Chapter 15

READING CENTER PROCEDURES

15.1 STAFFING AND ORGANIZATION

The primary function of the AREDS Reading Center is to evaluate age-related maculopathy from fundus photographs and lens opacities from slit lamp and Neitz retro-illumination photographs. The Reading Center is located within the Department of Ophthalmology and Visual Sciences at the University of Wisconsin in Madison, Wisconsin. The staff includes the following:

- Co-directors
- Associate Directors for Photography and Grading
- Research Program Manager
- Administrative Specialist
- Coordinator, Clerical and Secretarial Staff
- Biostatistician
- Data Manager
- Programmer/Analyst
- Senior Photograph Graders
- Photograph Graders
- Photograph Technician
- Photography Protocol Monitor

The Co-directors, Associate Directors, Research Program Manager, Senior Graders, and the Photography Protocol Monitor participate in the development of the Manual of Operations for Phase II and have major responsibility for the scientific methodology of the systems and procedures used by the Reading Center to evaluate fundus and lens photographs. The Associate Directors and the Research Program Manager manage Reading Center operations. The Associate Director for Photography and the Photography Protocol Monitor certify photographers and monitor the quality of photographs. The Senior Graders also train graders, supervise the quality of grading, and take corrective action as needed. The Senior Graders perform preliminary grading of photography quality and estimated AMD level, and adjudicate major differences between the preliminary estimate and the detailed grading of AMD. The Photograph Technician prepares photographs for grading by affixing grids to the slides. The Biostatistician, Data Manager, and Programmer/Analyst design and implement the databases for grading data (including attention to data quality) and collaborate in developing and operating the grading quality control program. The Data Manager edits, summarizes, and transmits files of grading data to the Coordinating Center. The responsibilities of the Coordinator and Clerical staff are to receive, check, and inventory photograph sets; to route photographs to grading staff for evaluation; to operate the AREDS Interactive Data Entry System; and to file photographs and forms. The Secretary provides support to the Directors for correspondence, reports, and manuscripts.

15.2 OVERVIEW OF GRADING PROGRAMS

The grading programs are of three general types, concerned with: (1) photographic quality, (2) characteristics of age-related macular degeneration (AMD) observed in fundus photographs, and (3) lens opacities, lens color, and iris pigmentation observed in slit lamp, Neitz, and Zeiss red reflex photographs. The quality of all types of Qualifying Visit photographs is assessed concurrently with a preliminary evaluation of eligibility (Section 15.3). Follow-up photographs are assessed using the same photographic quality grading protocol, and a preliminary estimate of AMD status is performed.

Fundus photographs taken at baseline and follow-up visits are graded for AMD according to the Summary Grading protocol (see Section 15.4.3); eyes without advanced AMD are evaluated in more detail for drusen features (the drusen extension, see Section 15.3.4). Gradings of lens opacities and lens color are carried out at each photographic visit (Qualifying and 2-year Follow-up Visits and annually thereafter), and gradings of iris pigmentation only at the Qualifying Visit (see Section 15.5).

Gradings are also performed on the unscheduled fundus and lens photographs submitted when a participant's visual acuity has decreased by 10 or more letters for the first time, and upon the lens photographs taken at the first Annual Visit of a subset of those participants who had any posterior subcapsular opacities at the Qualifying Visit.

15.3 PRELIMINARY QUALITY AND ELIGIBILITY GRADING OF PHOTOGRAPHIC AMD STATUS

At the Qualifying Visit, the Reading Center uses a two-step process to establish eligibility and AMD category of participants, basing this on photographic quality, media clarity, and retinal characteristics. In the first step, a Senior Grader performs a preliminary grading using the form shown as Exhibit 15-1. The grader determines if the photographs are of adequate quality, if the ocular media are sufficiently clear for retinal assessment, and if any disqualifying ocular disorders are present. Problematic cases are referred to one of two retinal specialists among the Co-Directors. If the participant appears to be eligible for the study, the grader assigns a tentative AMD category, including an estimate of the poorest level of visual acuity readily explainable by AMD. When photographs are found to be of inadequate quality, the grader requests that they be retaken (unless the participant is clearly ineligible because of ocular status). The retake request includes the grader's estimate of AMD category to help the Clinical Center decide whether to attempt retakes.

If photographic quality is satisfactory and disqualifying ocular disorders are absent, other Graders carry out the second step by performing a summary grading (Section 15.4.3) to officially establish the baseline AMD category and to further describe maculopathy status. Participant AMD category is extracted from the details of the summary grading, and if it disagrees with the preliminary assessment, both the preliminary and summary gradings accompanied by the photographs are referred to another Senior Grader (one who performed neither the preliminary nor the summary grading) for adjudication of the findings.

The adjudicating Grader first examines the photographs independently to form a tentative conclusion, next reviews the discrepant results from the preliminary and summary gradings, and then

determines the final result, taking the various gradings into account. The adjudicator may consult one of the two retinal specialists who are Reading Center Co-Directors or another Senior Grader if the case seems problematic. The adjudicator is required to consult one of the two Co-Directors, who are retinal specialists, in either of the following circumstances: (a) the adjudicator determines a result that differs substantially from both the preliminary and summary gradings (and is not a compromise between them), or (b) the protocol is unclear regarding the case in question.

Followup Visit photographs also undergo a preliminary review for photographic quality and AMD status, using the form shown as Exhibit 15-2. Since participants with followup visit photographs have already entered the study, eligibility is no longer an issue. Consequently, all photographs proceed from preliminary review into the main grading programs: summary and detailed grading for AMD and lens grading.

If the preliminary review determines that quality of any of the photographs is inadequate, retakes are requested. Given that retakes are onerous for the participant and Clinical Center, the Reading Center utilizes a multi-step review process to ensure that all information is taken into account in determining whether to request retakes. The Senior Grader performing the preliminary grading initiates the retake request by filling in the first section of an internal retake request form. Another Senior Grader compares the photographs in question with previous photographs from that participant's file to ascertain whether a substantial improvement in quality could likely be attained, and records the conclusion on the internal form. (This review is done by a separate grader so that the preliminary Grader is not biased by historical knowledge in estimating the AMD level at the current visit.) If the reviewer judges that better photographs are not likely, the retake request is denied. Otherwise the Associate Director for Photography or the Photography Protocol Monitor examines the photographs, considers any explanation provided by the Clinical Center Photographer along with the information already recorded by the Senior Graders, and records a conclusion on the internal form. If the photographic reviewer judges that better photographs should be attainable, an external retake request form is completed with further description of the problems observed and any advice that might promote success, and the retake request is formally issued. Otherwise the retake request is adjudicated by one of the Co-directors, who reviews the photographs, considers all of the information provided, and makes a final determination.

Since retakes during follow-up are at the discretion of the Clinical Center staff, it is uncertain whether replacement photographs will be received. Before attempting to grade any photographs that have an outstanding retake request, the Reading Center waits eight months from the date of the original photographs to allow the Clinical Center to retake photographs at the next semi-annual visit (allowing two months after the visit for handling). If retakes are received later, these are also graded and their results replace the earlier results if the quality of the retakes is superior to the original photographs.

As with Qualifying Visit photographs, results of the preliminary and summary gradings of AMD status are compared. If the results are discrepant for either eye, a Senior Grader adjudicates the final result as described above.

If a Clinical Center Ophthalmologist disagrees with the Reading Center determination of eligibility and AMD category, he/she can appeal the finding to the Senior Graders. The case at issue is reviewed with one of the two retinal specialists among the Co-Directors, and the original finding

is either confirmed or altered (the latter by transmitting a modified grading to the Coordinating Center).

Photographs taken at follow-up visits are graded for quality according to the same protocol (see Section 15.6).

15.4 PHOTOGRAPHIC CLASSIFICATION OF AGE-RELATED MACULAR DEGENERATION

15.4.1 Introduction

Fundus photographs are graded using the Wisconsin Age-Related Maculopathy Grading System as presented in Appendix 15A, with modifications by AREDS as described in Appendix 15B. The protocol for standardized AREDS photography (described in Chapter 8) provides Zeiss 30-degree color stereoscopic photographs of the macula and the disc, plus a non-stereo photograph centered just temporal to the macula.

Prior to grading, the Photograph Technician affixes a grid, made up of 3 circles concentric to the macula and 4 radial lines, to one member of the stereo pair of the macula, thereby demarcating a central, 4 inner, and 4 outer subfields (see Figure 1, Appendix 15A). When gridding follow-up photographs, the Technician first checks the location of the grid on the Qualifying Visit photographs and then positions the grid on the follow-up photographs to match.

15.4.2 Detailed Grading

The Wisconsin System (Appendix 15A) includes an evaluation of various features of drusen (maximum size, worst type, and extent), retinal pigment epithelial (RPE) degeneration (depigmentation), increased pigmentation, geographic atrophy, and detachment of the sensory retina and/or RPE. These characteristics are assessed and recorded for each of the 9 subfields.

For the AREDS, a modified version of this grading protocol has been developed to provide information similar to that of the original detailed grading, but with a smaller investment of grader time (Appendix 15B). In the AREDS detailed grading the presence and extent of each characteristic graded is not assessed separately in each of the nine subfields of the grid, but within the area of the grid as a whole (or, for some lesions, in Field 2 as a whole instead). In addition, some characteristics are also graded separately in the area within 500 μm of the center of the macula (the central subfield) and/or in the area within 1500 μm of the center of the macula (the central and four inner subfields combined, designated herein "the central zone").

The assessment of detachment of the sensory retina and/or RPE has been modified to separate these two types of detachment from each other and to subdivide RPE detachments into several types. Detailed grading is performed at the baseline and at each photographic visit thereafter, whether annual or specially scheduled to document an event. The AREDS modified detailed grading form is presented as Exhibit 15B-1.

For those eyes without advanced AMD the grader also completes a more detailed assessment of drusen features (extracted from the original Wisconsin Classification), recording for each of the nine subfields the maximum size of drusen, the worst type of drusen, and the longest dimension of any drusen confluence. Referred to as the "drusen extension," this addition to the modified detailed grading form is presented as Exhibit 15B-2.

15.4.3 Grading Procedures

As Qualifying Visit photographs are received at the Reading Center, preliminary grading is performed in the order that photographs are received. Thereafter, for detailed grading the fundus photographs are organized into randomized "reading lists" comprising 10 or fewer eyes. During preliminary grading, right and left eyes of a participant are examined concurrently to determine adequacy of photographic quality and eligibility of ocular status for the study. For detailed grading, right and left eyes are graded separately.

As they examine the photographs on their light boxes, Graders enter results directly into microcomputers, which edit for completeness and internal consistency. Before transmitting the information to the Coordinating Center, completed gradings are further processed to summarize the data. Documentation of the rules for completeness and consistency editing, and of the algorithms for data summarization, are available from the Reading Center upon request.

15.5 PHOTOGRAPHIC CLASSIFICATION OF LENS OPACITIES AND IRIS PIGMENTATION

Lens photographs are graded using the Wisconsin System for Classification of Cataract from Photographs (Appendix 15C), further modified for application in the AREDS (Appendix 15D). The protocol for standardized lens photography (described in Chapter 8) includes a slit lamp photograph to document nuclear sclerosis and color, anterior and posterior Neitz retro-illumination photographs to document cortical and posterior subcapsular lens opacities, and a stereoscopic pair of the red reflex taken with the Zeiss camera to assist in grading lens opacities and to document iris pigmentation. The grading form used for both types of lens photographs is provided as Exhibit 15D-1.

15.5.1 Slit Lamp Photographs

Slit lamp photographs are assessed primarily for nuclear sclerosis, defined as increased optical density or relucency ("opalescence") and loss of definition of nuclear landmarks. The grader compares the unknown photograph with a series of seven standard photographs, and places it in the appropriate interval using a decimalized scale. In other words, the grader mentally divides the interval between the two closest standards into 10 steps, and selects the step thought to best match the unknown photograph. Nuclear color is assessed using three standard photographs in the slit lamp series (two of those used for grading nuclear sclerosis, and a third provided only for grading nuclear color). The prefix "SL" is attached to the number of the standard photographs (i.e., SL Standards 1-8) to differentiate them from the maculopathy and iris pigmentation standard photographs.

15.5.2 Neitz Retro-illumination Photographs

Neitz photographs are evaluated chiefly for cortical lens opacities (documented in both the anterior and posterior photographs) and posterior subcapsular or PSC lens opacities (seen primarily in the posterior photograph). If cortical and/or PSC opacities are present, the Grader positions a concentric lens grid over (or under) the photograph to demarcate subfields. Then the Grader estimates the percentage of involvement of each subfield by cortical and PSC opacities respectively. The presence of any other lens opacities (such as vacuoles and "white anterior cortical opacities") is noted.

15.5.3 Zeiss Stereo Red Reflex Photographs

The Grader refers to the stereoscopic red reflex photograph taken with the Zeiss fundus camera to detect any opacities not captured in the Neitz photographs, and to determine the nature and antero-posterior location of opacities when these cannot be satisfactorily determined from the Neitz photographs alone. These photographs are also used for evaluating the degree of iris pigmentation (Section 15.5.5).

15.5.4 Grading Procedures

As with maculopathy grading, the photographs are organized into randomized "reading lists" comprising 10 or fewer eyes. Right and left eyes are graded separately. Slit lamp, Neitz, and Zeiss red reflex photographs are graded at the same sitting. To expedite the establishment of AMD category from the Qualifying Visit photographs (needed for a participant to enter the trial), the summary maculopathy grading is performed first, and the lens grading is performed later at a separate sitting after the participant has entered the trial. For follow-up photographs, the maculopathy and lens gradings are done at the same sitting (unless a grader is not certified to perform both types). Procedures for direct data entry by graders parallel those used for grading of fundus photographs (see 15.4.3)

15.5.5 Photographic Classification of Iris Pigmentation

Degree of iris pigmentation is evaluated only at the Qualifying Visit, using the protocol presented in Appendix 15D. This determination is made from the stereoscopic red reflex photographs taken with the Zeiss fundus camera, as described in Chapter 8. The unknown photograph is compared to a series of three standard photographs and placed in the proper interval. To avoid the inconvenience of a separate photographic session, the red reflex photographs taken with the pupil dilated (for retinal and lens photography) are used to grade iris pigmentation. Correspondingly the standard photographs also present eyes with dilated pupils, although undilated variants of two of the standards are also furnished to illustrate iris anatomy and to allow the graders to appreciate the effect of dilation. The iris pigmentation standards are labeled Standards I1-I3 ("I" to denote iris).

15.6 QUALITY CONTROL PROCEDURES FOR GRADING

15.6.1 Overview

The quality control program has three components: initial grader training and certification, ongoing grading exercises that provide feedback to the Graders to help them maintain and/or improve their performance, and masked replicate gradings of random samples to document the variability of grading for the information of AREDS committees and for inclusion in future publications. There is some overlap in the latter two of these three components, in that both furnish information to the Reading Center that is useful in monitoring performance in the grading programs.

The quality control program emphasizes the grading protocols that produce the data to be used in analyses: the detailed grading of maculopathy, the grading of lens opacities, and the grading of iris pigmentation.

15.6.2 Grader Training and Certification

Training of Graders at the Reading Center is based on a tutorial approach, utilizing written protocols and referring to teaching sets of photographs for which accepted grades have been established. When Graders have completed training, they are required to become certified for grading AMD and/or lens opacities by satisfactorily completing grading tests that include a wide range of varieties and severities of those conditions.

After Graders have completed the certification test, they gain further experience by grading several reading lists of eyes which have already been graded by experienced Graders and comparing their results with those of the experienced Graders. The grades from the new Graders are not utilized as study data, but serve to provide the Grader with further practice and identify any areas that may need remediation. Statistics summarizing these comparisons are produced, including proportions of agreement and degrees of disagreement. Retraining sessions are held if necessary to deal with problematic lesions.

15.6.3 Ongoing Grading Exercises

Each month the Senior Graders conduct quality control meetings of the grading groups, with separate meetings for maculopathy and lens opacity grading. Prior to most meetings the Senior Grader selects from eyes graded earlier a small sample having abnormalities relevant to the topic chosen for that meeting. These eyes are chosen by the Senior Grader in part on the basis of questions brought by Graders seeking help with difficult or unusual appearances. Topics are also proposed by Graders individually or through their quality control committee. Lesions already known to be difficult or subtle are included on a revolving schedule. A log is kept of the proceedings of the monthly quality control meetings.

Graders are required to perform a masked grading of this quality control sample for the specified features. Results are tabulated before or during the meeting, and Graders receive data from their own gradings as well as those of other members of the group so that they can compare

themselves to the overall profile of grading (especially the consensus). Any areas of important disagreement are identified, and the group discusses the proper application of the protocol. The Senior Grader clarifies problematic points, and if necessary selects example photographs illustrating the desired grading approach. Documentation from the quality control meetings is filed chronologically in a binder, so that graders can refer to it later should the need arise.

To promote uniformity of interpretation, the Reading Center maintains a collection of photographs designed to illustrate the desired "thermostat setting" for the presence and severity of various abnormalities. Periodically, graders are encouraged to review this collection as a "tuning" exercise.

15.6.4 Monitoring Contemporaneous Variability of Grading

The principal goal of this element of the program is to obtain periodic estimates of variability over the course of the study that exercise all parts of the grading scale for abnormalities and represent the usual range of photographic quality. These will be part of the primary data used to document reproducibility of the gradings in study publications.

Each calendar quarter the statistician selects samples of a variable number of eyes from those graded during the previous quarter, with separate samples for maculopathy and lens opacity grading. (To facilitate selection of a sample with the desired balance of abnormalities, eyes rather than participants are chosen.) Before selecting the sample, the statistician consults with the Senior Graders to determine whether there should be any special emphases in the selection process. Otherwise, the sample is constructed to achieve reasonable representation over the major categories of the grading scales. To make the selection, the gradings from the previous quarter are stratified into subgroups and individual eyes chosen randomly from within strata. This quarterly procedure yields an annual sample of about 140 eyes, which over the course of the trial should be sufficiently large to represent even somewhat rare conditions.

The samples selected receive masked replicate grading, with assignment of reading lists controlled so that an eye is never regraded by the same Grader who evaluated it originally. Results from this procedure are analyzed quarterly, and provided to the Graders as feedback regarding their concordance. (Eyes provoking disagreement are identified from a data listing provided to the Senior Grader, and often provide material for the monthly quality control meetings.) Contingency tables or plots are produced, with summary statistics describing the proportions of agreement and various degrees of disagreement, as well as the kappa statistic or intra-class correlation coefficient. Annually these data are used to prepare reports to AREDS on the variability observed in the grading programs.

15.6.5 Monitoring Temporal Variability of Grading

The principal goal of this element of the program is to monitor the grading programs for temporal drift. At the end of the first year of Phase 2, samples of 100 eyes of 50 participants (separate samples for maculopathy and lens opacity gradings) were selected from those graded during that period for masked regrading during the second and subsequent years. These samples

were stratified to represent different types and degrees of abnormalities, but were chosen randomly within those strata so as to include cases with a range of grading difficulty and photographic quality.

It proved necessary to select different samples for maculopathy and for lens opacities to obtain the distributions desired for each. For maculopathy, the stratification corresponds to the proposed severity scale presented in Chapter 3 of the AREDS Manual of Operations concerning study endpoints. Prior to the second regrading of the temporal drift sample, an additional 40 eyes (20 participants) were added to the sample to increase representation of lower levels of maculopathy (the initial sample accentuated advanced AMD). For cataract, the stratification accords with the severity scales for the several types of cataract presented in Chapter 3 (for results expressed as percentages, tentative ranges are suggested). Prior to the fourth regrading of the temporal drift sample, an additional 100 eyes (50 participants) was added to the sample to increase representation of greater levels of cortical and PSC opacities (these were rare at baseline).

To evaluate possible temporal drift of the system (which includes multiple graders), the maculopathy and lens opacity samples will receive masked replicate gradings during the second and subsequent years.

Assignment of reading lists for the temporal drift sample is uncontrolled, because reading lists are normally assigned without regard to who performed the original grading. In other words, a grader who did the original grading may grade the next visit from the same subject, but is unlikely to do so given the number of graders in the program.

Results from this procedure will be analyzed annually, considered carefully, and reported to the study. Cross-tabulations for ordinal scales and graphical plots for continuous scales will be produced and then further summarized as to proportions of agreement, including computation of the kappa statistic or intra-class correlation coefficient. While the trends revealed will undoubtedly be used by the Reading Center investigators to guide the direction of the quality control program, data from the exercise will not be shared with the graders themselves. In particular, they will not be allowed to examine the photographs in the sample (otherwise it would be invalid for further use).

15.6.6 Data Display and Analysis

Results of the formal exercises are reported as cross-tabulations or graphical plots, further summarized by percentage of agreement exactly and within specified degrees. For ordinal scales (typical of the AMD data), unweighted kappa statistics are used to further summarize the results and to adjust for chance agreement. Chi-square tests of marginal homogeneity may be performed to reveal if the categorization of the sample has shifted significantly. For continuous scales (typical of the lens data), intra-class correlations are used to summarize the results.

15.7 QUALITY CONTROL PROCEDURES FOR PHOTOGRAPHS

15.7.1 Clinical Center Photographer Training and Certification

The Reading Center program to promote good photographic quality has several components: preliminary testing of photographic protocols, orientation sessions for photographers, mandatory initial certification, and ongoing monitoring of photographic quality. After a period of detailed review, photographers become "fully certified" based on their submission of photographs that demonstrate general technical competence and specific knowledge of the photographic protocols (see Chapter 9).

15.7.2 Photographic Quality

Fundus and lens photographs from the Qualifying and Follow-up Visits are graded soon after arrival at the Reading Center to assess their quality. This initial grading also establishes the eligibility of the participant for Qualifying Visit photographs, and provides an estimate of AMD status for Followup Visit photographs. Each type of photograph receives a quality grade, based upon the criteria presented in Appendix A of Chapter 8. This grading is conducted by one of several Senior Graders, who confer regularly to maintain consistency in their evaluation. Photographs from both eyes are reviewed together, and the Photographic Quality and Preliminary Eligibility Assessment Form is completed (Exhibit 15-1). During follow-up, the items pertaining to eligibility are modified to simply provide an estimate of AMD status, since eligibility is no longer an issue (Exhibit 15-2).

Photographic quality is monitored throughout the study. On an *ad hoc* basis, the Senior Graders performing the preliminary grading refer serious quality problems to the Associate Director for Photography or the Photography Protocol Monitor. Based upon these cases and upon statistical summaries of the quality grades assigned to all photographs, Reading Center photographic staff contact individual Photographers to discuss problems and resolve them. Statistical summaries of the photographic quality grades, stratified by Clinical Center and time period (most recent period vs. previous periods), are sent to the Coordinating Center for clinic monitoring and for presentation to the Data and Safety Monitoring Committee. Semi-annually, statistical summaries of the photographic quality grades are sent to the Clinical Centers, with the Principal Investigator receiving results for all Photographers within the Clinic and with each Photographer receiving only his/her results. Data are stratified by time period, the most recent vs. previous periods, to allow Clinic Staff to detect any temporal trends. To provide a frame of reference, Clinic staff also receive the results for the study overall. Individual Photographers may receive supplementary information specifying the particular features of photographic quality (e.g., field definition) determining the quality grades.

Periodically, the Reading Center photographic staff conduct structured telephone interviews with each Clinical Center, talking with either the chief of photography or the most active AREDS Photographer, as appropriate. A summary of these scheduled telephone calls is sent to the Protocol Monitor at the Coordinating Center.

The Reading Center photographic staff conduct site visits to all Clinical Centers as needed, for the purposes of (1) orienting any new Photographers who may have joined the study and (2)

inspecting and maintaining the AREDS camera equipment, particularly the customized lens cameras. A written report regarding the site visit is provided to Clinic staff and to the AREDS Operations Committee.

Occasionally, the Reading Center circulates newsletters containing additional information on study photographic issues to the Photographers and other Clinic staff. In addition the Reading Center conducts central meetings for study Photographers, which review study progress, demonstrate how photographs are graded, discuss photographic equipment and procedures, and explore photographic quality problems.

15.8 PHOTOGRAPH FILE MANAGEMENT

To ensure that all AREDS photographs are correctly identified, the Coordinator or her clerical assistants immediately check the contents of each package of photographs received from a Clinical Center against the enclosed Shipping Manifest. If inconsistencies, omissions, or damage in shipping are noted, the originating center is contacted immediately by telephone. If the problem cannot be rectified over the phone, the package is returned to the clinic for resolution.

If the package is complete, the Shipping Manifest that accompanies the photograph sets is separated from them so that the information on the list can be entered into the computerized inventory file, which enables immediate identification of all photographs received and their grading status. Once a participant identity has been established in the inventory system at the Qualifying Visit, further submissions are checked for consistency of namecode with this original entry.

After the photographs have been graded, they are filed permanently according to clinic and participant number in steel, fire-resistant filing cabinets. This arrangement and the computerized inventory system allow for ready access and retrieval.

15.9 HANDLING AND TRANSMISSION OF GRADING DATA

Data generated by the various grading programs are entered into computerized files for editing and additional processing. There are two distinct modes of entry, with different procedures for each.

Graders enter all grading data directly into interactive networked personal computers as they perform the evaluations. Shell files containing identifying information for the reading list selected are downloaded to the Graders' computers. After selecting a record to grade, the Grader must enter sufficient identifying information from the photograph set label to ensure a correct match. As the grader completes each screen of the grading form, the program edits for completeness and consistency before advancing to the next screen. Any errors found are presented to the grader, with an indication of the nature of the problems, so the grader can rectify them. Upon successful completion of a record, its status code indicates that it is ready for data transfer. When all records on a reading list have reached this status, the files are uploaded in a batch to a holding area on the main computer. After further checks, the Data Manager transfers these records into the main file.

Data not entered directly by graders (such as inventory information) are keyed by clerical assistants into networked personal computers. To check the accuracy of conventional data entry, a second complete verification entry is made. After the second entry is completed, an editing program compares the first and second independent entries, indicating data fields that require resolution. To prepare gradings for data analysis, the Reading Center maintains software to condense and summarize data from the various grading programs.

The computerized data storage system at the Reading Center provides for backup in the event that primary files are lost. For the Reading Center computer network file server, there are daily complete back-ups of all files onto tape cartridges. For the graders' personal computers, gradings in progress are periodically saved to disk after completion of each "screen," to guard against loss of transient data due to mechanical failure or power outage. A back-up copy of all gradings resides on the local hard disks of the graders microcomputers, until it is evident that the gradings have been processed into the files on the network file server. These procedures allow staff to regenerate any files as needed, whether from disk or tape.

The Reading Center computer network is used for the periodic processing of batches of grading data. As each batch is completed a summary of the results is transferred to the AREDS microcomputer (constituting the Reading Center node of the AREDS data system), at which point it undergoes further checks for completeness and internal consistency. Data are assembled into ASCII files, using record structures mutually agreed upon between the Reading Center and the Coordinating Center (copies of these are available from the Reading Center upon request).

Transmission of data files to the Coordinating Center is scheduled as follows. For Qualifying Visits, records of the preliminary grading for eligibility and photographic quality and of the summary grading of maculopathy are sent not less than weekly. All other files (grading of lens opacities, detailed grading of maculopathy during follow-up) are sent monthly.

Data are transmitted by the Data Manager to the Coordinating Center during a communications session on the AREDS data system (via modem). Direct computer transfer uses internal checking procedures to ensure that information is not garbled during telecommunication.

Exhibit 15-1a. PHOTOGRAPHIC QUALITY & PRELIMINARYASSESSMENT FORM

Exhibit 15-1b. PHOTOGRAPHIC QUALITY & PRELIMINARY ASSESSMENT FORM

Exhibit 15-2a. PHOTOGRAPHIC FOLLOWUP VISIT ASSESSMENT FORM

Exhibit 15-2b. PHOTOGRAPHIC FOLLOWUP VISIT ASSESSMENT FORM

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Appendix 15A

THE WISCONSIN AGE-RELATED MACULOPATHY GRADING SYSTEM

The Wisconsin Age-Related Maculopy Grading System, included as this appendix, has been deposited with the National Technical Information Service under accession number PB 91-184267.

A summary of the system and data on its reproducibility have been published elsewhere:

Klein R, Davis MD, Magli YL, Segal P, Klein BEK, Hubbard LD. The Wisconsin Age-related Maculopathy Grading System. *Ophthalmolog*y 1991;98:1128-1134.

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Appendix 15B

WISCONSIN AGE-RELATED MACULOPATHY GRADING SYSTEM
AREDS DETAILED GRADING PROTOCOL

Appendix 15B

Wisconsin Age-Related Maculopathy Grading System
AREDS Detailed Grading Protocol

1.0 INTRODUCTION

1.1 Goals

The first goal of the AREDS detailed grading is to provide information similar to that produced by the detailed grading of the original Wisconsin System (Appendix 15A), but with a smaller investment of grader time. The evaluation of drusen has been divided into two parts: a summary section within the main form that is utilized for all eyes, and a more detailed module separate from the main form (the "drusen extension") that is utilized only for eyes without advanced AMD. A second goal is to grade in separate items (1) detachment of the sensory retina from the retinal pigment epithelium (RPE) by serous fluid or blood, designated serous or hemorrhagic sensory retinal detachment (RD), and (2) detachment of the RPE from the choroid, designated pigment epithelial detachment (PED), and to distinguish between different types of PED (see Section 15B-7). It is of particular importance to distinguish drusenoid PED from other types of PED (and from RD), because presence of drusenoid PED does not place an eye in the "advanced AMD" category, whereas presence of any of the other types of detachment does.

1.2 Overview

Sections 15B-2 through 15B-5 summarize major changes from the original Wisconsin System. Section 15B-6 describes briefly the grading form, consisting of the main form and the drusen extension. Sections 15B-7 through 15B-18 deal with specific lesions. Section 15B-19 provides descriptions of example photographs that have been added to those used in conjunction with the original Wisconsin System. These are referred to in other sections when appropriate. Standard and example photographs are on file at the UW Fundus Photograph Reading Center, 610 N. Walnut St., Madison, Wisconsin 53705.

2.0 GRADING RULES

Familiarity with the original Wisconsin System (Appendix 15A) is necessary before reading this document. Most of the concepts, conventions, and definitions used in the original Wisconsin System are also used in the AREDS detailed grading, and only some of them are discussed further here.

The same definitions apply concerning the grades of absent, questionably present, definitely present, and cannot grade. Absent means that the lesion under consideration is not visible in the area

being graded and that at least 25% of this area can be seen to be free of the lesion. Cannot grade means that the lesion is not visible and that less than 25% of the area under consideration can be seen to be free of it, either because of an obscuring lesion or poor photo quality (code 8 is assigned in either case). Questionably present means that the grader is $\geq$ 50 but < 90% certain that the lesion is present in the area under consideration; absent is assigned if the lesion is present with < 50% certainty (and $\geq$ 25% of the area under consideration is gradable for it). Definitely present means that the grader is $\geq$ 90% certain that the lesion is present in the area under consideration. A different definition of the questionable grade is used for involvement of the center of the macula by geographic atrophy: questionable means that the grader cannot be $\geq$ 90% certain that the center is not involved nor $\geq$ 90% certain that it is involved, usually because of difficulty deciding exactly where the center is located.

As in the original Wisconsin System, right and left eyes are graded independently.

3.0 SUBDIVISIONS OF FUNDUS

3.1 Areas Graded

In the main section of the AREDS grading, the presence and extent of each characteristic graded is not assessed separately in each of the nine subfields of the grid, but in the area of the grid as a whole (or, for some lesions, in Field 2 as a whole instead). In addition, some characteristics are also graded separately in the area within 500 μm of the center of the macula (the central subfield) and/or in the area within 1500 μm of the center of the macula (the central and four inner subfields combined, designated herein "the central zone"). Geographic atrophy (only) is also graded in a fourth location, at the center of the macula. Gradings of a given characteristic in these 3 (or 4) different locations are inclusive, rather than mutually exclusive, e.g. a characteristic present in the central subfield is, by definition, also present in the central zone and within the grid as a whole, while a characteristic present only in one or more of the outer subfields is evaluated within the grid as a whole, but is graded absent in the other locations.

In the drusen extension section of the AREDS grading, however, the presence and extent of each characteristic *is* assessed separately in each of the nine subfields of the grid (and for some characteristics, in regions outside the grid), as in the original Wisconsin System.

3.2 Grid Centration

An additional guideline for grid centration (see Section 15A-7 of the original Wisconsin System) is added for eyes in which RD involving the macula makes the yellow macular pigment more easily recognizable. When this pigment is visible and other landmarks are not helpful, the center of this yellow spot is used to help in grid centration.

4.0 DRUSEN GRADING, CHANGES FROM ORIGINAL WISCONSIN SYSTEM

- In the main part of the AREDS form, maximum drusen size is graded only for the area within the grid as a whole, as is presence of soft drusen. In the AREDS drusen

extension, both these drusen characteristics are graded separately in each of the nine subfields of the grid, as well as for regions outside the grid, as in the original Wisconsin System. For both the “soft drusen” item on the main AREDS form and drusen type on the drusen extension, the "softest" druse present determines the grade, rather than the predominant type as in the original Wisconsin System. In assessing drusen size, type, and area on the AREDS form, drusen that are part of a PED are included.

- On the main AREDS form "reticular" has been removed from the scales of drusen size and softness, and presence of reticular and calcified drusen are assessed as separate characteristics. (On the drusen extension, “reticular” remains as a separate step on the size and softness scales.)

- On both the main AREDS form and the drusen extension, the grading scale for drusen area has been simplified, in that the same steps are used in each of the 3 locations.

- Drusen confluence has been deleted from the drusen section on the main AREDS form, although not from the drusen extension.

- A new item has been incorporated from the Beaver Dam Eye Study adaptation of the original Wisconsin System that allows the grader to record the presence of each type of drusen, and the predominant type among them, for groups of subfields.

5.0 OTHER CHANGES FROM ORIGINAL WISCONSIN SYSTEM

Specific items for retinal/choroidal degeneration (other, retinal edema, retinal hemorrhages/microaneurysms, and surface wrinkling retinopathy) have been deleted, but presence of these conditions, as well as others, is recorded in the "confounding ocular lesions" or "other ocular lesions" sections. The order of items on the grading form has been modified and gatekeepers added to facilitate the grading process.

6.0 GRADING FORM

The AREDS Maculopathy Grading Form consists of two parts: the main part (which includes a streamlined section for drusen characteristics), and the separate “drusen extension” (which records more detail regarding drusen).

The main part of the AREDS form (Exhibit 15B-1) begins with identifying information and a section for recording presence or absence of the fundus photographs specified in the AREDS protocol. Photographic quality is not graded on this form, but on the Photographic Quality and Preliminary Eligibility Assessment Form (Exhibit 15-1).

Section 1 of the main part of the form, "Maculopathy", includes all of the lesions of AMD except drusen, and begins with a gatekeeper allowing it to be bypassed if all of these conditions are

absent. The initial items in this section (RD, PED's, hard exudate, subretinal hemorrhage, subretinal fibrosis, and scars thought to represent photocoagulation for AMD) are graded first within all of Field 2 and then within the central zone. The remaining items (geographic atrophy, RPE depigmentation [termed RPE degeneration in the original Wisconsin System and non-geographic atrophy in the Macular Photocoagulation Study], and increased pigment) are graded first in the central subfield, then in the central zone, and finally within the grid as a whole. Geographic atrophy is also graded at the center of the macula.

Sections 2 and 3 of the form are used to record other lesions, Section 2 for those that exclude a subject ("Confounding Ocular Lesions") and Section 3 for those that do not ("Other Ocular Lesions"). Lists of conditions and code numbers are provided for each section (Exhibit 15B-3).

Sections 4 through 11 of the form are concerned with drusen, beginning with a gatekeeper that eliminates grading for drusen area if end-stage AMD is present, defined as presence of any of the following: RD, PED other than drusenoid, subretinal hemorrhage, subretinal fibrosis, scars of photocoagulation for AMD, or geographic atrophy definitely present in the central subfield and questionably or definitely involving the center of the macula. Section 12 is provided for comments.

The drusen extension part of the AREDS form (Exhibit 15B-2) begins with an identification section similar to that on the main part of the form. Next, the grader is required to confirm the order of subfields appropriate to that eye (clockwise for right eyes, counterclockwise for left eyes), since the subfield designations are a mirror image between left and right eyes.

The body of the drusen extension is concerned with various drusen characteristics: maximum size in each subfield, softest type in each subfield, presence of each type (and predominant type among them) by subfield group, and confluence of drusen (including longest continuous dimension of confluence).

7.0 SENSORY RETINAL AND RETINAL PIGMENT EPITHELIAL DETACHMENTS

7.1 Overview

(a) When the *sensory retina* (this term, or simply *retina*, is used here to designate all layers of the retina except the pigment epithelium) is normal and in its normal position adjacent to the pigment epithelium, it appears transparent, except for subtle reflections from its inner surface and for blood flowing through the vessels located in its inner layers. Elevation of the retina (i.e. displacement toward the center of the vitreous cavity), an important feature of AMD and several other retinal disorders, is assessed in stereo photographs in part by the position of the retinal blood vessels and in part by partial or complete obscuration of the RPE/choroidal pattern. Obscuration of this pattern occurs when the retina is separated from the RPE, particularly when the fluid responsible for the separation is opaque, but also to some extent when it is clear, because the normal retina is not perfectly transparent and this lack of complete transparency becomes obvious when the retina is separated even slightly from the RPE. Elevation of the retina occurs when it is pushed forward by accumulations of

fluid, blood or fibrovascular tissue between it and the RPE, or when the RPE and the overlying sensory retina are pushed forward together by such accumulations (or mounds of drusen) between the RPE and the choroid. The sensory retina also *appears* elevated when its vessel-containing inner layers are elevated because of thickening within the retina (edema) or splitting of the inner layers of the retina from its outer layers (retinoschisis), processes not usually seen in AMD.

(b) In this grading protocol retinal detachment (RD) is considered to be present when the retina is visibly elevated away from the RPE by an accumulation of clear or turbid fluid (serous sensory retinal [SSR] detachment) or by blood (hemorrhagic RD). In keeping with clinical convention, RD is *not considered to be present* over a thin layer of subretinal blood, when the retina does not appear visibly elevated. Similarly, by convention, RD is *not considered present* over a subretinal fibrous scar when the retina appears tightly apposed to the scar tissue without intervening fluid, even though elevation of the retina is clearly visible. Pigment epithelial detachment (PED) is considered to be present when the RPE (and overlying retina) are together visibly elevated away from the underlying choroid. Drusen, which usually lie between the basal lamina of the RPE cells (the inner layer of Bruch's membrane) and the deeper collagenous/elastic layers of Bruch's membrane, often are detached along with the RPE.

(c) In the AREDS grading, unlike the subfield-by-subfield grading of the original Wisconsin System, RD and PED are graded as separate items, and drusenoid PED's are considered separately from PED's of other types. The principal criterion for recognition of either RD or PED is the perception of elevation of the retina during stereoscopic viewing. This requires *normal stereopsis* on the part of the grader and *good quality stereoscopic fundus photographs*. The first task of the grader is to determine whether elevation is present, then, if it is, to characterize its type. RD is distinguished from PED principally by the obscuration of the RPE pattern (and the underlying choroidal pattern as well) that occurs when the translucent retina is separated from the underlying RPE. This obscuration increases both with increasing separation of the retina from the RPE (even when the subretinal fluid is clear) and with increasing turbidity of the subretinal fluid (even if the separation is very slight), becoming most obvious when the subretinal fluid is a thick layer of blood. Thus an area in which the retinal vessels appear elevated is graded as RD if the RPE/choroidal pattern is obscured and the RPE is presumed to be in its normal position, and as PED if the RPE pattern is clearly visible and appears to be elevated along with the retina and in apposition to it. Frequently both types of detachment are present together.

(d) There is one exception to the general rule that elevation must be perceived stereoscopically for RD to be recognized. When it is necessary to grade photographs with little or no stereoscopic effect (rather than having them retaken), obscuration of the RPE/choroidal pattern in a localized area may be sufficiently suggestive of RD to merit a grade of definitely present or questionable.

7.2 Total area of Detachment (RD plus PED)

If detachment of one or more types (including drusenoid PED) is definitely present, the total area within Field 2 occupied by detachment is estimated to the nearest disc area (if definitely present but < .5 DA, recorded as 0 to indicate the range 0.1 to 0.4).

7.3 Drusenoid PED

Drusenoid PED's are usually easily identified as elevated mounds that appear to be made up of one or more large soft indistinct drusen or many confluent drusen. See Examples #22 (59-385 RE) and #26 (61-398 RE). Deposits of pigment may be visible on the surface of the PED, but for the most part the RPE overlying the mound of drusen appears depigmented (and in histologic sections often appears thinned), so that the predominant color of a drusenoid PED is pale yellow to white. The margins of a drusenoid PED are usually fairly well-defined and its elevation low to moderate. Large drusen or clumps of confluent drusen must be at least the diameter of Circle I-2 in narrowest diameter *and must appear elevated* to be classified as drusenoid PED (see Example #21 [60-347 RE]). In very large drusenoid PED's there may be small areas between or adjacent to large drusen where the color is like that of normal RPE and the appearance suggests presence of a small amount of subRPE or subretinal fluid (see Example #27 [55-346 RE]). Such areas are not classified as serous PED or RD. Drusenoid PED is graded absent, questionable, or definite, first in all of Field 2 and then in the central zone.

7.4 Other Types of PED

(a) Serous or hemorrhagic PED's

Serous PED's are characterized by sharply defined, solid-looking, typically dome-shaped but sometimes shallow elevations of the RPE, usually 500 to 3000 μm in diameter (see Example #29, 58-011 RE, and Standard #12). These elevations are round, oval or kidney-shaped and usually have clearly visible margins and a smooth surface contour. They have a uniform orange color of normal RPE with or without visible drusen and/or pigment deposits. When many large drusen are present, the appearance may be similar to drusenoid PED (see Example #30, 61-431 RE). Shallow serous PED's typically have a smooth, gently sloping surface that thins to a narrow, somewhat less well-defined border (the PED has the cross sectional shape of a strong plano-convex lens, see Example #36, 61-364 LE). The term "hemorrhagic" is used clinically for PED's that are dark gray or black in color, indicating subRPE blood, but in this classification hemorrhagic and serous PED's are placed in the same category, and presence of subRPE or subretinal blood is graded as a separate item.

(b) Irregular (fibrovascular) PED's

Irregular (fibrovascular) PED's can be recognized reliably in color photographs only if good stereoscopic effect is present, and even then are subtle and easily overlooked,

because their elevation is low, their color is often similar to that of the surrounding RPE, and their margins are not well defined. See Example #33 (53-006 RE). The term "irregular" applies mainly to the surface contour of the PED. The surface contour of an irregular PED typically varies irregularly from one area to another, an appearance leading to the descriptive term "lumpy, bumpy RPE". Alternatively, the surface contour may be quite smooth, but the cross sectional shape of the PED is more like a low plateau than a plano-convex lens, i.e. the edges do not thin to a narrow border. The "plateau" may be tilted, i.e. higher along one edge than another, and its edges are often ill-defined. The color of an irregular PED may also be irregular, with foci of increased pigment intermixed with areas of depigmentation and/or drusen, but in some cases is more uniform and similar to a serous PED. See also Examples #32 (52-071 LE), #34 (58-327 LE) and, #35 (58-353 RE).

(c) Grading of non-drusenoid PED's

Typical, dome-shaped serous PED's are easily distinguished from typical irregular PED's, but many shallow PED's have an intermediate appearance and are difficult to classify. See Standard #16, Example #36 (61-364 LE), and Example #37 (59-058 RE). In grading serous and irregular PED's the grader first decides whether a PED of either type is absent, questionably present ($\geq$ 50% but < 90% certain) or definitely present, first in Field 2 as a whole and then within the central zone. If questionably or definitely present in one or both areas, a second item is completed indicating (for all of Field 2) the predominant type of PED: (1) dome-shaped serous or hemorrhagic, (2) shallow (with some features suggestive of serous/hemorrhagic or irregular, but without the degree of elevation typical of dome-shaped serous/hemorrhagic PED and without the unevenness of surface contour typical of an irregular PED), or (3) irregular (with obviously irregular surface contour).

7.5 Retinal Detachment (RD)

RD's may be seen alone or in combination with PED's. In AMD the most commonly observed RD is serous (serous sensory retinal [SSR] detachment). These RD's are slightly more pale in color than serous PED's, with decreased visibility of the underlying RPE pattern. Their margins are often ill-defined (see Standard #11, Example #41 [54-372 LE], and Example #45 [52-512 RE]). When subretinal hemorrhage is so extensive as to cause definite elevation of the retina, this area is included as RD (see Standard #15).

The reader should review the special conventions regarding classification of RD contained in Sections 15B-7.1.b & d at this point.

RD is graded absent, questionable, or definitely present, first in Field 2 as a whole and then in the central zone.

8.0 HARD EXUDATES

Hard exudates are small white or yellowish white punctate or linear deposits with distinct margins. When related to AMD, hard exudates are often arranged adjacent to PED's and/or under the peripheral parts of RD's. Pale spots that appear to be deposits on the posterior surface of detached sensory retina are included in the estimate of hard exudates. Hard exudates are graded absent, questionable, or definitely present, first in Field 2 as a whole and then in the central zone.

9.0 SUBRETINAL OR SUBRPE HEMORRHAGE

Hemorrhage between the sensory retina and the RPE usually appears red, like the color of venous blood, retinal hemorrhage or preretinal hemorrhage. When a layer of subretinal or preretinal hemorrhage is particularly thick, however, it may look reddish-black. SubRPE hemorrhage usually appears dark gray and may be difficult to distinguish from pigment. Often both may appear together. Subretinal/subRPE hemorrhage is graded absent, questionable, definitely present, or cannot grade, first in Field 2 as a whole and then in the central zone.

10.0 SUBRETINAL FIBROUS SCAR (OR FIBRIN)

Sheets or mounds of white material under the retina in eyes with age-related macular degeneration usually represent fibrous or fibrovascular tissue that has proliferated in areas previously occupied by serous or hemorrhagic subretinal fluid. Early in the development of such scars the white material may sometimes be fibrin. No attempt is made to distinguish between fibrin and fibrous tissue in the classification. See Example #47, 52-516 RE, and Example #45, 52-512 RE. Subretinal fibrous tissue is graded absent, questionable, definitely present, or cannot grade, first in Field 2 as a whole and then in the central zone.

If subretinal new vessels are visible, their presence is recorded in the "Comments" section.

11.0 SCARS OF PHOTOCOAGULATION FOR AMD

Scars classified as representing photocoagulation for AMD may be difficult to differentiate from geographic atrophy or other chorioretinal scarring. Factors to be considered are location, margins, and degree of preservation of the RPE and choroid. Photocoagulation scars are often located so as to avoid or minimize involvement of the center of the macula. Other locations may be central, resulting from treatment of a subfoveal neovascular membrane, or peripapillary, resulting from treatment of new vessels here. Within such scars the RPE usually appears to have been completely destroyed and the choroid severely damaged and/or obscured by fibrous tissue, with loss of the normal pattern of large choroidal vessels. This degree of destruction is greater than that usually seen in geographic atrophy or in the RPE depigmentation that occurs adjacent to subretinal fibrous scars. In some cases, however, a narrow zone of less severely damaged RPE and choroid may be seen adjacent to a typical photocoagulation scar. Large deposits of pigment may also be seen at the margin of photocoagulation scars. Photocoagulation scars are graded absent, questionable, definitely present, or cannot grade, first in Field 2 as a whole and then in the central zone.

12.0 GEOGRAPHIC ATROPHY

Geographic atrophy is one or more sharply defined, usually more or less circular patches of partial or complete depigmentation of the RPE, typically with exposure of underlying large choroidal blood vessels. To be classified as geographic atrophy, a patch must be at least as large in area as Circle I-1. In general, at least two of the characteristics mentioned above (sharp edges, more or less circular shape, and visibility of underlying choroidal vessels) are required for a patch to be classified as geographic atrophy. Thus, even if much of the RPE appears to be preserved and large choroidal vessels are not visible, a roundish patch of RPE depigmentation with sharp edges may still be classified as geographic atrophy. The criterion of "edge sharpness" may be fulfilled in either of two ways: (1) when the depigmentation within the patch is subtle, a "sharp" edge must be abrupt and smooth, like one made with a cookie-cutter, but (2) when contrast between depigmentation within a patch and the normal pigmentation around it is substantial, the edge of the patch may still be considered "sharp", even if the transition occurs gradually or irregularly over a zone 125 to 250 μm in width. In the latter case, observation of the patch without magnification may be helpful in supporting the overall impression that the edge is "sharp". However, increased visibility of large choroidal vessels is the single most important criterion and, when present, it is not necessary for all the edges of the patch to be sharp; 25% of its circumference may be sufficient.

A potential area of disagreement is the categorization of areas of RPE atrophy adjacent to (or forming the peripheral part of) disciform scars. These areas may have an appearance very similar to that of geographic atrophy. Because such areas have not conventionally been described as geographic atrophy, they will not be so classified here. Sarks & Sarks state, "Use of the term geographic atrophy should be restricted to the end result of the atrophic form of age-related macular degeneration" (Ryan, Ed., Retina, Vol. 2, pp. 167-171). RPE atrophy adjacent to disciform scars will be included in the estimate of RPE depigmentation, with a grade of questionable assigned to geographic atrophy if an appearance typical of geographic atrophy is present in such a location.

Presence of geographic atrophy is graded first at the center of the macula: grade 0 if the center is definitely uninvolved; grade 1 (questionable) if the grader can not be $\geq$ 90% certain whether the center is or is not involved; and grade 2 if the center is definitely involved. After grading the center point, the central subfield, central zone, and area within the grid are graded, according to total area of geographic atrophy within the zone being graded. The steps in the scale are listed below.

Grade	Definition
0	None
1	Questionable
2	Present, < Circle I-2
3	Present, $\geq$ Circle I-2, < Circle O-2
4	Present, $\geq$ Circle O-2, < 1/2 disc area
5	Present, $\geq$ 1/2 disc area, < 1 disc area
6	Present, $\geq$ 1 disc area, < 2 disc areas
7	Present, $\geq$ 2 disc areas

8	Cannot grade

13.0 RPE DEPIGMENTATION (RPE DEGENERATION, NON-GEOGRAPHIC ATROPHY)

Areas of depigmentation (atrophy) of the RPE that do not meet the requirements for geographic atrophy are placed in this category. Such areas are less well defined (i.e. have less sharp edges), less regular in shape (i.e. less circular or oval), and/or less severe (i.e. the underlying choroid is less visible) than geographic atrophy. Small areas of RPE depigmentation are often seen adjacent to foci of increased pigment. Detection of these sometimes subtle abnormalities is facilitated by careful examination of Fields 1M or 3M, where the central zone is less directly illuminated ("proximal illumination") and increased/decreased pigmentation located here is often more clearly visible (see Example #34, 58-327 LE). Large areas of RPE depigmentation are often seen partially or completely surrounding subretinal fibrous scar tissue (see Example #47, 52-516 RE). RPE depigmentation is graded in the central subfield, central zone, and area within the grid, according to total area involved in each. The steps in the scale are listed below.

Grade	Definition
0	None
1	Questionable
2	Present, < Circle I-2
3	Present, $\geq$ Circle I-2, < Circle O-2
4	Present, $\geq$ Circle O-2, < 1/2 disc area
5	Present, $\geq$ 1/2 disc area, < 1 disc area
6	Present, $\geq$ 1 disc area, < 2 disc areas
7	Present, $\geq$ 2 disc areas
8	Cannot grade

14.0 INCREASED PIGMENT

Disturbances of the RPE sometimes lead to deposition of granules or clumps of gray or black pigment in or beneath the retina. Such pigment deposits are found in some eyes with age-related maculopathy, but may also be a result of previous traumatic, inflammatory, toxic, or congenital processes. Pigment deposits that the grader believes to be the result of such processes, or of photocoagulation, are graded 7 (cannot grade - pigment other), except that the halos of pigment surrounding drusen are excluded from consideration, as are peripapillary pigment deposits. Care must also be taken to distinguish pigment deposits from dirt on the viewing box or mounting sheet, or from other artifacts. Increased pigment is frequently most easily detected with proximal illumination. It is graded in the central subfield, central zone, and area within the grid, according to total area involved in each. The steps in the scale are listed below.

Grade	Definition
0	None
1	Questionable
2	Present, < Circle C-0
3	Present, ≥ Circle C-0, < Circle C-1
4	Present, ≥ Circle C-1, < Circle C-2
5	Present, ≥ Circle C-2, < Circle O-2
6	Present, ≥ Circle O-2
7	Pigment, other
8	Cannot grade

15.0 CONFOUNDING LESIONS

Presence of one or more non-AMD lesions that might interfere with assessment of AMD and its causal role in visual loss is indicated by a "yes" response to this item, followed by recording of the code number for the lesion(s) from a list (Exhibit 15B-3) and a grade of questionably or definitely present. As many as three lesions can be listed.

15.1 Surface Wrinkling Retinopathy

The mildest degree of this condition (cellophane reflexes) is seen as a patch or patches of irregular increased reflection from the inner surface of the retina, resulting from slight contraction of a thin transparent glial membrane on the inner surface of the retina, as seen in Standard Photograph #19 in the central and inner subfields. In some cases, shrinkage is sufficient to produce fine retinal traction lines, as in Standard Photograph #20. Visible fibrous (glial) tissue may also be present.

If traction lines (folds) are present, or if there is a patch of cellophane reflexes ≥ 1 DA in extent even without traction lines, this lesion is recorded in Section 2, Confounding Ocular Lesions, and disqualifies the subject from entry into the AREDS.

15.2 Abnormalities Attributable to Myopia

Subjects are excluded from AREDS if either eye is highly myopic as defined by any of the following: (1) refractive error of -8.00 diopters (spherical equivalent) or more, (2) myopic peripapillary crescent equalling or exceeding in width one-half the *greatest diameter* of the disc (vertical, horizontal, or oblique), (3) pigmentary abnormalities in the posterior pole considered by the clinic ophthalmologist or the Reading Center more likely due to myopia than AMD. It is unlikely that eyes with typical myopic degenerative lesions (lacquer cracks, gyrate atrophy of the RPE and choroid, Foerster-Fuchs spots) will be submitted for entry into AREDS (see Gass' Stereoscopic Atlas of Macular Diseases for examples).

16.0 OTHER OCULAR LESIONS

Non-AMD lesions that do not exclude a subject are recorded here as described in Section 15B-15, using the list shown in Exhibit 15B-3.

17.0 DRUSEN (See also Section 15B-4)

17.1 Main AREDS Form

17.1.1 Drusen Within the Grid

This is a gate-keeper question for items 5 through 7 on the main part of the AREDS form (Exhibit 15B-1). If the grade is 0 (none) or 8 (cannot grade), items 5 through 7 are omitted. If the grade is 7 (presence of advanced AMD), items 5 and 6 are completed, but drusen area (item 7) is omitted. If the grade is 2 (drusen questionably or definitely present and advanced AMD absent), all of items 5 through 7 are completed.

17.1.2 Maximum Drusen Size

Maximum drusen size is graded only within the grid as a whole, according to the guidelines in Sections 15A-9 and 10 of the original Wisconsin System.

17.1.3 Soft Drusen

Grade 0 is selected when maximum drusen size is < Circle C-0. When drusen size is ≥ Circle C-0 but < Circle C-1, drusen are placed in either a hard or soft category on the basis of uniformity of density (color) from center to periphery, sharpness of edges, and thickness: those with decreasing density from center to periphery and fuzzy edges generally are placed in the soft-indistinct category; those with uniform density, sharp edges, and a solid, thick appearance in the soft-distinct category; and those with sharp edges but without a solid, thick, nodular appearance in the hard category. Drusen as large as or larger than Circle C-1 are placed in either of the soft categories.

Grade 0 is selected when maximum drusen size is < Circle C-0, or when maximum size is ≥ Circle C-0 but < Circle C-1 and no drusen belonging to the soft-distinct or soft-indistinct category are present. Grade 1 is selected when one or more soft distinct drusen, but no soft-indistinct drusen, are present. Grade 2 is selected when one or more soft-indistinct drusen are present. Reticular drusen are included in the soft-indistinct category.

17.1.4 Drusen Area Within the Grid

Area covered by drusen is estimated by mentally moving together all drusen graded 2 through 5 for size and comparing this area to areas of standard circles, and to the area of the standard disc

(using the subfields of the grid as an aid: central subfield = 4/9 DA, each inner subfield = 8/9 DA). Three areas are graded, the central subfield, the central zone, and the area within the grid. The steps in the scale are listed below.

Grade	Definition
0	Drusen absent or questionable, or area covered by drusen < Circle C-0
1	Area covered by drusen ≥ Circle C-0 but < Circle C-1
2	Area covered by drusen ≥ Circle C-1 but < Circle C-2
3	Area covered by drusen ≥ Circle C-2 but < Circle I-2
4	Area covered by drusen ≥ Circle I-2 but < Circle O-2
5	Area covered by drusen ≥ Circle O-2 but < 1/2 disc area
6	Area covered by drusen ≥ 1/2 disc area but < 1 disc area
7	Area covered by drusen ≥ 1 disc area
8	Cannot grade

17.1.5 Drusen Area Outside the Grid

All area outside the grid is considered, including Fields 1M and 3. The goal is only to identify eyes with drusen ≥ Circle O-2 in extent, all lesser amounts being pooled with absent.

17.1.6 Reticular Drusen

The term *reticular drusen* has been chosen for the yellowish material that looks like soft drusen arranged in ill-defined networks of broad interlacing ribbons. A good example of reticular drusen is visible in Standard Photograph #10 in the outer superior and temporal subfields on either side of the 1:30 meridian. When reticular drusen are present, they are often more prominent outside than inside the grid. Grade 1 is selected for eyes with questionable reticular drusen, grade 2 when reticular drusen are definitely present but only in the area outside the grid, grade 3 when reticular drusen are present within the grid (with or without presence outside the grid).

17.1.7 Calcified Drusen

This term is used for drusen that are chalky-white or shiny, suggesting deposition of calcium. Absence, questionable presence, or definite presence is indicated, considering all of the area included in the fundus photographs.

17.2 Drusen Extension Form

This part of the AREDS grading form is separate from the main part of the form, and is designed to provide further detail regarding drusen characteristics. The drusen extension is completed only for eyes without advanced AMD.

17.2.1 Maximum Drusen Size

Maximum drusen size is graded in each of the nine subfields within the grid, within Field 2 outside the grid, and within Field 1 nasal to the disc, according to the guidelines in Sections 15A-9 and 10 of the original Wisconsin System. As in that system, "reticular" constitutes the most severe step on the scale. This item also allows the grader to indicate whether the center point of the macula is involved by a druse, and if so whether that druse is reticular.

17.2.2 Worst Drusen Type

Worst drusen type is graded in each of the nine subfields within the disc, and in Field 2 outside the grid, according to the guidelines in Section 15A-12 of the original Wisconsin System. For the AREDS grading, however, worst type rather than predominant type is recorded. As in the original Wisconsin System, "reticular" constitutes the most severe step on the scale. This item also allows the grader to indicate whether the center point of the macula is involved by a druse, and if so the type of that druse.

17.2.3 Multiple Drusen Types (BDES "Grid type")

This item, which has been incorporated from the Beaver Dam Eye Study (BDES) adaptation of the original Wisconsin System, allows the grader to record the presence of each type of drusen, and the predominant type among them, for the center subfield, the grouped inner subfields, and the grouped outer subfields. Types of drusen evaluated consist of hard distinct, soft distinct, soft indistinct, and reticular, as defined in Section 15A-12 of the original Wisconsin System. For each drusen type, presence is recorded utilizing the following codes:

Grade	Definition
0	Absent
1	Questionable
2	Present (but not predominate)
3	Predominate
8	Cannot grade

17.2.4 Drusen Confluence

Confluence of drusen, and if confluent the longest continuous dimension of confluence, is graded according to the guidelines of 15A-14 of the original Wisconsin System. Only the item pertaining to all of Field 2 (rather than the items specific to each subfield with the grid) has been retained in the AREDS grading.

18.0 COMMENTS

The main part of the AREDS grading form concludes with a section for comments.

19.0 EXAMPLE PHOTOGRAPHS

These photographs and their descriptions are provided to assist graders in applying the protocol in a standard way that will be reproducible within and between graders and over time. Many borderline cases have been included deliberately to help define the limits of the "questionable" grade and the choices between different types of detachments (RD versus PED, types of PED) and different degrees of depigmentation (RPE degeneration versus geographic atrophy).

19.1 **Drusenoid PED's** (Review Section 15B-7.3)

(a) Example #21 (60-347 RE)

Small, intermediate, and large drusen are present in this eye. In the inner inferior subfield near the 4:30 meridian, there is a small mound of drusen material larger than Circle I-2 in diameter, with pigment clumps on its surface. It is slightly but definitely elevated and should be graded as a definite drusenoid PED.

(b) Example #22 (59-385 RE)

A small drusenoid PED with pigment on its surface can be seen in the central, inner nasal, and inner inferior subfields in the 4:30 meridian. It is larger and a little more elevated than the PED in Example #21. Total area of detachment is < 0.5 DA.

(c) Example #23 (52-071 RE)

In the central subfield in the 4:30 meridian there is an accumulation of drusen with overlying pigment. Although there is some substance to this lesion, it is not elevated enough to be called even a questionable drusenoid PED.

(d) Standard #13 (UW/C14318-34 LE)

There is a large druse in the central subfield that shows slight elevation. In the original Wisconsin System grade 1, questionable, or perhaps even grade 2, definite, was considered appropriate, but 3 of 5 experienced graders now consider the correct grade to be absent, while 2 favor questionable.

(e) Example #24 (58-366 RE)

In the lower part of the central subfield there is a mass of confluent large drusen large enough (≥ Circle I-2) to be considered a definite drusenoid PED, but not elevated enough. Of 5 experienced graders, 3 chose absent, 2 questionable. Compare with Examples #21 and #22.

(f) Example #25 (55-344 RE)

Most of the drusen appear to be of intermediate size. Just above the center of the macula there is a small, low mound about 400-500 μm in diameter that appears to be made up mainly of confluent drusen. Other smaller mounds are present nasal, inferior, and temporal to the center of the macula. Although these mounds appear to be made up mostly of confluent drusen < Circle C-1 in size, the largest mound has drusen material spreading beyond the central confluent clump, and this would lead most graders to choose ≥ Circle C-2 for maximum drusen size and soft indistinct for type. This largest mound meets the minimum size criterion for drusenoid PED (≥ Circle I-2), but its degree of elevation is borderline. Of 5 experienced graders 2 chose absent, 3 questionable for drusenoid PED. One of the graders choosing absent commented that the camera artefact overlying the nasal part of the mound may be exaggerating the degree of elevation.

(g) Example #26 (61-398)

A low drusenoid PED is present in the inner nasal and inner inferior subfields, extending almost to the 1:30 and 7:30 meridians. The contrast between the choroidal background and the color of the drusenoid PED is not quite as marked as it is in Example #22, perhaps making the elevation less obvious. However, definite elevation is present and this area should be graded definite drusenoid PED. There is perhaps a suggestion of RD (SSR detachment) in the inferior and nasal part of the central subfield adjacent to the PED, but this was considered less than 50% likely and RD was graded absent. Total area of detachment is slightly less than 0.5 DA (the area of each inner subfield is 8/9 DA, that of the central subfield 4/9 DA).

(h) Examples #27 (55-346 RE) & 28 (55-346 LE, Fields 1M & 2)

In both eyes there are many large soft drusen, some of which form confluent masses occupying most of the area with 1 disc diameter of the center of the macula. In the right eye there is good stereoscopic effect and definite RPE elevation, most of which appears to be made up of yellowish-white drusen, although the superior nasal aspect of the mound has a darker appearance suggestive of detachment of intact RPE (serous PED). The Reading Center considered this to be a drusenoid (only) PED. Some observers suggested that serous RD might be present temporal to the PED. Note, however, that the quality of the left member of the stereo pair is poor, especially temporally. This makes it impossible to be sure whether serous RD is present or not; the Reading Center considered it less than 50% likely and thus graded it absent.

In the left eye the elevation of the large confluent masses of drusen is not so obvious, particularly when Field 2 only is considered. Field 1 is helpful (and would be more so if it were centered at the temporal disc margin, as specified for Field 1M in the revised protocol) in documenting a low PED, which the Reading Center considered to be definite. The total area of detachment is about 3 DA in each eye. Compare with Example #30 (61-431 RE).

19.2 Dome-shaped Serous PED's (Review Section 15B-7.4.a)

(a) Example #29 (58-011 RE)

There is a dome-shaped serous PED centered in the temporal part of the outer inferior subfield, with a narrow rim of RD (SSR detachment) adjacent to it (most prominent in the outer temporal subfield and below the outer inferior subfield). A thin light line just temporal to the 7:30 meridian defines the temporal edge of the PED (beyond this line is SSR detachment). The edge of the PED can be followed most easily upwards along the 7:30 meridian. It then crosses into the lower corner of the inner temporal subfield, then into the lower portion of the inner inferior subfield, then cuts diagonally through the center of the outer inferior subfield, extends just below its lower edge at about 7 o'clock, and returns to cross the 7:30 meridian again. The shallow SSR detachment extends for another 500-700 μm below and temporal to the PED. The surface of the PED is very smooth, with the reddish-orange color and finely granular pattern of intact RPE visible over its entire elevated dome. This granular RPE pattern is blurred in the areas of SSR detachment. The total area of detachment is 3 or 4 DA. Centered in the lower posterior part of the inner nasal subfield some observers suggest that there is a small, low, subtle elevation of the RPE that might be a PED of the irregular type. If this alone were present, some graders might assign a grade of questionable for PED, but most would consider the likelihood less than 50% and assign a grade of absent.

(b) Standard #12 (FES/3605 LE)

A sharply defined, dome-shaped serous PED is centered near the upper edge of the inner inferior subfield and extends into the remaining inner subfields, the central subfield, the outer inferior subfield, and a very small part of the outer nasal subfield. The intermittent light areas, most prominent in the inner inferior subfield, are drusen material pulled up along with the RPE. Several clumps of pigment are present on the surface of the PED. In the central subfield the color of the PED is reddish-orange and the fine granular RPE pattern is visible. Elsewhere the color is more pale and the RPE pattern is less visible, suggesting SSR detachment, but the presence of drusen leaves no doubt that the RPE is detached from the choroid, not the retina from the RPE. The surface of the PED is smooth, its edges are easily defined, and there is no surrounding SSR detachment. Total area of detachment is 2 DA.

(c) Example #30 (61-431 RE)

A dome-shaped serous PED is centered near the junction of the central and inner temporal subfields and extends also into the inner superior and inner inferior subfields. Its edges are well defined and there is no obvious surrounding or overlying RD. Perhaps there is a suggestion of SSR detachment at the junction of the inner and outer nasal subfields in Field 2, but this is not confirmed in Field 1M. The surface of the PED is smooth and in most areas its color is the reddish-orange of normal RPE. However, near the center of the PED there are several foci of pigment and a hint of several large drusen buried within it. If all of the PED had this appearance, it might be classified as drusenoid, rather than dome-shaped serous. Total area of detachment is 1 DA.

(d) Example #31 (60-345 RE)

A large "U" shaped, shallow to moderately elevated serous PED can be seen encircling the center of the macula from about 2 to 10 o'clock. It occupies part of the central subfield as well as all of the inner inferior subfield, most of the inner nasal and temporal subfields, and parts of the outer nasal, inferior, and temporal subfields. The surface of the elevated area is smooth and its edges fairly well demarcated in some, but not all, areas. There is subretinal and/or subRPE hemorrhage near the edge of the PED, and a vertical streak of subretinal hemorrhage in the inner and outer inferior subfields. There are scattered foci of pigment and a few drusen on the surface of the PED, but otherwise its color is the reddish-orange of intact RPE, except for a tiny light area in the inner temporal subfield at 10:30, which would be graded questionable or definite RPE depigmentation. There appears to be RD (SSR detachment) adjacent to the PED in the outer inferior subfield. Total area of detachment is 6 or 7 DA (including both PED and RD). There is little doubt that this PED is serous, as opposed to irregular, and its elevation is sufficient to place it in the dome-shaped category.

19.3 Irregular (fibrovascular) PED's ("lumpy-bumpy RPE") (Review Section 15B-7.4.b)

(a) Example #32 (52-071 LE)

There is a subtle, shallow elevation of the RPE centered in the inner temporal subfield and extending into adjacent subfields. The highest part of this elevation is in the inner temporal subfield, and it slopes gradually into the outer temporal, inner superior, and inner inferior subfields. Just after entering the central subfield the PED dips to a lower plateau, and the elevation gradually disappears in the inner nasal subfield. There are many pigment clumps on the surface of this detachment, and in the central subfield there is a faint whitish haze that is probably subretinal fibrous tissue. This PED is very shallow, its surface contour is irregular, and its edges are poorly defined, as is characteristic of irregular (fibrovascular) PED's. Total area of detachment is 2 or 3 DA.

(b) Example #33 (53-006 RE)

There is a very subtle, low elevation best seen near the junction of the inner superior, inner temporal, and central subfields. The temporal and superior edges of this elevation can be recognized about 3/4 of the way from the posterior to the peripheral limits of the inner temporal and inner superior subfields, and parallel to them. The nasal and inferior edges of the elevation are very ill-defined. There are scattered foci of pigment, drusen, and some small depigmented spots (RPE depigmentation) over and adjacent to the area of elevation. In the surface contour of the elevated area there appear to be many very subtle irregularities, but perhaps the impression of irregular contour results from the irregular surface pigmentation. At any rate, this elevated area does not have the smooth, "inflated" appearance of a shallow serous PED (see Example #36 61-364 LE) and there is little doubt that it fits best in the irregular (fibrovascular) category. There is no suggestion of any SSR detachment. Total area of detachment is a little greater than 1 DA. Good stereopsis is essential to the above description; monocular viewing of the right member of the pair gives little or no hint that a PED is present.

(c) Example #34 (58-327 LE, Fields 1M, 2, & 3M)

Even though both members of the Field 2 stereo pair have borderline to poor focus/clarity, there is excellent stereoscopic effect, which allows recognition of a low, donut-shaped elevation encircling the center of the macula in the central subfield and involving one-half or more of each inner subfield. A further portion of this elevation, shaped like a linear Indian burial mound oriented East to West, extends into the outer temporal subfield just above the 3 o'clock meridian. This extension, too, is low, making its edges difficult to define. In the 2:30 to 7:30 segment of the donut the elevation appears to involve mainly the RPE (i.e. to be a low PED). In the 7:30 to 1:00 segment the retina appears slightly pale and the underlying RPE/choroidal pattern is more blurred than elsewhere, and in the 1:00 to 2:30 segment the retina appears slightly elevated away from the RPE. From Field 2 alone, the best interpretation would appear to be that this is definitely an irregular PED (at least the 2:30 to 7:30 segment of the donut and its temporal extension) with associated definite low SSR detachment (the 7:30 to 2:30 segment of the donut, where the presence of underlying PED is uncertain). Fields 1M and 3 M confirm the impression of pallor and blurring of the RPE/choroidal pattern in the upper nasal part of the "donut", but are not otherwise very helpful, in spite of fairly good stereoscopic effect in Field 1M. Substituting Field 3M for the left member of the Field 2 stereo pair is also not very helpful; if anything, the impression of SSR detachment is strengthened and that of PED weakened. Total area of detachment is 3 DA.

(d) Example #35 (58-353 RE, Fields 1M, 2, & 3M)

There is a very shallow, plateau-like elevation of the RPE involving most of the area included in the central and inner subfields (the "central zone") and extending into the outer temporal and perhaps the outer superior subfield. The surface of this elevation has an irregular contour. There are heavy deposits of increased pigment and more

subtle areas of decreased pigment (RPE depigmentation) over most of the surface of the elevated area. There are more extensive areas of RPE depigmentation involving most of the area included in the outer subfields and particularly prominent in the outer nasal subfield, where the appearance is very similar to that of geographic atrophy. At the lower nasal corner of the inner nasal subfield (and extending slightly into the adjacent subfields) there is an elevated nubbin of subretinal fibrous tissue, with no more than a suggestion of SSR detachment just temporal to it. In the lower nasal corner of the outer temporal subfield there is also perhaps a suggestion of SSR detachment, in that a small distance can be seen between the vertically-running small venule and the underlying choroidal pattern. There is also a suggestion of obscuration of the RPE/choroidal pattern in the posterior one-half of the inner temporal and inner superior subfields from 9 to 12 or 1 o'clock. None of these three "suggestions", nor all of them taken together, is enough to support a grade of even questionable RD. Field 1 M is helpful in confirming that the upper nasal edge of the PED is indeed elevated; substituting Field 3M for the right member of the Field 2 stereo pair is not helpful. All of 5 experienced graders agreed that this was a definite PED, of the typical irregular type ("lumpy-bumpy RPE"). Total area of detachment is 3 DA.

19.4 **Shallow PED's** (Review Section 15B-7.4)

This category includes shallow PED's that may be either serous (or hemorrhagic) or irregular. This category is provided because of the frequent difficulty in distinguishing between shallow serous and irregular PED's in color stereo photographs alone.

(a) Example #36 (61-364 LE, Fields 1M, 2, & 3M)

A shallow but definite elevation of the RPE occupies essentially all of the inner inferior subfield and extends into adjacent subfields. Its shape is similar to that of a strong convex lens, with a smooth surface that curves gradually to its thin, sharp, fairly well defined edges. Its color is the reddish-orange of intact RPE and similar to that of the uninvolved fundus. These characteristics indicate that this is definitely a PED, probably of the shallow serous type. However, it is possible this could be an irregular fibrovascular PED with an unusually smooth surface. Because of the difficulty in making this distinction both types are included in the "shallow" category. Field 1m is helpful (but unnecessary) in confirming the definite, but shallow, elevation of the PED.

In a narrow ring adjacent to the PED for most of its circumference the RPE/choroidal pattern is slightly blurred and/or pale, and in the upper one-half of the inner temporal subfield the retinal vessels appear slightly elevated and out of focus. All of these features suggest accompanying SSR detachment. In the lower part of the outer inferior subfield and below it there are many small white spots that appear to be either hard exudates or drusen. Their white color, and the slightly linear (i.e. not perfectly round) contour of some of them suggest hard exudate. Field 1M is helpful in showing that at least some of these spots, those near the branching of the small

vein that approaches the PED from below, are on the posterior surface (or within) the retina, which is slightly elevated in this area, indicating that the spots are hard exudates. Field 3M is also helpful in documenting RD adjacent to the PED; when the left member of the Field 2 stereo pair is replaced by it, the elevation of the retina in the area described above and in the upper part of the inner temporal subfield are more clearly evident (definite SSR detachment).

There are two areas of subretinal hemorrhage, a sheet centered near the lower nasal corner of the inner nasal subfield and extending into adjacent subfields, and a small round spot near the upper border of the inner inferior subfield. The small linear hemorrhages in the lower part of the central subfield and the lower temporal corner of the inner nasal subfield look more superficial and are probably in the retina (record in "other ocular lesions" section). There are streaks of dark pigmentation in the central and inner nasal subfields over and adjacent to the PED. These appear deep and probably represent merely exaggerated choroidal pattern, rather than actual foci of increased pigment, or subRPE hemorrhage. Total area of detachment is 4 DA.

(b) Standard #16 (CSC/637625-5 RE)

A shallow oval elevation of the RPE occupies all of the central subfield and most of each of the inner subfields. Most of the temporal margin of this shallow PED is clearly visible, but much of its nasal margin is obscured by overlying SSR detachment, which forms a narrow rim adjacent to the PED nasally and then extends inferiorly into the outer nasal and outer inferior subfields (and below the latter). The contour of the PED appears to be plateau-like, sloping slightly from a thicker (more elevated) upper edge downwards to a thin lower edge. The color of the PED is that of intact RPE, with occasional drusen. There are sheets of subretinal hemorrhage nasal and temporal to the PED and perhaps one horizontally linear intraretinal hemorrhage at 3 o'clock in the outer part of the inner nasal subfield. This eye has a definite PED, which is probably best placed in the shallow category, and definite RD. Total area of detachment is 7 DA.

(c) Example #37 (59-058 RE)

A shallow elevation of the RPE occupies almost all of the central zone. Its edges are well defined, except from 4 to 6 o'clock, where shallow SSR detachment overlies the edge of the PED and extends slightly beyond it. There is a linear retinal hemorrhage in the area of RD and hard exudates temporal to and below it. Much of the surface of the PED has the reddish-orange color and fine granularity of intact RPE, but there are some paler areas (particularly in the central subfield) that appear to be confluent drusen and some foci of increased pigment. The surface contour (not color) of the PED is fairly smooth, and it slopes gradually to a thin edge (like a strong convex lens). This definite PED should be placed in the shallow category. Total area of detachment is about 4 DA.

(d) Example #38 (53-543 LE)

In this eye the shallow PED, which occupies small parts of the inner and outer superior and temporal subfields where they intersect, is overshadowed by the low SSR detachment that surrounds it and extends across nearly all of the central zone and into the upper edge of the outer inferior subfield. Surrounding the superior and temporal sides of the PED there is a red fringe, beneath the shallow SSR detachment; this could well be the edge of a subretinal neovascular network. Stringy subretinal vessels also appear to be present inferonasal to the PED. Fine hard exudates are present in and/or beneath the retina over parts of the PED and in the inner nasal, superior and temporal subfields and in the outer superior subfield. The yellow-orange color normally present in and around the center of the macula is more prominent because of the low SSR detachment. Both PED and RD are definitely present. The surface contour of the PED appears fairly smooth (and slopes to thin margins), indicating that it should be placed in the shallow, rather than the irregular category, although this may well actually be an irregular (fibrovascular) PED. Total area of detachment is about 6 DA.

(e) Example #39 (58-038 RE)

There are three small, shallow PED's in this eye, each a bit less than one-half DA in size, in the outer subfields centered in the 5:30, 10:00, and 11:30 meridians. The definite PED at 5:30 is hemorrhagic, and is partially surrounded by a horseshoe of subretinal hemorrhage. It has a smooth, evenly convex surface. The PED's at 10:00 and 11:30 are near the borderline between questionable and definite. The upper part of the PED at 10:00 has an appearance suggestive of early (questionable) subretinal fibrous tissue. Temporal to it there are many hard exudates. The PED at 11:30 is easily overlooked. Its upper edge lies just outside the grid, its lower edge near the more temporal branch of a small vein that bifurcates just above the exact center of the outer superior subfield. Adjacent to it are many large soft indistinct drusen. There appears to be considerable distance between the RPE and the retina in the inner and outer superior subfields, and to a lesser extent in the remaining inner subfields as well. Compare the distance of the retina from the RPE here with that outside the grid temporally. It is difficult to decide whether this appearance is the result of SSR detachment or of unusually good stereoscopic effect. RD should be graded no more than questionable. The predominant PED type is shallow. Total area of detachment is about 1-2 DA.

(f) Example #40 (61-372 RE)

A shallow, round PED centered near the junction of the central and inner temporal subfields occupies most of these two subfields and extends into the inner superior and inferior subfields as well. It has a fairly smooth, evenly convex surface and its margins can be distinguished fairly well (although somewhat obscured by very shallow overlying and adjacent SSR detachment). The otherwise rather darkly pigmented PED appears to be covered in some areas by a grayish-white film of fibrous tissue or fibrin. There is one collection of bright white hard exudate temporal

to the PED and another duller collection in the nasal part of the outer inferior subfield. The RD appears to involve nearly all of the central zone and the part of the outer temporal subfield occupied by hard exudate, with total area of detachment about 5 DA. The yellow color of the retina at and around the center of the macula is increased because of the SSR detachment. The dark slightly reddish areas in the inner superior and nasal subfields at 12:30, 1:30, and 3:00 may be subretinal/subRPE hemorrhage (a grade of questionable may be best).

19.5 Retinal Detachment (Review Sections 15B-7.1 and 15B-7.5)

Many examples of RD associated with PED have been given above. This section provides examples of eyes in which RD is a more prominent feature than PED, or exists without associated PED.

(a) Example #41 (54-372 LE)

A low SSR detachment covers the entire central subfield, extends a short way into the inner superior subfield, and then fans out to cover approximately one-half or a little more of the inner nasal and inner temporal subfields and all of the inner inferior subfield, as well as the lower one-third of the outer nasal subfield and all but the inferior temporal corner of the outer inferior subfield. The subretinal fluid is fairly turbid throughout, making it difficult to decide whether a shallow PED is present (most likely at the site of the large drusen and adjacent pigment located near the junction of the central and inner inferior and nasal subfields). Of 5 experienced graders, 1 graded PED questionable, 4 PED absent. Total area of detachment is about 5 DA.

(b) Example #42 (54-427 RE, Fields 1M, 2, & 3M)

A disc-shaped, very low SSR detachment occupies the central subfield and about two-thirds of each inner subfield. Its edges are quite well defined as a circle within which the fine granularity of the RPE pattern is blurred and the RPE/choroidal background looks slightly darker. As they cross this circle, the small retinal vessels appear to turn forward slightly as they climb the low sloping elevation of the RD, and they become slightly out of focus. The subretinal fluid is clear enough to allow small drusen to be seen. Field 3M is helpful as a replacement for the left member of the Field 2 stereo pair, providing greater stereoscopic effect (and suggesting that perhaps some of the "drusen" beneath the RD are exudates on the posterior surface of the retina). No PED is present. Total area of detachment is 2 DA.

(c) Example #43 (53-493 RE)

A fairly obvious SSR detachment occupies all of the inner and outer nasal subfields and adjacent parts of the inner and outer inferior, the central, and (barely) the inner and outer superior subfields. Below the horizontal meridian under the posterior part of the RD, drusen can be seen in the plane of the RPE. Between the 1:30 and 3:00

meridians there is an oval pale area with a ring of surrounding pigment (and some drusen partially surrounding the pigment). If the oval pale area appeared elevated, it might be interpreted as a PED or is subretinal fibrous tissue. There is a history of previous photocoagulation, and this lesion may represent a photocoagulation scar.

(d) Example #44 (61-414 LE)

There is a shallow SSR detachment centered near the junction of the central, inner temporal, and inner inferior subfields, and involving nearly all of these subfields and parts of the inner nasal and perhaps the inner superior subfields as well. The good stereoscopic effect provided by this stereo pair makes it easy to detect the elevation of the retinal vessels. The loss of the normal fine granular RPE pattern in the elevated area strongly supports the interpretation that this is RD, not PED, as does the blurring of the few drusen still visible beneath the elevated retina *and* their apparent position in the plane of the attached RPE. The first two of these features (loss of the RPE pattern and blurring of the drusen) are not dependent on stereoscopic effect and in this case would be sufficient to allow a grade of definite RD, even if only one member of the stereo pair were present. The temporal and inferior edges of the RD are fairly well defined, but the nasal and superior edges are not (compare with the sharp edges of PED's in Example #30 (61-431 RE) and Standard #12. There is a fleck of subretinal hemorrhage near the lower temporal corner of the inner inferior subfield and several tiny dots of such hemorrhage in the temporal part of the inner superior subfield. At the junction of the central and inner superior subfields there is a collection of foci of increased pigment with very subtle adjacent partial depigmentation. This oval area of pigment disturbance appears to be very slightly elevated. Its more posterior part (in the central subfield) is blurred by the overlying RD, while its more peripheral part (in the inner superior subfield) is in contact with the overlying attached (or very slightly detached) retina. There is a history of photocoagulation in this eye, and this lesion probably is a photocoagulation scar. If it were less pigmented and more elevated, it might be interpreted as a shallow PED. Total area of detachment is 2 or perhaps 3 DA.

(e) Standard #11 (UW/G637-5 LE)

There is a shallow elevation of the retina centered near the junction of the inner and outer inferior and the inner and outer temporal subfields and extending into all subfields except the outer superior and outer nasal. The elevation is low and its borders somewhat indistinct, characteristics of SSR detachment. In the central and inner temporal subfields the RPE pattern is obscured and the detachment appears to be purely SSR. This is true as well for the tiny extensions of the detachment into the inner superior and nasal subfields. In the outer temporal and inferior subfields, near the middle circle on either side of the 4:30 meridian, drusen are seen clearly, suggesting that the RPE is elevated. This appearance is different from that seen elsewhere in the detached area, in particular along its lower edge near the outer circle from 3:45 to 5:00, suggesting that the RPE may be detached and close to or in contact with the sensory retina in the area where drusen are clearly visible. All of 5 experienced graders agreed on the presence of SSR detachment; 1 graded PED

absent, 1 questionably present, and 3 definitely present (shallow type). Total disc areas of detachment equal approximately 5: outer temporal 2 disc areas, outer inferior 1 disc area; inner temporal and its central extension 1 disc area; inner inferior and its central extension 1 disc area, with room at its inferior nasal corner for the tiny extensions occupying the inner nasal and superior subfields and for part of the superior nasal half of the central subfield not yet accounted for; leaving less than one-half disc area in the central subfield, not enough to bring the total to 5.5 DA (which would be rounded to 6).

(f) Standard #15 (CSC/637625-5 LE)

There is a shallow elevation of the retina involving nearly all of the area within the grid. In the upper one-third of the outer temporal subfield the appearance is that of a very shallow SSR detachment, with slight elevation of the retinal vessels and slight blurring of underlying drusen. In the nasal part of the central subfield, and in adjacent parts of the inner inferior, nasal, and superior subfields, the dark brownish-orange color suggests a very shallow PED. Temporal to this the black color indicates subRPE blood, with some elevation of the RPE and overlying retina (about the same amount of elevation as in the area of SSR detachment described above), i.e. hemorrhagic PED. Most of the remaining area within the grid is occupied by a layer of subretinal blood that is thick enough to elevate the retina to about the same level as the SSR detachment and hemorrhagic PED. This eye would therefore be graded as having: (1) RD (SSRD and hemorrhagic RD are considered together as one lesion), (2) PED (shallow), and (3) subretinal/ subRPE hemorrhage. Total area of detachment within Field 2 is about 15 DA (the grid contains 16 DA).

19.6 RD and Subretinal Fibrous Tissue

(a) Example #45 (52-512 RE)

A low elevation of the retina occupies all of the central zone and extends into the outer nasal and inferior subfields and inferiorly beyond them. Perhaps small parts of the outer temporal and superior subfields, on either side of the 10:30 meridian, are also involved; it is difficult to be sure of this because focus/clarity is poor in this area in both members of the stereo pair. The margins of the elevated area are not well defined. There is no doubt that this is an RD (SSR detachment). The subretinal fluid is clear and the choroidal/RPE pattern and flat sheets of subretinal fibrous tissue are clearly visible in the plane of the attached RPE. In fact, these features are so well seen that the presence of RD could not be detected with certainty without stereoscopic effect. In the outer nasal subfield and below it at 4 o'clock there is a solid (3 dimensional) band of subretinal fibrous tissue. Along its nasal edge there is a thin line of subretinal hemorrhage. There are also small spots of subretinal hemorrhage outside the grid at about 6:45, 7:15, and 9:00, and several tiny spots near the temporal end of the outer superior subfield. There is some hard exudate inside, but more outside, of the grid between 7:30 and 9:00. Most of the whitish area within the grid is subretinal fibrous tissue. At least some of the smaller, less intensely white

depigmented spots on either side of the 1:30 meridian in the inner superior and nasal subfields and on either side of the 7:30 meridian in the inner inferior and inner temporal subfields represent RPE depigmentation (some may be drusen).

(b) Example #46 (52-500 RE)

In the central subfield and in a portion of all the inner subfields there is dense subretinal fibrous tissue. The elevation of the fibrous tissue is due to the thickness of the subretinal tissue itself, not to the presence of PED pushing it forward. There is also RPE depigmentation surrounding the mound of fibrous tissue. This is evident by the change in the color of the RPE. There are thin fibrous strands in this area as well. The retina appears to be in contact with the fibrous tissue in most areas, but peripheral to the fibrous tissue in some areas the retina is elevated by serous fluid; this is seen most clearly from 11:00 to 12:00 in the inner superior subfield (SSR). All or some of the hemorrhages seen nasally are probably in the retina (they are too high to be subretinal).

(c) Example #47 (52-516 RE)

In the central zone a wad of subretinal fibrous tissue is present, with pigment deposits at its inferotemporal edge and a depression in its center. The elevation of the surface of the fibrous tissue is probably due to the tissue itself and not to an underlying PED. There is a narrow rim of subtle SSR detachment adjacent to the fibrous tissue along its superior and nasal edges. A fairly broad band of RPE depigmentation surrounds this entire area. It is most extensive in the outer temporal subfield, occupying most of it, but being most obvious between 8 and 9 o'clock, where the appearance is very similar to geographic atrophy.

(d) Example #48 (58-357 LE)

A large mass of subretinal fibrous tissue occupies most of the central zone and extends into parts of all the outer subfields. Over much of the fibrous tissue and temporal to it there is a shallow SSR detachment. At about 3 o'clock in the outer temporal subfield there are several faint reddish spots that may be subretinal hemorrhage (graded no more than questionable). It is difficult to decide whether a PED is present beneath the fibrous tissue. Along the temporal edge of the mound, there seems to be a gradual sloping upward of the tissue, suggesting that PED is present. In addition, in the inner superior subfield, beneath the small branch of the venule, some choroidal vessels can be seen. They appear to be on an incline which, again, suggests PED is present (graded questionable).

(e) Example #49 (54-414 LE)

This case is similar to Example #48, but the amount of subretinal fibrous tissue is less and evidence of a PED underlying it stronger (at the borderline between definite and questionable PED, of the shallow type). Shallow SSR detachment is present

throughout the central zone and extends part way into each of the outer subfields. The mass beneath the retina is most highly elevated in the inner superior and temporal subfields, where the fibrous tissue is located, and slopes downward into the inner inferior subfield. The hemorrhage partially surrounding the PED is obviously beneath the retinal vessels and is dark red in color rather than grey-black, which indicates that it is subretinal not subRPE. There also appears to be some hard exudate outside the grid at about 11:00 and some in the outer nasal and inferior subfields, most notably at 7:30.

19.7 Abnormalities of the RPE

Three types of abnormalities are graded, each as a separate item:

Increased pigment
RPE depigmentation (degeneration) } Pigmentary abnormalities
Geographic atrophy

There are two principal difficulties in grading: (1) deciding whether to categorize small, flat depigmented spots as drusen or as RPE depigmentation, and (2) deciding whether to categorize depigmented areas that have some, but not all, of the characteristics of geographic atrophy (GA) as GA or as RPE depigmentation. The examples to follow will focus on these problems.

(a) Standards #1 (UW/C246-9 LE), #2 (UW/C9188-7 RE), #4 (UW/G637-16 RE), & #5 (UW/-G2260-14 RE)

Standard Photographs #1 and #4 have no increased pigment, even at the questionable level. All of the pigmentation in Standard Photograph #2, including the more prominent area in the inner inferior subfield, is considered pigment mottling, so that increased pigment is graded 0 here as well. In Standard Photograph #5 in the central subfield at 11:00 touching the edge of the large druse is a grey spot that should be graded questionable. Definite increased pigmentation, however, can be seen in the inner superior subfield.

(b) Example #50 (58-016 RE)

There are several small drusen mainly in the outer temporal subfield. Near the edge of the central subfield from 1 to 4 o'clock there are several foci of increased pigmentation with adjacent decreased pigmentation. Both increased pigment and RPE depigmentation (degeneration) clearly should be graded definitely present (and there is no suggestion of GA).

(c) Example #51 (58-342 LE, Fields 1M, 2, & 3M)

Straddling the inner circle at 9 o'clock there is a small area of depigmentation that could be described equally well as "roundish" or "squarish". Its edges are clearly

defined, but not "cookie-cutter" sharp. No large choroidal vessels are visible within it. It should be graded as definite RPE depigmentation. In Field 2, two small foci of pigment are visible, one near the center of the depigmented area and one on its margin at 1:30 o'clock. Many other areas of dark pigmentation are visible, but all of these are part of the choroidal pattern. In Field 1M, focus is better and several pigment dots can be seen within the depigmented area; they appear to be definite increased pigment.

(d) Standard #3 (FES/491-S-1 RE)

There is a pale area straddling the inner circle from 10 to 12 o'clock. Within this area several small drusen are visible, but it does not appear that all of the area can be ascribed to drusen. Therefore RPE depigmentation should be graded definite. This area may well be unrelated to age-related macular degeneration but because the RPE appears to be the principal tissue involved and is depigmented, this area is graded as RPE depigmentation.

(e) Example #52 (53-563 RE)

In the central and inner nasal subfields there are subtle but definite foci of increased pigment. In the nasal one-half of the central subfield and in the posterior part of the inner nasal subfield adjacent to the increased pigment, there is definite RPE depigmentation. In the upper part of the outer temporal subfield there are some obvious drusen (many of them $\geq$ 63 μm in size). In the inner superior subfield and upper part of the inner nasal subfield there are some smaller, more subtle drusen. The remaining obvious pale areas, in the inner nasal, inferior, and temporal subfields, are less easy to categorize. Most of these are round, intensely white spots, and they should probably be considered to be confluent drusen (most $<$ 63 μ, some perhaps $\geq$ 63 μ). Adjacent to these spots, and elsewhere in the inner temporal subfield, there are ill-defined areas of very subtle depigmentation, too subtle to classify even as questionable RPE depigmentation.

(f) Example #53 (54-425 LE, Fields 1M, 2, & 3M)

There are many foci of increased pigment, most prominent in the central subfield but also present in each inner subfield. How should the paler areas adjacent to the pigment be classified, as drusen or as RPE depigmentation? Within the central subfield many of the pale spots are small and round, strongly suggesting drusen (presumably confluent between 6 and 7 o'clock). In the inner subfields the spots are larger, most have fuzzy edges, and there is a suggestion of visible thickness in many of them; all these characteristics suggest large, soft indistinct drusen. From Field 2 it would be difficult to defend an interpretation of RPE depigmentation in any area. From Field 1M, which is in better focus, the pale area in the lower part of the central subfield between 6 to 7 o'clock is suggestive of RPE depigmentation, but should be graded no more than questionable.

(g) Standard #18 (UW/G3229-25 RE)

A roughly round patch of RPE atrophy occupies most of the central zone. Its edges are clearly defined (superotemporally cookie-cutter sharp) and large choroidal vessels are visible at its base. Clearly this is geographic atrophy with the center of the macula involved. There is increased pigment, quite definite along the temporal margin of the atrophic area.

(h) Example #54 (61-394 LE)

All of the atrophic areas have clearly defined edges and exposed choroidal vessels. Most are round, or appear to result from confluence of multiple smaller round areas. Even the smallest round patch at 12:30 is larger (slightly) than Circle I-1. All of these areas are geographic atrophy. The center of the macula is not involved by GA, but there is increased pigment here. There are many large and smaller confluent drusen, some of which are very shiny, meriting a definite grade for calcified drusen.

(i) Example #55 (54-008 RE)

This case has 4 roundish areas of RPE atrophy, all with "cookie-cutter" sharp edges, all $\geq$ Circle I-1 in size, and with varying degrees of visibility of underlying choroidal vessels (at 7, 10, 1:30, and 3 o'clock in the inner subfields). All of these should be graded as definite GA. If only the 3 o'clock lesion were present, a grade of questionable might be considered. Some of the drusen are calcified.

(j) Example #56 (56-389 LE, Fields 1M & 2)

There are several foci of increased pigment in the upper part of the inner inferior subfield. Nasal to this pigment there is an ill-defined area almost as large as the disc (centered above the lower nasal corner of the inner nasal subfield) in which there is a subtle increase in the visibility of the choroidal vessels. Only in the upper part of this area (between the 8 and 9 o'clock meridians in the nasal part of the inner nasal subfield) is there definite RPE depigmentation (and increased pigment within it); the rest of the area might well be considered within normal limits.

(k) Example #57 (58-368 LE, Fields 1M, 2 & 3M)

There is a roundish depigmented area in the lower part of the central subfield, with some increased visibility of choroidal vessels within it. Its nasal and temporal edges are sharp, its upper and lower edges less well defined. There are many foci of increased pigment superior to the depigmented spot and one within it. It is difficult to decide whether to classify this as geographic atrophy or RPE depigmentation. A questionable grade for GA and definite for RPE depigmentation would be appropriate.

(l) Example #58 (61-349 RE)

In the area outside the grid, in most of the outer temporal subfield, and in some outer parts of the remaining outer subfields the brownish-orange color of the RPE is visible. This color is also present in most of the upper nasal one-half of the central subfield, in adjacent parts of the inner superior and nasal subfields, and extending across the inner and outer nasal subfields between the 3:45 and 4:30 meridians. In much of this area large soft drusen are visible. In the remainder of the photo, the large choroidal vessels are faintly visible, the color is more reddish-orange, and there are few or no drusen; this appearance presumably results from partial atrophy of the RPE and strongly suggests geographic atrophy. However, the atrophic area is not round or oval and its edges are ill defined. Compare with Example #55 (54-008 RE). Grades of definite for RPE depigmentation and questionable or absent for geographic atrophy best categorize this eye. The foci of pigment in the temporal one-half of the central subfield merit a grade of definite for increased pigment. It is less clear how the pigment in the nasal one-half of the central subfield and in adjacent parts of the inner superior and nasal subfields should be graded (if it alone were present); either questionable or definite would be appropriate.

(m) Example #59 (52-509 RE)

There are about 6 or 7 roundish spots of (partial) atrophy of the RPE contiguous with one another lying mostly in the inner superior and nasal subfields. The margin of these areas are sharp and the reddish-orange color of the choroidal vessels barely visible in some areas. These lesions are probably best classified as definite geographic atrophy, although near the borderline of questionable. There are many foci of increased pigment.

(n) Example #60 (53-490 LE)

Occupying all of the central subfield and adjacent parts of all the inner subfields is a roughly oval area of RPE atrophy with exposure of large choroidal vessels beneath most of its base. Its nasal and upper edges are sharp (with pigment foci) and its temporal and lower edges somewhat ill-defined. It meets the criteria for definite geographic atrophy, with involvement of the center.

(o) Example #61 (56-364 LE)

Straddling the junction of the inner and outer nasal subfields is a patch of definite geographic atrophy, over which some drusen are still present. In a corresponding position temporally is an ill-defined area with some increase in visibility of choroidal vessels. This would *not* meet the criteria for geographic atrophy and it is doubtful whether RPE atrophy is definite enough for a grade of more than questionable RPE depigmentation. Compare with Examples #55 (54-008 RE) and #58 (61-349 RE).

(p) Example #62 (61-389 LE)

A low mound of subretinal fibrous tissue occupies a large part of the outer superior subfield and extends into adjoining subfields. There is little or no RD over or adjacent to it. An area of partial RPE atrophy involves all of the central zone, most of the outer temporal subfield, and smaller parts of the outer inferior and nasal subfields. Scattered over this atrophic area there are additional more subtle flat patches and bands of subretinal fibrous tissue, as well as foci of increased pigment. The atrophic area is roughly circular and there is some increased visibility of choroidal vessels, but its edges are ill-defined. It should be graded as RPE depigmentation, not geographic atrophy. The prominent vessels in the central subfield may be subretinal/subRPE new vessels. There are some tension lines in the retina, probably related to contraction in the fibrous tissue.

(q) Example #63 (58-366)

Rather faint subretinal fibrous tissue (or fibrin) straddles the inner circle from 10 to 4:30 o'clock. Peripheral to it there is a narrow parallel band of SSR detachment. There are areas of RPE atrophy occupying much of the central zone with extensions into adjoining parts of the outer subfields. The most clearly defined patch of atrophy straddles the middle circle at 9 o'clock; it is round, has fairly well defined edges, and exposed choroidal vessels are visible in it. This could be a patch of geographic atrophy, as could some (or all) of the other patches, and the exudative features could have occurred subsequent to development of the GA. On the other hand, exudative AMD could have occurred first, with the RPE atrophy occurring as part of the disciform scar. The clearly defined patch at 9 o'clock could be a photocoagulation scar (but there is no history of such treatment). All of the atrophy should be graded RPE depigmentation, because it appears to be related to the fibrous scar, except perhaps for the round patch at 9 o'clock, which should be graded questionable or definite GA, definite if it is known that this eye did not have photocoagulation.

19.8 Surface Wrinkling Retinopathy (Epiretinal membrane) (Review Section 15B-15.1)

(a) Standard #20 (UW/C19179-8 LE)

There are obvious tension lines in all subfields.

(b) Example #64 (59-369 RE)

There are subtle tensions lines about 1 disc diameter temporal to the temporal margin of the disc, running through parts of the inner and outer nasal and inner and outer superior subfields. Although subtle, these are enough to disqualify the subject. The pigment beneath the tension lines between 3 and 4 o'clock is part of the choroidal pattern and would not be graded as increased pigment (nor would the nevus at 7:30 at the edge of the photo).

(c) Example #65 (59-326 LE)

Even though there are no tension lines, an area of visible epiretinal membrane occupying one disc area or more is sufficient to disqualify a subject from AREDS.

19.9 Myopia (Review Section 15B-15.2)

(a) Example #66 (53-505 RE)

The disc appears fairly typical of high myopia, with a temporal crescent slightly wider than one-half the vertical disc diameter. There are also fine areas of depigmentation in the macula and few, if any, obvious drusen. The temporal crescent is sufficient to exclude the subject, and this decision is perhaps supported to some extent by the pigmentary changes.

(b) Example #67 (60-160 LE)

The disc qualifies (barely) for exclusion on the basis of myopia. Just nasal to the center of the macula there is a pale area (it is difficult to decide whether to grade this as drusen or RPE depigmentation). Superonasal to the center of the macula there is a suggestion of tension lines, which should be graded questionable SWR. If the disc were more normal and myopia were < 8.00, the eye would be eligible.

Exhibit 15B-1. AREDS MACULOPATHY GRADING FORM - MAIN SECTION

Exhibit 15B-1. AREDS MACULOPATHY GRADING FORM - MAIN SECTION (continued)

Exhibit 15B-2. AREDS MACULOPATHY GRADING FORM - DRUSEN EXTENSION

Exhibit 15B-3. APPENDIX FOR THE AREDS MACULOPATHY GRADING FORM

2. Confounding ocular lesions (use only for non-AMD)

18	Pup Sz	Pupil < 5 mm diameter
19	Media	Media opacity precludes adequate photos
20	Ang stk	Angioid streaks
21	DR>10RS	Diabetes ≥ 10 red spots (Ma's and/or small RHS) and/or < 10 red spots with more severe lesion(s)
23	Drug	Drug related maculopathy (e.g. chloroquine)
24	Nevus +	Nevus within grid with associated pigmentation, depigmentation or drusen
25	H/T/C	Healed chorioretinal scar to include Histo, Toxo, Chorioretinitis
26	Mac ed	Macular edema < 1500 microns from center
27	Mac hle	Macular hole/cyst < 1500 microns from center
28	Mac scr	Macular scar < 1500 microns from center
29	Mac oth	Macular other lesion < 1500 microns from center
30	Occ art	Occlusion, central or branch artery
31	Occ vn	Occlusion, central or branch vein
32	Op at	Optic atrophy
33	Op ed	Optic disc edema
34	PC oth	Photocoagulation scars, other (i.e. non-AMD)
35	P/V hem	Preretinal or vitreous hemorrhage
36	Ret det	Retinal detachment
37	Dq oth	Other disqualifying lesions (specify under comment)
38	SWR>Stds	Surface wrinkling retinopathy more severe than that in examples 68-71
39	Cat	Cataracts preclude satisfactory photos
40	Myope	Myopic crescent > 1/2 longest diameter of disc

3. Other ocular lesions

41	Ast hyl	Asteroid hyalosis
42	Art nar	Arteriolar narrowing ≥ Std 19
43	Chr scr	Chorioretinal scar > 1500 microns from center
44	DR < 10RS	Diabetic retinopathy level 20 or 30 or < 10 small red spots
45	Op dr	Drusen of the optic nerve
46	Hollenh	Hollenhorst plaque
47	Nevus Only	Nevus (< #24 of Confounding ocular lesions)
48	Peri at	Peripapillary atrophy
49	Cello R	Cellophane reflex only, no patch ≥ 1 disc area in extent
50	Vit/gl	Vitreous opacity or glial remnant
51	Other	Other (specify under comment)
52	Lg Cup	Large cup (add under comment if present; asymmetry, undercutting, notching, or cup-to-rim)
53	SWR≤Stds	Surface wrinkling retinopathy w/traction lines ≤ examples 68-71 and OS 9 and 13 (any category)

February 2000

Appendix 15C

ASSESSMENT OF CATARACTS FROM PHOTOGRAPHS IN THE BEAVER DAM EYE STUDY

February 2000

Appendix 15D

WISCONSIN CATARACT GRADING SYSTEM
AREDS LENS OPACITY GRADING PROTOCOL

Appendix 15D

Wisconsin Cataract Grading System
AREDS Lens Opacity Grading Protocol

1.0 OVERVIEW

The AREDS lens opacity grading protocol is an adaptation of the Wisconsin System for Classification of Cataracts from Photographs.

A single nonstereoscopic photograph taken with a modified Topcon slit lamp camera according to a specified protocol (Section 8.3) is used to grade nuclear sclerosis and nuclear color. Degree of nuclear sclerosis is graded by comparing the photograph with a series of seven standard photographs. Both the interval into which the photograph being assessed falls and its approximate position within that interval are estimated. The principal characteristics evaluated are the optical density of the nucleus and the clarity of its normal landmarks (Sections 15D-2.2 and 15D-2.3). Nuclear color is graded on a four-step scale by comparing the color of the specular reflection near the posterior surface of the lens in the photograph being assessed with the comparable feature in a series of three standard photographs (Section 15D-2.4).

Two nonstereoscopic photographs taken with a modified Neitz retro-illumination camera according to a specified protocol (Section 8.3) are used to estimate the extent of cortical and posterior subcapsular lens opacities and to record the presence of other opacities. A grid superimposed on the photographs divides the dilated pupil into 17 subfields, so that the area of each occupied by opacity can be estimated (Sections 15D-3 and 15D-4). The area within a 5 mm diameter circle (the "central zone", comprising 9 of the subfields) is considered of primary importance, since it is expected that pupillary dilation to at least this degree will be achieved at most visits in most AREDS participants, thus facilitating analyses of change between baseline and follow-up visits.

A stereoscopic pair of photographs of the red reflex taken with the Zeiss fundus camera according to a specified protocol (Section 8.2.3) is used to assist grading of the Neitz photographs and to recognize opacities not visible in them. This stereo pair (albeit taken through a dilated pupil) is also used to grade degree of iris pigmentation (iris color) on a four-step scale, by comparison with three standard photographs (Section 15D-5).

The results of the grading are recorded on the AREDS Lens Grading Form, (Exhibit 15D-1). The form includes a comments section for recording unusual, presumably non-age-related lens opacities. The grading grid is illustrated in Exhibit 15D-2. The standard photographs are on file at the UW Fundus Photograph Reading Center, 610 Walnut St., Madison, Wisconsin 53705.

2.0 SLIT LAMP PHOTOGRAPHS

2.1 Camera features and artifacts

The Topcon Model SL-6E photo slit lamp camera has been modified so that the angle between the illumination beam and the observation system, the beam width and intensity, and the magnification remain the same for all cameras for all subjects. Fixation targets have been added (viewed with the eye being photographed) so that the path of the slit beam through the lens is the same for right and left eyes (the beam is to the examiner's left of the observation system, for both right and left eyes, so that the posterior surface of the lens is always to the observer's right). A detailed protocol is specified, including focusing of the camera at the center of the lens nucleus. A single (nonstereoscopic) slit lamp photograph of the lens is mounted in a plastic sheet along with the red reflex and retro-illumination photographs for that eye. The right and left eyes are mounted and graded separately.

2.2 Slit lamp appearance of the lens and definitions

As the slit lamp beam transverses the normal adult lens, differences in refractive indices result in alternating brighter and darker bands of varying widths (See SL Standard Photograph l). Because the depth of focus in the photographs is fairly shallow, these bands become less well defined the farther they are from the center of the lens, the ideal focal point of the camera. In SL Standard 1 a wide dark band can be seen running vertically through the center of the lens. This is termed the *central dark interval* or the *sulcus* of the nucleus (and corresponds to the *embryonal nucleus*). Bordering the sulcus anteriorly and posteriorly are two broad, short, bright bands. The surfaces of these bands facing the sulcus tend to be flat or only slightly curved, while the surfaces facing the lens capsule are more steeply curved. In SL Standard 1 the posterior of these two bright bands is rather steeply curved both posteriorly and anteriorly, i.e., is bean-shaped. This is a common appearance and has led to the use of the descriptive term *lentils* for these bright bands, which are part of the fetal nucleus. The anterior and posterior Y-sutures can sometimes be seen in the anterior and posterior lentils. They are not clearly visible in SL Standard 1, but part of the posterior suture can be seen in SL Standard 3.

There are differences in interpretation regarding the remaining bands between the lentils and the lens capsule. According to Berliner[2] the bright bands immediately external to the lentils, visible as narrow, tall, relucent bands with dark bands of equal or slightly narrower width adjacent to them, represent the anterior and posterior surfaces of the lens at birth, the "fetal nucleus". In the Oxford System, these bands are described as the anterior and posterior limits of "the nucleus"[1]. In this grading system these bands will be referred to as the anterior and posterior *nuclear surface bands*. That part of the lens between (and including) these bands is considered the *nucleus* and is the only part of the lens evaluated in the slit lamp photographs. The term *nuclear landmarks* will be used to refer to all the parts of the nucleus described above, i.e., the sulcus, the lentils, the nuclear surface bands, and the dark bands between the lentils and the nuclear surface bands.

In SL Standard 1, three additional bright bands are visible: (1) a broad one at the posterior surface of the lens, (2) a narrower one at the anterior surface of the lens, and (3) another relatively narrow one between the anterior surface of the lens and the anterior nuclear surface band. The third of these bands is considered by Berliner to represent the anterior surface of the "adolescent" or "adult" nucleus; in the Oxford System it is considered to be part of the lens cortex. In SL Standard

1 the reflection of the slit beam from this band and from the posterior lens surface is particularly bright ("specular reflection"). The anterior chamber lies between the surface of the anterior capsule and the wide steeply curved band of the cornea. The downward pointing arrow that appears to be within the anterior chamber is a reflex from a mirror in the slit illumination system and ideally should fall midway between the anterior surface of the lens and the posterior surface of the cornea, as it does here.

2.3 Grading nuclear sclerosis

2.3.1 Characteristics graded

In grading the severity of nuclear sclerosis two factors are considered: (1) the optical density (perceived as brightness or relucency, sometimes described as "opalescence") of the nuclear landmarks, especially the sulcus, and (2) the definition of these structures (contrast between the bright and dark bands). Optical density is given greater weight, in part because it is less influenced by suboptimal focus than is definition of nuclear landmarks. In the early stages of nuclear sclerosis, increased optical density is noticeable only in the normally dark bands, particularly the sulcus (see SL Standards 2, 3, and 4), but in advanced stages the density of all bands becomes greater (see SL Standards 5, 6 and 7). With increasing nuclear sclerosis, the definition of nuclear landmarks decreases, and finally disappears.

When the focus of the photograph being graded is too anterior, posterior landmarks will be blurred, and vice versa. In judging the definition of landmarks in such cases, primary emphasis should be placed on the part of the lens that is in better focus. The optical density of the sulcus also may appear to increase as the plane of focus moves farther from it, but it is difficult for the grader to make any allowance for this, and no such attempt should be made. "Cannot grade" may be assigned in extreme cases of incorrect focus (see Sections 8.3.4.1 and 15D-2.6). When analyses of change between two visits are carried out, the plane of focus grades from the Quality Gradings (see 8.3.4.1) of these visits will be compared and eyes with disparities flagged for special consideration (such as exclusion, assignment to a special category, or editing by an algorithm to be developed, or by a direct side-by-side comparison).

2.3.2 The grading scale

The grader compares the photograph being graded with seven standard photographs, which show progressively increasing severity of nuclear sclerosis (SL Standards 1-7). The grader first determines the interval between adjacent standards into which the photograph being graded falls and then estimates its position in the interval to the nearest tenth. For example, if the lens being graded is considered to have nuclear sclerosis only slightly more severe than that in SL Standard 2, the grade 2.1 is assigned; if half way between SL Standards 2 and 3, the grade 2.5 is assigned. Photographs with less optical density and greater definition of landmarks than Standard 1 (virtually a normal lens) are assigned the grade 0.9; those with nuclear sclerosis exceeding that of SL Standard 7 are assigned the grade 7.1.

2.3.3 Description of slit lamp standard photographs

To be comprehensive, this description of standard photographs includes a description of the Y-sutures. However, their status is ignored in judging definition of the lentils. Not only is visibility of the sutures highly vulnerable to changes in the plane of focus, but they may in fact become more distinct as the relucency of the lentils increases (i.e., with the onset of mild sclerosis).

In **SL Standard 1** the nuclear landmarks are easily identified. The sulcus is well defined and appears dark throughout the vertical extent of the nucleus. (The small circular red dot on the anterior edge of the sulcus is a reflection of the fixation target.) The density of the posterior lentil is greater than that of the anterior, and its edges are more clearly defined. The Y-sutures are not visible in this photograph, except perhaps for a faint line centrally in the posterior lentil. The anterior and posterior nuclear surface bands and the narrow dark bands bordering them are easily discerned. As one would expect because of their distance from the point of focus, the remaining bright bands are out of focus.

In **SL Standard 2** the sulcus is denser (or more relucent, thus less black) and is less well defined, particularly superiorly and inferiorly. Although the anterior and posterior nuclear surface bands are still well defined, the dark bands between them and the lentils are denser.

In **SL Standard 3** the density of all the dark bands has increased, leading to a decrease in distinctness of the landmarks. The density of the sulcus has increased to the point that its definition has been lost, except for its central one-third. The anterior nuclear surface band cannot be distinguished at all, except perhaps centrally. The posterior nuclear surface band can only be distinguished centrally. The anterior lentil has become denser. Part of the posterior Y-suture is easily identified in the posterior lentil.

In **SL Standard 4** there appears to have been a further increase in the density of the dark bands. Only a suggestion of the sulcus can be detected. Towards the upper and lower ends of the sulcus segments of what appears to be the equator of the fetal nucleus (or a zone just beneath its surface) are visible as steeply curved white lines. Only a small part of the anterior lentil is visible. The posterior nuclear surface band cannot be seen at all and the anterior one is very faint.

In **SL Standard 5** there has been a further increase in density of both the dark and bright bands. A very faint shadow centrally marks the sulcus; the normally dark bands separating the nuclear surface bands from the lentils have increased in density to equal the increased density of the remaining nucleus. Only the dark bands external to the nuclear surface bands are well defined, and these are not included in the assessment of nuclear opacity.

In **SL Standard 6** there has been a further increase in density of both dark and bright bands. The sulcus and lentils cannot be distinguished and the density of the area assessed is greater than that in SL Standard 5.

In **SL Standard 7**, nuclear landmarks are indistinguishable due to increased density, which in the area assessed is even greater than that in SL Standard 6.

SL Standard 8 is used only in grading lens color (see below). Its grade for nuclear sclerosis would be near the lower end of the 4.0-4.9 range, because the optical density of the nucleus is a little greater than that of SL Standard 4 (although nuclear landmarks are better defined).

2.4 Grading lens color

2.4.1 Characteristics graded

In most adults, the gray-blue nucleus typical of youth begins to yellow with increasing age, although there is great variation in the age at which this begins. Yellowing may not develop at the same rate in both eyes of an individual and in rare cases may appear in only one eye[2]. The color may continue to deepen and intensify, turning from pale yellow to gold to orange and finally to brown ("brunescent"). In rare cases the nucleus may appear nearly black in color. The greatest intensity of the color change is seen in the specular reflection from the central zone of the posterior surface of the lens. It is at this point that the grader should assess the color, comparing it with the same area in the standard photographs.

2.4.2 The grading scale and descriptions of standard photographs

Slit lamp Standard Photographs 2, 4, and 8 are used as standards for grading lens color. The grader compares the photographs to the standards both with and without the Donaldson stereo viewer. Sometimes subtle changes in color can be perceived more easily without the stereo viewer. The standards for lens color and their use in grading are described below.

In **SL Standard 2** slight yellowing can be seen at the posterior surface of the lens and extending forward into the posterior part of the nucleus. This is best appreciated by comparison with SL Standard 1, in which there is no yellowing. If color in the photograph being graded is less yellow than that in SL Standard 2, the grade is 1; for yellowing $\geq$ SL Standard 2 but < SL Standard 4 the grade is 2.

In **SL Standard 4** a broad, bright, pale yellow reflex can be seen at the posterior pole of the lens. If yellowing in the photograph being graded equals or exceeds that in SL Standard 4 (but < SL Standard 8), the grade is 3. SL Standard 3 provides an example of yellowing very nearly the same as that in SL Standard 4, but with less specular reflection. For example in SL Standard 5 color is slightly more yellow than in SL Standard 4 and would receive the grade 3.

In **SL Standard 8** the reflex from the posterior pole of the lens has a deeper yellow color than that in SL Standards 3 or 4. If color in the photograph being graded is as yellow as or more yellow than that in SL Standard 8, the grade is 4. To illustrate, in SL Standard 6 color is substantially more yellow than in SL Standard 8 and would receive the grade 4.

If lens color cannot be graded the grade is 8.

2.5 Cortical flecks

Small, discrete white flecks or dots are often visible in the peripheral cortex of the lens in the slit lamp photograph. Although such opacities occur commonly with some systemic (metabolic) diseases, they are also often found in healthy individuals. The relationship of cortical flecks to other age-related changes is unclear. These small snowflake-like opacities may be found scattered throughout the lens periphery, but are most often seen, in photographs taken according to the AREDS protocol, at the superior and inferior poles of the cortex. Their presence or absence is recorded for the lens as a whole.

2.6 Gradability of slit-lamp photographs (use of "cannot grade")

Three factors determine gradability of slit-lamp photographs: focus, placement of the slit beam, and area of the lens visible (determined by pupil size and position of the eyelids). The depth of focus of the slit lamp camera is shallow (1 - 2 mm), but broad enough so that the entire thickness of the nucleus can be in satisfactory focus simultaneously when the plane of focus is in the sulcus. If the plane of focus is at or anterior to the anterior lens capsule in the optic axis, or at or posterior to the posterior capsule in the optic axis, photo quality is graded inadequate (see 8.3.4.1). However, if such photographs are presented to the grader, a grade is assigned if possible.

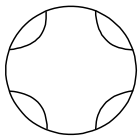
If the slit beam is displaced laterally so that an imaginary vertical line through the sulcus does not fall between vertical lines that would cross the pupil margin from 10:30 to 7:30 and from 1:30 to 4:30, too little of the nucleus will be visible to allow grading. Similarly, if a small pupil or drooping upper lid allows less than one-half of the vertical extent of the nucleus to be seen, cannot grade is assigned.

3.0 NEITZ RETRO-ILLUMINATION PHOTOGRAPHS

3.1 Camera features and artifacts

Because the illuminating and viewing axes of the Neitz camera coincide, the image it records is provided by light reflected from the fundus. This image is reddish-orange because of pigment in the retinal pigment epithelium and choroid, and because of blood in the choroidal, and to a lesser extent, the retinal vessels. Lens opacities (other than nuclear sclerosis) are visible as dark spots because they partially or completely block the light reflected from the fundus behind them (retro-illumination). Two nonstereoscopic color photographs are taken with the Neitz CT-R cataract camera through the dilated pupil, one focused on the iris (corresponding to the anterior cortex of the lens) and one focused 3-5mm more posteriorly (at or near the posterior capsule).

To reduce the bright reflection from the cornea of the Neitz camera's flash, polarizing filters are placed (at opposite axes) in front of the light source and in front of the film. In the Neitz photograph there is a characteristic unevenness in color in the form of a darker orange cross, similar in shape to the central part of a celtic cross, as illustrated below.



In the four peripheral areas not covered by the orange cross, the fundus reflex is lighter and more yellow in color. This nonuniformity is normal for the system and should not be confused with lens abnormality.

Frequently in the anterior Neitz photograph a pale white rectangular reflection from a mirror in the illuminating pathway can be seen centrally (with a longer axis vertical). A similar but fainter, out-of-focus image can be seen in many posteriorly focused Neitz photographs. These images should be ignored when grading.

3.2 Appearance of lens opacities in Neitz retro-illumination photographs

Lens fibers grow in concentric layers and continue to develop throughout life. Each new layer grows beneath the capsule and around the older fibers internal to it pushing these fibers inward. For this reason opacities of the lens tend to be location-specific, depending on the stage of lens development at which they occur. For example , a common type of congenital cataract is confined to a zone within the nucleus ("zonular cataract").

In retro-illumination, the normal lens appears uniformly transparent. Discrete lens opacities are visible as dark interruptions of this transparency, even when their appearance in direct illumination is subtle. The principal types of age-related lens opacities assessed in the Neitz photographs are *cortical* and *posterior subcapsular*. Typical cortical opacities are wedge-shaped and oriented radially. Another, less common, appearance of cortical opacities is a collection of fine granular dots ("stippling"). Posterior subcapsular opacities are located just beneath the posterior lens capsule. Typically they are centered at or near the posterior pole of the lens and extend for varying distances towards the lens equator. The areas involved by cortical and posterior subcapsular opacities are estimated separately for each of the 9 subdivisions of the central zone of the grading grid (within the 5 mm diameter circle). In addition, the number of cortical "vacuoles" in each of these subdivisions is counted up to a limit of 10 (excluding any that form part of a cortical spoke or a posterior subcapsular opacity and are therefore included in those estimates). Vacuoles have the appearance of small, round or oval, clear cyst-like spaces (see Training Photograph 9). The presence or absence of anterior cortical opacities that appear white from directly reflected light rather than black from blocking of light reflected from the fundus (white anterior cortical opacities, or WACOS) is also recorded for each of these subdivisions. The 8 outer subdivisions of the grid are graded for cortical lens opacities (see 15D-3.3.2).

In nonstereoscopic retro-illumination photographs, artifacts can mimic lens opacities because they also block light reflected from the fundus. Common problems are debris on the cornea (such

as mascara, eyelashes, or strands of mucus) and irregularities of the cornea following examination procedures (such as applanation tonometry or use of a diagnostic contact lens). A broad tear meniscus may form above the lower lid margin, appearing as a narrow blurred area in the Neitz photograph; care should be taken not to confuse this with an abnormality in the lens cortex. Many of these problems can be detected by careful scrutiny of the Zeiss stereo red reflex photograph.

3.3 Grading Neitz photographs

3.3.1 Measurement of pupil diameter

The diameter of the pupil is measured from the anterior Neitz photograph using a magnifier with a built-in millimeter scale (Bausch and Lomb, 7X). Both the horizontal diameter from 9:00 to 3:00 and the vertical diameter from 12:00 to 6:00 are measured on the film and recorded to the nearest tenth of a millimeter (these may not always be the widest and narrowest dimensions). If the pupil is particularly distorted the grader measures the horizontal and vertical meridians as specified and notes the distortion under the Comments section. Because the Neitz camera has a magnification of 2X, the film measurements will be twice the actual pupil size, that is, in an eye with a 5mm pupil the measurement on film will be 10mm.

3.3.2 Lens grading grid

In order to allow the grader to specify the location and extent of lens opacity more precisely, a grid is used to divide the Neitz photograph into subfields. The grid is formed by three concentric circles: a central circle with radius 2mm; an inner circle with radius 5mm and an outer circle with radius of 8mm. The outer circle is used only to facilitate placement of the grid, <u>not</u> to define the limits of the outer subfields, which are defined by the pupillary margin.

Equally spaced radial lines (meridians) at 10:30, 12:00, 1:30, 3:00, 4:30, 6:00, 7:30, and 9:00 o'clock divide the zones between the central and inner circles and between the inner circle and the pupillary margin into eight subfields each. The grid therefore has 17 subfields: the central subfield; eight equal inner subfields; and eight outer subfields, the areas of which vary with pupil size. On the grading form the subfields are designated as follows:

Central,

1A (10:30-12:00),	1B (12:00-1:30),
2A (1:30-3:00),	2B (3:00-4:30),
3A (4:30-6:00),	3B (6:00-7:30),
4A (7:30-9:00),	4B (9:00-10:30).

Thus for right eyes inner and outer subfields 2A and 2B are nasal, while for left eyes inner and outer subfields 4A and 4B are nasal. A diagram of the grid is provided as Exhibit 15D-2. The central and inner subfields are referred to as the "central zone".

Short perpendicular ticks are spaced at 1mm intervals along each meridian to facilitate placement of the grid. The grid is affixed to the front of the anterior Neitz transparency so that the central circle is equidistant from the pupillary margins vertically and horizontally. Occasionally the eyelid may obscure a portion of the pupil superiorly, making placement of the grid more difficult. Despite possible interference from the lid, the best determination of the center of the pupil should be made and the grid placed accordingly.

With the grid placed on the anterior photograph, both the anterior and posterior Neitz photographs are mounted side-by-side in the plastic sheet so that they can be viewed simultaneously with the stereoscopic viewer. This allows the grader to combine opacities seen in the anterior cortex with those seen in the posterior cortex, resulting in a single grade for each type of cortical opacity. To determine whether a posterior lesion falls within a particular subfield without attaching an additional grid to the posterior photograph, both the anterior and posterior photographs are viewed simultaneously with the stereo viewer as a pair, thus allowing the grid to be visually superimposed over the posterior photograph. Another technique is to close one eye and then the other in rapid succession, so that the immediate memory of the position of the grid on the anterior photograph helps determine the location of an opacity seen in the posterior photograph.

For both cortical and PSC opacities, each of the 9 subfields comprising the central zone (those within the 5 mm diameter circle) will be graded for presence and extent of opacities. For cortical opacities alone, each of the outer subfields will also be graded. Although opacities in the outer subfields have little or no effect on visual function, cortical cataract typically begins here and almost 50% of lens area visible with a 7 mm pupil lies outside the central zone. Thus it seems undesirable to exclude this area totally from consideration.

However, variations in degree of pupillary dilation from visit to visit, and the tendency for dilation to decrease with increasing age, suggest that for most analyses assessing change in extent of lens opacities between visits only the central zone should be considered. Pupillary dilation of at least 5 mm should be attainable at nearly all visits for nearly all AREDS participants.

3.3.3 Grading rules

When determining the area of each subfield involved by definite cortical or posterior subcapsular opacities, the grader records the percentage to the nearest whole number. However, when the total percentage of the subfield involved is less than one percent (for example when one or two small isolated dots are present), the grader by convention records the percentage as 1%.

When it cannot be determined with $\geq$90% certainty that the lesion being graded is indeed that lesion, but the grader is $\geq$50% although <90% confident of the identity of the lesion, the grade is "questionable" and is recorded in the appropriate box for that lesion as "Q". If the grader is <50% confident, the grade is "absent," code 0. If a subfield cannot be graded the grade is recorded as "CG" (see 15D-3.6).

3.4 Grading cortical lens opacities

Cortical opacities vary in shape, size, location in the pupil, and depth within the anterior and/or posterior cortex of the lens. The lesions graded are cortical opacities (spoking or stippling), vacuoles, and WACOS.

3.4.1 Cortical spokes and cortical stippling

Cortical spokes are linear or wedge-shaped radially oriented opacities that partially or completely block light reflected from the fundus. Their appearance varies from dense black solid opacity to diffuse collections of dots with intervening clear areas. They usually originate near the peripheral edge of the lens (the equator) and extend toward the center of the pupil. They are frequently broader at the base, tapering as they extend centrally. Spokes are more often seen in the anterior cortex, although they often appear in both the anterior and posterior cortex and occasionally only in the posterior cortex. Occasionally strings of vacuoles are aligned in radial spoke-like formations, (see Training Photograph 14); these, too, are graded as cortical spokes (not vacuoles, see 15D-3.4.2).

Cortical opacities may also appear as collections of uneven granular dots that do not form spokes; these are referred to as stippling. Typically, in zones of stippling much of the lens between the dots is clear. Therefore, in estimating area involved by stippling the grader mentally sweeps the opacities together and estimates the area they would cover if contiguous. An example of stippling can be seen in Training Photograph 12 in the anterior image at 12:00.

When grading cortical opacities, the grader mentally combines the anterior and posterior images, then estimates and records the percentage of area in the composite image covered by opacities (spokes and stippling combined) in each subfield. Care should be taken to confirm that the opacities seen in the posterior photograph are not merely out-of-focus images of the same opacities seen anteriorly, so as not to over-estimate the area involved.

3.4.2 Vacuoles

Vacuoles appear as small round or oval, clear, cyst-like spaces with sharply defined borders. With retro-illumination some or all of the borders of a vacuole usually appear dark. Vacuoles may be found at any level in the cortex. Isolated vacuoles are counted up to a maximum of ten in each of the 9 subfields of the central zone. If vacuoles appear as part of a cortical spoke or if their configuration is spoke-like, they are considered as spoking and are not tallied in the vacuole count. Similarly, if vacuoles appear to be part of a posterior subcapsular opacity (see 15D-3.5), they are considered PSC and not included in the vacuole count.

3.4.3 White anterior (and/or posterior) cortical opacities (WACOS)

In the Neitz photographs cortical opacities sometimes are seen as white or yellow-white spots of variable size and shape with hazy, ill-defined borders. WACOS are located mainly in the anterior

cortex, but may be seen in both the anterior and posterior Neitz photographs. WACOS do not appear to be flat but rather to have some volume. These opacities vary greatly in number and are usually located centrally rather than peripherally. WACOS are graded in each of the 9 subfields of the central zone as being absent (code 0), questionably present (code 1), present (code 2), or cannot grade (code 8).

Often WACOS appear as pale *gray* opacities in the red reflex photographs. Because of the color difference, there is a risk that the grader may fail to identify them as WACOS and erroneously indicate the presence of an opacity in the red reflex photograph not present in the Neitz photograph (item 300 on the form). Careful comparison of the location of the appearances in the two photographs is necessary to avoid this error.

3.5 Grading of posterior subcapsular (PSC) opacities

Posterior subcapsular (PSC) lens opacities are a less frequent but visually important finding in the older population. They are usually located in the central part of the pupil, and are often accompanied by cortical opacities. PSC opacities develop in what appears to be a single layer immediately anterior to the posterior lens capsule, and thus can be in sharp focus only in the posterior Neitz photograph. Because of the camera's shallow depth-of-field, if the focus is not directly on the PSC opacities they may be somewhat out-of-focus even in the posterior photograph, but will still be sharper than in the anterior photograph. PSC opacities may vary from a darkly opaque network to a thin brown or gray barely discernible haze. These opacities are usually lacy in configuration, often with discrete round or oval "bubbles"or vacuoles within them. Less frequently PSC opacities may appear granular. Any vacuole touching or part of the PSC network is graded as PSC opacity and not included in the vacuole count. Usually PSC opacities have irregular edges, are asymmetrical, and are limited to the central and inner subfields. The Zeiss stereoscopic red reflex photograph may be helpful in determining whether a central opacity that is visible but out-of-focus in the posterior Neitz photograph is in fact a PSC opacity.

The grader evaluates the area covered by PSC opacities by positioning the grid on the posterior Neitz photograph and estimating the percentage of involvement in each of the 9 subfields of the central zone. Because PSC opacities are usually fairly compact, extent of opacity is estimated without any attempt to subtract clear spaces even if a PSC opacity is lacy with small open areas. If PSC is so large or eccentrically located that it extends beyond the central zone, the grader notes this fact in the comments section.

Care should be taken not to confuse a Mittendorf dot, a remnant of the fetal hyaloid vascular system sometimes seen on the posterior capsule, with PSC opacities (Section 15D-4.1).

3.6 Gradability of Neitz photographs (use of "cannot grade")

3.6.1 Anterior Neitz photograph

To grade for cortical opacities, vacuoles, and WACOS, the anterior Neitz photograph must be present and gradable; that is, the anterior photograph must be in reasonably good focus and at

least two-thirds of the subfield being graded must be visible and free from major artifacts. Thus, if actual pupillary diameter were less than 4mm (defined by the first tick posterior to the middle circle on each meridian, corresponding to 4mm radius on the grid or 2mm radius of the pupil), all inner subfields would be assigned cannot grade. When grading each of the outer subfields the procedure followed is similar to that used for grading the inner subfields, except that the total area of each subfield used as the denominator in applying the two-thirds rule is variable rather than fixed. However, if a portion of one of the outer subfields is obscured by an eyelid, it is easy to estimate the size of the portion obscured, and this is considered part of the ungradable portion in applying the two-thirds rule.

3.6.2 Posterior Neitz photograph

To grade for posterior subcapsular cataract, the posterior Neitz photograph must be present and at least the central subfield must be gradable. The distance between the anterior and posterior surfaces of the lens varies from subject to subject, and increases with age. The protocol takes this variability into consideration by allowing the posterior photograph to be taken from 3 to 5mm posterior to the anterior photograph. If the distance recorded by the photographer between the anterior and posterior photograph differs substantially from this range (< 2.5mm or > 6.0mm) and no PSC opacities are visible, "cannot grade" is assigned. However, if PSC appears to be present, though out of focus, the grader should attempt to grade it if at all possible, without regard to the distance recorded.

3.7 Opacities absent in the Neitz photographs but present in the Zeiss red reflex photograph

Occasionally opacities not apparent in the Neitz photographs can be identified in the Zeiss red reflex stereo photograph. One explanation is that the very shallow depth of field of the Neitz camera (approximately 1mm) does not allow opacities outside this range to be seen while the greater depth of field of the Zeiss camera captures them. Another reason is that since some stereoscopic effect is present in Zeiss fundus reflex photographs (even though this effect is less than in fundus photographs or in external stereo photographs taken with slit lamp, Donaldson, or other cameras), the grader can determine that opacities are within the portion of the lens under consideration. In contrast, the location of out-of-focus opacities in the Neitz photograph (if they can be seen at all) may not be determinable. The presence of such opacities is recorded in item 300 of the form for the lens as a whole (absent; questionable; definite, but not PSC opacity; definite PSC opacity, with or without other opacities; or cannot grade). Care should be taken not to record any gray opacities seen in the fundus reflex photograph, and identifiable as white cortical opacities in the Neitz photographs, as opacities <u>not</u> present in the Neitz photograph (see WACOS, Section 15D-3.4.3). In addition, because of the optics involved, a slight shift in gaze may change the perceived position of an opacity seen in the fundus reflex photograph from the position observed in the Neitz photograph, thus giving the erroneous impression of the presence of two opacities instead of one.

4.0 OTHER OPACITIES (OBSERVED IN ANY TYPE OF PHOTOGRAPH)

Other opacities are assessed for the lens as a whole.

4.1 Mittendorf dot

Infrequently, a Mittendorf dot, a remnant of the fetal hyaloid vascular system, can be seen attached to the surface of the posterior lens capsule. It is usually located slightly nasal to the center of the lens (see Training Photograph 36 LE) and appears as a small, round or oval, dense black dot approximately 125-350 μm in diameter. It should not be confused with PSC opacities. When a Mittendorf dot is present, the grader checks the appropriate box.

4.2 Pseudoexfoliation of the lens capsule

Occasionally pseudoexfoliation of the lens capsule, a deposit on the anterior lens capsule that has the appearance of a curling or scrolling back of a thin transparent membrane, can be seen in a circular zone inside the edge of the dilated pupil. The everting free ends of the tissue sometimes may appear to curl toward the lens equator in strips of varying widths. Pseudoexfoliation is often very subtle and easily can be missed or mistaken for cortical opacities. The origin of pseudoexfoliation is unknown, but it is sometimes associated with glaucoma. When pseudoexfoliation is present, the grader checks the appropriate box.

4.3 Miscellaneous opacities

Presence of opacities other than those described above is indicated by checking the "other" box and describing the opacities in the Comments section. There are many types of non-age-related lens opacities, which may be seen in any layer of the lens. These include polar cataracts (white or gray circular or oval opacities within the fetal nucleus which may or may not extend beyond it, as in Training Photograph 41); stellate cataracts associated with the Y-sutures, traumatic cataracts (one type of which appears as a central rosette formation in Training Photograph 33), and cataracts of unknown origin (such as the "barbed-wire" opacity seen posteriorly in Training Photograph 39). Vitreous opacities may also confound grading. For example, in Training Photograph 38 a scattered granular pattern can be seen in the posterior photograph; these opacities are asteroid bodies in the anterior vitreous.

5.0 GRADING IRIS PIGMENTATION (COLOR) IN ZEISS STEREO RED REFLEX PHOTOGRAPHS

5.1 Introduction

The iris is a thin membrane separating the anterior and posterior chambers. Peripherally the iris is continuous with the ciliary body; anteriorly, in the undilated state, the pupillary margins rest on the surface of the lens. The iris consists of a layer of mesothelium anteriorly, a stroma made up

mostly of blood vessels centrally and two layers of pigment epithelium posteriorly. Located within the stroma are melanin-containing pigment cells which vary greatly in number. The color of the iris depends mainly on the presence and number of these cells. When light passes through the translucent stroma unimpeded by stromal pigment cells, the rays of shorter wavelength (blue) are reflected back preferentially, resulting is a blue-appearing iris.(2) This phenomenon is analogous to the sky appearing blue due to scattering (diffraction) of light as it passes through atmospheric haze. As the melanin-containing pigment cells in the stroma increase in number, the iris color changes from blue to various shades and combinations of blue, green, yellow and brown.

In the lightly-pigmented iris the radial, thick-walled, opaque iris blood vessels are well defined, appearing as slightly curving white lines that run from the periphery of the iris to within about 1mm of the pupillary margin, where they end by joining a circular vessel at the "collarette". Between the collarette and the pupil margin, the color of the iris often appears darker, in part because the stroma is thinner, allowing the dark color of the pigment epithelium to be seen more clearly, and in part because of the black fringe of pigment epithelium that is directly visible at the pupil margin (see Iris Standard Photograph 1, with undilated pupil). The zone of iris between the collarette and the pupil margin is called the pupillary zone to distinguish it from the remainder of the iris, called the ciliary zone. When the pupil is dilated the pupillary zone is pulled partially under the ciliary zone, so that it appears narrower and is often in partial shadow (see Iris Standard Photograph 1, with dilated pupil). When grading iris pigmentation the pupillary zone is excluded from consideration. Also excluded are iris crypts and iris freckles (see below). The characteristic assessed is the degree of *browness* of the iris stroma, on the blue-green-yellow-light brown-dark brown continuum.

The unknown photograph to be classified, taken with the pupil dilated, is compared with a series of standard photographs, also taken with the pupil dilated. An undilated iris photograph might be preferable, but since AREDS lens and fundus photographs require dilation, obtaining the undilated photograph would necessitate an additional session (considered unjustifiably inconvenient for the participant). Undilated variants of two of the standard photographs are provided to illustrate iris anatomy.

5.2 Conditions which may confound grading

Several conditions may make it difficult to judge the density of the stromal pigmentation. A portion of the iris may be obscured (for example, when a broad arcus senilis of the cornea is present). Overall pigmentation may appear darker (blacker) because of the presence of many iris crypts, through which the dark pigment epithelium of the iris is plainly visible. Similarly, the presence of many iris freckles or nevi may give the impression of a browner iris. These conditions, described below, should be ignored when assessing iris pigmentation.

Arcus senilis, an aggregate of lipid material ringing the cornea, is seen as a white or grayish-white opaque or nearly opaque band located near the limbus and separated from it by a narrow uninvolved clear band. The opacity may involve only one or two clock hours or may encircle the cornea completely. If the opaque band is broad and completely encircles the cornea, it may make grading for iris pigmentation difficult when the pupil is dilated. The grader should select an area where the band is narrowest and grade the area between the posterior edge of the band and the collarette (or the pupil margin, if the collarette is not visible).

Iris crypts are openings or spaces in the stroma through which the dark pigment epithelium below can be seen. The blackness of the exposed pigment epithelium is not a consideration in the evaluation of iris pigmentation.

Iris freckles are isolated spots of brown or reddish brown pigment located in the superficial layers of the iris. They appear to be "thin" (as opposed to the dense or "solid" appearance of a nevus) and vary widely in shape and size. Prominent iris freckles can be seen in Iris Standard Photograph 2 (undilated pupil) at 11:30 and 5:30. At 4:30, two smaller, lighter brown freckles can be seen (almost touching one another). Near them (toward the pupil margin) is an iris crypt. All of these features can also be seen in Iris Standard Photograph 2 (pupil dilated), but less clearly. A small freckle is visible at 5:00 near the limbus in Iris Standard Photograph 3.

An **iris nevus** is a solid-appearing dark area with regular or irregular borders. Nevi are usually darker, fewer in number and appear to extend deeper into the stroma than freckles. They are thought to be composed of groups of melanophores within the stroma and are benign.

5.3 Grading iris pigmentation (color)

In **Iris Standard 1** there is little or no evidence of stromal pigment. Except for a tiny freckle at 6:00 over the collarette, no brown pigmentation can be seen in the iris. The gray-white radial blood vessels are prominent when the pupil is small (i.e., in the undilated variant of Iris Standard 1), but are less distinct when it is dilated. Because of the paucity of stromal melanophores, the dark pigment epithelium beneath the stroma can be seen easily through the iris crypts (to be ignored when evaluating the degree of pigmentation present). Photographs with iris pigmentation equal to or less than that in Iris Standard 1 are graded 1. The dilated pupil versions of the Iris Standard Photographs are to be used in grading.

In **Iris Standard 2** there is an increase in pigmentation, which results in the appearance of a very faint wash of pale brown throughout the iris and leads to a muted graying of the color. The radial blood vessels are prominent (in the undilated variant) but appear more yellow-gray in color, reflecting the increase in pigmentation. The iris crypts are not as noticeable as in Iris Standard 1. The iris freckles, described above (Section 15D-5.2) are to be ignored. Eyes with iris pigmentation greater than Standard 1, but equal to or less than Standard 2, are graded 2.

In **Iris Standard 3** there is a marked increase in pigmentation from the previous standard, giving the iris an overall appearance of a light to medium brown. Eyes with iris pigmentation greater than Standard 2, but equal to or less than Standard 3, are graded 3.

Eyes with iris pigmentation greater than Standard 3, are graded 4. Cannot grade, code 8, is assigned when iris pigmentation cannot be determined.

6.0 REFERENCES

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Exhibit 15D-1. DETAILED LENS GRADING FORM

Exhibit 15D-2. GRADING GRID