patients. Al-

**Table 3. Randomization Group Comparisons for Older Age Group (13-17 Years)\***

	Responder Rate†			Maximum Improvement			Interocular Difference‡		
	Treatment Group, No. (%) of Patients	Optical Correction Group, No. (%) of Patients	Unadjusted/Adjusted P Value§	Treatment Group, Mean Letters	Optical Correction Group, Mean Letters	Unadjusted/Adjusted P Value§	Treatment Group, Mean Letters	Optical Correction Group, Mean Letters	Unadjusted/Adjusted P Value§
All patients n = 55/48	14 (25)	11 (23)	.38/.22	9.2	6.2	.03/.01	23.5	27.4	.06/.03
Severity of amblyopia									
Moderate (20/40-20/80) n = 33/29	7 (21)	6 (21)	.48/.35	8.3	5.6	.07/.05	17.3	20.8	.18/.17
Severe (20/100-20/400) n = 22/19	7 (32)	5 (26)	.35/.15	10.4	7.1	.13/.05	32.0	37.3	.13/.09
Cause of amblyopia									
Strabismus n = 11/14	3 (27)	5 (36)	.67/.66	8.5	9.5	.64/.82	23.6	24.4	.22/.93
Anisometropia n = 20/17	3 (15)	3 (18)	.59/.56	9.9	5.1	.07/.04	23.7	31.7	.03/.02
Combined n = 24/17	8 (33)	3 (18)	.14/.15	9.0	4.6	.04/.07	23.2	25.6	.19/.26
Prior amblyopia treatment									
Yes									
n = 38/28	6 (16)	7 (25)	.82/.72	7.1	6.3	.33/.34	25.1	25.1	.55/.49
No									
n = 17/20	8 (47)	4 (20)	.04/.03	14.2	6.1	.002/.002	19.7	30.6	.002/.003

\*Maximum improvement and interocular difference columns exclude 6 patients who were randomized but dropped out with no follow-up visits.

†Responder has improved at least 10 letters. Among the 14 responders in the treatment group, the responder criterion was met at the 6-week visit by 6 (43%), at the 12-week visit by 4 (29%), at the 18-week visit by 3 (21%), and at the 24-week visit by 1 (7%). Among the 11 responders in the optical correction group, the number of patients meeting the criterion at each visit was 7 (64%), 1 (9%), 3 (27%), and 0, respectively.

‡At visit of maximum improvement.

§Adjusted *P* values were adjusted for age (continuous), baseline amblyopic eye acuity (continuous), cause (strabismus/anisometropia/combined), prior treatment (yes/no), and current optical correction at enrollment (yes/no). *P* values under responder rate are from logistic regression models. *P* values under maximum improvement and interocular difference are from analysis of covariance models, adjusting for baseline acuity and baseline interocular difference, respectively.

though a number of patients reported occasional diplopia when specifically queried, in almost all cases the diplopia was infrequent and inconsequential.

The use of multiple modalities (patching, atropine, near visual activities) in the treatment regimen was an effort to maximize the therapeutic response. Nevertheless, the results of the trial must be viewed in the context of the treatment regimens that were prescribed. It is possible that prescribing patching or atropine alone could have produced a response similar to the combination therapy. It is also possible that prescribing more intensive patching or other treatment modalities could have produced greater improvement in visual acuity. Patching was prescribed to be 2 to 6 hours a day to limit patch wear to nonschool hours and because our prior studies of 3- to 6-year-olds demonstrated that as few as 2 hours of patching a day (when combined with near visual activities) is as effective as a greater number of hours.<sup>29</sup> Instructing patients to perform at least 1 hour of near activities while wearing the patch was based on the unproven postulate that near activities can augment the effect of the occlusion therapy.<sup>30-33</sup> Atropine placed in the sound eye once a day has been demonstrated in younger children to improve visual acuity,<sup>34,35</sup> presumably because of its cycloplegic effect blurring vision in the sound eye at near fixation.

Patients 13 years and older were prescribed patching but not atropine because of concern that the continual

blur from the atropine could have a deleterious effect on their ability to drive and perform other activities. Therefore, we cannot determine whether the lack of appreciable visual acuity improvement from patching in the older age group compared with the younger age group was due to their age alone or could be related to the use of atropine as well as patching in the younger group. We also are unable to assess whether the lack of effect may have been owing to poorer compliance with patching in the older patients than in the younger patients. Poor compliance is an often-cited reason for a lack of response to amblyopia treatment.<sup>17,36</sup> In this study, we had limited ability to assess compliance. We asked the patients to record the treatment received each day on a calendar. However, only about half of the patients returned the calendar. In the future, occlusion dose monitors currently under development<sup>37-40</sup> may prove feasible for monitoring compliance in multicenter trials. Nevertheless, the response of a proportion of 13- to 17-year-olds to optical correction alone suggests that the sensitive period for treatment of amblyopia had not ended before these teenage years, and therefore, it is possible that efforts to improve compliance with patching might result in better results with augmented treatment in this age group.

The proportion of patients who responded to optical correction alone substantially exceeded our expectations in designing the study. Improvement, and even resolution of amblyopia, with optical correction alone has been



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reported by other investigators.<sup>41-45</sup> This “refractive adaptation” is more than just the immediate effect of wearing spectacles but represents actual treatment of amblyopia since the visual acuity improves in a gradual and sustained manner.<sup>37</sup> Another consideration for the improvement seen in the optical correction group is a learning effect; however, this is likely not the explanation for most of the responder cases based on the fact that 2 visual acuity tests were performed to establish the baseline and based on prior test-retest studies that did not demonstrate a meaningful learning effect.<sup>25,26</sup> In designing the trial, had we known that there would be such a large proportion of patients who had never been treated for amblyopia and were not wearing optimal optical correction, we might have included a no treatment arm as part of the randomization of patients with uncorrected refractive error. Alternately, we might have followed up all patients with spectacle correction alone until improvement stopped prior to randomizing those patients who still had amblyopia.

We could identify no sources of bias or confounding to explain our findings. Accounting for differences in the distribution of baseline factors between groups in the analyses did not alter the interpretation of the results. The follow-up visit rate was similar in the 2 groups, and analyses that included and excluded the dropped patients provided similar results. Although the patients and investigators were by the nature of this study unmasked to the treatment group assignments, responder-nonresponder status was based on a visual acuity test administered by an individual masked to the treatment assignment. In addition, the computerized method of visual acuity testing used in the trial minimizes the possibility that knowledge of treatment group will bias the results. The responder definition of a 10 or more letter ( $\geq 2$  lines) improvement from baseline was selected for this protocol to provide a measure of acuity improvement that exceeded testing variability. This was based on prior studies that determined that a change of 7 or more letters is unlikely to be due to measurement variability.<sup>25,26</sup>

In translating the results into clinical practice, it is important to recognize that patients participating in a clinical trial may differ from patients in usual practice, and our patients’ level of compliance may have been better than what may be achieved in clinical practice. Although our results indicate that visual acuity can be improved by treating amblyopia in older children, it is not known whether the improvement will be sustained after treatment is discontinued. Therefore, a conclusion regarding the long-term benefit of treatment and the development of treatment recommendations for amblyopia in children 7 years and older will need to await the results of a follow-up study we are conducting on the patients who responded to treatment.

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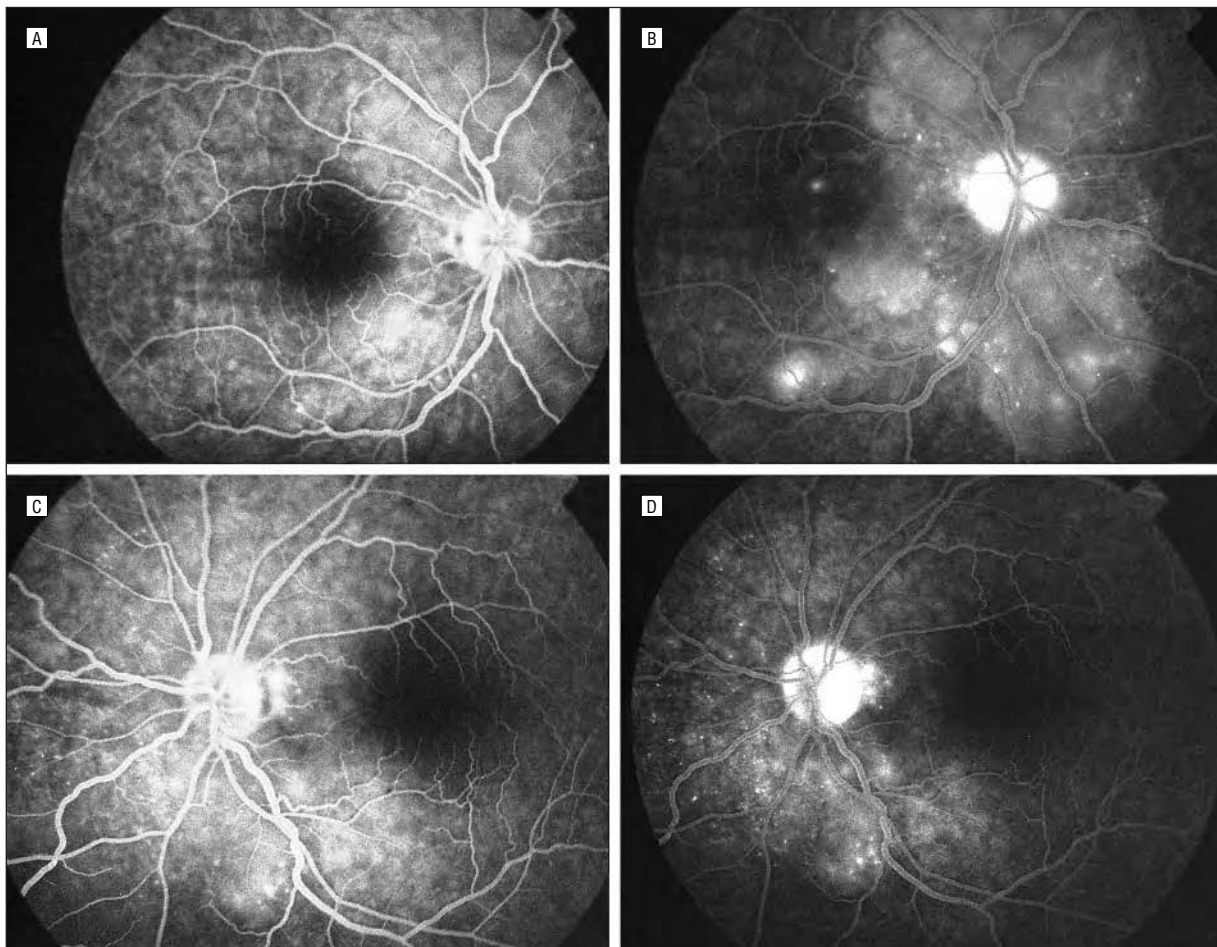
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**ARCHIVES Web Quiz Winner**

December 2004 Web Quiz Winner

**C**ongratulations to the winner of our December quiz, Amani A. Fawzi, MD, Doheny Retina Institute, University of Southern California, Los Angeles. The correct answer to our December challenge was multifocal choroiditis and serous retinal detachment due to brucellosis. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the January ARCHIVES (Rabinowitz R, Schneck M, Levy J, Lifshitz T. Bilateral multifocal choroiditis with serous retinal detachment in a patient with *Brucella* infection. *Arch Ophthalmol*. 2005;123:116-118).



Be sure to visit the *Archives of Ophthalmology* Web site (<http://www.archophthalmol.com>) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also be able to choose one of the following books published by AMA Press: *Clinical Eye Atlas*, *Clinical Retina*, or *Users' Guides to the Medical Literature*.