The Ocular Hypertension Treatment Study (OHTS) is a prospective, multicenter investigation that seeks to evaluate the safety and efficacy of topical ocular hypotensive medications in preventing or delaying the onset of visual field loss and/or optic nerve damage in ocular hypertensive subjects at risk for developing primary open-angle glaucoma. This study evaluates the baseline visual field test characteristics (visual field status, reliability properties, etc.) of patients who underwent eligibility visual field testing for entry to the OHTS.

**Purpose:** The Ocular Hypertension Treatment Study (OHTS) seeks to evaluate the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the onset of visual field loss and/or optic nerve damage in ocular hypertensive subjects at risk for developing primary open-angle glaucoma. This study evaluates the baseline visual field test characteristics (visual field status, reliability properties, etc.) of patients who underwent eligibility visual field testing for entry to the OHTS.

**Design:** Cross-sectional study of baseline data as part of a longitudinal randomized clinical trial.

**Participants:** Two thousand eight hundred nineteen ocular hypertensive individuals, aged 40 to 80 (mean age, 55).

**Methods:** Subjects underwent at least two Humphrey Field Analyzer Program 30-2 Full Threshold visual field examinations in both eyes for study eligibility. A third examination was performed if a prior test was abnormal, questionable, or unreliable. For final eligibility, two sets of visual field examinations had to meet OHTS criteria for reliability and had to be classified as “normal.” All OHTS visual field tests of potential subjects were submitted for eligibility assessment to the OHTS Visual Field Reading Center.

**Main Outcome Measures:** The percentage of visual fields that were normal and reliable according to OHTS criteria.

**Results:** Of the subset of 2304 subjects who completed the eligibility assessments, 1828 (79%) were OHTS-eligible based on visual field test requirements. A third eligibility test was required for 11% of all eyes because of unreliable, questionable, or abnormal test results. With the 33% fixation loss cutoff in the OHTS, 97% of all eligibility visual field examinations were reliable and 3% were unreliable. The most frequent cause (69.5%) of unreliability was excessive fixation losses.

**Conclusions:** Permitting one repeat test after an abnormal or unreliable test allowed an extra 560 patients to be “eligible” for the study based on visual field tests. A clinical screening review of otherwise normal and reliable tests was not restrictive. The adoption of a 33% fixation loss cutoff significantly reduced the number of required retests and prevented study rejection of 89 patients. *Ophthalmology* 2002;109:432–437 © 2002 by the American Academy of Ophthalmology.
OHTS, and (3) to determine how changing the Humphrey Field Analyzer fixation loss cutoff from 20% to 33% impacted the OHTS recruitment.

Material and Methods

The visual field test protocol used for the OHTS is a modification of the protocol used in the Optic Neuritis Treatment Trial (ONTT). The visual field examinations consist of the full threshold test strategy for program 30-2 on the Humphrey Field Analyzer (Humphrey Systems, Inc., Dublin, CA), with a 31.5 asb (10 cd/m²) background luminance and a size III target with foveal threshold and short-term fluctuation testing enabled. An appropriate, near-lens correction is placed before the eye to be tested, and the fellow eye is occluded. The patient’s pupils are dilated before visual field testing if their pupil diameter is less than 3 mm. All OHTS visual field tests are performed by OHTS-certified technicians.

For final OHTS eligibility, patients had to produce two “reliable” and “normal” visual field test results from each eye during a maximum of three testing sessions. The visual field testing sessions during eligibility assessment had to be separated by a minimum of 1 hour and a maximum of 12 weeks. The results of all eligibility visual field tests were sent to the VFRC for clinical review and for eventual archiving of enrolled patients’ tests.

For purposes of the eligibility assessment, “normal” visual field test results were determined by Humphrey Field Analyzer STATPAC 2 criteria for age-adjusted normal visual field test indexes for: mean deviation, pattern standard deviation, short-term fluctuation, corrected pattern standard deviation, and glaucoma hemifield test, and by clinical review by two senior readers at the VFRC. All visual field test printouts were also reviewed by VFRC readers for any suspicious clusters of points on the Humphrey Field Analyzer 30-2 deviation plots that might indicate early glaucomatous loss, regardless of STATPAC 2 classifications of “normal” or “abnormal.” Thus, a field was determined to be normal if STATPAC 2 criteria were met and if readers found no suspicious clusters.

“Reliable” and “unreliable” visual field tests were determined by Humphrey indexes using the Humphrey 33% reliability cutoff rates for false-negative and false-positive responses. However, the standard Humphrey 20% cutoff for fixation losses (FL) was not used. Instead, a more lenient 33% cutoff rate was used for fixation losses. Previous investigations had indicated that a 33% fixation loss criterion produced results in normal observers that seemed to be in better accordance with a 5% probability level cutoff (i.e., approximately 5% of normal subjects exceeded 33% fixation losses). A pretest examination of patient data at the University of California, Davis and at Washington University using OHTS entrance and endpoint criteria predicted that, with the more relaxed 33% fixation loss cutoff, identification of defects would not be compromised, fewer field tests would be required, and more patients would be classified as eligible for the study. Consequently, the OHTS criterion defined “reliable” as tests recording no more than 33% false-positive errors, false-negative errors, or fixation losses.

Altogether, 3328 patients were referred to the OHTS for consideration. Telephone screenings with patients’ physicians or representatives and initial eligibility visits with these patients reduced the number of subjects who began visual field testing to 2819 (This reduction also reflects 108 subjects who withdrew from consideration). Overall eligibility for the OHTS was determined by a comprehensive eye examination, medical and ocular history, masked evaluation of Humphrey 30-2 visual field test printouts by the VFRC, and masked evaluation of stereoscopic optic disc photographs by the OHTS Optic Disc Reading Center. Clinical eligibility and exclusion criteria are described at length in a previous publication. To be confident of the subset of all patients considered for eligibility and to record how enrolled subjects differed from subjects not enrolled, the OHTS incorporated a one-page form on which information would be captured as a screening assessment of all patients. This form was to be used at all centers that were interviewing, screening, and testing potential OHTS patients. During the first 6 months of study recruitment, the OHTS Data and Safety Monitoring Committee (DSMC) advised that capturing data about ineligible subjects was tangential to the study’s primary purpose. Also, it was apparent that any information recorded by the OHTS Data Coordinating Center (ODCC) could not have adequately described the screening process at different participating clinics. Thus, clinical data regarding ineligible patients—other than that reflecting total visual field testing abnormality and reliability rates—was not collected by the ODCC.

Approvals from appropriate institutional review boards and ethics committees were obtained before commencement of the OHTS. These have been renewed each year as necessary. In addition, since the outset of the study, the OHTS DSMC has monitored the ethical conduct of the study and the accumulating data for evidence of adverse and beneficial treatment effects.

Results

Altogether, 11,584 OHTS eligibility visual field tests were performed and evaluated by the OHTS VFRC. Of these, 9251 (80%) were normal according to Humphrey 30-2 full-threshold printouts, and 2333 (20%) were abnormal. Of all OHTS eligibility tests, 11,269 (97%) were reliable, and 315 (3%) were unreliable (according to OHTS standards for reliability). Of the subset of 9251 normal tests, 9080 (98%) were reliable, and 171 (2%) were unreliable. Of the subset of 2333 abnormal tests, 2189 (94%) were reliable, and 144 (6%) were unreliable. Overall, 9080 (78%) OHTS eligibility visual field tests were technically both normal and reliable according to Humphrey indexes and OHTS reliability standards. However, of these normal and reliable visual field tests, 388 were identified by VFRC readers as questionable because of the presence of suspicious clusters of points with abnormal sensitivity. Figure 1 displays the distribution of all OHTS eligibility visual tests according to normality and reliability.

Fixation losses were the most frequent cause of unreliable tests among the 11,584 total OHTS eligibility tests. Of the subset of 315 unreliable tests, 219 (69.5%) were disqualified because of excessive fixation losses. Excessive false-positive responses on 56 (17.8%) tests accounted for the next highest percentage of unreliable tests; 20 (6.3%) unreliable tests reflected a combination of excessive fixation losses and false-negative responses; 15 (4.8%) of the tests were invalidated because of excessive false-negative responses; 3 (1%) of the tests had both excessive fixation losses and false-negative responses; 2 (0.6%) tests were unreliable because of both excessive false-negative and false-positive responses. No OHTS eligibility visual field test had all three reliability indexes beyond the 33% limit. Figure 2 illustrates the distribution of excessive reliability errors among the 315 unreliable OHTS eligibility visual field tests.

Of the total 11,584 OHTS eligibility visual field tests, 1031 (9%) registered fixation losses between 20% and 32%, which, under normal Humphrey test protocol, would have been classified as unreliable.

The 1636 patients permanently enrolled in the study produced
a total of 7256 visual field tests in the completion of their eligibility requirements (1637 patients were randomized, but data have been deleted from one patient who lacked documentation of informed consent). The number of eligibility visual field tests of patients enrolled reflects 712 extra retests needed to complete the required 2 normal and reliable sets of visual field tests. The rate of normal tests of patients permanently enrolled in the study was 91%. The rate of unreliable tests of patients enrolled was 1.4%. In 71% of these unreliable tests, fixation losses were the cause of unreliability. Of the patients enrolled, 89 (5%) had an unreliable eligibility visual field test. Eleven patients (1%) had an unreliable test with both left and right eyes. Of patients enrolled, 63 (4%) had tests that recorded a fixation loss of 33% or more, and 5 (0.3%) had such tests in both eyes. Of the 7256 eligibility visual field tests from patients enrolled, 613 (8.5%) were tests that reflected fixation losses between 20% and 32%. These tests would have been considered unreliable according to Humphrey standards. The mean fixation loss rate of these 613 fields was 24%; the median fixation loss rate was 23%.

The data presented in Table 1 are a profile of reliability errors in the eligibility visual field tests of patients eventually enrolled in the OHTS. The minimum number of questions asked for fixation losses was 12, and the maximum was 34; the minimum number of questions asked for false-positive responses was 2, and the maximum was 30; the minimum number of questions for false-negative responses was 7, and the maximum was 20. The average error rate (per test/eye) for fixation losses was 7.5%; the average false-positive error rate was 3%; the average false-negative error rate was 1%.

Altogether, 1021 eyes required a third eligibility visual field test to meet the OHTS' entry requirement for two of a maximum of three normal and reliable visual field tests. The rate of third tests was only slightly lower for eyes eventually determined eligible for the trial compared with the rate of eyes determined ineligible. Of eligible eyes, 705 of 3274 required retesting—a rate of 22%. Of ineligible eyes, 316 of 1390 (23%) required retesting. However, the rate of third tests for both eyes was considerably higher in patients eventually considered ineligible for the study. Only 145 of the 560 patients (26%) ultimately eligible required retests in both eyes, although 94 of 222 (42%) ultimately ineligible patients required retests in both eyes. Of patients ultimately eligible for the study, 415 of 560 (74%) required tests in 1 eye; 128 of 222 (58%) ultimately ineligible patients required retests in 1 eye. Figure 3 illustrates the rate of retests required by eligible and ineligible patients for one eye and for both eyes.
The production of abnormal results was the most frequent cause of retests. Of the set of 1021 eyes, 861 (84%) required retests because of an abnormal Humphrey visual field index. A much smaller number of eyes, 91 (9%), had to be retested because of unreliable tests; 40 eyes (4%) were retested because of questionable tests; 29 eyes (3%) were retested because they had produced tests that were both abnormal and unreliable. Figure 4 illustrates the reasons for requesting a third screening visual field by eligible and ineligible eyes.

Of the 2819 patients who began the series of OHTS eligibility visual field tests, 2304 (82%) completed all of the required visual field tests. Of the set of patients who completed all eligibility field tests, 1828 (79%) patients successfully met the OHTS eligibility requirements for visual field tests. The remaining 476 (21%) patients were determined ineligible because of abnormal and/or unreliable visual field test indexes and/or clinical review. Of the set of patients (476) who were ineligible because of visual field test abnormalities, 273 (57%) were ineligible based on indexes alone. Fifty-six patients (12%) were ineligible based on judgment of a reproducibly suspicious cluster of points (e.g., a small cluster of points suspicious for a subtle nasal step). Finally, 147 (31%) were ineligible because of both clinical review and abnormal indexes. Figure 5 shows the eligibility rates and the rates for factors determining ineligibility of those patients who completed all visual field tests.

As reported previously, of the 3328 patients referred to the OHTS, 108 withdrew before the eligibility assessment, 1371 did not meet all of the study eligibility criteria, and 210 declined to participate or withdrew before randomization. Two patients died before randomization, and one randomly assigned subject was excluded because of lack of documentation of informed consent. The final OHTS enrollment was 1636 subjects.

Discussion

The data collected from the OHTS eligibility visual field tests provide new information regarding baseline visual field characteristics in ocular hypertensive patients. It will also be useful as comparison data in following trends and in assessing final outcomes in the OHTS. Eighty percent of all OHTS eligibility visual field tests were “normal” by Humphrey standards. Overall, the OHTS reliability rate for all eligibility tests was 97%; only 3% of OHTS eligibility visual field tests were unreliable.

Based on either the adopted 33% fixation loss cutoff or on the Humphrey fixation loss cutoff of 20%, the rate of reliability for OHTS eligibility visual field tests compares favorably with the results of other studies in which normal control subjects or patients with normal or nearly normal visual field tests have been evaluated. Table 2 presents OHTS data on unreliable visual field tests (for both a 33% and 20% fixation loss cutoff) compared with other studies that have evaluated either normal control subjects or patients with normal or nearly normal visual field tests (e.g., ocular hypertensive patients or fellow eyes of patients with optic neuritis). Using a 20% fixation loss cutoff, the 12% rate of the OHTS would have been comparable to the findings for fellow eyes in the ONTT (Keltner JL, Samuels S, Johnson CA, et al. Invest Ophthalmol Vis Sci 1995;
The indexes would still cause a visual field test to be considered “questionable” if the cluster were suspicious for early glaucomatous loss. The concern that the VFRC might overly classify visual field tests with subtle changes as abnormal was not supported by the data. Of the 2304 patients who completed all eligibility tests, only 476 (21%) were ineligible. Of the same 2304 patients, as seen in Figure 5, 2% (56 of 2304) were ineligible by judgment alone; 12% (273 of 2304) were ineligible by abnormal Humphrey Field Analyzer indexes, and the remaining 7% (147 of 2304) were ineligible by both clinical review and indexes. Note that in 1% of the eligible patients and in 10% of the ineligible patients, a third visual field test was performed because a prior field had been considered questionable. This information reaffirms that the study’s strict eligibility criteria were appropriate. Thus, the clinical review screening did not have a large impact on the eligibility of patients.

Quality control procedures previously established in the ONTT are currently being used by the OHTS VFRC. By using highly monitored quality control procedures in the ONTT, we found a smaller number of unreliable visual field tests compared with reports from prior studies. We believe the overall OHTS quality control program (technician certification, standardized protocols, quality control assessment procedures, and related factors) helped to produce high-quality, reliable visual field baseline tests. Although visual field tests can sometimes exhibit variability in patients, we believe the procedures used by the VFRC can greatly improve the reliability and quality of visual field information. The relationship between OHTS visual field technician performance, reliability, and quality-control procedures will be the subject of a future report.

Acknowledgments. The authors are indebted to Bhupinder Dhillon and John O. Spurr for their assistance in the analysis of data associated with this manuscript.

References

6. Bickler-Bluth M, Trick GL, Kolker AE, Cooper DG. As-

Table 2. Comparison of Ocular Hypertension Treatment Study Rate of Reliable Eligibility Visual Field Tests to Rates in Previous Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total Number of Visual Field Tests</th>
<th>Number of Unreliable Visual Field Tests</th>
<th>% Unreliable Visual Field Tests</th>
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<tr>
<td>33% Fixation loss cutoff</td>
<td>OHTS eligibility visual field tests</td>
<td>11,584</td>
<td>315</td>
</tr>
<tr>
<td>20% Fixation loss limit</td>
<td>OHTS eligibility visual field tests</td>
<td>11,584</td>
<td>1,346</td>
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<td>Keltner et al</td>
<td></td>
<td>3,881</td>
<td>490</td>
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<tr>
<td>Johnson et al</td>
<td></td>
<td>180</td>
<td>38</td>
</tr>
<tr>
<td>Bickler-Bluth</td>
<td></td>
<td>120</td>
<td>31</td>
</tr>
<tr>
<td>Katz et al</td>
<td></td>
<td>248</td>
<td>73</td>
</tr>
</tbody>
</table>

OHTS = Ocular Hypertension Treatment Study.

36(Suppl):$455). Thus, both the ONTT and the OHTS have reported percentages of unreliable visual field tests that are approximately 50% lower than other investigations.

The use of the 33% fixation loss cutoff did not seem to adversely affect the quality and reliability of visual field test data in the OHTS. The average short-term fluctuation for all eligibility assessment visual field tests was 1.3 dB (SD, 0.39 dB). The difference in average short-term fluctuation values between eligibility assessment visual field tests with less than 20% fixation losses and those with fixation losses between 20% and 32% was less than 0.1 dB.

If the 20% fixation loss cutoff had been used in the OHTS, 12% (1346) of the eligibility assessment visual field tests would have been classified as unreliable, and 89 more patients would have been excluded from the study—17 of these based on fixation losses alone. The lower fixation loss cutoff would have generated a 69% increase in retests, placing a heavier burden on patients and clinical centers and extending the study recruitment. As reported, the median fixation loss between 20% and 32% was only 23% (mean, 24%).

Permitting an extra screening test was considered appropriate to avoid the unnecessary exclusion of patients whose single abnormal or unreliable test might actually be the result of inexperience or long-term variability. In the OHTS, the confirming requirement for conducting/permitting a third test to meet study eligibility allowed an extra 360 subjects to be identified as eligible based on visual field tests. A later study of the OHTS population may link some of the patients who required third tests to subsequent developments of defects or to persistently unreliable patients; however, no major connection has become apparent to date. The implementation of a clinical review undoubtedly helped to screen out patients with other abnormalities.

The various Humphrey standards for normality of visual field tests were supplemented with a VFRC reader clinical review. Initially, several investigators expressed concern that this review might be too stringent for eligibility visual field tests. For example, a small cluster of abnormal points on an eligibility visual field examination that did not trigger the review might be too stringent for eligibility visual field tests. For example, a small cluster of abnormal points on an eligibility visual field examination that did not trigger

Historical Image

These four stamps were issued by Ghana to commemorate World Health Day on April 7, 1976. The series was dedicated to the eradication of onchocerciasis, also known as river blindness. It is caused by the filarial parasite *Onchocerca volvulus*. The disease is endemic in equatorial Africa and in parts of Central and South America. As many as 50 million people worldwide may be infected by the parasite and 1 million persons blinded by it.

In Africa the disease is transmitted by the blackfly, *Simulium damnosum*. Male flies do not bite but the female requires a blood meal to begin ovulation. She then mates and lays her eggs in rapidly flowing cold water. This assures an oxygen rich environment for the maturing fly larvae. When the larvae reach adult stage they are ready to renew their reproductive cycle.

Microfilariae of *O. volvulus* enter a female blackfly when she bites an infected individual. The microfilariae enter the fly's stomach, penetrate its gut wall and migrate to the flight muscles, where they undergo a series of molts. They become infectious larvae, migrate to the fly's proboscis and are injected into the next human host at a subsequent blood meal.

(Continued on page 547)

Text and images courtesy of John Kearney, MD and Stephen Tanaka, MD, Hayward, California.