Atherosclerosis Risk in Communities Study Protocol

Manual 14b

Retinal Reading Protocol

Visit 3

Version 1.0

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FOREWORD

This manual, entitled Retinal Reading, is one of a series of protocols and manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study. The complexity of the ARIC Study requires that a sizeable number of procedures be described, thus this rather extensive list of materials has been organized into the set of manuals listed below. Manual 1 provides the background, organization, and general objectives of the ARIC Study. Manuals 2 and 3 describe the operation of the Cohort and Surveillance Components of the study. Detailed Manuals of Operation for specific procedures, including those of reading centers and central laboratories, make up Manuals 4 through 11, 13 and 14. Manual 12 on Quality Assurance contains a general description of the study's approach to quality assurance as well as the details for quality assurance for the different study procedures.

ARIC Study Protocols and Manuals of Operation

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4	Pulmonary Function Assessment - (Retired)
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DIAGRAMS AND EXHIBITS

1.0 INTRODUCTION

The Atherosclerosis Risk in Communities (ARIC) Study is an epidemiological examination of the major factors contributing to the occurrence and trend of cardiovascular disease in middle-aged (age 35-74) adults in the United States. The study has two main objectives: (1) to investigate factors associated with both atherosclerosis and incidence of clinical cardiovascular disease, and (2) to measure coronary heart disease (CHD) occurrence and trends and relate them to community levels of risk factors, medical care and atherosclerosis.

The study will examine 14,500 participants including men, women, blacks and whites. Examinations will be conducted in four USA communities located in Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland. Initially, 4,000 persons aged 45-64 were selected to represent each community. Follow-up examinations will be performed on all remaining participants.

At the third examination visit (contact year 7), a 45-degree non-mydriatic retinal photograph is taken of one randomly-selected eye of each study participant. The photographs are taken with the Canon CR-45UAF non-mydriatic (i.e., not requiring pharmacologic dilation of the pupil) camera. The ARIC 45° photographic field, diagrammed in Exhibit 1, is centered between the optic disc and the macula, providing photographic documentation of the optic disc, the macula, substantial portions of the temporal arcades and about two disc diameters of retina nasal to the optic disc. The procedures for obtaining the retinal photographs are described in ARIC Manual 14A, Retinal Photography.

The retinal photographs are sent to the ARIC Retinal Reading Center for assessment of retinal status. The retinal photographs are used to evaluate abnormalities in the retinal vasculature (presumed to be related to hypertension and/or arteriosclerosis) that may be prognostic for various cardiovascular outcomes. Generalized narrowing of arterioles is assessed quantitatively by measuring the caliber of arterioles and veins in the retina. Focal narrowings of arterioles and arterio-venous crossing abnormalities are evaluated. Although rare, signs of "malignant" hypertension (hemorrhages and microaneurysms, soft exudates or "cotton-wool spots", and swelling of the optic nervehead) are also assessed. Other significant retinal conditions are noted, such as diabetic retinopathy or vascular occlusions.

2.0 STAFFING AND ORGANIZATION

The primary function of the ARIC Retinal Reading Center is to evaluate abnormalities, primarily vascular, visible in the retinal photographs, and to detect generalized narrowing of arterioles by measuring the caliber of arterioles and veins in the retina. The Retinal Reading Center is part of the department of Ophthalmology at the University of Wisconsin in Madison, Wisconsin. The staff includes the following:

- Director
- Associate director
- Photography consultant
- Senior grader
- Photograph graders
- Acquisition technician
- Data manager
- Systems analyst
- Coordinator, clerical and secretarial staff.

The director, associate director, photography consultant and senior grader develop the ARIC Retinal Reading Center protocols and have major responsibility for the scientific methodology of the systems and procedures used to evaluate retinal photographs. The director also serves as the consulting ophthalmologist for retinal notification letters. The associate director manages Reading Center operations. The photography consultant monitors the quality of the retinal photographs, and provides feedback on photographic quality to the field centers. The senior grader trains the graders, designs and leads quality control exercises for the grading program, and provides backup for grading, technical, and data management functions. The senior grader also prepares reports to the Steering Committee and serves as liaison between the Retinal Reading Center and other study Centers. The - photograph graders, or readers, evaluate retinal abnormalities and measure the caliber of retinal vessels. The acquisition technician prepares the photographs for grading by scanning the slides to produce computerized digital images. The data manager compiles and edits files of grading data and transmits them to the Coordinating Center. The systems analyst participates in the selection and configuration of the computer hardware and software. The coordinator and clerical staff receive, check, and file photographs and forms. The secretary to the director provides support for correspondence, reports and manuscripts.

3.0 OVERVIEW OF RETINAL READING CENTER FUNCTIONS

The ARIC Retinal Reading Center uses the retinal photographs in two distinct grading programs. The first evaluates abnormalities visible in the original retinal slides, using a magnifying viewer and a light box. The abnormalities noted include hypertensive and sclerotic lesions, and other abnormalities, such as diabetic retinopathy and vascular occlusions. The second program measures the caliber of retinal vessels, in order to detect generalized arteriolar narrowing. The quantitative assessment is done on a computerized digital image of the retinal photograph.

The major functions of the Reading Center, including both grading programs and support functions, can be summarized as follows in temporal sequence:

- receipt and computer inventory of photographs,
- monitoring photographic quality,
- reading retinal abnormalities from the retinal photograph,
- acquiring retinal photographs as computerized digital images,
- measuring caliber of retinal vessels on the computerized digital image,
- managing and transmitting data, and
- storing photographs.

These functions are diagrammed in Exhibit 2, showing the flow of retinal photographs and data within the Retinal Reading Center.

4.0 FLOW OF PHOTOGRAPHS WITHIN THE READING CENTER

4.1 Receipt of Photographs

The ARIC Field Centers regularly ship retinal photographs to the ARIC Retinal Reading Center. Each shipment is accompanied by a shipping list and photographers' log (see Examples 5 and 2, respectively, of ARIC Manual 14A, Retinal Photography).

Each shipment is identified by a batch identifier in the standard ARIC format ARxR3nnn where:

- AR is the two character study code for ARIC,
- x is a one character code for the sending agency, in this case the Field Center sending the photographs, where the acceptable values are:
  - F Forsyth County, North Carolina
  - J Jackson, Mississippi
  - M Minneapolis suburbs, Minnesota
  - W Washington County, Maryland,
- R is the one character code for the receiving agency, the Retinal Reading Center,
- 3 is the visit number, and
- nnn is the sequential batch number, i.e., 001 for the first batch from a center and 002 for the second.

Each Field Center sees from 20 to 30 study participants in one week. Thus, a typical shipment would consist of about 25 retinal photographs in 2" x 2" cardboard slide mounts, which in turn are mounted in three plastic photograph-mounting sheets (10 photographs in each of the first two and 5 photographs in the third), the photographers' log for that week's roll of film, and the shipping list. The photographers' log is completed at the time of photography and documents the order in which the photographs are taken, developed and mounted in the plastic mounting sheets. An ARIC ID label showing the study name ARIC, contact year 07 and the participant identification number is affixed to both the photographers' log and to each slide mount. The shipping list is completed at the ARIC Field Center and shows the total number of photographs and mounting sheets in the shipment and the date shipped.

Upon receipt at the Retinal Reading Center, the coordinator or clerical assistant opens each package and checks the contents against the shipping list and photographers' log. He/she reconciles the ID information on the photographs with the photographers' log. If any damage to the shipping package, inconsistencies in the identifying information, or missing photographs are noted, the coordinator's office contacts the originating Field Center by telephone. Any corrections to the identifying information are made on the photograph labels and accompanying paper forms. If the problem cannot be resolved by phone, the shipment, or the problematic portion, is returned to the Field Center.

If the shipment is complete, the coordinator or an assistant mails a postcard to the Field Center acknowledging receipt of the shipment (see Exhibit 3). The coordinator stamps the date received on the shipping list, and on the batch label of each mounting sheet of photographs.

4.2 Computer Inventory of Photographs

The coordinator or his/her assistant inventories each study participant's photograph in a computerized database. The inventory record for each photograph includes the study participant's ID number, the Field Center, the

shipping batch identifier, and the sequence number in the batch as shown on the shipping list. The record also includes the date of photography, the date shipped from the Field Center, the date received at the Reading Center, and the photographer's certification number.

Each inventory record includes three additional fields indicating: (1) that the photograph is an original or a retake, (2) that the inventory record is active or inactive, and (3) that the record is a either an original (standard or ST) reading or a quality control rereading. For most inventory records, these fields are automatically set to original, active and standard. If a retake photograph is submitted, then one of the two photographs is labeled inactive, and the other is labeled active and used for grading. For quality control rereads, the third field indicates whether this record is a light box reread (values Q1, Q2, etc.) or an image processing reread (values R1, R2, etc.).

Quality control rereads are integrated into regular grading batches, usually no more than two quality control rereads per sheet of photographs. Each reread photograph is inventoried in the batch, using the code value 999 for the photographers' certification number, and indicating the type of reread (Q1, Q2, R1, R2, etc.).

4.3 Routing of Photographs for Grading

The coordinator's office files the shipping lists in a central location, labels a file folder for each shipping batch, and forwards the photographs for retinal light box grading. Each sheet of photographs becomes, in effect, a reading list, and the photographs in a sheet are read together at each step in the grading program.

For the first three months of the study, all photographs are routed first to the photography consultant to facilitate immediate feedback on photographic quality and mounting problems. Thereafter, the photographs are routed directly for grading. The photograph graders and the acquisition technician will then refer problematic photographs to the photography consultant (see section 5.3).

The workbaskets for ARIC readings are located in a room designated for the ARIC project, which is locked when not in use. The sheets are evenly distributed between the individual light box readers' workbaskets and a free choice workbasket. Sheets which include quality control eyes are assigned to a particular grader as indicated by the ARIC Coordinating Center. The light box grader pulls one sheet of photographs from either his/her workbasket or the free choice workbasket, choosing the sheet with the oldest received date. After completing the retinal light box reading (described in Section 6.), the grader initials and dates the label on the mounting sheet, and forwards the photographs to the workbasket for completed gradings.

The senior grader collects the completed sheets and, when all sheets in a shipping batch are completed, prepares a report to the Field Center on the notification status of all participants in the batch. The senior grader then consolidates the sheets in each batch in the appropriate labeled folder, and files the folders in the ARIC permanent file.

At a later date, the photograph technician pulls the batch folders for the image processing reading. The photographs are reviewed on a light box with a magnifying viewer, and ungradable photographs are tagged with green labels, and omitted from the scanning process. Quality control rereads are integrated into the batches at this time. The photograph technician then scans the retinal slides, producing computerized digital images, and stores them under

the participant ID number. The digital images are then transferred to the Sun workstation, and the sheets of photographs are distributed into workbaskets for the image processing readers. (This process is discussed in more detail in Section 7.2.)

The image processing reader pulls one sheet of photographs from either his/her workbasket or the free choice workbasket, and performs the image processing readings (described in Section 7.3). After completing the measurements, the reader initials and dates the label on the mounting sheet, and forwards the photographs to the workbasket for completed work. When all sheets in a batch are completed, the batch is refiled in the ARIC permanent file. The image processing reader transfers the measuring data from the Unix workstation to the PC and the Novell network, and archives the images and data on tape.

The check-in of the photographs, the initial review by the photography consultant during the first three months of the study, and the computer inventory are all completed within eight working days of receipt. The light box reading of the photograph and, after the initial three months of the study, any referrals to the photography consultant, are completed within three weeks of receipt. The reports to the Field Centers are completed within 30 calendar days of receipt.

4.4 Storage of Photographs and Forms

When the grading process is complete, the photographs are filed permanently in steel, fire-resistant filing cabinets. The shipping lists are filed in binders. Both photograph batches and shipping lists are filed by the sequential batch identifier (and thus by the date received at the Reading Center) within each Field Center. If a study participant's photograph must be retrieved, the computer inventory is used to determine the batch identifier and sequence number, and access the photograph in the files.

The photographers' logs are filed with the shipping list. These are filed in a central location for easy reference by the photographic consultant and the graders.

5.0 QUALITY CONTROL OF PHOTOGRAPHS

The ARIC quality control procedures for photography include documentation and testing of the photography protocol, training and certification of photographic technicians, and ongoing monitoring of photographic quality. The photography consultant has primary responsibility for monitoring photographic quality. The photograph graders evaluate photographic quality as part of the light box grading. The photography consultant produces reports on photographic quality, based upon the light box data.

5.1 Training of Retinal Photography Technicians

The ARIC Retinal Reading Center, in conjunction with Canon USA, provides the initial training of the Field Center photography technicians. The designated chief photography technician receives special training in maintenance and repair of the camera. Both a Canon USA representative and the photography consultant visit each Field Center early in the study to provide additional training and technical support. The photography consultant is scheduled for one additional visit to each Field Center at some later point in the study, to check the state of repair of the camera, observe photography in the setting of the examination site, and provide corrective feedback for any photographic problems.

The retinal photography procedures are documented in ARIC Manual 14A, Retinal Photography. Each Field Center is provided with a copy of the protocol as well as the Canon CR-45UAF camera manual for reference.

5.2 Certification of Retinal Photography Technicians

Each photography technician at a Field Center is required to submit 10 retinal photographs of non-study subjects for certification. The senior grader reviews the certification photographs for quality, and notifies the Field Center and the Coordinating Center if the application for certification is successful. The technician is then certified for the duration of the study. If the certification photographs are not of adequate quality, the photography consultant communicates with the technician about photographic quality and technique. The technician may then submit a second certification application.

A technician may be decertified if photographic problems remain unresolved for a period of several months despite corrective feedback from the Retinal Reading Center.

5.3 Monitoring of Photographic Quality

For the first three months of the study, all photographs received at the Retinal Reading Center are routed to the photography consultant immediately upon receipt. The photography consultant telephones the Field Center and communicates directly with the retinal photography technicians about any problems observed. In the absence of problems, the consultant contacts the Center monthly to provide positive feedback.

For the remainder of the study, problematic photographs will be referred to the photography consultant by the photograph graders and the acquisition technician. The photography consultant may also request photographs, based on problems noted in the photographic quality statistics. The consultant telephones each Field Center quarterly, and more frequently if quality problems are evident.

The referral of any batch sheet of photographs to the photography consultant is noted on a photocopy of the sheet to insure that the photographs can be located if needed. When the consultant reviews any sheet of photographs, he/she initials the punched border of the photograph mounting sheet with indelible magic marker to deter repeat referrals.

5.4 Evaluation of Photographic Quality

The photograph graders evaluate photographic quality as part of the light box grading (see Section 7.3). The grader evaluates the overall gradability of the photograph, focus, adherence of field definition to the study protocol, and any artifacts present. Problematic photographs are referred to the photography consultant.

Periodically, the graders and the photography consultant meet to present and discuss problematic photographs. This promotes uniformity in the evaluation and referral of quality problems.

5.5 Photographic Quality Reports

A brief summary of ungradable photographs is included in the reports to the Field Centers on the retinal notification status of the photographs in each shipping batch.

Summary reports on photographic quality over longer periods are prepared for the ARIC Quality Control Committee by the photography consultant. The reports provide frequency distributions for the overall gradability of the photographs, observed artifacts, shifts in field definition, and degree of focus. Reports are stratified by Field Center and by technician; the chief retinal photography technician at each Field Center receives the quality report for that Center. The report is done quarterly.

6.0 READING RETINAL PHOTOGRAPHS ON LIGHT BOX FOR ABNORMALITIES

Each ARIC study participant has a 45° retinal photograph taken of one eye, showing the disc, macula, temporal arcades and an area nasal to the disc, as shown in Exhibit 1. The retinal photographs are read by the photograph graders and the data recorded on the ARIC Retinal Grading Form, Exhibit 4. The features evaluated include arteriolar and other hypertensive and sclerotic abnormalities, diabetic retinopathy, other retinal and vitreous lesions, and photographic quality. Retinal notification letters are prepared and sent to the Field Centers when appropriate.

6.1 Equipment

The photograph grader views the retinal photograph with a monocular 8X stand magnifying viewer on a daylight fluorescent light box (Kelvin color rating of 6200°).

The light box grader has as reference materials the protocol (Retinal Light Box Reading, Appendix A of ARIC Manual 14B), and photographic examples and standards. The grader overlays a grid, produced on transparent film, upon the retinal photograph. The ARIC grid, shown in Exhibit 1, has three circles outlining an average disc, the zone from the disc margin to 1/2 DD from the disc margin (Zone A), and from 1/2 DD to 1 DD from the disc margin (Zone B). The four lines radiating from the central circle are used to divide the 45° photograph into four quadrants centered on the disc: superior temporal, superior nasal, inferior nasal and inferior temporal.

6.2 Abnormalities Evaluated

6.2.1 Arteriolar Abnormalities

Abnormalities are evaluated both in the arteries on and near the disc, and in the arterioles distally. Within the disc margin and within 1/2 DD of the disc margin, where the vessels are more truly arterial in nature, the grader evaluates focal narrowings. Outside 1/2 DD of the disc margin, the grader first records a subjective impression of generalized narrowing of the arterioles in the eye as a whole. The grader then notes specific abnormalities in each of the four quadrants including focal narrowing of arterioles, arteriolar sheathing, and arterio-venous crossing abnormalities.

6.2.2 Other Hypertensive Abnormalities

Lesions of malignant hypertension include retinal hemorrhage, soft exudate, microaneurysms, hard exudate and papillary swelling. Assessment of these as hypertensive abnormalities is confounded by the fact that they may also be diabetic abnormalities, and the retinal photograph readers are masked to a study participant's diabetic and hypertensive status.

The amount and type of retinal hemorrhage, the number of microaneurysms and the presence of soft exudate and hard exudate are all assessed under the heading of lesions of hypertension and diabetes. Papilledema, or papillary swelling, is also assessed.

6.2.3 Diabetic Retinopathy

The photograph grader assigns an overall severity level of diabetic retinopathy according to the Early Treatment Diabetic Retinopathy Study (ETDRS)[1], and specifies the supporting evidence for that level. The grader also grades the presence and severity of individual diabetic lesions, including the lesions listed above as hypertensive or diabetic. The grader provides an estimate of macular edema based on clues such as hard exudates, retinal hemorrhage pattern and color abnormalities. The presence of laser photocoagulation scars is noted.

6.2.4 Other Retinal and Vitreous Lesions

The list of other retinal and vitreous lesions includes features of other vascular diseases, glaucoma, and age-related maculopathy. The noted features of age-related maculopathy are soft drusen, retinal pigment epithelium (RPE) degeneration, hyperpigmentation, serous detachment, subretinal hemorrhage, subretinal fibrous proliferation, and geographic atrophy.

6.3 Photographic Quality Evaluation

The photograph grader evaluates the overall gradability of each retinal photograph. In addition, he/she assesses focus, photographic artifacts and shifts in field definition. These evaluations are used to produce the photographic quality reports, and are an important resource for the photography consultant. The photograph grader may refer photographs to or consult with the photography consultant while evaluating photographic quality.

6.4 Retinal Notification Letters

The Retinal Reading Center completes retinal notification letters concerning conditions for which referral to an ophthalmologist may be advisable, or where the observed conditions may be of interest to the primary care physician. There are two types of notifications, based on immediacy: (1) retinal alerts, and (2) routine retinal notifications. Suggested wordings for letters are detailed in ARIC Manual 2.

6.4.1 Retinal Alerts

Retinal alerts are sent for conditions where timely referral to an ophthalmologist is advised. The light box grader refers alert conditions to the consulting ophthalmologist before completing the alert. The ophthalmologist suggests an appropriate time frame for an eye exam, to be included in the alert. Retinal alerts are completed as soon as possible after receipt of the photographs at the Reading Center. Conditions which may trigger an alert include:

(1) Recent, fresh vascular occlusions, whether arteriolar and venous;
(2) Signs suggestive of malignant hypertension such as extensive flame-shaped retinal hemorrhages, with soft exudates and/or hard exudates (the alert for this finding includes a disclaimer that the lesions present could be hypertensive retinopathy, diabetic retinopathy or some other disease process);

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[1]Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy, ETDRS Report 12. Ophthalmology 1991; 98: 823-833.

(3) Papillary swelling, only if severe and accompanied by retinal hemorrhage and/or exudates;

(4) Presumed diabetic retinopathy with an overall retinopathy level characterized as:
    (a) High Risk Characteristics (ETDRS retinal severity levels 71, 75, 81 or 85),
    (b) proliferative retinopathy (ETDRS retinal severity levels 61 and 65), or
    (c) severe non-proliferative retinopathy (ETDRS retinal severity level 53);
(5) Macular edema threatening or involving the center as inferred from hard exudates, hard exudate rings, or changes in retinal transparency;
(6) Retinal detachment;
(7) Advanced maculopathy characterized by evidence of subretinal neovascularization;
(8) Active chorioretinitis;
(9) Possible melanoma or choroidal tumor.

If the grader observes a condition not listed but which may be of medical concern, and the consulting ophthalmologist concurs, the grader completes an alert.

Retinal alerts are sent as soon as possible after receipt of the photographs at the Reading Center. The immediate referral alerts are sent to the Field Center via fax with a follow-up telephone call to insure that the alert was received. The original is mailed to the Field Center after it has been faxed.

6.4.2 Routine Retinal Notifications

Routine retinal notifications are sent for conditions where routine observation by an ophthalmologist may be advisable, or where the observed conditions may be of interest to the primary care physician. Conditions resulting in routine notifications include:

(1) Presumed diabetic retinopathy characterized as early, mild to moderate, background retinopathy (ETDRS retinal severity levels 20, 31, 43 and 47) (the letter will include a disclaimer that the lesions could be due to diabetes, hypertension or some other disease process);
(2) Questionable diabetic retinopathy characterized by diabetic lesions without microaneurysms (ETDRS retinal levels 14 and 15) (the letter will include the disclaimer that the lesions may be due to hypertension, diabetes or some other disease process);
(3) Signs suggestive of glaucoma such as hemorrhage within the disc or crossing the disc margin, or a cup to disc ratio greater than or equal to 0.7 accompanied by disc pallor, notching of the rim, or undercutting of retinal vessels at the edge of the cup.

Routine notification letters may be completed at the time the photographs are read, or may be deferred and completed as part of a larger group of letters within seven working days of the reading of the photographs. Routine notifications are faxed to the Field Centers, and the originals are mailed to the Field Centers as backup. No phone call is required.

6.4.3 Retinal Notification Status Reports to the Field Centers

The Retinal Reading Center provides each Field Center with a report on the retinal notification status of all participants in a batch when light box readings for that batch are completed. In the retinal light box database, the grader indicates the retinal notification status for each participant on the grading form as follows:

- no retinal notification,
- retinal alert sent,
- routine retinal notification sent, or
- cannot grade for retinal notification conditions.

If a notification letter was sent, the grader enters the date on which the letter was prepared and faxed to the Field Center.

The report lists all participants in the batch, by sequence number. For each participant, the report shows the eye photographed, the date of photography, the notification status based on the retinal light box data, and the date of the letter if a notification was sent. The cover memo makes special note of photographs which were ungradable for notification conditions, detailing the photographic problems seen.

7.0 MEASURING VASCULAR CALIBER ON COMPUTERIZED IMAGES OF RETINAL PHOTOGRAPHS

Generalized narrowing of the retinal arterioles is quantified by measuring the caliber of arterioles and veins in a specified zone of the retina. These measurements are then used to calculate a central arteriolar equivalent and a central venous equivalent, using pragmatic formulas developed by Parr et al[2,3] and the Retinal Reading Center[4]. The ratio of the arteriolar and venous central equivalents provides a quantitative measure of generalized arteriolar narrowing.

The measurement of vessel caliber is done on a computerized image. This image is produced by acquiring the retinal slide transparency as an image with a scanning camera. Converting the photograph to a digital image allows the use of image processing techniques to optimize the image for measurement and to easily quantify vessel calibers. The image processing reader measures each retinal vessel within a given area (Zone B using the ARIC grid). The measurements are stored as a data file on the computer file, and used to calculate the derived variables which describe generalized narrowing.

7.1 Equipment

The retinal slides are converted to digital images using a Nikon LS 3510 AF 35mm film scanner with a 5000 line resolution. The scanner software is a module of Aldus Photostyler, operating in a Windows environment on a Gateway PC. The image files are stored on the PC.

The image processing reader measures the retinal vessels at a Unix workstation. This workstation is composed of a Sun SparcStation 5 with a high resolution 17" color monitor, running Solaris as the operating system environment. The grading module was custom-designed at the Retinal Reading Center using Khoros, an image processing software package available from the University of New Mexico - Albuquerque. The images are transferred to the workstation from the scanner PC via an ethernet connection. After the measuring work is completed, the images are archived on 8mm digital audio tapes (DAT). The data files resulting from the measuring are archived on the tapes, and stored on the network as ASCII files.

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[2]Parr JC, Spears GFS. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. Am J Ophthalmol 1974; 77:472-477.

[3]Parr JC, Spears GFS. Mathematic relationships between the width of a retinal artery and the widths of its branches. Am J Ophthalmol 1974; 77:478-483.

[4]Hubbard LD, Ehrhardt E, Klein R, Messing SP, Brothers RJ, Moss SE, Meuer SM. The association between arteriolar narrowing and blood pressure. Presented at the May 1992 of the Association for Research in Vision and Ophthalmology, Sarasota, FL.

7.2 Acquisition Procedures

The retinal photographs are translated into digital images with the scanning camera specified above. The images are scanned through a green filter to acquire the portion of the color spectrum providing the best contrast between the retinal vessels and the background color of the retina, and therefore the most useful black-and-white image. Standard settings developed at the beginning of the project are used for the camera. These are checked by the acquisition technician prior to acquiring each group of photographs. One aspect of the settings is adjusted to one of three possible settings, based on the color saturation of the retinal slide. Only the portion of the retinal photograph used for measuring is scanned, reducing the file size and storage requirements. As the technician scans the slides, each image is saved in a DOS file labeled with the participant ID number, and the files are saved in DOS directories labeled with the batch identifiers (for example, F001). The technician scans from one to three batches (30 to 90 photographs) in one work session, providing an economy of scale.

7.3 Measuring Procedures

The grader recalls the stored image onto the image processing workstation, using the batch and participant ID number on the photograph labels. He/she places the original retinal slide on an adjacent light box for reference. The grader evaluates the suitability of the image for measuring; if the image is inadequate, no measurements are taken and the grader marks the image as ungradable. Problematic photographs are referred to the photography consultant.

If the image is gradable, the grader affixes the ARIC grid (diagrammed in Exhibit 1) to the image. The ARIC grid consists of three circles: an inner circle demarcating the margin of an optic disc of average diameter, and two circles 1/2 DD and 1 DD from the disc margin. The image processing reader measures retinal vessels in the area between the 1/2 DD and 1 DD circles (Zone B). The image processing system is calibrated to 1850u per standard disc diameter.

The grader then measures the retinal vessels. The grader first refers to the original retinal slide to ascertain the identity of each vessel as an arteriole or a vein, and to note the presence of focally narrowed or distended parts of each vessel to avoid when measuring. He/she chooses the segment of each vessel within the measuring zone, Zone B, which is best for measurement, and marks that region of interest. This region of interest is then enlarged and enhanced in a subsidiary window. The determination of vessel edges is made by the grader, using the image processor readings of the gray scale values as an aid. The grader uses a mouse to mark the two edges of the retinal vessel, using a circle with its center on one edge of the vessel and one point on the circle on the opposite edge of the vessel. The radius of the circle is the shortest distance across the retinal vessel.

If any arteriole measured in Zone B is larger than a given cut-off size, then the grader moves outside of Zone B to measure the branches of that arteriole, also.

7.4 Image Processing Data

The measuring process results in two data files for each image, one with the vessel measurements and the second with the coordinates of the areas of interest and the edges of the vessels. The gridded picture image and the data file with the coordinates are archived on tape. The data file with the vessel measurements is transferred to the network and imported into a Paradox

database, where the derived variables are calculated by a Paradox program. A sample print of the measurements and derived variables is provided in Exhibit 5.

8.0 DATA MANAGEMENT

The Retinal Reading Center maintains the ARIC data sets in Paradox for Windows in a Windows/DOS environment. Data are entered at personal computers linked into a Novell network. Photographs are inventoried in a Paradox database within eight working days of receipt. The inventory is entered from the shipping list and verified with a second entry. The Retinal Light Box (RLB) data is entered directly by the photograph readers. Verification of identifying information with inventory and completeness are checked at the time of the grading. All Paradox databases are backed up nightly. The Retinal Image Processing (RIP) data is collected in a Solaris/Unix environment on a Sun workstation. The digitized images and all related data files are backed up on tape as each photo batch is completed. Measurement data only are transferred to the DOS environment over the network.

Data are exported to the ARIC Coordinating Center monthly. Editing and summarization are done in Paradox. The inventory is checked for duplicate records. The RLB data are checked for internal inconsistencies. Any edits are returned with the photographs to the original readers for corrections. Any record failing the consistency edits is held out of the data send until the inconsistencies are resolved. The RIP data set is formatted to the Coordinating Center's specifications after the derived variables are calculated. RIP records are deleted from the data set if there are inconsistencies. These eyes are returned to the original readers to measure again. Verification of identifying information with the inventory is checked at the time of export.

The RLB and RIP data sets are exported to the Foxpro format specified by the Coordinating Center. The data records in Paradox are locked at the time of export. The Foxpro data sets are copied onto 3.5" diskettes and shipped to the Coordinating Center monthly.

9.0 QUALITY CONTROL OF GRADING

The grading program has several components to insure quality. Graders use standardized procedures, guided by formal written protocols. After the initial training and certification, graders participate in ongoing quality control exercises and meet regularly to discuss quality issues. Finally, masked replicate gradings of randomly selected eyes are done to document the variability of the grading for reports to the ARIC Quality Control Committee and for publication in study results.

9.1 Standardized Procedures

The standardized grading procedures are described for the graders' reference in Appendices A (Retinal Light Box Reading) and B (Retinal Image Processing Reading) of this manual. Both protocols discuss their companion photographic standards and examples. The Retinal Light Box protocol uses photographic standards to document cut-points between different degrees of severity for lesions, and includes photographic examples of artifacts and diabetic retinal levels. The Retinal Image Processing protocol includes photographic examples and diagrams illustrating decisions about the identity of vessels and the best vessel segment to measure. The protocols also employ standard measuring devices to define the disc zone and the four quadrants.

9.2 Grader Training and Certification

The light box readers' initial training includes units on the translation of the Modified Airlie House grading of diabetic retinopathy to the Canon 45° photographs, the evaluation of photographic quality and, in particular, the evaluation of arteriolar abnormalities in 45° photographs. The training uses a tutorial approach, utilizing written protocols and selected teaching photographs.

The image processing readers receive training in the general use of the image processing system, followed by measurement exercises designed to improve reproducibility. These include exercises where graders attempt to reproduce their own results on selected eyes, to reproduce standardized results derived from several measurements of the same eye, and to produce similar results from well- and poorly-focused images of the same eye.

After training, graders become certified by satisfactorily grading a set of test eyes which include a wide range of the pathologies evaluated, and a range of artery to vein ratios.

9.3 Quality Control Exercises

9.3.1 Quality Control Meetings

Both grading groups meet regularly to discuss quality issues. Photographs for discussion are suggested by the graders, selected by the senior grader from the final review of the data, or chosen from the ongoing duplicate gradings used to measure inter- and intra-grader reproducibility. The selected eyes are graded by all graders prior to the meeting, and differences are discussed and reconciled at the meetings.

During the training period, the grading groups meet weekly. In the six month period following certification and the initiation of study readings, the grading group meets monthly. Thereafter the grading group meets quarterly with the primary emphasis of the meetings being discussion of selected eyes.

9.3.2 Tuning Exercises

For the evaluation of retinal abnormalities, the Reading Center builds and maintains a collection of photographs to illustrate the desired "thermostat setting" for the presence and severity of lesions. Graders review this collection periodically as a "tune-up" exercise.

The analogous collection for the measurement process contains eyes with established measurements based on multiple readings by several readers. Graders retune their measuring skills by rereading one of these eyes periodically. In their daily work, graders may use retuning exercises such as remeasuring vessels in one quadrant and comparing the two sets of results.

9.4 Monitoring Grading Quality

The ARIC Coordinating Center provides the Retinal Reading Center with lists of eyes to be reread for quality control, designating the grader chosen to reread each eye. There are two types of rereads: (1) library rereads, and (2) inter- and intra-grader reproducibility rereads.

A library of eyes is reread several times over the course of the study to monitor temporal drift in the grading program. At the end of the second quarter, the original readings for all eyes are stratified to represent different types and degrees of abnormalities. Eyes are randomly selected from within each strata for the library, although some strata may be proportionally over-represented to exercise the full range of severity of all lesions.

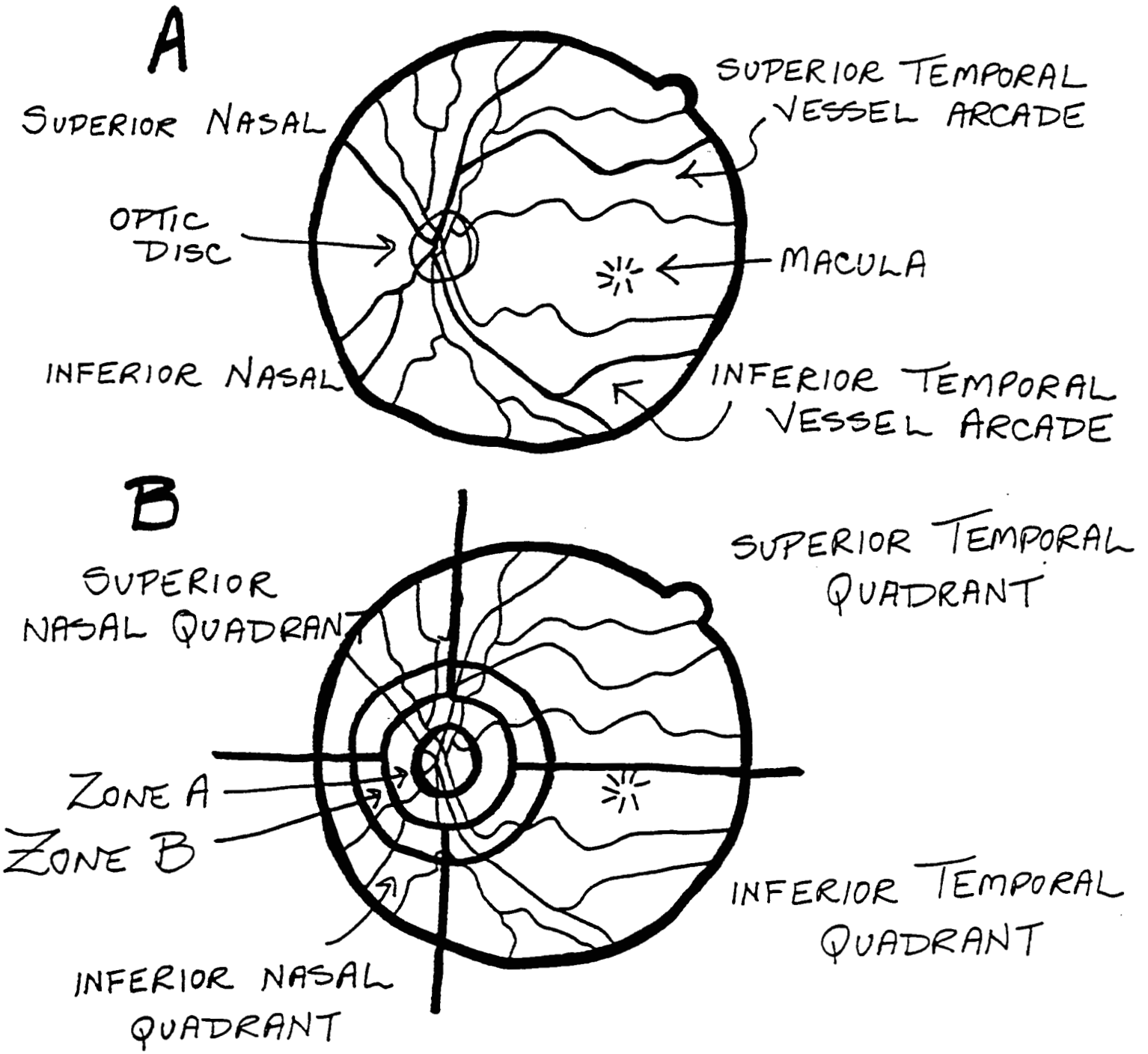
Eyes to test inter- and intra-grader reproducibility are selected on an ongoing basis to monitor contemporaneous variability in the grading program. Again, the original readings are stratified and the quality control rereads are randomly selected from within the strata, with strata of particular interest being over-represented.

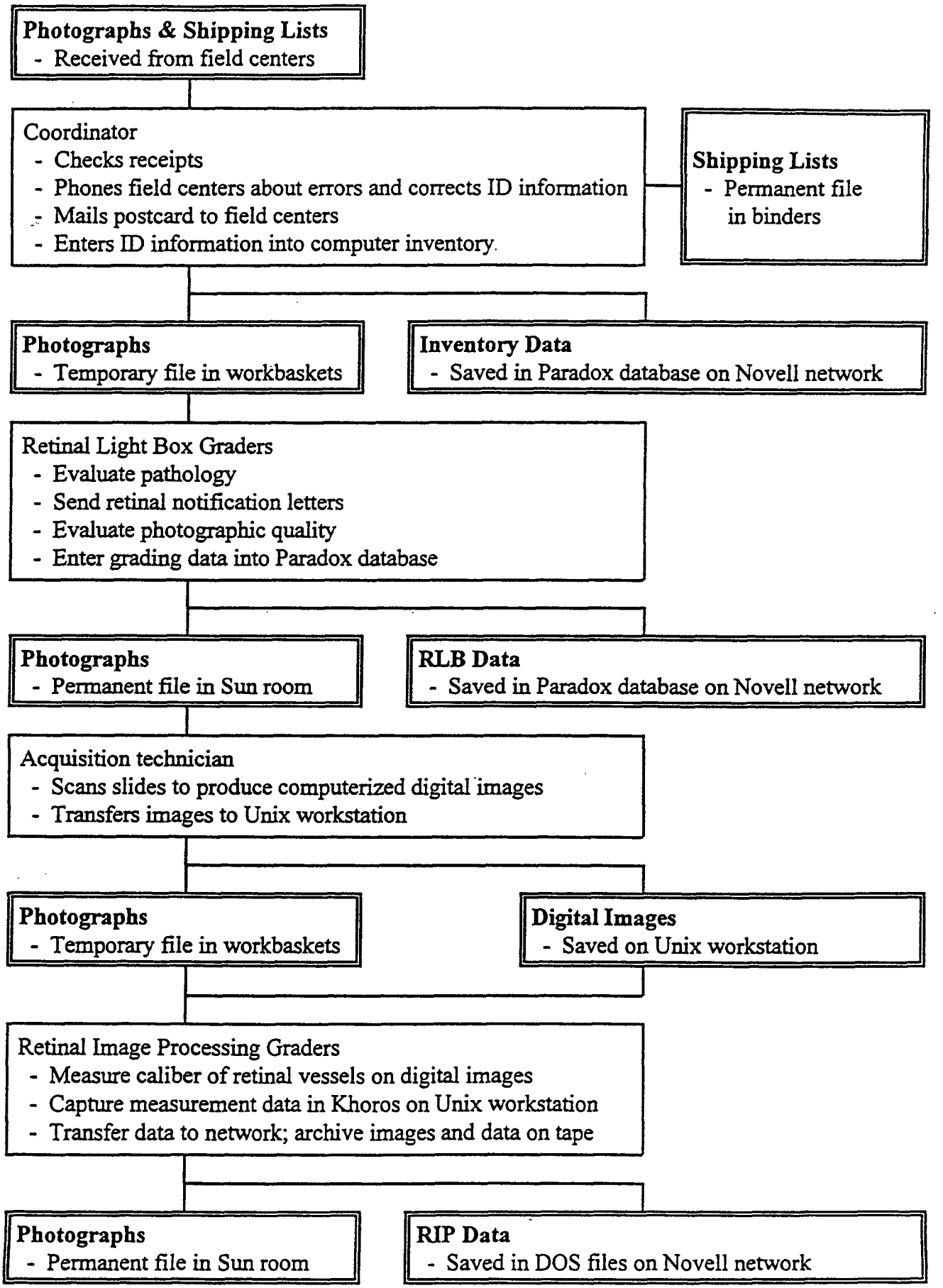
At the Retinal Reading Center, the quality control rereads are pulled from their original batches and inserted into a current reading batch, working within the same Field Center. The quality control eyes are inserted in the middle of the mounting sequence to promote masking, and no more than one or two rereads are inserted into each sheet, or reading list. Placement of individual duplicate gradings in original reading lists allows regular accrual of duplicate gradings with a minimum impact on the timely processing of the original gradings. This scheme also promotes proportional representation of an individual grader in original and reproducibility data sets.

The quality control gradings are specially marked when sent to the ARIC Coordinating Center. The Coordinating Center periodically produces reports on inter- and intra-grader reproducibility. The Retinal Reading Center may use cases of disagreement from these rereadings for retraining of the readers. However, graders will remain masked to the results of the library rereadings and, in particular, will not see the photographs between rereads.

This section will be expanded by the ARIC Coordinating Center.

Exhibit 1
Part A - Diagram of a Canon 45° Photographic Field
Part B - Diagram of Grid Application





See Part B for Key, and editing and compilation of data sets.

Exhibit 2, Part B
Workflow in Retinal Reading Center, Data

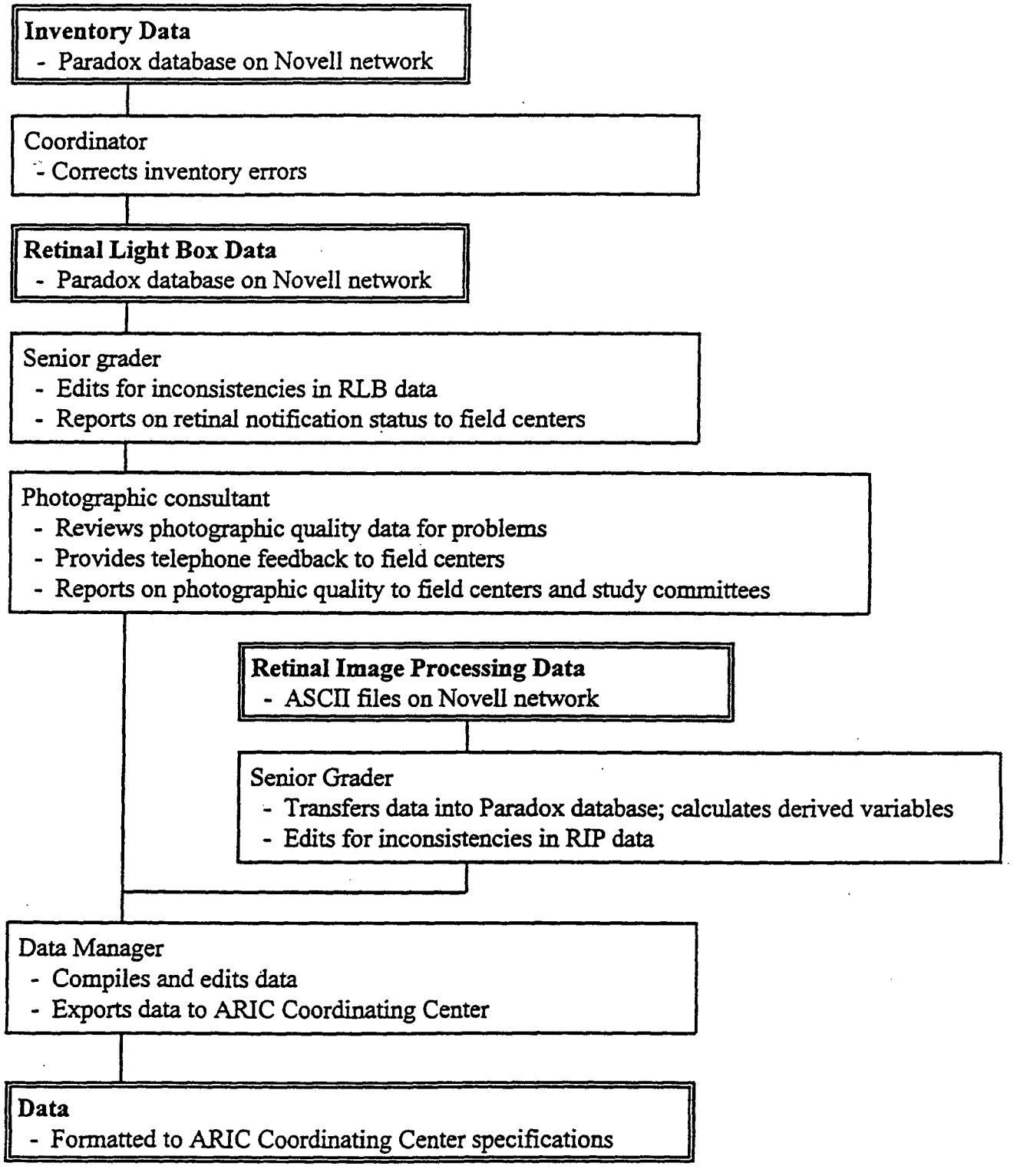


Exhibit 3
Postcard Acknowledging ARIC Receipts

ARIC

ARIC SHIPMENT RECEIPT CARD

Field Center ____

Batch Identifier **AR** ___ **R3** ___ ___ ___ ___

has been received at the Reading Center on _____

Comments:

Exhibit 4
Retinal Light Box Reading - Paper Form

FIELD CENTER ___ PATIENT ID _ _ _ _ _ _ EYE ___ Grader ____ Date Graded _ _ / _ _ / _ _

PHOTOGRAPHIC QUALITY

Focus		Field Definition	
1	Good	1	Good
2	Fair	2	Fair
3	Borderline	3	Borderline
4	Inadequate	4	Inadequate
8	Cannot grade	8	Cannot grade

Artifacts	No	Yes
Haze	0	2
Dust / dirt	0	2
Lashes	0	2
Arc	0	2
Uneven illum / macula	0	2
Uneven illum / edge	0	2
Uneven illum / disc zone	0	2
Total blink	0	2
Other	0	2

Gradability

1	Entire field gradable
2	Disc zone gradable, macula ungradable
3	Macula gradable, disc zone ungradable
4	Disc zone and macula ungradable
5	Entire field ungradable

Comments _____

_____

ARTERIOLAR Abnormalities

Arterial Abnormalities:
W/i Disc Margin Zone to 1/2 DD

0	0	None
1	1	Questionable
2	2	Definite
3	3	Severe
8	8	Cannot grade

Generalized Narrowing of Arterioles

0	None
1	Questionable
2	Definite
3	Severe
8	Cannot grade

Focal Narrowing of Arterioles (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Mild
3	3	3	3	Moderate
4	4	4	4	Severe
8	8	8	8	Cannot grade

Papillary Swelling

0	None
1	Questionable
2	Definite
3	Severe
8	Cannot grade

Sheathing of Arterioles (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Mild
3	3	3	3	Moderate
4	4	4	4	Severe
8	8	8	8	Cannot grade

Abnormalities in A/V Crossings (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Definite
3	3	3	3	Severe
8	8	8	8	Cannot grade

LESIONS OF DIABETIC RETINOPATHY

Number of Microaneurysms

0	None
1	Questionable
2	1 Ma
3	2 Ma's
4	3 Ma's
5	4 Ma's
6	≥ 5 Ma's
8	Cannot grade

Number of Retinal Hemorrhages

0	None
1	Questionable
2	1 RH
3	≥ 2 RH's
8	Cannot grade

Type of Retinal Hemorrhage

0	None
1	Questionable
2	Flame hemorrhage only
3	Blot hemorrhage only
4	Blot and flame hemorrhages
8	Cannot grade

Hemorrhages/Microaneurysms

0	None
1	Questionable
2	Definite
3	≥ Std. Photograph #1 in all 4 quadrants
4	≥ Std. Photograph #2A
5	≥ Std. Photograph #2A in 2 or 3 quadrants
6	≥ Std. Photograph #2A in all 4 quadrants
8	Cannot grade

Hard Exudate

0	None
1	Questionable
2	Definite
8	Cannot grade

Soft Exudate

0	None
1	Questionable
2	Definite
8	Cannot grade

IRMA

0	None
1	Questionable
2	Definite
3	Definite in all 4 quadrants
4	≥ Std. Photograph #8A
8	Cannot grade

Venous Beading

0	None
1	Questionable
2	Definite
3	Definite in 2 or more quadrants
8	Cannot grade

NVD

0	None
1	Questionable
2	< Std. #10A
3	≥ Std. #10A
8	Cannot grade

NVE

0	None
1	Questionable
2	< 1/2 DA
3	≥ 1/2 DA
8	Cannot grade

VH/PRH

0	None
1	Questionable
2	< 1 DA
3	≥ 1 DA
8	Cannot grade

FP

0	None
1	Questionable
2	Definite
8	Cannot grade

Macular Edema

0	None
1	Questionable
2	Present, inferred from HE/other
3	CSME, inferred from HE/other
4	Center involved, inferred from HE/other
8	Cannot grade

Laser Photocoagulation

0	None
1	Questionable
2	Focal Rx only
3	Scatter and/or local Rx
4	Focal and scatter Rx
8	Cannot grade

Diabetic Retinal Level	Supporting Evidence
90 Cannot grade	903 Cannot grade for proliferative retinopathy
	902 Cannot grade for background retinopathy; no proliferative retinopathy present
	901 Cannot grade for microaneurysms; no other background retinopathy present
85 Advanced PDR	852 Retinal detachment at center of macula
	851 Macula obscured by VH and/or PRH
81 Advanced PDR	811 VH and/or PRH, cannot grade for NVD and/or NVE, center attached
75 DRS HRC	751 NVD $\geq$ Std Photograph #10A with VH and/or PRH
71 DRS HRC	714 NVD $\geq$ Std Photograph #10A
	713 NVD < Std Photograph #10A with VH and/or PRH
	712 NVE $\geq$ 1/2 DA with VH and/or PRH
	711 VH and/or PRH $\geq$ 1 DA
65 Moderate PDR	654 NVE < 1/2 DA with VH and/or PRH
	653 NVD < Std Photograph #10A
	652 NVE $\geq$ 1/2 DA
	651 VH and/or PRH < 1 DA
61 Mild PDR	612 NVE < 1/2 DA
	611 FPD and/or FPE
53 Severe NPDR	534 Venous beading in 2 or more fields
	533 IRMA $\geq$ Std Photograph #8A
	532 H/Ma $\geq$ Std Photograph #2A in 4 or 5 fields
	531 Any two or three of level 47 characteristics
47 Moderately severe NPDR	474 Venous beading in one field
	473 H/Ma $\geq$ Std Photograph #2A in 2 or 3 fields
	472 IRMA in 4 or 5 fields
	471 Both IRMA and H/Ma characteristics from level 43
43 Moderate NPDR	433 IRMA in 1 to 3 fields
	432 H/Ma $\geq$ Std Photograph #2A in 1 field
	431 H/Ma $\geq$ Std Photograph #1 in 4 or 5 fields
35 Mild NPDR	355 Soft exudate
	354 Hard exudate
	353 Retinal hemorrhage
	352 Questionable SE, IRMA or venous beading
	351 Venous loop $\geq$ code 2
20 Microaneurysms only	201 Microaneurysms only
15 DR questionable	151 Retinal hemorrhage, no microaneurysms
14 DR questionable	143 IRMA, no microaneurysms
	142 Soft exudate, no microaneurysms
	141 Hard exudate, no microaneurysms
10 DR absent	101 Microaneurysms and other lesions absent

OTHER OCULAR LESIONS

N	Q	Y		N	Q	Y	
0	1	2	Central artery occlusion	0	1	2	Cellophane reflex
0	1	2	Branch artery occlusion	0	1	2	Surface wrinkling retinopathy with or without tension lines
0	1	2	Central vein occlusion				
0	1	2	Branch vein occlusion				
0	1	2	Hollenhorst plaque	0	1	2	Soft drusen
0	1	2	Asteroid hyalosis	0	1	2	RPE depigmentation
				0	1	2	Hyperpigmentation
0	1	2	Lg cup/disc ratio	0	1	2	SSR detachment
0	1	2	RH within disc margin	0	1	2	Subretinal hemorrhage
0	1	2	Peripapillary atrophy	0	1	2	Subretinal fibrous
0	1	2	Other disc abnormality	0	1	2	Geographic atrophy
0	1	2	Glial / vitreous thickening	0	1	2	Chorioretinal scars
0	1	2	Medullated nerve fibers	0	1	2	Nevus
				0	1	2	Retinal detachment

COMMENTS _____

_____

Draft 2-19-93

Exhibit 5
Retinal Image Processing - Sample Data Set

BATCH ID: F001
PARTICIPANT: F999999
GRADER: 33
DATE GRADED: 01/01/95

	ARTERIES					VEINS	
	TRUNK	B1	B2		EQUIV		VEIN
A_1	68			B_1_AE	68	V_1	39
A_2	63			B_2_AE	63	V_2	109
A_3	91	96	78	B_3_AE	114	V_3	35
A_4	41			B_4_AE	41	V_4	42
A_5	83	55	68	B_5_AE	80	V_5	34
A_6	55			B_6_AE	55	V_6	110
A_7	35			B_7_AE	35	V_7	86
A_8	39			B_8_AE	39	V_8	90
A_9	63			B_9_AE	63	V_9	79
A_10	64			B_10_AE	64	V_10	68
A_11				B_11_AE		V_11	54
A_12				B_12_AE		V_12	90
A_13				B_13_AE		V_13	
A_14				B_14_AE		V_14	
A_15				B_15_AE		V_15	
A_16				B_16_AE		V_16	
A_17				B_17_AE		V_17	
A_18				B_18_AE		V_18	

CRAE_T: 152
CRAE_B: 162
CRVE: 198
AV_RATIO_T: 0.77
AV_RATIO_B: 0.82

Arteries requiring branch measurements: A_REQ_B: 2
Branch pairs measured: A_MEAS_B: 2
Proportion measured: A_B_RATIO: 1.00

Retinal Light Box Reading

1.0 INTRODUCTION

1.1 Objective

The objective of this procedure is to evaluate retinal photographs taken of participants in the Atherosclerotic Risk in Communities (ARIC) Study for hypertensive and/or sclerotic changes. Photographs are evaluated in semi-quantitative fashion by a reader using a magnifying viewer to examine the slide transparencies on a light box. Among the features evaluated are focal narrowing of arterioles, arteriolar sheathing, arterio-venous (AV) crossing abnormalities, and other retinopathy (including microaneurysms, intraretinal hemorrhages, soft exudates or "cotton wool spots," and papillary edema). In addition, photographs are assessed for lesions characteristic of diabetic retinopathy and age-related maculopathy, and other conditions (some of which may affect visual function). Generalized narrowing of arterioles is evaluated separately by measuring vessels upon a digital image processing system, a procedure described in Appendix B.

1.2 Rationale

The major purpose of evaluating changes in the retinal vasculature associated with hypertension and/or arteriolar sclerosis is to explore their prognostic value for cardiovascular outcomes. It may be that changes in the retinal vasculature provide information about status (such as length and severity of exposure to hypertension, and degree of structural damage) not provided by standard measurement of blood pressure, particularly in subjects taking antihypertensive medications. Because the retina can be assessed noninvasively, this procedure may be a practical way to identify risk factors for clinically important pathology.

1.3 Background

Observers have associated retinal changes with hypertension and/or sclerosis for decades. Recently, Freeman and Sperduto[5] reviewed the classification of ocular signs and evaluated their suitability for further research. Focal arteriolar narrowing, AV crossing changes, and hypertensive retinopathy were included in the landmark classification of clusters of signs proposed by Keith, Wagener, and Barker[6,7,8]. Later,

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[5]Freeman RW, Sperduto RD. A review of hypertensive and arteriolosclerotic changes in the ocular fundus: implications for epidemiologic research. Unpublished manuscript, provided by Robert D. Sperduto, MD, Biometry and Epidemiology Program, National Eye Institute, National Institutes of Health, DHHS, Bethesda, MD 20892.

[6]Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1939; 197:332-343.

[7]Wagener HP, Keith NM. Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine 1939; 18:317-430.

[8]Wagener HP, Clay GE, Gipner JF. Classification of retinal lesions in the presence of vascular hypertension. Report submitted to the American Ophthalmological Society by the Committee on Classification of Hypertensive Diseases of the Retina. Trans Am Ophthalmol Soc 1947; 45:57-73.

Sheie[9], Leishman[10], and Evelyn[11] also proposed classifications that included several of these features. As Freeman and Sperduto[1] note, focal narrowing and AV crossing changes have been linked with hypertension and other clinical outcomes in various studies. Other changes, particularly the cluster referred to as "malignant" or "fulminant" hypertensive retinopathy, while also important, have presumably decreased in prevalence as high blood pressure has become better controlled in the general population. Traditionally, changes in arteriolar light reflex have been considered important and were included in early classifications. However, Kagan et al[12] demonstrated that this sign probably cannot be graded with sufficient reproducibility.

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[9]Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. Arch Ophthalmol 1953; 49:117-138.

[10]Leishman R. The eye in general vascular disease: hypertensions and arteriosclerosis. Brit J Ophthalmol 1957; 41:641-701.

[11]Evelyn KA, Nicholls JV, Turnbull W. A method of grading and recording the retinal changes in essential hypertension. Am J Ophthalmol 1958; 4(2):165-179.

[12]Kagan A, Aurell E, Dobree J, et al. A note on signs in the fundus oculi and arterial hypertension: conventional assessment and significance. Bull WHO 1966; 34:955-960.

2.0 EQUIPMENT AND MATERIALS

A single 45° retinal photograph, taken with Ektachrome 100 ASA film on the Canon CR-45UAF non-mydriatic camera, is read for each ARIC participant. The ARIC 45° photographic field is centered between the optic disc and the macula, providing photographic documentation of the optic disc, macula, substantial portions of the temporal arcades, and about two disc diameters of retina nasal to the optic disc. The standard ARIC photographic field is diagrammed in Exhibit 1, part A.

The photograph reader views each retinal photograph with a monocular magnifying viewer on a fluorescent light box, and references the written protocol and the photographic standards and examples to evaluate retinal abnormalities. The photograph reader directly enters his/her evaluations in a micro computer database. The following materials are used in the reading process:

(a) a monocular 8X stand viewer;
(b) a daylight fluorescent light box, Logan #1055 with opal glass cover, modified to hold three 14 watt fluorescent tubes with a Kelvin color rating of 6200° to approximate normal daylight, and with a modified direct current power source to eliminate flicker;
(c) subfield grid to demarcate the grading subfields, as described in Section 3;
(d) photographic standards and examples, discussed throughout the protocol and listed in Exhibit 2; and
(e) the direct entry software, a series of data collection screens (Exhibit 3) built in Paradox for Windows (a relational database from Borland International Incorporated) available to the photograph readers on networked IBM-compatible personal computers, and based on the paper data collection form in Exhibit 4.

The Canon 45° retinal photograph provides about 2X magnification, further magnified by the 8X viewer to about 16X, closely approximating the 15X magnification obtained with Zeiss 30° photographs and 5X Donaldson stereo viewers.

3.0 SUBFIELD GRID

The reader overlays a grid of black lines printed on a transparency to determine the grading subfields in each retinal photograph. The grid, developed for use with Canon 45° retinal photographs, is based on the diameter of an average optic disc as calculated by comparing Zeiss 30° and Canon 45° photographs of the same eye from several individuals and appropriately scaling down from the standard disc diameter (DD) for Zeiss 30° photographs.

The grid consists of three concentric circles centered on the optic disc and four spokes at 12:00, 3:00, 6:00 and 9:00, as diagrammed in Exhibit 1, part B. The inner circle approximates the disc margin assuming an average size disc (diameter = 1 DD or one disc diameter, radius = 1/2 DD); the second circle demarcates a zone extending to 1/2 DD from an average disc margin (radius of circle = 1 DD), hereafter referred to as Zone A; and the outer circle demarcates a zone extending from 1/2 DD to 1 DD from the disc margin (radius of circle = 1 1/2 DD), hereafter referred to as Zone B. The four spokes extend outward from the edge of Zone A and demarcate the four quadrants named for their relationship to the posterior pole (the most posterior retinal region which contains the optic disc and the macula, or center of acute vision). Beginning at the upper left and moving clockwise, the four quadrants in the right eye are the superior temporal, superior nasal, inferior nasal and inferior temporal; in the left eye, the superior nasal, superior temporal, inferior temporal and inferior nasal.

When evaluating any retinal abnormalities present, the photograph reader places the grid over the photograph to determine the subfield in which any lesion occurs. The reader centers the inner circle on the optic disc and places the temporal spoke to evenly bisect the relatively open retina between the major blood vessels of the superior and inferior temporal arcades. In most eyes, the macula will fall just below this spoke. When the temporal spoke extends horizontally from the disc margin at 9:00 (right eye) or 3:00 (left eye), the macula will generally fall on a parallel line intersecting the disc margin at 7:30 (right eye) or 4:30 (left eye). The example photograph PQ1 shows a correctly placed grid.

4.0 PHOTOGRAPHIC STANDARDS AND EXAMPLES

The ETDRS photographic standards for diabetic retinopathy have been appropriately scaled down for the Canon 45° photographs by copying the Zeiss 30° originals of ETDRS standards at a reduced scale appropriate to Canon 45° photographs, based on comparisons of Zeiss 30° and Canon 45° photographs of the same eye of five individuals. Each ETDRS photographic standard is represented by a single scaled down photograph. In the ARIC 45° photograph, the photograph reader considers an area of retina approximately equal to that of the ARIC reduction of an ETDRS standard when determining if the amount of the lesion present is equal to or greater than the standard. When the reader evaluates the severity of a lesion equal to or greater than a standard, the reader uses the ARIC subfield grid to locate the four quadrants and then compares the total amount of the lesion present in each quadrant to the total amount of the lesion present in the ARIC reduction of the ETDRS standard.

Each photographic example consists of a single Canon 45° or Topcon 45° photograph. Many of the photographic examples have corresponding Zeiss 30° photographs of the same eye, available to the photograph readers as a reference collection in a central location.

5.0 READING PROCEDURES AND DATA COLLECTION

5.1 Reading Procedures

After computer inventory at the Reading Center, each sheet of up to 10 retinal photographs is handled as one reading list. The photograph reader selects a reading list from his/her workbasket at the beginning of a grading session. Upon completion, the reader initials and dates the mounting sheet label and forwards the list to the basket provided for completed lists.

5.2 Data Collection Form

The data collection form exists in both an original paper format (Exhibit 4) and the derived direct entry screens (Exhibit 3). In both, the data collection begins with identifying information and an evaluation of photographic quality, and is followed by the collection of substantive grading data and information on retinal notifications.

The identifying information (field center, participant identification number and eye) is entered in screen 1 of the direct entry screens and at the top of page 1 on the paper data collection form. In direct entry, the reader must correctly enter the field center and participant identification number, which are then checked against the photograph inventory, before entering data for the eye. The direct entry software does not permit data entry for an uninventoried identification number, and shows the grader if data are already present for the identification number.

The reader completes all questions for photographic quality (screen 2 of direct entry, page 1 of paper form) and arteriolar abnormalities (screen 3 of direct entry, page 1 of paper form). The questions regarding diabetic retinopathy and other ocular lesions are organized under gatekeeper questions. The first gatekeeper asks the reader if any lesions of diabetic retinopathy are questionably or definitely present, or ungradable (screen 4 in direct entry, page 2 on paper form). If yes, the reader completes all questions for lesions of diabetic retinopathy (screens 4 and 5 in direct entry, page 2 of paper form). If no, the reader proceeds directly to the overall diabetic retinal level (screens 6 and 7 in direct entry, page 3 of paper form). In all cases, the reader completes the overall diabetic retinal level. Another gatekeeper asks if there are any other ocular lesions questionably or definitely present in the eye (screen 8 of direct entry, page 4 of paper form). If yes, the reader completes all questions for other ocular lesions. If no, the reader proceeds to the comment section (same page as the other ocular lesion questions). Comments may annotate arteriolar abnormalities, lesions of diabetic retinopathy or other ocular lesions.

Finally, the photograph reader records information about retinal notifications to the field centers on screen 9 of direct entry or on page 4 of the paper form.

6.0 GRADING RULES

Photograph readers (graders) at the Reading Center use the following conventions in evaluating the presence and severity of abnormalities:

a) None is used to indicate that a lesion is absent. If there is a suggestion that a lesion may be present, but the reader is less than 50% certain that the lesion is in fact present, the reader uses none, or absent, for that lesion.

b) Questionable is used to indicate the probable presence of the lesion. If the reader is more than 50% certain but less than 90% certain that the lesion is present, he/she selects questionable as the answer. Stated alternatively, if the reader thinks that the lesion is present but is unsure that all observers would agree, he/she marks the lesion as questionably present.

When an abnormality is present but the reader is uncertain of its identity, the reader chooses questionable for the lesion considered most likely and answers none, or absent, for the lesion(s) considered less likely.

c) Definite indicates the definite presence of a lesion. If the reader is at least 90% certain that the lesion is present, he/she marks the lesion as definitely present.

d) In questions with several codes for definite presence of the lesion, there may be several steps to indicate ascending severity of the lesion. The ascending severities may be described in general terms as mild, moderate and severe. The severities of a lesion are usually defined either in terms of the number, length, or area present, or in relation to photographic standards.

e) Cannot grade is used to indicate that the lesion is ungradable due to impaired photographic quality or a confounding condition. In general, if no evidence of the lesion is seen and more than 50% of the subfield is missing or obscured, the reader selects cannot grade rather than none. For focal narrowing and sheathing of arterioles in the quadrants, at least 1 1/2 DD total length of arterioles should be visible in the quadrant; if no abnormality of the arteriole is seen and less than 1 1/2 DD of arterioles are available for assessment, the reader selects cannot grade as the appropriate answer. Cannot grade is also used where the subfield is present and unobscured but impaired to a degree that the typical appearance of the lesion in question could not be identified.

If a specific lesion can be seen in any part of the subfield, it should be assessed as such even if the remainder of the subfield is ungradable.

f) Lesions occupying more than one subfield are assessed as present in each subfield and the number, length, or area involved is estimated in each subfield separately.

7.0 PHOTOGRAPHIC QUALITY

The photograph reader separately evaluates the four aspects of photographic quality which most affect how useable the photograph is for light box reading: focus and clarity, field definition, visibility of the optic disc and visibility of the macula. The reader also marks the presence of any photographic artifacts. Presence of artifacts sometimes offers further explanation of the four major aspects of quality. Information on artifacts is also useful to the photographic consultant in providing feedback to the field centers. Finally, the reader evaluates the overall gradability of the retinal photograph.

Example photograph PQ1 provides an example of ideal photographic quality. Example photographs PQ2 through PQ11 show common photographic problems. A photographic quality evaluation for all of these is contained in Exhibit 5.

7.1 Focus and Clarity

The photograph reader evaluates the focus and clarity for the retinal photograph as a whole, based on the impact of focus and clarity on the detection and assessment of subtle abnormalities such as focal narrowing of arterioles or retinal microaneurysms. In some cases, the clarity may be impaired due to overall haze, possibly from lens or vitreous opacity. Such photographs are marked as having reduced focus and clarity; this reflects the useability of the photograph rather than adequacy of photographic technique. For example, PQ5 and PQ6, both taken of the same individual, show overall haze suggesting media opacity. In PQ5 the camera is focused, but the overall haze reduces the focus and clarity to borderline. In PQ6 the haze is compounded by true focus problems, resulting in inadequate focus and clarity. If some portions of the photograph are well-focused but other portions are problematic for grading, the reader may describe the overall focus and clarity as fair or borderline. Each reader is provided with Canon 45° photographic originals showing good, fair, borderline and inadequate focus, in addition to the examples here.

Code	Definition	
1	Good -	Crisp and well-focused throughout (see PQ1).
2	Fair -	Slightly soft, or soft only in some areas; subtle abnormalities such as arteriolar narrowing and microaneurysms are fully gradable (see PQ3).
3	Borderline -	Impaired focus and clarity complicates the reader's decision-making process, but ultimately is adequate to assess arteriolar narrowing and microaneurysms; or, some portions are good and others are inadequate (see PQ4).
4	Inadequate -	Impaired focus and clarity prevent the assessment of arteriolar narrowing and microaneurysms (see PQ6).
8	Cannot grade -	Cannot evaluate focus and clarity, usually because of an obscurity such as a total blink (see PQ9).

7.2 Field Definition

The reader evaluates field definition on the basis of correct positioning of the two major retinal landmarks, the optic disc and the macula, within the retinal photograph. Ideally, the optic disc should be from 1 1/2 DD to 2 1/2 DD from the nasal edge of the photograph and should be centered vertically between top and bottom of the photograph (see Exhibit 1 and example photograph PQ1). If any portion of the disc or its surrounding Zones A and B is omitted from the photograph, it is inadequate for the measuring process and the field definition is evaluated as poor; as in example photograph PQ2. If either disc or macula is omitted from the photograph, it is inadequate for the light box reading and the field definition is evaluated as poor. If the disc is not centered between top and bottom of the photograph, the evaluation of arteriolar abnormalities in some quadrants may be compromised and the field definition is evaluated as fair.

Code	Definition	
1	Good -	Disc is 1 1/2 DD to 2 1/2 DD from nasal edge, and centered vertically; macula is within photograph (see PQ1).

2 Fair - Disc is at least 1 DD from nasal edge; macula is within photograph.

3 Poor - Disc is omitted or less than 1 DD from nasal edge of photograph (see PQ2); or macula is omitted from photograph.

8 Cannot grade - Cannot evaluate field definition, usually because of an obscurity such as a total blink (see PQ9).

7.3 Disc Obscured or Missing

The photograph reader evaluates the disc as obscured or missing if any portion of the disc is either obscured by artifact such as a dark shadow or a blink, or omitted from the photograph because of poor field definition. If the disc is obscured or missing, the following lesions should be marked as ungradable: focal narrowing within the disc margin, papillary swelling, new vessels on the disc and overall diabetic retinal level.

Code Definition

0 No - disc is visible.
2 Yes - disc is either obscured or missing (see PQ9).

7.4 Macula Obscured or Missing

The reader evaluates the macula as obscured or missing if the macula is either obscured, most commonly by the dark shadow resulting from small pupillary dilation, or omitted because of poor field definition. To be recorded as obscured, the area should be greater than one disc area (1 DA) and, in the case of uneven illumination, truly obscured rather than merely shadowed. The dark artifact over the macula only shadows about 1 DA in example photograph PQ10, but definitely obscures more than 1 DA in example photograph PQ11. When the area obscured is substantial, the number of microaneurysms, overall diabetic retinal level, and macular edema should be marked as ungradable.

Code Definition

0 No - macular area is visible.
2 Yes - macular area is either obscured or missing (see PQ11).

7.5 Artifacts

Photographic artifacts are evaluated as either present or absent; severity is not considered. The photograph reader uses example photographs of the various artifacts to aid decisions about their presence.

Code Definition

0 No - absent.
2 Yes - present.

7.5.1 Haze

Two types of haze are noted: overall haze and edge haze. Overall haze is characterized by an overall reduction in clarity and generally produces a dimmer and yellower color than is usually seen. The affect is one of something sheer or gauzy between the retina and the observer. Example photographs PQ5 and PQ6 exhibit overall haze. As discussed in section 7.1, the clarity of these two photographs is reduced. Edge haze is a white, hazy appearance at the edge of the retinal photograph, generally whitest and most opaque at the periphery and diffusing towards the center of the photograph. Example photographs PQ3 and PQ4 show edge haze. In PQ4, arteriolar abnormalities are ungradable in the two nasal quadrants because of the edge haze, lowering the overall photographic quality to impaired.

7.5.2 Dust and Dirt

The artifacts resulting from dust spots on the camera lens are usually small gray-white, soft-edged circular spots. Example photograph PQ1, although excellent in every other way, exhibits one small dust spot at 5:00 near the field periphery. Larger irregular artifacts may result from body oil smudges if the lens has been touched by a nose or finger. If the lens has been improperly cleaned, the resulting artifact may form an arc or arcs following the circular motion used to clean the lens, as shown in photographic examples PQ10 and PQ11. Dust and dirt artifacts are soft-edged and out of focus because dirt on the lens is far anterior to the retina and therefore in a very different plane of focus than retinal features.

7.5.2 Lashes

Artifacts from lashes or partial blinks are a bright yellow-white and flare from the edge of the field toward the center, most often extending upwards from the bottom edge of the photograph, as in example photographs PQ7 and PQ8. Linear or rounded shapes from the individual lashes are frequently evident. Lash artifacts are soft-edged and out of focus because the lashes are anterior to the retina and in a different plane of focus.

7.5.3 Arc

Arcs are hard-edged white, yellow, or rainbow-shaded artifacts at the field periphery.

7.5.4 Uneven illumination/Macula

Uneven illumination refers to the dark shadow which occurs in non-mydriatic photographs when the pupillary dilation is less than optimal. This dark shadow is usually centered over the macula. The photograph reader assesses uneven illumination as present in the macula if the macular area is lightly shadowed, darkly shadowed or totally obscured. Uneven illumination over the macula is seen in example photographs PQ8, PQ10 and PQ11.

7.5.5 Uneven illumination/Edge

If the dark shadow is placed on the edge or periphery of the field, or extends from the center of the field to the edge, then uneven illumination is marked as present on the edge. Example photographs PQ8 and PQ11 show illumination problems on the edge of the field nasally.

7.5.6 Uneven illumination/Disc

If any dark shadow extends over any part of the optic disc, then uneven illumination is marked as present on the disc.

7.5.7 Total Blink

A total blink results in bright yellow-white artifact obscuring all or most of the field. A total blink will sometimes have uneven color or linear shapes from the individual lashes. If the retinal photograph is obscured by a total blink, focus and field definition are usually ungradable. Both disc and macula are obscured resulting in an ungradable photograph. Example photograph PQ9 shows a total blink.

7.6 Gradability

The overall gradability of the retinal photograph is based on all aspects of photographic quality and the degree to which they impact the reading of retinal abnormalities. The retinal photograph is assessed as gradable if most of the substantive questions can be answered.

In general, the important substantive questions in the retinal light box reading can be grouped under two headings: arteriolar abnormalities and lesions of diabetic retinopathy. If photographic quality negatively impacts only one of these two groupings, the photograph is assessed as gradable but impaired. For example, if the number of microaneurysms and diabetic retinal level are ungradable because the macular area is obscured by dark shadow, but good focus and field definition allow accurate assessment of arteriolar abnormalities, then the photograph is gradable but

impaired. Alternatively, if artifacts and obscurities on the field periphery prevent assessment of arteriolar abnormalities in several subfields, but the central retinal landmarks (disc and macula) are clearly visible and the diabetic retinal level can be established, then the photograph is gradable but impaired.

If both major groupings of questions cannot be answered, then the retinal photograph is assessed as ungradable. The most common causes of ungradable retinal photographs are inadequate focus and clarity, dark shadows obscuring both macula and field periphery, and total blinks. Some photographs may be ungradable because they are obscured by media problems (such as asteroid hyalosis); the assignment of ungradable reflects the usefulness of the photograph for data collection, not necessarily photographic technique.

8.0 ARTERIOLAR ABNORMALITIES

The arteriolar abnormalities assessed are: focal narrowing of arterioles, generalized narrowing of arterioles, sheathing of arterioles, and arterio-venous crossing abnormalities (arterio-venous nicking). The reader uses the ARIC normotensive examples N1 to N5, the ARIC arteriolar abnormality examples A1 to A8, and a reduction of ETDRS Standard Photograph #9 as references (all listed in Exhibit 2). Exhibit 6 is a table showing assessment of focal narrowing and arterio-venous nicking in example photographs A1 to A8.

8.1 Focal Narrowing

The photograph reader assesses all marked constrictions of arteries and arterioles as focal narrowing. Focal narrowing is assessed separately for the disc and Zone A, where the vessels may be more arterial in nature, and the quadrants beyond Zone A where the vessels are arteriolar in nature. Definite focal narrowing is marked when the involved vessel is at least 50u (42u ETDRS) in diameter, or about 1/3 of the diameter of a vein at the disc margin, and the constricted area has a caliber less than or equal to 2/3 the caliber of proximal and distal vessel segments. If the reader observes constriction in vessels less than 50u (42u ETDRS) in diameter, such constrictions should be assessed as questionable focal narrowing. If the reader feels that subtle constriction of vessels is present, but the segment in question has a diameter greater than 2/3 of the diameter of adjacent segments, then the reader marks questionable focal narrowing.

8.1.1 Focal Narrowing, Disc and Zone A

The reader assesses focal narrowing within the disc margin, using the natural disc margin even if it is smaller or larger than an average disc (as approximated by the inner circle of the ARIC grid), and in Zone A, defined as the zone from the natural disc margin to the second circle on the grid (1/2 DD from an average disc, radius of second circle = 1 DD from a point at the center of the disc).

Special care must be taken to exclude apparent changes in the diameter of arteries as they come up through the optic cup and course over the margin of the optic disc. The normotensive example N1 shows an artery crossing the disc margin at 12:00 where the apparent diameter of the artery within the disc margin is less than the apparent diameter in Zone A. The Zeiss stereo view shows that the apparent tapering of the artery on the disc is due to its position down the slope of the rim into the optic cup. The nerve fiber layer is frequently more visible near the disc margin and may subtly obscure vessel margins, giving the illusion of a decrease in vessel caliber. Such appearances are excluded. The normotensive examples N2 and N3 show arteries leaving the disc nasally which appear subtly smaller in caliber immediately distal to the disc margin. Close examination of both Canon and Zeiss photographs reveals that these arteries are partially obscured by the feathery, sheer white of the nerve fiber layer; focal narrowing in Zone A of these eyes would be marked as absent.

The severity of focal narrowing within the disc margin and in Zone A is determined by the number of substantial vessels affected, substantial vessels being defined as arteries with a diameter greater than or equal to 50u (42u ETDRS), or about 1/3 the diameter of a vein at the disc margin. If only one or two substantial vessels are affected, the abnormalities are considered definite, mild; if three or more substantial vessels are affected, the abnormalities are severe.

Example photograph A1 shows definite focal narrowing of the arteries leaving the disc margin at 1:00 and 2:00. The artery leaving the disc at 1:00 exhibits two distinct pinched areas, one just within the disc margin and one in Zone A. (Moving towards the center of the disc, this vessel is more subtly narrowed just after it splits off the superior arterial branch.) The artery leaving the disc at 2:00 is distinctly pinched shortly after it splits from the superior arterial branch. This vessel appears "beaded" in Zone A, an appearance usually noted as questionable because the constrictions are not definitively less than 2/3 the normal vessel caliber, but in this case the vessel appears subtly narrower through all of Zone A and possibly into the superior nasal (SN) quadrant when contrasted with more distal lengths of the same vessel. This vessel would be assessed as having definite focal narrowing in Zone A, and questionable narrowing in the SN quadrant.

Example photograph A2 exhibits a trifurcation of the inferior artery within the disc margin. All three of the branches are constricted immediately after the trifurcation. The temporal branch is only subtly narrowed and quickly regains a larger caliber which is then maintained in Zone A and the inferior temporal (IT) quadrant; the appearance of this branch alone would be graded as questionable narrowing within the disc margin. The middle branch is markedly irregular within the disc, showing two definite focal narrowings, and may also exhibit a thickened wall. This vessel is questionably narrowed in Zone A: it is more subtly irregular here and may be narrower than in the inferior nasal quadrant (IN) distally. The nasal branch exhibits a very robust caliber after the initial constriction, and then narrows as it leaves the disc margin at 3:00, courses through Zone A and branches in the superior nasal quadrant, never regaining a caliber close to that within the disc margin. The change in caliber seems too great to be explained by undulations of the vessel within the optic disc; both the initial constriction of this branch and the narrowing at the disc margin are evaluated as definite narrowing. It is difficult to say if this vessel should be evaluated as focally narrowed in Zone A, because the appearances in the superior nasal quadrant suggest generalized narrowing (see section 8.4).

The superior artery in example photograph A2 has two large branches feeding the superior temporal (ST) quadrant. The temporal branch narrows shortly after the branching point within the disc and remains narrow well into Zone A, and then approximately doubles in caliber. This definite focal narrowing in the disc brings the number of vessels with definite narrowing within the disc to three, meeting the requirement for severe focal narrowing within the disc. Focal narrowing in Zone A is definite. This vessel may be subtly irregular and narrower between Zone A and the macula; this appearance would be marked as questionable focal narrowing in the ST if it was the only segment in question. However, the superior branch (leaving the disc margin at 12:00) appears relatively constant in caliber within the disc margin and in Zone A, but exhibits four short segments of distinct focal narrowing in the ST quadrant.

Code	Definition
0	No focal narrowing.
1	Questionable focal narrowing.
2	Definite focal narrowing in one or two substantial arterioles (definite).
3	Definite focal narrowing in three or more substantial arterioles (severe).
8	Cannot grade.

8.1.2 Focal Narrowing in Quadrants

Focal narrowing or constriction of arterioles is assessed in each of the four quadrants, excluding the area within 1/2 DD of the disc (Zone A). The photograph reader carefully examines all arterioles greater than or equal to 50u (42u ETDRS) in diameter, or about 1/3 the diameter of a vein at the disc margin, and estimates the combined length of all constricted segments. There is sometimes a gradual tapering from the original caliber of the arteriole to the most constricted caliber; only the length of constriction to 2/3 or less of the original caliber is considered definite. If a quadrant has more than one focally narrowed segment, the lengths of all narrowed segments are added together. If focal narrowing extends from one quadrant to another, the length involved is estimated separately in each quadrant.

Example photograph A2, chosen for pronounced focal narrowing of the arteries on the disc, also exhibits definite focal narrowing of the arterioles in the ST quadrant, as discussed in section 8.1.1.

Example photograph A3 exhibits classic focal narrowing in both superior quadrants. The superior temporal arteriole bifurcates in Zone A, and the more robust branch exhibits two segments of focal narrowing, one in Zone B and one just distal to Zone B. In the superior nasal (SN) quadrant, there is a short but distinct area of focal narrowing about 1/2 DD from the nasal edge of the photograph at 10:30. (Please note that the SN arteriole is also narrowed in Zone A.)

Example photograph A4 demonstrates more pronounced focal narrowing. The more superior arteriole in the superior nasal (SN) quadrant exhibits one segment of distinct focal narrowing, about 1/3 DD in length and beginning about 2/3 DD from the disc margin. The inferior nasal (IN) quadrant exhibits a subtle constriction in the arteriole leaving the disc at 4:00, about 3/4 DD from the disc margin. In the inferior temporal (IT) quadrant, there are constricted segments in three arterioles.

The arteriole leaving the disc at 7:30 (note that the entire length within the disc margin is markedly narrowed) is subtly constricted beyond Zone A. The artery leaving the disc at 6:00 immediately bifurcates, giving rise to two arteriolar branches. The more temporal branch exhibits at least two short segments of focal narrowing. The arteriole coursing straight inferiorly exhibits a segment of focal narrowing, beginning about 1 1/4 DD from the disc margin, which exceeds 1/2 DD in length. The total length of focal narrowing in the IT quadrant may be as much as 1 1/4 or 1 1/2 DD, meeting the definition of moderate focal narrowing.

For severe focal narrowing, all segments of focal narrowing in a quadrant are similarly added up and must total 2 DD or more. Given that the Canon 45° photographs usually provide about 6 DD of arterioles for evaluation in each temporal quadrant and only about 3 DD in each nasal quadrant, it is unusual to find more than 2 DD of focal narrowing in any given quadrant.

Example photographs 5 and 6 show cases that, although less pronounced, are evaluated as definite focal narrowing. In example photograph A5, the superior nasal artery bifurcates at the disc margin. The more superior arteriolar branch is irregular along its length. This vessel is probably about 60u (50u ETDRS) in caliber, approaching the lower limit at which focal narrowing can be confidently assessed at this magnification, and the narrowings are brief, making an assessment of the degree of constriction difficult. The appearances in this eye suggest possible generalized narrowing. However, there are two areas of definite focal narrowing: one in the SN quadrant about 1 DD from the disc margin in the more superior vessel, and one in Zone A in the vessel coursing nasally.

Example photograph A6 is also subtle. The arteriolar branch leaving the photographic field at 2:30 shows one short segment of definite focal narrowing about 1 DD from the edge of the field.

If the total length of arterioles available for examination in a quadrant totals less than 1 1/2 DD, then the reader marks that quadrant ungradable, code 8. Cannot grade is also used if the arterioles in a given subfield are out-of-focus or obscured by artifact.

Code	Definition
0	No focal narrowing.
1	Questionable focal narrowing.
2	Definite focal narrowing, combined length $<$ 1/2 DD (mild).
3	Definite focal narrowing, combined length $\geq$ 1/2 DD, but $<$ 2 DD (moderate).
4	Definite focal narrowing, combined length $\geq$ 2 DD (severe).
8	Cannot grade.

8.2 Arteriolar Sheathing

The reader assesses opacification of the arteriolar column as arteriolar sheathing in the four quadrants, excluding the area within 1/2 DD of the disc (Zone A). Arteriolar walls which are partially opaque, that is, a ribbon of blood can still be seen with white lines on one or both sides, and complete opacification of the arteriolar column, or white threads, are assessed as definite arteriolar sheathing. The lengths of all sheathed segments are added for each quadrant, as described for focal narrowing above.

If the total length of arterioles available for examination in a quadrant totals less than 1 1/2 DD, then the reader marks that quadrant ungradable, code 8.

Code	Definition
0	No arteriolar sheathing.
1	Questionable arteriolar sheathing.
2	Definite arteriolar sheathing, combined length $<$ 1/2 DD (mild).
3	Definite arteriolar sheathing, combined length $\geq$ 1/2 DD, but $<$ 2 DD (moderate).
4	Definite arteriolar sheathing, combined length $\geq$ 2 DD (severe).
8	Cannot grade.

8.3 Arterio-venous Crossing Abnormalities

The photograph reader assesses abnormalities of arterio-venous crossings, or arterio-venous nicking, in each quadrant. Crossings within 1/2 DD of the disc margins are excluded, as are the atypical crossings where the vein crosses over the artery. The reader examines all crossings of artery over vein, and evaluates crossings where the venous blood column is narrowed as abnormal.

Tapering or narrowing of the venous blood column on both sides of the crossing is required for definite AV nicking. If the venous blood column appears tapered on only one side of the crossing, and the appearance is not due to normal vessel undulation, then the reader assesses AV nicking as questionable. The grader discounts any apparent diminishments in venous caliber if the vein appears to be partially obscured by nerve fiber reflex as it approaches and crosses under the artery.

The reader compares any definite arterio-venous nicking to that in the ARIC reduction of ETDRS Standard Photograph #9; if the appearance is as pronounced as that in ETDRS Standard Photograph #9, it is assessed as severe. In ETDRS Standard Photograph #9, the venous blood column is reduced to about 1/2 its original diameter on both sides of the crossing.

Example photograph A6 exhibits one definite arterio-venous crossing abnormality in the superior temporal (ST) quadrant. Subtle tapering of the venous blood column can be seen on both sides of the crossing, and the Z-shaped deviation in the path of the vein further suggests that the pressure relationships at the crossing are not normal. The arterio-venous crossing in the inferior temporal (IT) quadrant is similar in appearance but the tapering of the venous blood column cannot be seen distinctly on the proximal side of the crossing; therefore, the IT quadrant would be marked questionable for arterio-venous crossing abnormalities.

The arterio-venous crossing abnormalities in example photograph A7 are more pronounced. Both the inferior nasal (IN) and superior temporal (ST) quadrants exhibit marked narrowing of the venous caliber on both sides of the arterio-venous crossing in question. In the ST quadrant, the caliber of the vein narrows to about 1/3 of its normal caliber, resulting in a grade of severe. The inferior temporal (IT) quadrant has an arterio-venous crossing immediately adjacent to a venous trifurcation. The venous branch involved in the this crossing is visibly narrowed distally, but the proximal side cannot be assessed because of the proximity to the trifurcation. Because the venous narrowing is visible on only one side, arterio-venous nicking would be assessed as questionable in the IT quadrant.

Example photograph A8 exhibits definite, although somewhat more subtle, arterio-venous nicking in both temporal quadrants. The abnormal arterio-venous crossing in the IT quadrant is adjacent to a venous bifurcation. In this case, the crossing is somewhat distal to the bifurcation and the venous caliber can be assessed on both sides of the crossing. The venous caliber on both sides is narrower than the caliber of the vein distally in the field. The ST quadrant shows narrowing of the vein on both sides of the crossing, although the narrowing on the proximal side is more subtle than that seen in the other examples.

Code	Definition
0	No A/V nicking.
1	Questionable A/V nicking.
2	Definite A/V nicking, < ETDRS Std. Photo. #9 (definite).
3	Definite A/V nicking, ≥ ETDRS Std. Photo. #9 (severe).
8	Cannot grade.

8.4 Generalized Narrowing

Generalized narrowing is difficult to evaluate, given that normal arterioles in the same eye may not be available for comparison. The reader provides an estimate of generalized narrowing based on comparison with the corresponding veins in the eye or, where the arterioles appear normal in some quadrants, with other arterioles.

If the reader has a general impression that the arterioles in the eye are narrow in comparison with the veins, he/she marks generalized narrowing as questionable. If some arterioles in the eye are markedly narrowed, or thready, but other quadrants appear more normal, then the reader marks generalized narrowing as definite.

Sometimes only the nasal quadrants may have thready arterioles. Example photograph A8 may have questionable generalized narrowing: the arterioles in the SN quadrant are narrower than one might expect given the caliber of the parent artery. If the arterioles are small threads throughout the entire eye, then the reader assesses generalized narrowing as severe.

Code	Definition
0	No generalized narrowing.
1	Questionable generalized narrowing.
2	Definite generalized narrowing.
3	Severe generalized narrowing, threads throughout.
8	Cannot grade.

9.0 LESIONS OF DIABETIC RETINOPATHY

The photograph reader assesses all lesions of diabetic retinopathy for presence or absence. Individual lesions are assessed for severity where relevant to the supporting evidence for the diabetic retinal level. A brief description of each lesion and special considerations for non-stereo 45° photographs are provided here; more detailed descriptions of the individual lesions are available in ETDRS Report #10, An Extension of the Modified Airlie House Classification[13].

Some of these lesions, notably microaneurysms, retinal hemorrhages and soft exudates, or cotton-wool spots, are also characteristic of hypertensive retinopathy. Recent data from a study by Klein et al[14] suggest that a single retinal microaneurysm is more typically found in hypertensive rather than diabetic individuals.

9.1 Retinal Hemorrhages and Microaneurysms

The photograph reader counts microaneurysms up to a total of five, counts retinal hemorrhages up to two, characterizes the retinal hemorrhage(s) as blot or flame, and estimates the total area of retina covered by retinal hemorrhages and microaneurysms.

9.1.1 Number of Microaneurysms

Retinal microaneurysms, small sacs or balloonings of the retinal capillaries, appear as small red dots. A red spot which is less than 150u (125u ETDRS) in its longest dimension (approximately the width of a vein at the disc margin) and which has sharp margins and even density is considered a microaneurysm. A red spot which is equal to or greater than 150u (125u ETDRS) in its longest dimension is assessed as a microaneurysm only if features such as round shape, smooth margins and a central light reflex suggest that it is probably a microaneurysm; otherwise, it is assessed as a retinal hemorrhage. Microaneurysms are typically round, but may more rarely appear fusiform, or sausage-shaped. They are typically red, but more rarely appear pink or dull white if opacified.

Code	Definition
0	No microaneurysms.
1	Questionable microaneurysm.
2	One microaneurysm.
3	Two microaneurysms.
4	Three microaneurysms.
5	Four microaneurysms.
6	Five or more microaneurysms.
8	Cannot grade.

9.1.2 Number of Retinal Hemorrhages

Retinal hemorrhages, the leaking of blood into the retina, typically appear as red spots in the retina with irregular margins and shapes. A red spot less than 150u (125u ETDRS) in its longest dimension is assessed as a retinal hemorrhage only if it has irregular margins and/or uneven density. Any red spot greater than or equal to 150u (125u ETDRS) in its longest dimension is considered a retinal hemorrhage, unless its features strongly suggest that it is a microaneurysm as described above.

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[13]Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs - an extension of the Modified Airlie House Classification, ETDRS Report 10. Ophthalmol 1991; 98:786-806.

[14]Klein R, Klein BEK, Moss SE, and Wang Q. Blood pressure, hypertension, and retinopathy in a population of people without diabetes. Submitted for publication.

Code	Definition
0	No retinal hemorrhage.
1	Questionable retinal hemorrhage.
2	One retinal hemorrhage.
3	Two or more retinal hemorrhages.
8	Cannot grade.

9.1.3 Type of Retinal Hemorrhage

The reader characterizes any retinal hemorrhage present as either flame-shaped or blot-shaped, or notes that both types are present. Flame-shaped hemorrhages are elongated and pointed at one or both ends; if small, they may appear linear. The density of the hemorrhage may be greater centrally, and it may have a central white spot (Roth's spot). Flame-shaped hemorrhages are oriented parallel to the nerve fiber layer and characteristically appear in the vessel arcades or radiating from the optic disc. Blot hemorrhages are roughly round or irregular in outline, and may occur anywhere within the retina. Example Photograph T2, diabetic retinal level 35, shows retinal hemorrhages and microaneurysms, including a linear flame hemorrhage in the inferior temporal arcade and several blot hemorrhages.

Code	Definition
0	No retinal hemorrhage.
1	Questionable retinal hemorrhage (retinal hemorrhage questionably present).
2	Definite retinal hemorrhage(s), flame-shaped only.
3	Definite hemorrhage(s), blot only.
4	Definite hemorrhages, blot and flame-shaped.
8	Cannot grade.

9.1.4 Hemorrhages and Microaneurysms (H/Ma)

The photograph reader estimates the total area of retina covered by hemorrhages and/or microaneurysms (H/Ma), in comparison to the ARIC reductions of ETDRS Standard Photographs #1 and #2A. All punctate, blot and linear hemorrhages, and all microaneurysms are included. The amount of retinal hemorrhage and microaneurysms is assessed in some detail because of its importance in determining diabetic retinal level.

Code	Definition
0	No hemorrhages or microaneurysms.
1	Questionable microaneurysm and/or retinal hemorrhage.
2	Definite microaneurysms and/or retinal hemorrhages, but the amount is < ETDRS Std. Photo. #1, or ≥ ETDRS Std. Photo. #1 in only one to three quadrants.
3	Definite, ≥ ETDRS Std. Photo. #1 in all four quadrants.
4	Definite, ≥ ETDRS Std. Photo. #2A in an area approximating an ETDRS field.
5	Definite, ≥ ETDRS Std. Photo. #2A in two or three quadrants.
6	Definite, ≥ ETDRS Std. Photo. #2A in all four quadrants.

9.2 Hard Exudates and Macular Edema

9.2.1 Hard Exudates (HE)

Hard exudates are lipid deposits within the retina. They are characteristically bright yellow-white deposits with sharp margins, and often appear waxy, shiny or glistening. Hard exudates may be arranged as individual dots, confluent patches, or in rings partially surrounding zones of retinal edema and/or groups of microaneurysms. Hard exudates are shown in Example Photographs T3, T4, T6, and T8.

Code	Definition
0	No hard exudate.
1	Questionable hard exudate.
2	Definite hard exudate.
8	Cannot grade.

9.2.2 Macular Edema

Macular edema is thickening of the retina in the macular area, resulting from the leakage of fluid into the retina from microaneurysms and/or compromised capillaries. In a non-stereo photograph, the reader cannot directly assess thickening of the retina and must rely on other appearances to estimate areas of edema.

Hard exudates, particularly confluent hard exudates or hard exudate rings, are characteristic of eyes with macula edema. More rarely, edematous eyes have large amounts of retinal hemorrhages and microaneurysms concentrated temporally or arranged concentrically around the macula. In addition, changes in the transparency of the retina within hard exudate rings or at the center of the macula may suggest retinal thickening.

Example Photographs T6, T8 and T10 show hard exudate patterns suggestive of macular edema. T6 exhibits a hard exudate ring superior to the macula with one confluence of hard exudate adjacent to the macula at 10:00, suggesting retinal thickening in this area; the Zeiss stereo photographs confirm thickening in this area. The proximity of the hard exudates to the center suggests "clinically significant macular edema" by the ETDRS definition[15], in the Topcon 45° photograph. T8 exhibits massive edema throughout the posterior pole; the presence of edema extending to center can easily be deduced from the hard exudate rings and the several patches of confluent hard exudate encroaching on the center. The partial ring of hard exudate in T10 is a more subtle appearance and, in the absence of stereo in the 45° photograph, the grade of choice may be questionable macular edema.

The photograph reader assesses any inferred edema within the temporal arcades, but less than clinically significant macular edema, as definite. Clinically significant macular edema is defined as: (a) an area of edema greater than or equal to 1 DA and extending within 1 DD of center, or (b) edema extending within 500u of center. The reader may assess definite thickening at center based on the presence of hard exudates at center, a central color change or loss of transparency, or cystoid spaces at center. Example Photograph T8 exhibits definite thickening at center, based on the proximity of the hard exudates to center.

Code	Definition
0	No macular edema.
1	Questionable macular edema.
2	Macular edema present but less than clinically significant, inferred from hard exudates and/or other appearances.
3	Clinically significant macular edema present, but center is not definitely involved, inferred from hard exudates and/or other appearances.
4	Clinically significant macular edema with center definitely involved, inferred from hard exudates and/or other appearances.
8	Cannot grade.

9.3 Other Non-Proliferative Lesions

9.3.1 Soft Exudate (SE)

Soft exudates indicate areas of ischemia in the retina. They appear as superficial white, pale yellow-white or gray-white areas with feathery edges, frequently showing striations parallel to the nerve fibers.

Soft exudates appear in Example Photographs T3, T4, T5, T6, T7 and T9; Example Photograph T2 shows a questionable soft exudate.

Code	Definition
0	No soft exudate.
1	Questionable soft exudate.
2	Definite soft exudate.
8	Cannot grade.

[15]See 10.

9.3.2 IRMA

Intraretinal microvascular abnormalities (IRMA) are tortuous intraretinal vascular segments varying in caliber from barely visible to 35u (30u ETDRS) or larger. In the absence of stereo, it may be difficult to distinguish IRMA from new vessels. In general, IRMA are more delicate, more angular or jagged in their tortuosity, less likely to cross themselves or other retinal vessels, and more likely to occur in relatively open areas between major vessels. The amount of IRMA is assessed relative to the ARIC reduction of ETDRS Standard Photograph #8A.

Example Photographs T5, T6 and T7 show definite IRMA; Example Photograph T9 exhibits IRMA greater than Standard Photograph #8A in the superior temporal quadrant.

Code	Definition
0	No IRMA.
1	Questionable IRMA.
2	Definite IRMA, < ETDRS Std. Photo. #8A, in one to three quadrants.
3	Definite IRMA, < ETDRS Std. Photo. #8A, in all four quadrants.
4	Definite IRMA, ≥ ETDRS Std. Photo. #8A in any given area approximating an ETDRS field.
8	Cannot grade.

9.3.3 Venous Beading (VB)

Venous beading refers to localized increases in the venous caliber (segmental dilation), sometimes resembling a string of beads and typical of diabetic retinopathy.

An example of venous beading may be found in Example Photograph T8. Example Photograph T9 suggests the difficulty of assessing venous beading in 45° photographs: venous beading is evident in the superior temporal arcade in the Zeiss photographs but is more difficult to identify in the Topcon photograph.

Code	Definition
0	No venous beading.
1	Questionable venous beading.
2	Definite venous beading in one quadrant only.
3	Definite venous beading in two to four quadrants.
8	Cannot grade.

9.4 Proliferative Lesions

The proliferative lesions assessed include new vessels on the disc, new vessels elsewhere, fibrous proliferations and vitreous and/or preretinal hemorrhage. In a non-stereo photograph, proliferative lesions which are elevated from the retinal surface are in a different plane of focus from the retinal vessels, and may therefore be out of focus when the retinal vessels and other retinal detail are in focus.

9.4.1 New Vessels on the Disc (NVD)

New vessels on the surface of the optic disc or on the retina within 1 DD of the disc margin (within Zone B), or in the vitreous cavity anterior to this area are considered NVD. However, when new vessels originating elsewhere than the disc extend within 1 DD from the disc (within Zone B) but not within 1/2 DD of the disc (within Zone A), and no other new vessels are present closer to or on the disc, they are graded as new vessels elsewhere (NVE). The amount of NVD is assessed in relation to the ARIC reduction of ETDRS Standard Photograph #10A.

Example Photographs T11, T12 and T13 show new vessels on the disc, with that in Examples T12 and T13 greater than Std. Photo. #10A.

Code	Definition
0	No NVD.
1	Questionable NVD.
2	Definite NVD, < ETDRS Std. Photo. #10A.
3	Definite NVD, ≥ ETDRS Std. Photo. #10A.

8 Cannot grade.

9.4.2 New Vessels Elsewhere (NVE)

Any new vessels which are on the surface of the retina or further forward in the vitreous cavity are considered new vessels elsewhere, excluding those considered as NVD as described in Section 10.4.1. In the absence of stereo, it may be difficult to distinguish subtle new vessels from IRMA. In general, new vessels are bolder, more curvilinear, more likely to cross and recross both themselves and the retinal vessels, and more likely to be sited over retinal vessels.

Example Photographs T11, T12 and T13 exhibit new vessels elsewhere. Example Photograph T9 has an area in the superior temporal arcade which could reasonably be assessed as either IRMA or NVE from the non-stereo 45° photograph.

Code	Definition
0	No new vessels elsewhere.
1	Questionable new vessels elsewhere.
2	Definite new vessels elsewhere, < 1/2 DA.
3	Definite new vessels elsewhere, ≥ 1/2 DA.
8	Cannot grade.

9.4.3 Vitreous and/or Preretinal Hemorrhage

Vitreous hemorrhage (blood in the vitreous cavity) and preretinal hemorrhage (blood on the surface of the retina) are considered together. Vitreous hemorrhage is frequently diffuse and may obscure part or all of the photographic field. If localized, it is usually irregular in shape and outline. Preretinal hemorrhages may be boat-shaped, indicating a fluid level in a pocket between the retina and the detached posterior hyaloid, or flat and blot-shaped. Small preretinal hemorrhages may be distinguished from intraretinal hemorrhages by their distinctive shape or by a darker, more purple-red color.

Example Photographs T13 and T14 both show diffuse vitreous hemorrhage. Example Photograph T12 exhibits small hemorrhages at 7:00 in the 45° field. Their distinct edges and dark color suggest that they are not retinal but, without stereo effect to differentiate them, they could be either preretinal or vitreous.

Code	Definition
0	No vitreous and/or preretinal hemorrhage.
1	Questionable vitreous and/or preretinal hemorrhage.
2	Definite vitreous and/or preretinal hemorrhage, totalling < 1 DA.
3	Definite vitreous and/or preretinal hemorrhage, totalling more than 1 DA.
8	Cannot grade.

9.4.4 Fibrous Proliferation (FP)

Fibrous proliferations are white sheets or fine strands of fibrotic tissues formed subsequent to neovascularization, and are therefore sited similarly. Fibrous proliferations on the disc (FPD) and elsewhere (FPE) are considered together.

Example Photograph T10 shows an eye where fibrous proliferations are the only evidence of neovascularization.

Code	Definition
0	No fibrous proliferation.
1	Questionable fibrous proliferation.
2	Definite fibrous proliferation.
8	Cannot grade.

9.5 Papillary Swelling

Papillary swelling is detectable in non-stereo photographs only by blurring of the disc margin. The reader assesses papillary swelling as severe if at least 270° of the disc margin is blurred and the appearance of the disc suggests swelling comparable to that in ETDRS Example Photographs E and F.

Marked papillary swelling may be accompanied by engorged capillaries on the disc, retinal hemorrhage and/or soft exudate.

Code	Definition
0	No papillary swelling.
1	Questionable papillary swelling.
2	Definite papillary swelling.
3	Severe papillary swelling.
8	Cannot grade.

9.6 Laser Photocoagulation Treatment

The photograph reader assesses the presence of photocoagulation treatment, and its type based on his/her inference of the intent of the treating physician, given the location and appearance of the photocoagulation scars.

Focal photocoagulation treatment for macular edema is characterized by burn scars within the temporal arcades. Focal treatment may be scattered, indicating treatment of microaneurysms or other focal sources of leakage, or, more rarely, arranged in a grid pattern around the macula. Focal burns tend to be smaller and lighter, i.e., with less pigment disturbance, than scatter treatment burns.
Scatter treatment, usually administered for severe non-proliferative or proliferative retinopathy, characteristically consists of an even pattern of burns in all four quadrants and sparing the macula and the papillomacular bundle. Scatter treatment may be accompanied or, rarely, replaced by local treatment, areas of confluent burns used to treat neovascularization directly.

Example Photograph T6 shows focal treatment only. Scatter photocoagulation treatment is present in all of Example Photographs T10 through T14. Example T12 shows definite focal and scatter treatment. In Example T10, the Zeiss photographs show subtle focal treatment but one is able to assess only scatter treatment as definitely present in the Topcon 45° photograph.

Code	Definition
0	No photocoagulation treatment.
1	Questionable photocoagulation treatment.
2	Definite photocoagulation treatment, focal only.
3	Definite photocoagulation treatment, scatter and/or local only.
4	Definite photocoagulation treatment, focal and scatter and/or local.
8	Cannot grade.

10.0 DIABETIC RETINAL LEVEL

The photograph reader assigns an overall diabetic retinopathy severity level according to the ETDRS scale[16] and marks the appropriate supporting evidence, based on his/her assessments of the individual lesions of diabetic retinopathy. The table below lists the diabetic retinal levels in ascending severity, along with the supporting evidence and rules for marking that evidence for each level. Levels 14 and 15 indicate retinopathy which is questionably diabetic because of the lack of microaneurysms, the hallmark of diabetic retinopathy. Level 20, or microaneurysms only, is commonly considered the earliest stage of diabetic retinopathy. The ascending severity of the non-proliferative diabetic retinopathy levels 35 to 53 indicate increased risk of the eye becoming proliferative within the next one to five years, based on ETDRS results[17]. Ascending proliferative levels 61 to 85 indicate increased risk of moving to DRS High Risk Characteristics or severe visual loss (need reference).

ETDRS Scale of Diabetic Retinopathy Severity	Supporting Evidence	Rules for Marking Supporting Evidence
10 Diabetic retinopathy absent	101 Microaneurysms (Ma's) and other lesions absent	
14 Diabetic retinopathy questionable	141 Hard exudate, no Ma's 142 Soft exudate, no Ma's 143 IRMA, no Ma's	Reader may select one, two or three of the supporting evidence codes.
15 Diabetic retinopathy questionable	151 Retinal hemorrhage, no Ma's	
20 Microaneurysms only	201 Microaneurysms only	
35 Mild non-proliferative diabetic retinopathy	351 Venous loop ≥ code 2 352 Questionable soft exudate, IRMA or hard exudate 353 Retinal hemorrhage 354 Hard exudate 355 Soft exudate	Reader may select from one to five of the supporting evidence codes.
43 Moderate non-proliferative diabetic retinopathy	431 H/Ma ≥ Std Photo #1 in four quadrants 432 H/Ma ≥ Std Photo #2A in one "field" 433 IRMA in one to three quadrants	Reader may select only one of the supporting evidence codes; reader may not select both 431 and 432, and either 431 or 432 paired with 433 moves the eye up to level 47.

[16]Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy, ETDRS Report 12. Ophthalmol 1991; 98: 823-833.

[17]See 12.

47 Moderately severe non-proliferative diabetic retinopathy	471 Both IRMA and H/Ma characteristics from level 43 472 IRMA in all four quadrants 473 H/Ma ≥ Std Photo #2A in two or three quadrants 474 Venous beading in one quadrant	Reader may select only one of the supporting evidence codes; either 472 or 473 supersedes 471, and any two codes moves the eye up to level 53.
53 Severe non-proliferative diabetic retinopathy	531 Any two or three of level 47 characteristics 532 H/Ma ≥ Std Photo #2A in four quadrants 533 IRMA ≥ Std Photo #8A 534 Venous beading in two to four quadrants	Reader may select only code 531, or any one, two or three of the other codes; any of codes 532, 533 or 534 supersedes code 531.
61 Mild proliferative diabetic retinopathy	611 FPD and/or FPE 612 NVE < 1/2 DA	Reader may select one or both supporting evidence codes.
65 Moderate proliferative diabetic retinopathy	651 VH and/or PRH < 1 DA 652 NVE ≥ 1/2 DA 653 NVD < Std Photo #10A 654 NVE < 1/2 DA, with VH and/or PRH	Reader selects only the highest supporting evidence code.
71 DRS High Risk Characteristics	711 VH and/or PRH ≥ 1 DA 712 NVE ≥ 1/2 DA with VH and/or PRH 713 NVD < Std Photo #10A with VH and/or PRH 714 NVD ≥ Std Photo #10A	Reader selects only the highest supporting evidence code.
75 DRS High Risk Characteristics	751 NVD ≥ Std Photo #10A with VH and/or PRH	
81 Advanced proliferative diabetic retinopathy	811 VH and/or PRH partially obscures retina; cannot grade for NVD and/or NVE but the center of the macula is attached	
85 Advanced proliferative diabetic retinopathy	851 Macula obscured by VH and/or PRH 852 Retinal detachment at the center of the macula Reader selects only the highest supporting evidence code.	Reader selects only the higher supporting evidence code.
90 Cannot grade	901 Cannot grade for microaneurysms; no other background retinopathy is present 902 Cannot grade for background retinopathy; no proliferative retinopathy is present 903 Cannot grade for proliferative retinopathy	Reader selects only the highest supporting evidence code.

11.0 OTHER OCULAR LESIONS

Other ocular lesions are evaluated as not seen, questionably present, or definitely present. The other ocular lesions specifically assessed are listed below, loosely grouped by topic:

Occlusions:
- **Central artery occlusion**
- **Branch artery occlusion**
- **Central vein occlusion**
- **Branch vein occlusion**

Lipids:
- **Hollenhorst plaque**
- **Asteroid hyalosis**

Glaucoma indicators:
- **Large cup/disc ratio** (.6 to .69 = questionable, $\geq$ .7 = definite)
- **Retinal hemorrhage on the disc or crossing the disc margin**

Other disc abnormalities:
- **Peripapillary atrophy**
- **Other disc abnormality**

Non-pathological confounding lesions:
- **Glial tissue and/or vitreous thickening**
- **Medullated nerve fibers**

Surface wrinkling retinopathy:
- **Cellophane reflex**
- **Surface wrinkling retinopathy with tension lines and/or glial tags**

Maculopathy:
- **Soft drusen within 2 DD of the center of the macula**
- **RPE depigmentation**
- **Hyperpigmentation**
- **SSR detachment**
- **Subretinal hemorrhage**
- **Subretinal fibrosis**
- **Geographic atrophy**

Other:
- **Chorioretinal scar**
- **Nevus**
- **Retinal detachment**
- **Other**

12.0 RETINAL NOTIFICATIONS

The photograph reader prepares letters for retinal alert conditions and routine retinal results, as discussed in the Reading Center Procedures Chapter, Section 7.4. The readers use the guidelines for notification procedures detailed in Exhibits 7 and 8. The direct entry software shows a plus next to all retinal alert conditions and an asterisk next to all routine retinal notification conditions to assist the reader in identifying eyes which need letters. When completing the grading, the reader notes if either a retinal alert or routine notification was sent, and the date of the letter. If either of the two major retinal landmarks, the disc and the macula, is missing or obscured, or if the diabetic retinal level in ungradable for any other reason, and no lesions prompting notification are seen, then the eye is marked cannot grade for notification conditions.

Code	Definition
0	No retinal notification sent.
1	Retinal alert notification sent.
2	Routine retinal notification sent.
8	Cannot grade for notification conditions.

Exhibit 1
Part A - Diagram of a Canon 45° Photographic Field
Part B - Diagram of Grid Application

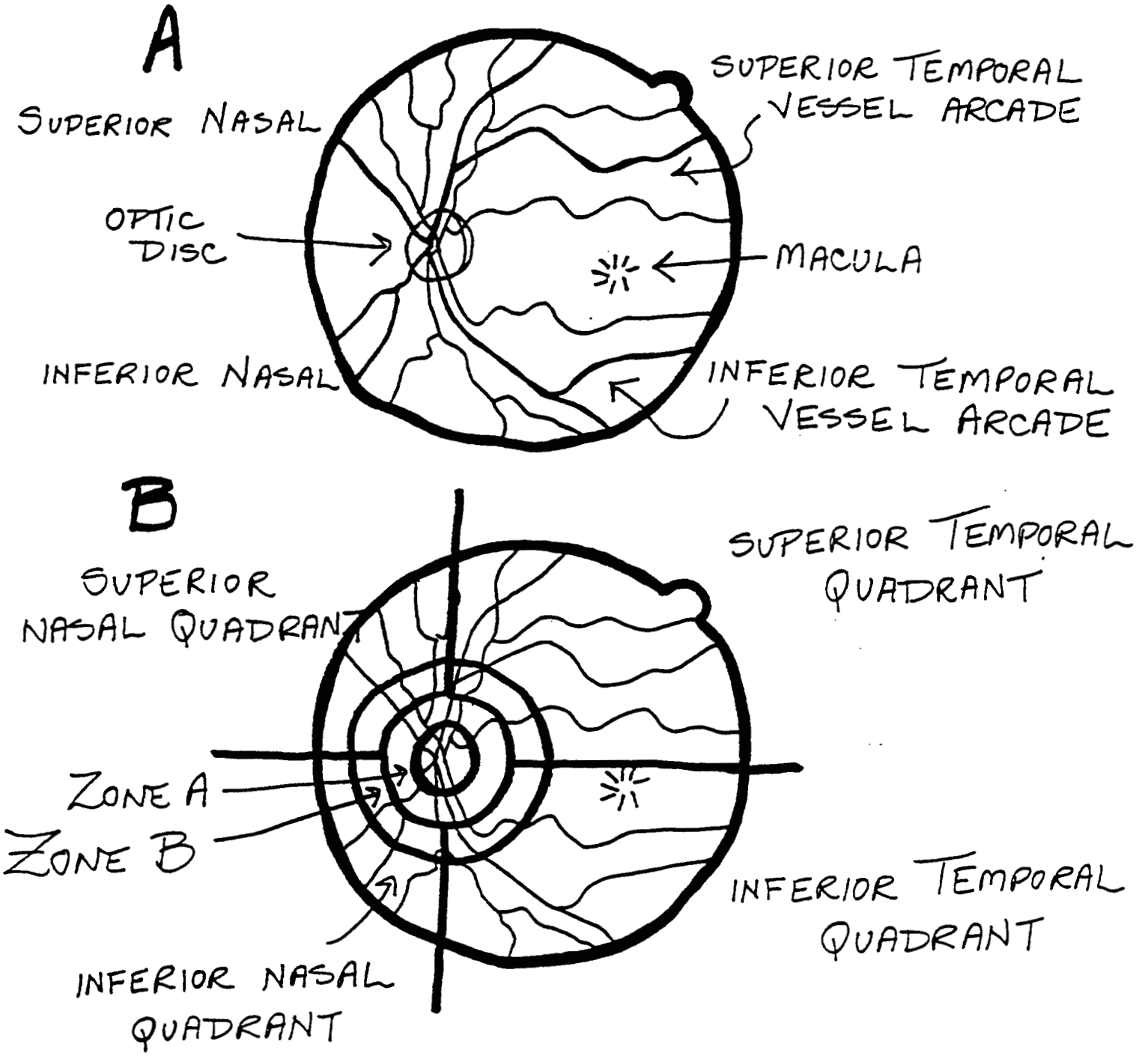


Exhibit 2
ARIC Photographic Standards and Examples

ARIC Canon 45° Example Photographs for Photographic Quality

PQ1	Excellent photographic quality; appropriate grid application
PQ2	Field definition problems
PQ3 & 4	Edge haze
PQ5 & 6	Overall haze; focus and clarity problems
PQ7 & 8	Lashes
PQ9	Total blink
PQ10 & 11	Uneven illumination in the macula; dust and dirt

ARIC Canon 45° Example Photographs for Arteriolar Abnormalities

A1 & 2	Focal narrowing, disc and Zone A
A3, 4, & 5	Focal narrowing, quadrants
A6, 7, & 8	Arterio-venous crossing abnormalities, quadrants

ARIC reductions of ETDRS Standard Photographs:

Std Photo #9	A/V nicking
Std Photo #1	H/Ma
Std Photo #2A	H/Ma
Std Photo #8A	IRMA
Std Photo #10A	NVD

Canon 45° Example Photographs, with corresponding Zeiss 30° photographs in the ARIC reference collection:

N1	Normotensive
N2	Normotensive
N3	Normotensive
N4	Normotensive
N5	Normotensive

Topcon 45° Example Photographs, with corresponding Zeiss 30° photographs in the ARIC reference collection:

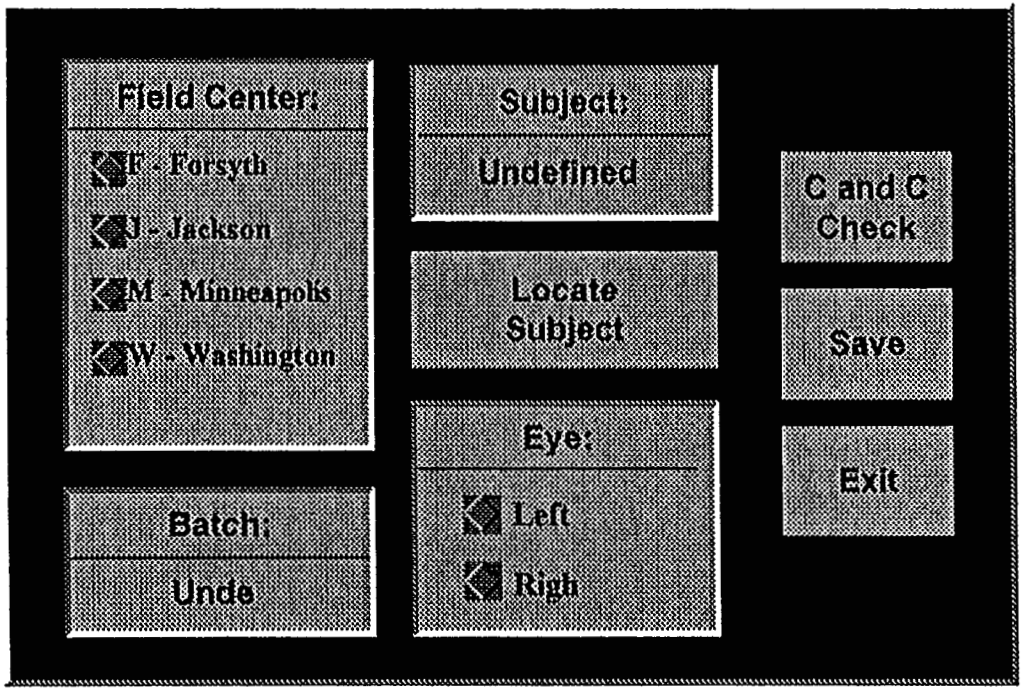
T1	Level 10
T2,T3,T4	Level 35
T5	Level 43
T6	Level 47
T7,T8	Level 53
T9	Level 53/61
T10	Level 61
T11	Level 65
T12	Level 71
T13	Level 75
T14	Level 81

Grader:

Page:

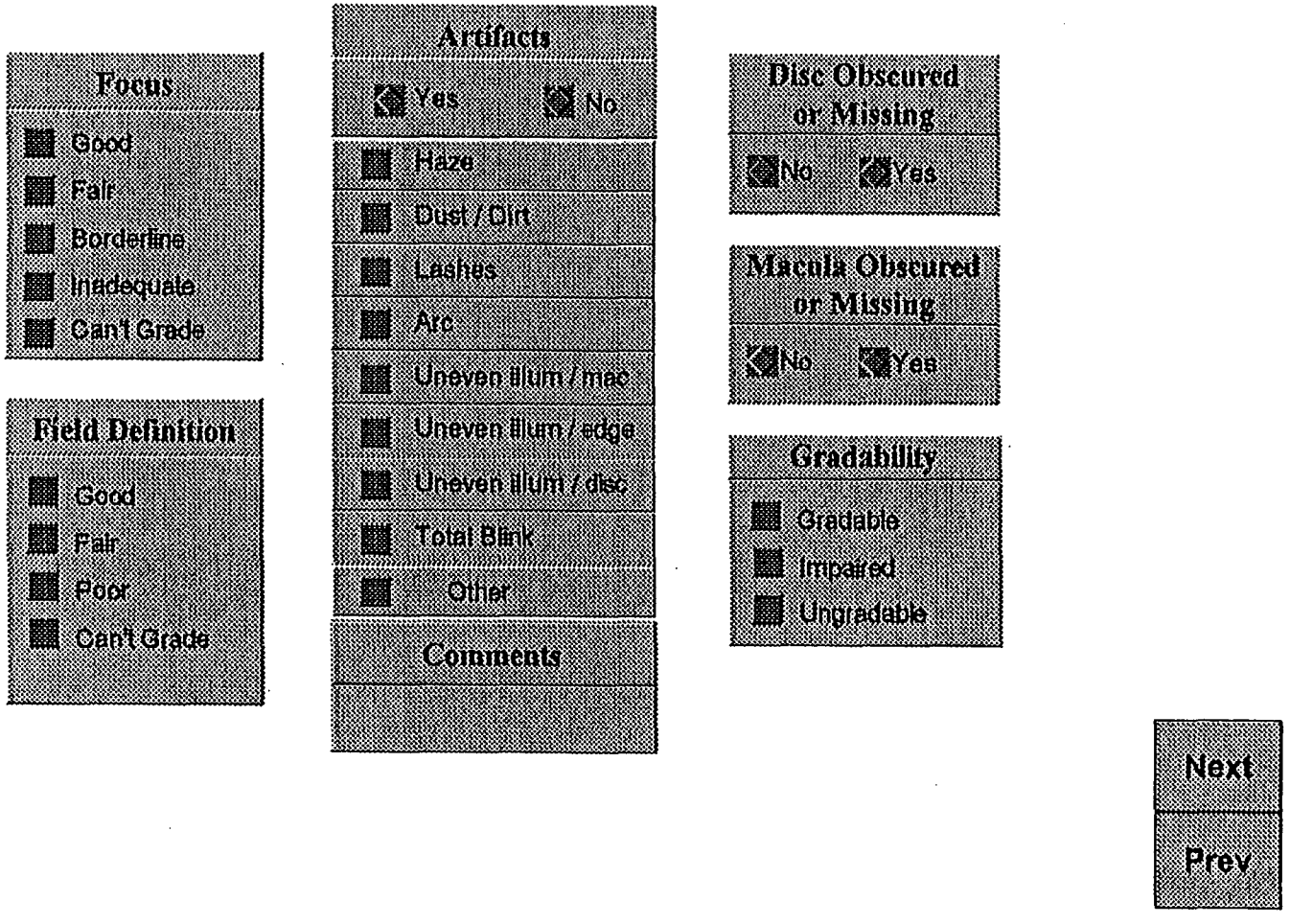
Date:

Exhibit 3
Direct Entry Grading Form



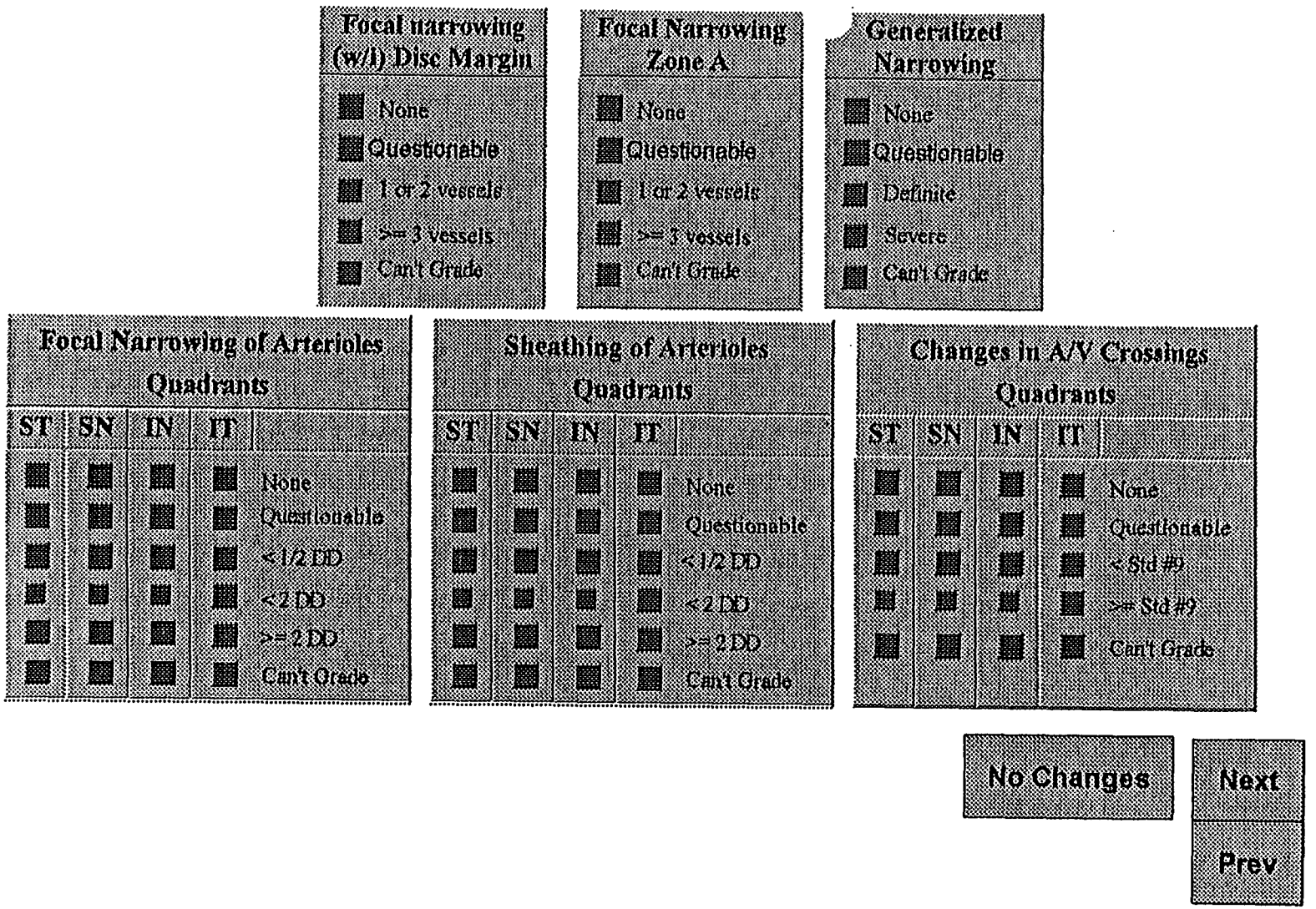
Photographic Quality

Page:



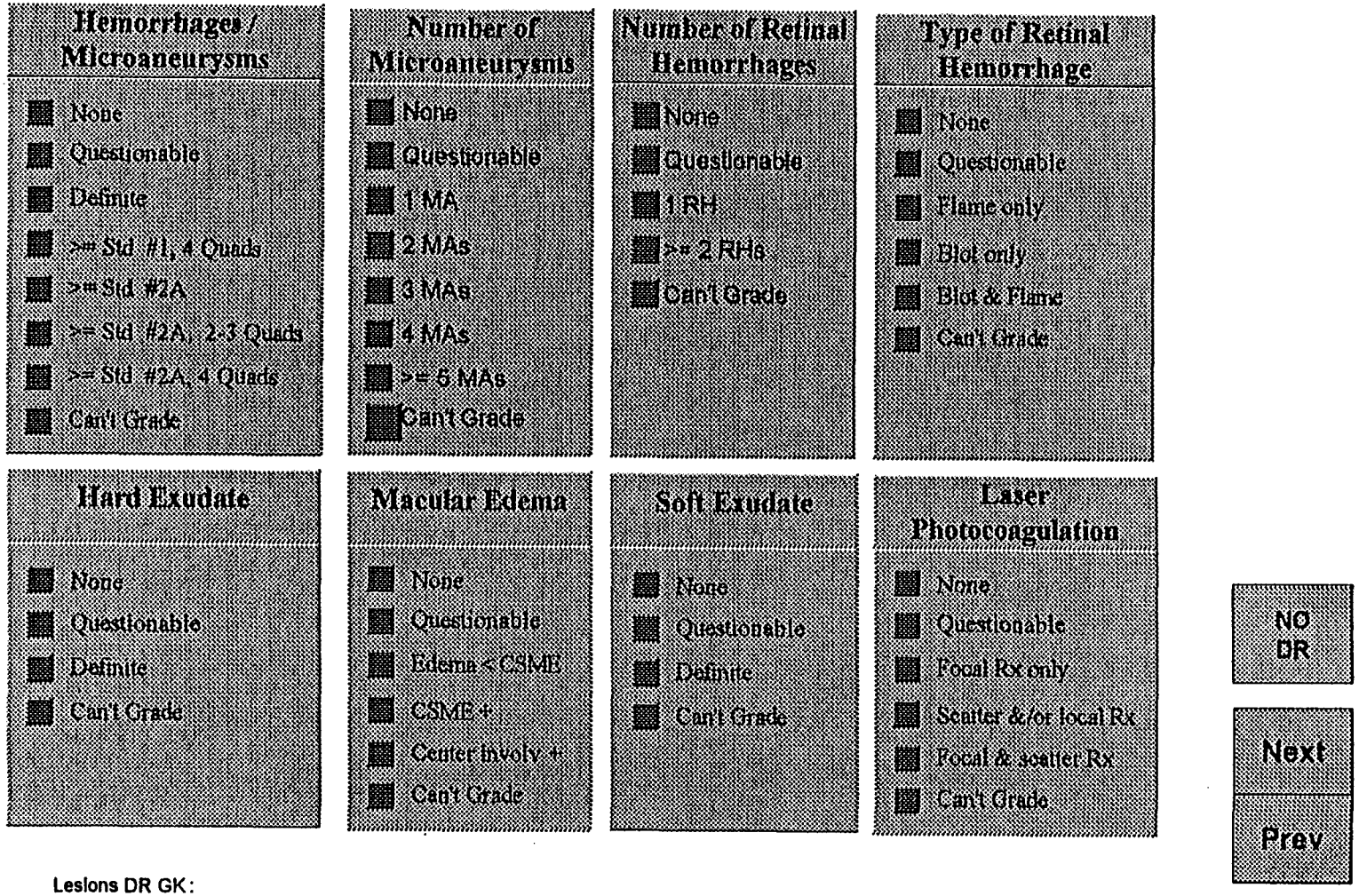
Arteriolar Changes:

Page:



Lesions of Diabetic Retinopathy I

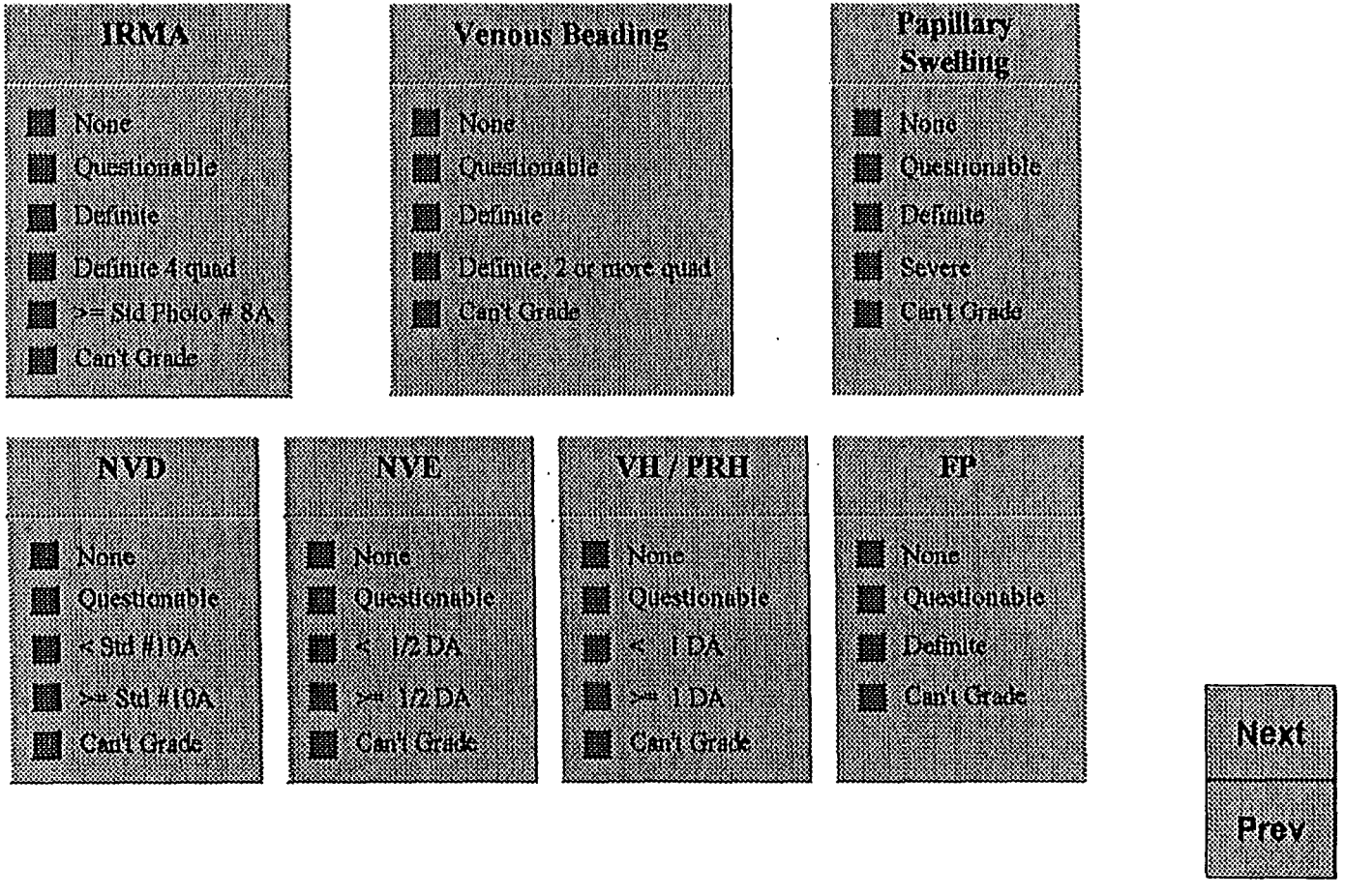
Page:



Lesions DR GK:

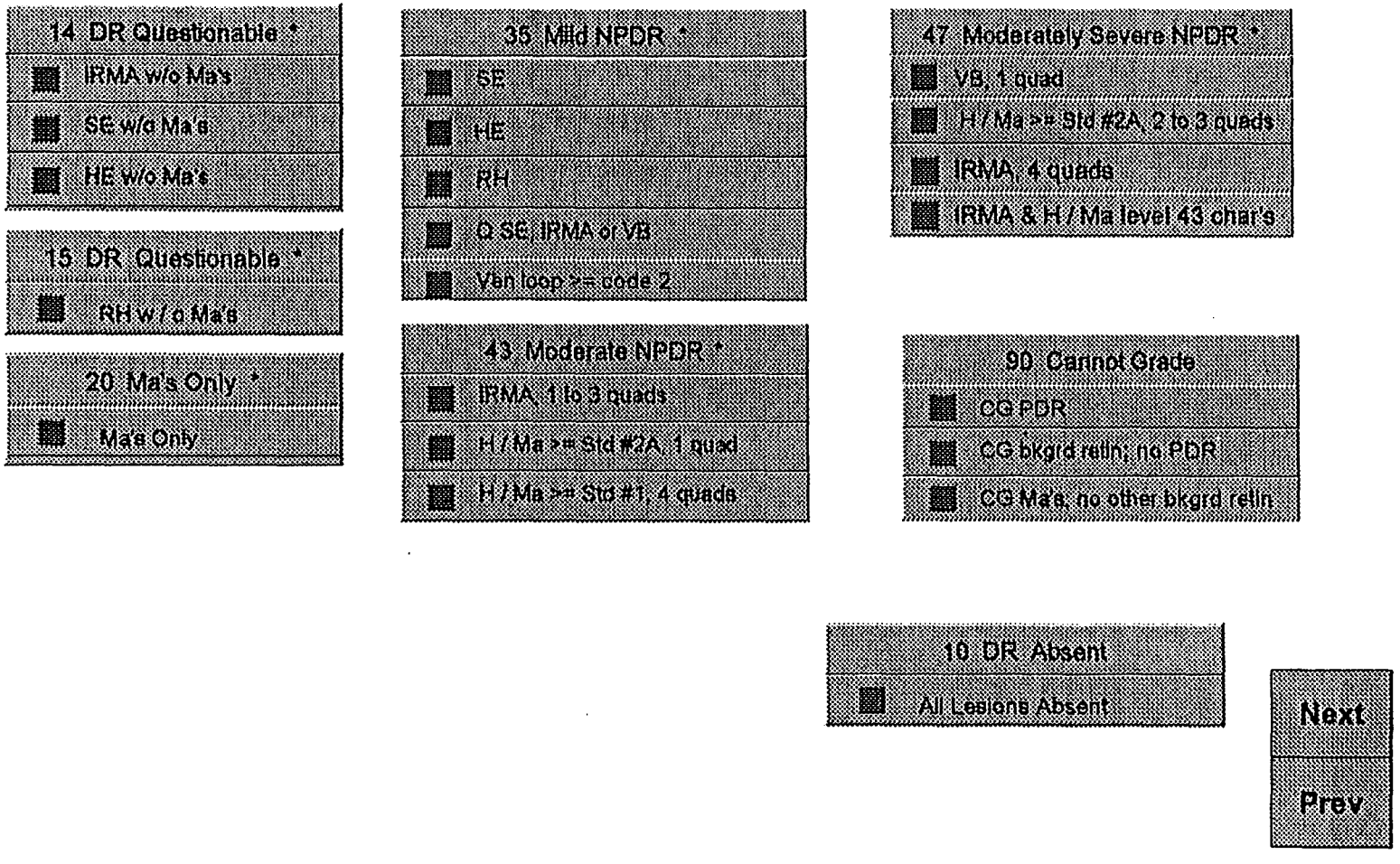
Lesions of Diabetic Retinopathy II

Page:



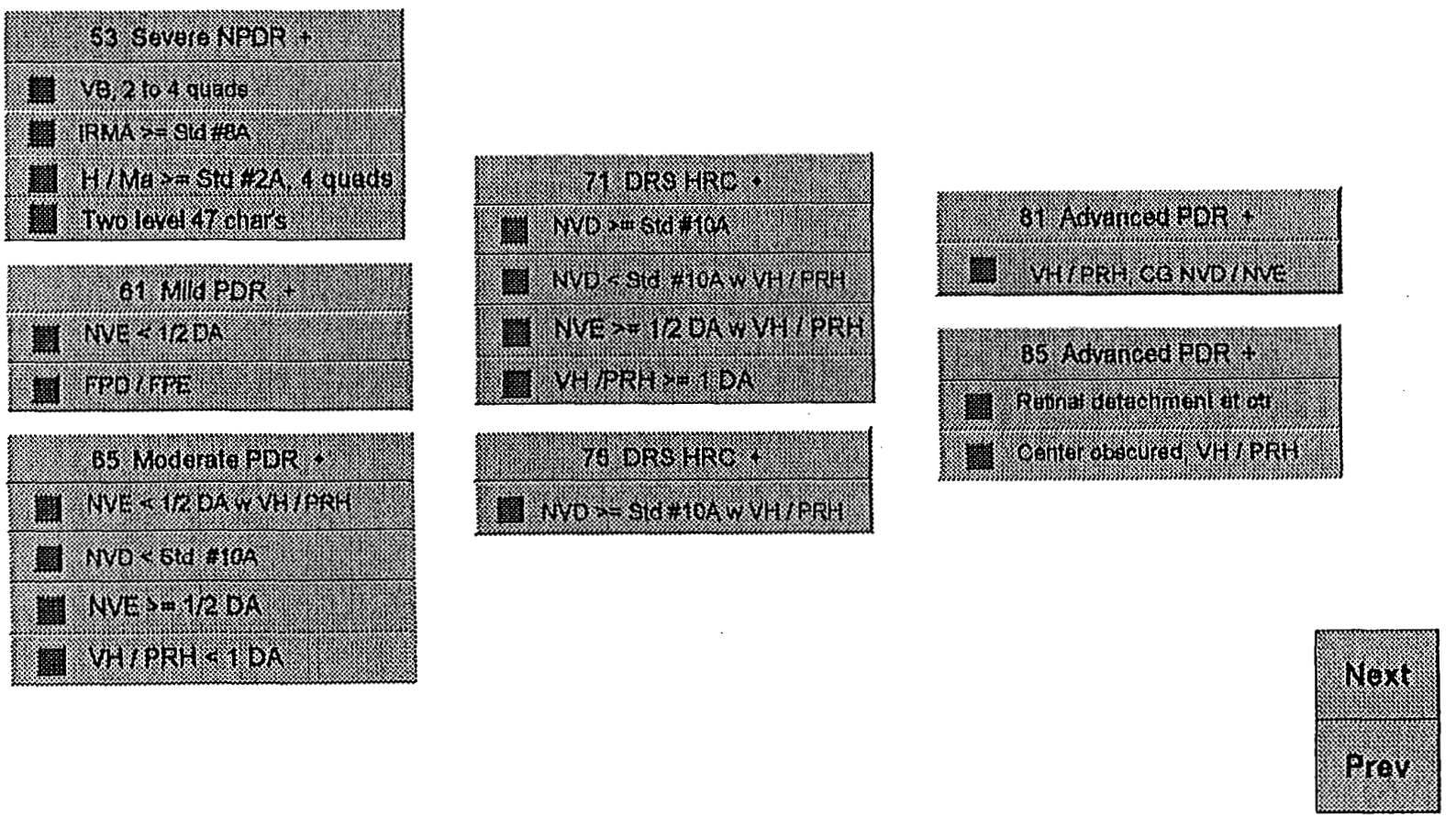
Diabetic Retinal Level I

Page:



Diabetic Retinal Level II

Page:



Other Ocular Lesions

Page:

No	Q	Yes	
◇	◇	◇	Central artery occlusion +
◇	◇	◇	Branch artery occlusion +
◇	◇	◇	Central Vein Occlusion +
◇	◇	◇	Branch Vein Occlusion +
◇	◇	◇	Hollenhorst plaque
◇	◇	◇	Asteroid hyalosis
◇	◇	◇	Large cup/disc ratio *
◇	◇	◇	RH within disc margin *
◇	◇	◇	Peripapillary atrophy
◇	◇	◇	Other disc abnormality
◇	◇	◇	Glial / vitreous thickening
◇	◇	◇	Medullated nerve fibers
◇	◇	◇	Cellophane reflex
◇	◇	◇	SWR w or w/o tension lns

No	Q	Yes	
◇	◇	◇	Soft drusen w/i 2 DD
◇	◇	◇	RPE depigmentation
◇	◇	◇	Hyperpigmentation
◇	◇	◇	SSR detachment
◇	◇	◇	Subretinal hemorrhage +
◇	◇	◇	Subretinal fibrosis
◇	◇	◇	Geographic atrophy
◇	◇	◇	Chorioretinal scar
◇	◇	◇	Nevus
◇	◇	◇	Retinal detachment +
◇	◇	◇	Other (see comment)

Comment

NO OOL

Next

Prev

OOLGK:

Page:

Retinal Notification Sent

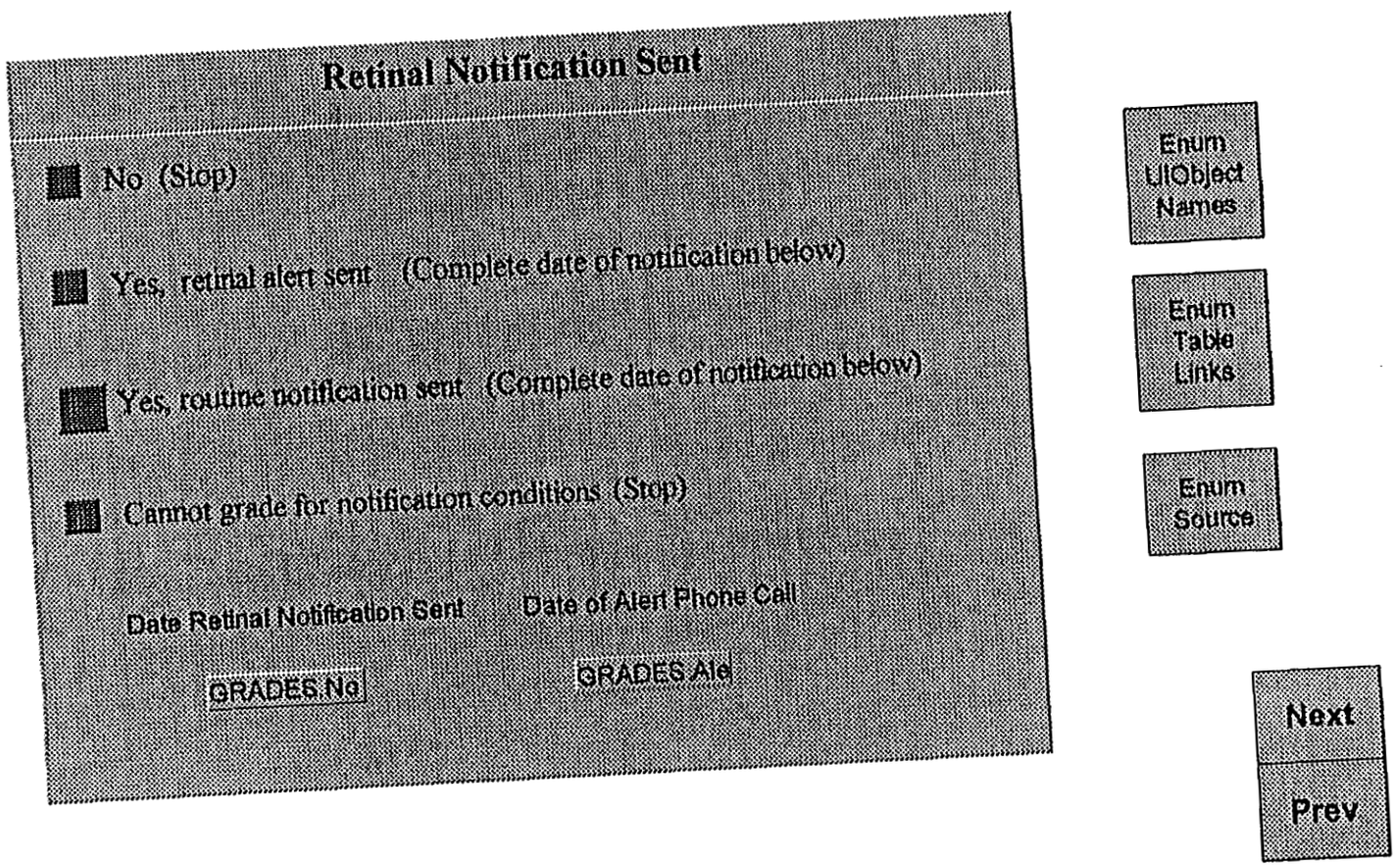


Exhibit 4
Retinal Light Box Reading - Paper Form

FIELD CENTER ___ PATIENT ID _ _ _ _ _ _ EYE ___ Grader ___ Date Graded _ _ / _ _ / _ _

PHOTOGRAPHIC QUALITY

Focus		Field Definition		Artifacts	No	Yes
1	Good	1	Good	Haze	0	2
2	Fair	2	Fair	Dust / dirt	0	2
3	Borderline	3	Borderline	Lashes	0	2
4	Inadequate	4	Inadequate	Arc	0	2
8	Cannot grade	8	Cannot grade	Uneven illum / macula	0	2
				Uneven illum / edge	0	2
				Uneven illum / disc zone	0	2
				Total blink	0	2
				Other	0	2

Gradability

1	Entire field gradable
2	Disc zone gradable, macula ungradable
3	Macula gradable, disc zone ungradable
4	Disc zone and macula ungradable
5	Entire field ungradable

Comments _____

_____

ARTERIOLAR Abnormalities

Arterial Abnormalities:

W/i Disc Margin Zone to 1/2 DD

0	0	None
1	1	Questionable
2	2	Definite
3	3	Severe
8	8	Cannot grade

Generalized Narrowing of Arterioles

0	None
1	Questionable
2	Definite
3	Severe
8	Cannot grade

Focal Narrowing of Arterioles (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Mild
3	3	3	3	Moderate
4	4	4	4	Severe
8	8	8	8	Cannot grade

Papillary Swelling

0	None
1	Questionable
2	Definite
3	Severe
8	Cannot grade

Sheathing of Arterioles (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Mild
3	3	3	3	Moderate
4	4	4	4	Severe
8	8	8	8	Cannot grade

Abnormalities in A/V Crossings (in Quadrants)

ST	SN	IN	IT	
0	0	0	0	None
1	1	1	1	Questionable
2	2	2	2	Definite
3	3	3	3	Severe
8	8	8	8	Cannot grade

LESIONS OF DIABETIC RETINOPATHY

Number of Microaneurysms

0	None
1	Questionable
2	1 Ma
3	2 Ma's
4	3 Ma's
5	4 Ma's
6	$\geq$ 5 Ma's
8	Cannot grade

Number of Retinal Hemorrhages

0	None
1	Questionable
2	1 RH
3	$\geq$ 2 RH's
8	Cannot grade

Type of Retinal Hemorrhage

0	None
1	Questionable
2	Flame hemorrhage only
3	Blot hemorrhage only
4	Blot and flame hemorrhages
8	Cannot grade

Hemorrhages/Microaneurysms

0	None
1	Questionable
2	Definite
3	$\geq$ Std. Photograph #1 in all 4 quadrants
4	$\geq$ Std. Photograph #2A
5	$\geq$ Std. Photograph #2A in 2 or 3 quadrants
6	$\geq$ Std. Photograph #2A in all 4 quadrants
8	Cannot grade

Hard Exudate

0	None
1	Questionable
2	Definite
8	Cannot grade

Soft Exudate

0	None
1	Questionable
2	Definite
8	Cannot grade

IRMA

0	None
1	Questionable
2	Definite
3	Definite in all 4 quadrants
4	$\geq$ Std. Photograph #8A
8	Cannot grade

Venous Beading

0	None
1	Questionable
2	Definite
3	Definite in 2 or more quadrants
8	Cannot grade

NVD

0	None
1	Questionable
2	< Std. #10A
3	$\geq$ Std. #10A
8	Cannot grade

NVE

0	None
1	Questionable
2	< 1/2 DA
3	$\geq$ 1/2 DA
8	Cannot grade

VH/PRH

0	None
1	Questionable
2	< 1 DA
3	$\geq$ 1 DA
8	Cannot grade

FP

0	None
1	Questionable
2	Definite
8	Cannot grade

Macular Edema

0	None
1	Questionable
2	Present, inferred from HE/other
3	CSME, inferred from HE/other
4	Center involved, inferred from HE/other
8	Cannot grade

Laser Photocoagulation

0	None
1	Questionable
2	Focal Rx only
3	Scatter and/or local Rx
4	Focal and scatter Rx
8	Cannot grade

Diabetic Retinal Level	Supporting Evidence
90 Cannot grade	903 Cannot grade for proliferative retinopathy
	902 Cannot grade for background retinopathy; no proliferative retinopathy present
	901 Cannot grade for microaneurysms; no other background retinopathy present
85 Advanced PDR	852 Retinal detachment at center of macula
	851 Macula obscured by VH and/or PRH
81 Advanced PDR	811 VH and/or PRH, cannot grade for NVD and/or NVE, center attached
75 DRS HRC	751 NVD $\geq$ Std Photograph #10A with VH and/or PRH
71 DRS HRC	714 NVD $\geq$ Std Photograph #10A
	713 NVD < Std Photograph #10A with VH and/or PRH
	712 NVE $\geq$ 1/2 DA with VH and/or PRH
	711 VH and/or PRH $\geq$ 1 DA
65 Moderate PDR	654 NVE < 1/2 DA with VH and/or PRH
	653 NVD < Std Photograph #10A
	652 NVE $\geq$ 1/2 DA
	651 VH and/or PRH < 1 DA
61 Mild PDR	612 NVE < 1/2 DA
	611 FPD and/or FPE
53 Severe NPDR	534 Venous beading in 2 or more fields
	533 IRMA $\geq$ Std Photograph #8A
	532 H/Ma $\geq$ Std Photograph #2A in 4 or 5 fields
	531 Any two or three of level 47 characteristics
47 Moderately severe NPDR	474 Venous beading in one field
	473 H/Ma $\geq$ Std Photograph #2A in 2 or 3 fields
	472 IRMA in 4 or 5 fields
	471 Both IRMA and H/Ma characteristics from level 43
43 Moderate NPDR	433 IRMA in 1 to 3 fields
	432 H/Ma $\geq$ Std Photograph #2A in 1 field
	431 H/Ma $\geq$ Std Photograph #1 in 4 or 5 fields
35 Mild NPDR	355 Soft exudate
	354 Hard exudate
	353 Retinal hemorrhage
	352 Questionable SE, IRMA or venous beading
	351 Venous loop $\geq$ code 2
20 Microaneurysms only	201 Microaneurysms only
15 DR questionable	151 Retinal hemorrhage, no microaneurysms
14 DR questionable	143 IRMA, no microaneurysms
	142 Soft exudate, no microaneurysms
	141 Hard exudate, no microaneurysms
10 DR absent	101 Microaneurysms and other lesions absent

OTHER OCULAR LESIONS

N	Q	Y		N	Q	Y	
0	1	2	Central artery occlusion	0	1	2	Cellophane reflex
0	1	2	Branch artery occlusion	0	1	2	Surface wrinkling retinopathy
0	1	2	Central vein occlusion				with or without tension lines
0	1	2	Branch vein occlusion				
0	1	2	Hollenhorst plaque	0	1	2	Soft drusen
0	1	2	Asteroid hyalosis	0	1	2	RPE depigmentation
				0	1	2	Hyperpigmentation
0	1	2	Lg cup/disc ratio	0	1	2	SSR detachment
0	1	2	RH within disc margin	0	1	2	Subretinal hemorrhage
0	1	2	Peripapillary atrophy	0	1	2	Subretinal fibrous
0	1	2	Other disc abnormality	0	1	2	Geographic atrophy
0	1	2	Glial / vitreous thickening	0	1	2	Chorioretinal scars
0	1	2	Medullated nerve fibers	0	1	2	Nevus
				0	1	2	Retinal detachment

COMMENTS _____

_____

Draft 2-19-93

Exhibit 5
Photographic Quality Assessments for Photographic Examples PQ1 to PQ11

Example	Field Definition	Focus & Clarity	Disc Obscured or Missing	Macula Obscured or Missing	Artifacts	Gradability
PQ 1	Good	Good	No	No	-	Gradable
PQ 2	Poor	Good	No	No	Haze (edge)	Impaired
PQ 3	Good	Fair	No	No	Haze (edge)	Gradable
PQ 4	Good	Borderline	No	No	Haze (edge)	Impaired
PQ 5	Good	Borderline	No	No	Haze (overall) Uneven illumination/macula	Impaired
PQ 6	Good	Inadequate	No	No	Haze (overall) Uneven illumination/macula	Ungradable
PQ 7	Good	Good	No	No	Lashes	Gradable
PQ 8	Good	Good	No	Yes	Lashes Uneven illumination/macula Uneven illumination/edge	Impaired
PQ 9	Cannot grade	Cannot grade	Yes	Yes	Total blink	Ungradable
PQ 10	Good	Borderline	No	No	Dust and dirt Uneven illumination/macula	Impaired
PQ 11	Good	Borderline	No	Yes	Dust and dirt Uneven illumination/macula Uneven illumination/edge	Ungradable

Exhibit 6

Assessment of Arteriolar Abnormalities in Photographic Examples A1 to A8

Example Photograph	Focal Narrowing						Arterio-Venous Crossing Abnormalities (Arterio-Venous Nicking)			
	Arteries (disc)		Arterioles (Quadrants)							
	Disc	Zone A	ST	SN	IN	IT	ST	SN	IN	IT
A1	definite	definite	0	Q	0	0	0	0	0	0
A2	severe	definite	definite	0	0	0	0	0	0	0
A3	0	definite	definite	definite	0	0	0	0	0	0
A4	definite	0	0	definite	definite	severe	0	0	0	0
A5	0	definite	0	definite	0	0	0	0	0	0
A6	0	0	0	definite	0	0	definite	0	0	Q
A7	Q	Q	definite	0	0	definite	severe	0	definite	Q
A8	0	0	0	0	0	0	definite	0	0	definite

Key:
0 = none
Q = questionable
definite
severe

Exhibit 7

Notification Procedures for Lesions of Hypertension and Diabetes

Grading Item	Letter?	Suggested language	Referral to ophthalmologist?
Focal narrowing	No letter		
Sheathing	No letter Exception: if sheathing is associated with an occlusive process, *please see letter recommendations under Other/ Occlusions.*		
AV nicking	No letter		
Ma	Routine notification for definite appearance No letter for questionable appearances	". . . exhibits a single retinal microaneurysm. This could be due to diabetes, hypertension, or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.
RH	Routine notification for definite appearance No letter for questionable appearances	". . . exhibits a single retinal hemorrhage. This could be due to hypertension, diabetes, or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.
H/Ma	Routine notification. If definite H/Ma is present, but identity as Ma or RH is in doubt, send letter.	". . . exhibits a small red spot [or spots] which could be either retinal hemorrhage or a retinal microaneurysm[s]. This [these] could be due to diabetes, hypertension or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.

SE	Routine notification for definite appearance No letter for questionable appearances	". . . exhibits a single soft exudate, or cotton-wool spot. This could be due to hypertension, diabetes, or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.
CSME	Routine notification for questionable CSME Retinal alert for definite CSME	". . . exhibits [description of definite lesions]. These lesions are typical of [appropriate descriptive phrase for diabetic retinal level]. Based on the proximity of the hard exudates to the macula [or other suggestive appearances] . . ." Similar to above.	". . . routine observation by an ophthalmologist may be advisable." Time frame for referral per Retinal Reading Center ophthalmologist. ". . . observation by an ophthalmologist within the next __ months may be advisable."
[Other lesions of diabetic retinopathy]	*Please see letter recommendations for appropriate diabetic retinal level .*		
Laser PC scars	Routine notification. Consult Retinal Reading Center ophthalmologist for possible retinal alert if diabetic retinopathy ≥ DR level 65 persists.	". . . exhibits [description of definite lesions]. These lesions are characteristic of [appropriate descriptive phrase for diabetic retinal level]. The presence of photocoagulation treatment scars suggests that the participant has been under an ophthalmologist's care." Language as suggested by the Retinal Reading Center ophthalmologist.	None, if no lesions are seen. "Continued follow-up by an ophthalmologist may be advisable." if diabetic retinopathy is present. Referral as suggested by Reading Center ophthalmologist.

Papillary swelling	No letter for: Q papillary swelling, nerve head drusen. Consult Retinal Reading Center ophthalmologist for cases where grader is unsure of cause or significance. Retinal alert for papillary swelling with associated retinal hemorrhages and/or soft exudates, suggesting severe hypertensive retinopathy.	 Language as suggested by the Retinal Reading Center ophthalmologist. Language as suggested by the Retinal Reading Center ophthalmologist.	 Referral as suggested by Reading Center ophthalmologist. Time frame as suggested by Reading Center ophthalmologist.
DR 14	Routine notification	". . . exhibits a single soft exudate, or cotton-wool spot [IRMA, hard exudate]. This could be due to hypertension, diabetes, or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.
DR 15	Routine notification	". . . exhibits a single retinal hemorrhage. This could be due to hypertension, diabetes, or some other cause, and may be of little clinical significance."	None Information may be of interest to primary care physician.
DR 20	Routine notification	1 Ma: ". . .exhibits a single retinal microaneurysm. This could be due to diabetes, hypertension or some other cause, and may be of little clinical significance." $\geq$ 2 Ma's: ". . . exhibits several [or provide the number] retinal microaneurysms. These are typical of very early diabetic retinopathy, but could be due to hypertension or some other cause."	None Information may be of interest to primary care physician.

DR 35	Routine notification	". . . exhibits retinal hemorrhages and microaneurysms, and soft exudates (cotton-wool spots). These lesions are typical of early diabetic retinopathy."	None Information may be of interest to primary care physician.
	Exceptions: 1) if questionable CSME is present, or if HE is within 2 DD of center	". . . exhibits retinal hemorrhagesand microaneurysms, and hard exudates (lipid deposits). These are typical of early diabetic retinopathy. Based on the proximity of the hard exudates to the macula, . . ."	". . . routine observation by an ophthalmologist may be advisable."
	2) if the macula is ungradable	". . . exhibits [describe lesions]. These are typical of early diabetic retinopathy. We are unable to evaluate the macula because of a dark shadow [or other impairment]."	"Routine observation by an ophthalmologist may be advisable."
	3) if definite CSME is present (retinal alert)	Language as suggested by Reading Center ophthalmologist.	Time frame as suggested by Reading Center ophthalmologist.
DR 43	Routine notification	". . . exhibits moderate amounts of retinal hemorrhage and microaneurysms, [describe other lesions]." OR ". . . exhibits [describe other lesions] and IRMA (intraretinal microvascular abnormalities)." "These are typical of moderate non-proliferative diabetic retinopathy."	"Routine observation by an ophthalmologist may be advisable."
	Exceptions: 1) if definite CSME is present.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
	2) if photocoagulation scars are present.	" The presence of photocoagulation treatment scars suggests that the participant has been under an ophthalmologist's care."	"Continued follow-up by an ophthalmologist may be advisable."

DR 47	Routine notification	". . . exhibits moderate amounts of retinal hemorrhage and microaneurysms, [describe other lesions] and IRMA (intraretinal microvascular abnormalities). These are typical of moderate non-proliferative diabetic retinopathy."	"Routine observation by an ophthalmologist may be advisable."
	Exceptions: 1) if definite CSME is present.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
	2) if photocoagulation scars are present.	" The presence of photocoagulation treatment scars suggests that the participant has been under an ophthalmologist's care."	"Continued follow-up by an ophthalmologist may be advisable."
DR 53	Retinal alert	". . . exhibits [describe lesions]. These lesions are typical of severe non-proliferative diabetic retinopathy."	Time frame as suggested by Reading Center ophthalmologist.
DR 61	Routine notification if scatter photocoagulation treatment scars are present.	". . . exhibits [description of definite lesions]. These lesions are characteristic of proliferative diabetic retinopathy. The presence of photocoagulation treatment scars suggests that the participant has been under an ophthalmologist's care."	"Continued follow-up by an ophthalmologist may be advisable."
	Retinal alert if untreated. Consult the Retinal Reading Center ophthalmologist.	Language as suggested by Reading Center ophthalmologist.	Time frame as suggested by Reading Center ophthalmologist.
DR 65 DR 71 DR 75 DR 81 DR 85	Retinal alert. Consult the Retinal Reading Center ophthalmologist.	Language as suggested by Reading Center ophthalmologist.	Time frame as suggested by Reading Center ophthalmologist.

DR 90	No letter if no lesions are seen. Check "ungradable for notification conditions" for the Retinal Notification Sent item.		
	Routine notification if lesions such as retinal hemorrhage or soft exudate are seen, but other lesions are ungradable.	". . . exhibits retinal hemorrhage [or whatever lesions are visible]. The photographic quality is impaired by a dark shadow over the macula [or whatever impairment is present], and we may be unable to evaluate some other lesions of diabetic retinopathy."	"Routine observation by an ophthalmologist may be advisable."
	Consult Retinal Reading Center ophthalmologist for cases where grader is unsure of significance of visible lesions. Retinal alert if time frame for referral is provided.	Language as suggested by Reading Center ophthalmologist.	Routine observation or time frame for referral, as suggested by Reading Center ophthalmologist.

Exhibit 8
Notification Procedures for Other Ocular Lesions

Grading Item	Letter?	Suggested language	Referral to ophthalmologist?
Central artery occlusion Branch arteriole occlusion Central vein occlusion Branch vein occlusion	Consult with Retinal Reading Center ophthalmologist about occlusive processes. Possible outcomes are: 1) Retinal alert for fresh vein occlusion, or vein occlusion with associated macular edema. 2) Routine notification for old arteriolar or venous occlusion. 3) No letter for old occlusion of a very small branch.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Hollenhorst plaque	Routine notification for definite Hollenhorst plaque, and possibly for questionable Hollenhorst plaque. Consult with Reading Center ophthalmologist.	Language as suggested by Reading Center ophthalmologist.	None Information may be of interest to primary care physician.
Asteroid hyalosis	No letter.		
Large cup/disc ratio	No letter for questionable large cup/disc ratio (< 0.70). Routine notification for definite large cup/disc ration of 0.70 with appearances such as undercutting. Routine notification for cup/disc ratio $\geq$ 0.80.	". . . the optic disc exhibits a moderately large cup-to-disc ratio of 0.70, which could indicate glaucoma." Similar to above.	"Routine evaluation by an ophthalmologist may be advisable." Same as above.
RH within disc margin	Routine notification.	". . . exhibits a retinal hemorrhage on the optic disc. This is sometimes seen in eyes with glaucoma."	"Routine evaluation by an ophthalmologist may be advisable."
Peripapillary atrophy	No letter for most cases. Consult the Reading Center ophthalmologist if unsure of significance, or if associated with angioid streaks.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.

Other disc abnormality	No letter for: oblique insertion, scleral crescent, nerve head drusen, minor vessel anomalies. Possible letter for: some vessel anomalies, marked disc pallor. Consult with the Reading Center ophthalmologist about severity of vessel anomalies or disc pallor, or other disc appearances of unknown significance.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Glial/vitreous thickening	No letter for: glial tissue small vitreous thickenings. Consult the Reading Center ophthalmologist if any vitreous opacity suggests vitreous hemorrhage or an inflammatory reaction of the vitreous.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Medullated nerve fibers	No letter.		
Cellophane reflex	No letter.		
Surface wrinkling retinopathy	No letter if the surface wrinkling retinopathy encircles less than 180° of the macula, and the center of the macula is unaffected. Routine notification if the surface wrinkling retinopathy fully encircles the macula, or if the macula is dragged or crossed by tension lines and vision may be affected. Consult the Reading Center ophthalmologist about borderline cases.	". . . exhibits mild retinal distortion due to an epiretinal membrane in the macular area (surface wrinkling retinopathy). " Similar to above.	"The participant may be aware of this condition. If not, routine evaluation by an ophthalmologist may be advisable." Similar to above.

Soft drusen	No letter for most cases of early maculopathy. Consult the Reading Center ophthalmologist regarding routine notification if extensive soft drusen are present, or if abnormalities involve the center of the macula and may affect vision.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
RPE depigmentation			
Hyperpigmentation	Hyperpigmentation associated with POHS, fundus flavimaculatus other degenerative processes, or possible inflammatory processes may require routine notification. Consult with the Reading Center ophthalmologist.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
SSR detachment	Consult the Reading Center ophthalmologist regarding notification for all end-stage maculopathy.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Subretinal hemorrhage			
Subretinal fibrosis			
Geographic atrophy			
Chorioretinal scar	No letter for most small, peripheral chorioretinal scars. Notification for: 1) Toxoplasmosis scars, or other large scars suggesting an old inflammatory process. 2) Chorioretinal scars involving the macula, affecting vision. 3) POHS, as suggested by any two of the following appearances: a) round, "punched out" chorioretinal scars in the periphery, b) chorioretinal scars in the macular area, c) scarring around the optic disc.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Nevus	No letter for a nevus which appears flat, and has even pigmentation and regular or diffuse margins. Routine notification for a nevus which may be elevated, or has uneven pigmentation and/or irregular margins. Possible notification if only a small portion of what is clearly a larger lesion extends into the photographic field. Consult Reading Center ophthalmologist.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.

Retinal detachment	Consult Reading Center ophthalmologist regarding retinal alert or routine notification.	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.
Other	Other conditions which may require notification: macular hole choroidal folds angioid streaks fundus flavimaculatus POHS (*see description under chorioretinal scars*).	Language as suggested by Reading Center ophthalmologist.	Referral as suggested by Reading Center ophthalmologist.

Retinal Image Processing

1.0 INTRODUCTION

1.1 Objective

The primary objective of this procedure is to evaluate fundus photographs taken in the Atherosclerotic Risk in Communities Study (ARIC) for generalized changes in retinal arterioles, both narrowing and distention, presumed to be related to hypertension and/or arteriolar sclerosis. Slide transparencies are scanned into a digital image processing system for enhancement and measurement of retinal vascular caliber.

1.2 Rationale

The purpose of evaluating changes in the retinal vasculature associated with hypertension and/or arteriolar sclerosis is to explore their possible prognostic value for cardiovascular outcomes. It may be that changes in retinal vessels provide information about vascular status (such as length and severity of exposure to hypertension, and degree of structural damage) not provided by standard measurement of blood pressure, particularly in subjects currently taking antihypertensive medications. Since the retinal vasculature can be assessed noninvasively, this procedure may be a practical way to identify risk factors for clinically important pathology.

1.2.1 Arteriolar Narrowing

Observers have associated generalized narrowing of retinal arterioles with hypertension and/or sclerosis for decades. However, the etiology of this phenomenon is unclear. In their review of the literature of retinal vascular changes in hypertension, Freeman and Sperduto[18] postulate a vasoconstrictive phase, mediated by myogenic and/or metabolic mechanisms (as yet unidentified), and a sclerotic phase with hyperplasia of the arteriolar media followed by intimal thickening with atrophy of the media and replacement of muscle cells with hyaline.

Generalized arteriolar narrowing was included in the landmark classification of clusters of signs proposed by Keith, Wagener, and Barker[19,20,21]. Later, Sheie[22], Leishman[23], and Evelyn[24] also proposed classifications that prominently featured

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[18]Freeman RW, Sperduto RD. A review of hypertensive and arteriolosclerotic changes in the ocular fundus: implications for epidemiologic research. Unpublished manuscript, provided by Robert D. Sperduto, MD, Biometry and Epidemiology Program, National Eye Institute, National Institutes of Health, DHHS, Bethesda, MD 20892.

[19]Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1939; 197:332-343.

[20]Wagener HP, Keith NM. Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine 1939; 18:317-430.

[21]Wagener HP, Clay GE, Gipner JF. Classification of retinal lesions in the presence of vascular hypertension. Report submitted to the American Ophthalmological Society by the Committee on Classification of Hypertensive Diseases of the Retina. Trans Am Ophthalmol Soc 1947; 45:57-73.

[22]Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. Arch Ophthalmol 1953; 49:117-138.

[23]Leishman R. The eye in general vascular disease: hypertensions and arteriosclerosis. Brit J Ophthalmol 1957; 41:641-701.

generalized narrowing. All of these systems were relatively subjective, depending upon the observer's ability to detect reduction in arteriolar caliber by estimating what the original caliber might have been, or comparing the present caliber of specific arterioles with those of matching veins (the latter generally presumed to be little affected by hypertension).

Using this subjective approach to detection of generalized narrowing, Svardsudd et al[25] reported significant differences in systolic and diastolic blood pressure among subjects with and without narrowing. In contrast, van Buchem et al[26] failed to find such an association.

As more attention has been paid to the methodology itself, the reliability of subjective evaluation of generalized narrowing (among other signs) has been called into question. In particular, Kagan et al[27] found sufficient variability of the traditional technique that they recommended the development of more objective techniques. However, meaningful measurement of the retinal vessels is not straightforward. Stokoe and Turner[28] demonstrated that marked variability in branching pattern among individuals (both size and number of branches) prevented direct comparison of arteriolar measurements between individuals. It was also recognized that the range of normal arteriolar width is sufficiently broad that it overlaps extensively with the pathological.

Several investigators developed more quantitative approaches to address these difficulties, as described in a review by Parr[29]. Most measured vascular caliber upon photographs enlarged as prints or projected to a large scale. Boyd and de Margherie[30] gauged the widths of the four major arterioles and derived the total cross-sectional area of the retinal arterial supply. Kagan et al[31] measured veins and arteries as they crossed a circle one disc diameter from the optic disc margin, and counted their number. Measurements were combined in a variety of ways (sum of widths for arterioles and veins, respectively, and the ratio of the sums) in an attempt to discover a

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[24]Evelyn KA, Nicholls JV, Turnbull W. A method of grading and recording the retinal changes in essential hypertension. Am J Ophthalmol 1958; 4(2):165-179.

[25]Svardsudd K, Wedel H, Aurell E, et al. Hypertensive eye ground changes: prevalence, relation to blood pressure and prognostic importance. The study of men born in 1913. Acta Med Scand, 1978; 204:159-167.

[26]van Buchem FSP, van der Heuvel-Aghina J, ven der Heuvel J. Hypertension and changes of the fundus oculi. Acta Med Scand 1964; 176:539-548.

[27]Kagan A, Aurell E, Dobree J, et al. A note on signs in the fundus oculi and arterial hypertension: conventional assessment and significance. Bull WHO 1966; 34:955-960.

[28]Stokoe NL, Turner RWD. Normal retinal vascular pattern: arteriovenous ratio as a measure of arterial calibre. Brit J Ophthalmol 1966; 50:21-40.

[29]Parr JC. Hypertensive generalized narrowing of retinal arteries. Trans Ophthalmol Soc NZ 1974; 26(0):55-60.

[30]Boyd TAS, de Margerie J. Caliber of retinal arterioles in hypertension. Trans Canad Ophthal Soc, 1960; 23:65-76.

[31]Kagan A, Aurell E, Tibblin G. Signs in the fundus oculi and arterial hypertension: unconventional assessment and significance. Bull WHO 1967; 36:231-242.

relationship with blood pressure and other outcomes. Ramalho and Dollery[32] measured the diameter of all arterioles and veins as they crossed the margin of the disc, and expressed the A/V ratio by summing the measurements and their squares respectively. Michaelson et al[33] measured the widths of arterioles as they crossed a circle concentric with the disc, and classified their order in regard to vascular branching. Freeman and Sperduto[1] review the results obtained by these investigators, with some (e.g. Michaelson et al[16]) reporting significant associations between reduced arteriolar caliber and blood pressure.

In his review, Parr[36] made several critical points about the methodology of evaluating generalized arteriolar narrowing. First, smaller arterioles probably display more narrowing than larger ones (although the latter are easier to measure). Second, when major arterioles are measured, narrowing is likely most apparent at some distance from the disc margin, where these vessels become unambiguously arteriolar rather than arterial in their structure. Takahashi et al[34] demonstrated that arteriolar caliber decreases markedly out to one-half disc diameter from the disc (with any further decrease being gradual and limited) in narrowing associated with several systemic diseases. Third, arithmetic summing of arteriolar widths is inappropriate, since their capacity is a function of the square. Fourth, measurement of arterioles as they cross a circle concentric with the disc without taking account of branching pattern ignores the increase in total cross section of the arteriolar system occurring with each bifurcation.

Consequently, Parr et al[35,36] proposed a technique that attempts to standardize the measurement of arteriolar caliber by adjusting for branching pattern. To model the relationship between an arteriolar trunk and its branches, he computed a pragmatic "best fit" formula from measurements taken in a sample of normotensive young adults:

$$W_c = (0.87\ W_a^2 + 1.01\ W_b^2 - 0.22\ W_a W_b - 10.76)^{1/2}$$

in which W_c is the caliber of the trunk arteriole, W_a the caliber of the smaller branch, and W_b the caliber of the larger branch.

In the Parr technique, arterioles are measured in a zone from 0.5 to 1.0 disc diameter from the optic disc margin, and the caliber of the trunks from which they arise is estimated using the formula. This process is carried out successively until all arterioles have converged. Parr termed this result the "central retinal artery equivalent" (CRAE). It should be noted that the result is not intended to represent the true width of the central retinal artery. (Since that vessel is an artery rather than an arteriole, it should not display the generalized narrowing being investigated.) Rather, the result is a way of summarizing the caliber of the arterioles in the measurement area with normalization for branching pattern.

In his normotensive population, Parr demonstrated that this approach results in a

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[32]Ramalho PS, Dollery CT. Hypertensive retinopathy: calibre changes in retinal blood vessels following blood-pressure reduction and inhalation of oxygen. Circulation 1968; 37:580-588.

[33]Michaelson IC, Eliakim M, Avshalom A., et al. An approach to the investigation of the vascular changes in the fundus of the eye in hypertension and arteriosclerosis. Excerpta Medica International Congr 1966; 146:207:219.

[34]Takahashi S, Kawasuchi K, Yamanobe R. Hypertension and fundus change with special reference to narrowing of the retinal arteries. Ganka 1967; 9:921-31.

[35]Parr JC, Spears GFS. General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. Am J Ophthalmol 1974; 77:472-477.

[36]Parr JC, Spears GFS. Mathematic relationships between the width of a retinal artery and the widths of its branches. Am J Ophthalmol 1974; 77:478-483.

narrower range of measurements than either the summing of the widths (which has a 100% greater coefficient of variation) or of their squares (which has a 50% greater coefficient of variation). Applying his technique to a population containing hypertensive subjects, Parr found a trend toward a smaller equivalent artery caliber with higher blood pressure[37].

Although the Parr technique is innovative and elegant, it is laborious (particularly the delineation of the branching pattern, often obscured on the disc itself) and computationally intensive (measurements need to be combined according to their observed pairing in succession. Parr applied this technique to arterioles only, not addressing the measurement of veins.

Hubbard et al[38] explored application of the Parr approach in a sample containing both hypertensive and normotensive individuals. By measuring pairs of branches and trunks in the normotensives, they corroborated the Parr formula for predicting the caliber of trunk given the caliber of the branches. So that an A/V ratio could be obtained, they extended the technique by deriving a similar pragmatic "best fit" formula for veins (the "central retinal vein equivalent," or CRVE):

$$W_c = (0.72\ W_a^2 + 0.91\ W_b^2 + 450.05)^{1/2}$$

in which W_c is the caliber of the trunk vein, W_a the caliber of the smaller branch, and W_b the caliber of the larger branch.

Use of the ratio was introduced to counter several potential problems. First, it introduces some adjustment for the wide range of vessel caliber in the normal population. Second, by virtue of being a ratio it offers some protection against several potential problems: (a) variable magnification due to differences in refractive error among individuals, (b) apparent broadening of vessel caliber due to poor photographic focus or ocular media clarity, and (c) differences among graders regarding the precise determination of the vessel edge.

Hubbard et al also devised a simplified alternative computational technique for combining the measurements to yield the CRAE and CRVE. It combines pairwise the largest vessel with the smallest (disregarding the pairing actually observed), the next largest with the next smallest, and so on until all are accounted for. (If the number of vessels to be combined is odd, the single remaining vessel at the end of the pairing process is folded into the next iteration.) The estimate obtained typically agrees within a few microns with the result obtained using the original Parr computational technique.

Using their extension of the Parr approach, Hubbard et al examined the relationship between arteriolar caliber and blood pressure in a population of 74 nondiabetic volunteers examined in the Wisconsin Epidemiological Study of Diabetic Retinopathy. For subjects not taking antihypertensive medications, the correlation coefficient between the A/V ratio and diastolic blood pressure was -0.47 ($p = 0.02$) for 22 subjects 27-39 years of age (mean 33.8, SD 4.0) and -0.56 ($p = 0.001$) for 31 subjects 44-74 years of age (mean 57.9, SD 8.7). Similar associations were observed for systolic pressure in both groups.

1.2.2 Arteriolar Distention

Pathological broadening of retinal arterioles has been discussed much less commonly than generalized narrowing, both in the historical literature and in current reviews. In his observational study, Leishman[23] obtained fundus photographs of subjects showing

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[37]Personal communication from JC Parr, July, 1991.

[38]Hubbard LD, Ehrhardt E, Klein R, Messing SP, Brothers RJ, Moss SE, Meuer SM. The association between generalized arteriolar narrowing and blood pressure. Presented at the May 1992 of the Association for Research in Vision and Ophthalmology, Sarasota, FL.

this phenomenon. Leishman hypothesized that some large arterioles reach such an advanced state of sclerosis, with replacement fibrosis reducing muscular contractility, that they passively dilate under increased pressure when previously they would have constricted. Ramalho and Dollery[32] published experimental data from a study in which vessel response in older hyptertensives was observed as hypertensive stimulus was removed by various means. Their results suggested that the degree of arteriolar change may vary qualitatively and proportionally with caliber: large vessels are sometimes distended with hypertension (larger vessels distend more), and small vessels are constricted (smaller vessels constrict more).

Perhaps because arteriolar distention was more commonly observed during a period when hypertension was less well controlled, the existence of this phenomenon may not be widely known. However, Hayreh[39] cautioned that it must be taken into account for an adequate understanding of the relationship of arteriolar caliber to hypertension.

The possibility that larger arterioles with advanced sclerosis may display a qualitatively different response to hypertension (distention rather than constriction) complicates the task of relating vascular caliber to hypertension and other clinical conditions of interest. However, Leishman[23] observed that branch arterioles often continue to appear constricted even when their trunk arterioles appear to be distended. (Such a relationship would be consistent with the findings of Ramalho and Dollery[14], since branch arterioles are necessarily smaller then their trunks.)

Consequently, measurement of branch arterioles when trunk arterioles are wider than a set threshold offers the possibility of "correcting" the summarization of arteriolar caliber. The threshold chosen must take into account two factors: the existing experimental data regarding this phenomenon and the practical considerations of how many vessels have measurable branches (given the extent of retina documented) and how much time can be expended on the task.

The branch arteriole measurements may be used in two ways. First, they can be substituted for the measurement of the trunk arteriole in an alternative computation of the CRAE. Second, the predicted trunk caliber obtained from the (perhaps narrowed) branch arterioles can be compared with the observed caliber of the (perhaps distended) trunk arteriole, with a significant disparity between predicted and observed signaling by itself the presence of advanced sclerosis.

1.3 Technical Considerations Regarding Method

Following the work establishing the objective measurement techniques, there have been several reports examining the technical details of the methodology. Hodge et al[40] and Bracher et al[41] compared the efficacy of different ways of determining vessel caliber from photographs. There was agreement upon several points. First, a fundus camera with high resolution is used to take a photograph centered upon the optic disc, optionally with a green filter to enhance contrast of retinal vessels against the retinal pigment epithelium. Second, the image is recorded upon a film with reasonably fine grain to preserve the resolution. Third, the image is displayed with a method that allows the observer to further magnify the image and make precise measurements upon it.

More recently, computerized image processing techniques have been applied to the

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[39]Hayreh SS, Servais G, Virdi PS. Retinal arteriolar changes in malignant hypertension. Ophthalmologica 1989; 198:178-196.

[40]Hodge JV, Parr JC, Spears GFS. Comparison of methods of measuring vessel widths on retinal photographs and the effect of fluorescein injection on apparent retinal vessel calibre. Am J Ophthalmol 1969; 68:1060-1068.

[41]Bracher D, Dozzi M, and Lotmar W. Measurements of vessel width on fundus photographs. Graefes Arch Klin Exp Ophthalmol 1979; 211:35-48.

evaluation of the retinal vasculature. Pelli et al[42] suggested that enhancement of less-than-optimal fundus photographs through techniques such as digital sharpening ("high pass filtering") can facilitate their evaluation. Brinchmann-Hansen et al[43] have adopted a linear densitometric technique to automate the measurement of vessel caliber. Briefly, a profile of intensity measurements is obtained along a line intersecting the retina and extending beyond it into the retina (the latter to provide a contrasting reference value), an algorithm (the "half-height method") is applied to determine the boundary points, and the distance between the two points measured. This approach is being explored as an alternative to manual establishment of the boundaries by an observer.

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[42]Peli E, Schwartz B. Enhancement of fundus photographs taken through cataracts. Ophthalmology 1987; 94(S):10-13.

[43]Brinchmann-Hansen O, Engvold O. Microphotometry of the blood column and the light streak on retinal vessels in fundus photographs. Acta Ophthalmologica 1986; 179:9-19.

2.0 EQUIPMENT AND MATERIALS

The image processing system for this project consists of the following components:

(a) Scanner

Slide transparencies are converted to digital images via a Nikon LS 3510 AF scanner, with a resolution of 3,175 dots per inch. The scanner is controlled by a Gateway 2000 486/DX33 microcomputer (24 megabytes of random access memory, 200 megabytes of hard disk storage) running Aldus Photostyler under Microsoft Windows. The scanning system is linked over a network to the image processor itself.

(b) Image processor

Images are measured on a SUN consisting of the following components: SPARCstation LX graphics workstation (32 megabytes of random access memory), 19 inch color monitor for image display, 424 megabyte internal hard drive for software and working space, 2.3 gigabyte external hard drive for storage of images in process, and 5 gigabyte 8 mm tape backup drive for archival image storage. Customized software for image manipulation and vessel measurement was developed using Khoros, a general-purpose suite of image processing software developed at the University of New Mexico and running under the Solaris operating system.

(c) Light box and Magnifying Viewer

As the digital image is examined and measured, the grader has available for reference the original slide, viewed with an 8X stand magnifier and retroilluminated by a light box as described in Appendix A.

(d) Retinal photograph

A single 45° color fundus photograph is obtained on Ektachrome 100 film with the Canon CR-45UAF nonmydriatic camera, as described in the ARIC photography manual. This photograph is centered between the optic disc and the macula, providing photographic documentation of the optic disc, macula, substantial portions of the temporal arcades and about two disc diameters of retina temporal to the optic disc.

3.0 SCANNING THE SLIDE

The photographic technician acquires photographs onto the image processing system on a regular basis. The technician creates a directory in the database, named for the shipping batch, to accommodate the images as they are scanned. Each image is then saved in a file named with the participant identification number. For example, the photograph for participant F102304 received at the Retinal Reading Center in batch ARFR3001 would result in a digital image saved as F001\f102304.

Each slide is positioned in the scanner holder, the cover is closed, and a prescan is invoked. The scanner automatically determines the correct focus and exposure for the individual slide, and then scans a preview image at low resolution. The technician examines the preview image, and positions a mask to demarcate the area of interest: a rectangle including all of the retinal image nasal to the center of the macula. (The area temporal to the center of the macula, which rarely contains vessel branches of interest, is excluded from the final scan to increase processing speed and reduce storage.) Then the technician invokes the final scan at high resolution, inspects the image, and saves the image to the hard disk using the participant ID as the file name.

When all of the slides in a shipping batch have been scanned, the technician executes a batch processor which transmits the image files from the microcomputer driving the scanner to the image processing workstation, and clears the microcomputer disk to receive more images.

4.0 PROCESSING OF THE IMAGE

Prior to grading images are processed in two ways to improve their quality. First, an automatic contrast enhancement is performed to use the full dynamic range of the display monitor (making it easier for graders to discern vessels against the background). Second, a sharpening (or "high pass") filter is used to accentuate the vessel borders. Both of these processes are executed in a standardized fashion, so that the caliber of the retinal vessels is unaffected.

5.0 MEASURING THE VESSELS

5.1 Image Processing Computer Module

The image processing module for the measurement of vessels has a Windows interface. The interface is mouse-controlled, but the keyboard is used to type in the batch and participant identification numbers. The interface consists of two primary form windows, the Grade_form window and the Measure_form window, diagrammed in Exhibit 1. Each primary form window contains a digital image. The Grade_form contains a window showing a portion of the digital image of the eye (the full-resolution image of the eye is too large for the monitor screen). The grader uses the mouse to move the image within the window. The Measure_form window contains the enlarged and contrast-enhanced image of the retinal vessel being measured.

The Grade_form window is linked to two important subforms. The Select_subform window is used to recall the image for each participant. The Grade_subform window has buttons controlling several steps in the grading process.

5.1.1 Recalling the digitized image

The grader uses the Select_subform, shown in Exhibit 2, to recall the digitized image. The Select_subform window is brought up by pushing the "Select Image" button on the Grade_form. The grader then uses the keyboard to enter his/her grader number, the batch identifier, and the participant identification number. The computer module automatically fills in the date graded with today's date, and shows the grader name corresponding with the grader number. If the identifying information is correct, the digitized image is recalled into the available window on the Grade_form and is ready for the grading process. The grader then closes the Select_form window.

5.1.2 Preparatory Grading Steps

The grader opens the Grade_subform by pushing the button marked "Grade Image" (see Exhibit 3A). The Grade_subform offers menu options to: (1) overlay the Zone B grid on the digital image, (2) identify and number the arterioles, veins and arteriolar branches, and (3) choose the region of interest for each vessel.

5.1.2.1 Gridding the image

The gridding process allows the reader to apply a digital version of the ARIC grid on the picture image. The ARIC grid, diagrammed in Exhibit 1 of the Retinal Reading Center procedures chapter, demarcates: (1) an average optic disc, (2) Zone A from the disc margin to 1/2 DD from the disc, and (3) Zone B from 1/2 DD to 1 DD from the disc. Retinal vessels are measured in Zone B.

The grader initiates the gridding process by pushing the button marked "Grid" on the Grade_subform. A circle approximating the optic disc appears on the digitized image, and a small window labeled as the grid_subform appears. The grader uses the mouse to center the circle over the optic disc in the digitized image, and then pushed the "OK" button on the grid_subform. The computer then fixes the grid on the image, centered on the optic disc, as shown in Exhibit 3B.

5.1.2.2 Identifying the retinal vessel

After gridding the image, the reader pans through the image and selects an area of Zone B wherein to start the measuring process. The grader identifies the first vessel to be measured as either an arteriole, a vein, or an arteriolar branch, using the grading rules in Section 5.2.1, Identification of arterioles and veins. The first vessel is automatically marked with the ID number 1 for that vessel type (see Exhibit 4A). The computer keeps a count on the number of arteries and veins which have already been measured, and automatically increments the number in the vessel ID box. However, the grader can edit this number.

5.1.2.3 Selecting the region of interest

After identifying the vessel to measure, the grader selects the region of interest for that vessel, using the grading rules in Section 5.2.3, Choosing region of interest to measure. This process is diagrammed in Exhibit 4B. The grader initiates the process by pushing the button marked "Region". To choose the region of interest, the reader uses a mouse to mark the center of the vessel with a dot, and then uses the mouse to enlarge a circle centered on the dot until he/she has the desired region of interest within the circle. The grader then pushes the "Extract" button, and the region of interest is then enlarged four times within the Measure_form window.

5.1.3 Measuring the Vessel Caliber

The reader moves to the Measure_form window to measure the vessel caliber (see Exhibit 5A). The process is initiated by pushing the button marked "Measure". He/she then uses the mouse to mark one edge of the vessel with a dot, to enlarge a circle centered on that dot until one edge of the circle coincides with the opposite edge of the vessel, and to click and finalize the circle size. The diameter of the circle is the shortest distance across the retinal vessel. The image processor converts this distance from pixels to microns. The photograph reader is presented with the measurement in microns and can choose to accept or reject the measurement. An example is diagrammed in Exhibit 5B.

If the measurement is accepted, it is written to a data file along with the vessel identification from the Grade_subform. Also, the vessel identification is marked on the image of the eye contained in the Grade_form window. If rejected, the reader may mark and measure the vessel again.

5.1.4 Completing the Grading of the Eye

The photograph reader moves from the Grade_subform (where the vessel is identified and the region of interest for measurement is chosen) to the Measure_form (where the vessel is measured) for each vessel in Zone B. Finally, the reader reviews the digitized image of the eye, checking for any vessels not marked with an identifier (A1, A2, V1, etc.). The grader may also review the measurements by pushing the button marked "Review" on the Grade_subform. The measurements are presented in a format similar to that in Exhibit 6.

When the grader is satisfied that all retinal vessels in Zone B have been appropriately measured, the data file is saved by pushing the "Save Data" button on the Grade_form.

5.2 Grading Rules

5.2.1 Identification of Arterioles and Veins

The photograph reader identifies each vessel within Zone B as either an arteriole or a vein before selecting the region of interest for that vessel. Most vessels with a caliber greater than or equal to 50u can be identified as either arterioles or veins from the digital image on the picture monitor. For smaller vessels, the reader refers to the original retinal photograph on a light box. For either, the reader uses the guidelines below to identify each vessel:

(a) Arterioles are a lighter orange-red color with a strong central light reflex. The central light reflex may not always be apparent, especially in arterioles less than 50u in caliber. Arterioles tend to be straighter and smoother in outline; they are more regular in both path and outline.
(b) Veins are a darker purple-red color with little or no central light reflex. Veins are generally more tortuous, and more irregular in outline and diameter. Veins are broader in diameter at the disc margin than the corresponding arteries.
(c) As a general rule, arterioles do not cross arterioles and veins do not cross veins. This may not always be true on or near the disc, but is a reliable guideline more than 1 DD from the disc margin. If a vessel of unknown identity crosses a venous branch within or distal to Zone B, then the unknown vessel is an arteriole. If it crosses an arteriolar branch within or distal to Zone B, then

it is a vein. This rule is crucial in identifying small vessels.

(d) Smaller branches can be identified by tracing them proximally to their branching from a parent vessel, the identity of which may be evident from the first two guidelines. Angles between vessels may be useful in differentiating crossings and branchings. Crossings are frequently almost perpendicular (180°) or, if the two vessels are coursing in parallel, the angle of the crossing may be very shallow (less than 30°). Branchings are usually somewhat less than perpendicular (with the angle between the two branches from 30° to 45°).

5.2.2 Exclusion of Small Vessels

All vessels with a diameter of 25u or less are excluded from measurement. The reader may determine if a vessel should be excluded by measuring the vessel or by comparing the vessel with a standard dot of 25u on the image processing monitor [to be developed].

5.2.3 Choosing Region of Interest to Measure

For measuring each vessel, the reader chooses a region of interest which is zoomed to a 4X enlargement for measuring purposes. The region of interest should show enough retinal background to provide contrast with the vessel. A circular region of interest with a diameter from three times that of large vessels may be sufficient, while a diameter up to ten or twelve times the diameter of small vessels may be useful. The region of interest for each vessel is always chosen within Zone B (1/2 DD to 1 DD from the disc margin) as shown by the grid overlaid on the digital image. Working within Zone B, the reader uses the following guidelines to choose the region of interest:

(a) The reader chooses a vessel segment in the center third of Zone B unless contra-indicated.

(b) If a vessel bifurcates within Zone B, a single measurement of the vessel before the bifurcation is preferable to measuring the branches after the bifurcation.

(c) The reader chooses a stretch of vessel away from branchings and crossings to minimize any effect that branching or crossing, or the vessel undulations that may accompany them, may have on the apparent caliber of the vessel.

(d) A vessel segment which is relatively straight, rather than curving, is preferable, again to avoid vessel undulations which may affect the apparent diameter.

(e) The reader preferentially chooses areas with better focus, given that he/she remains within the measuring zone and away from branchings and crossings. If focus and contrast are acceptable anywhere within Zone B, the reader observes the guidelines above. If the focus is markedly better elsewhere, the reader may choose a region of interest in the inner or outer third of Zone B. The reader may also choose to measure the branches after a bifurcation if the branches show better focus or contrast.

5.2.3 Detection of Vessel Edges

The reader marks the vessel edges on the 4X enlargement in the Measure_form window. The enlarged image of the vessel shows a gradual change from the relatively paler gray of the retinal background to the darker gray of the vessels. The vessel edge is assumed to be the point at which the gray values become uniformly darker. The reader disregards the irregular medium gray halo, which is especially prominent on poorly focused vessels, and chooses a point where the color value is closer to the dark gray of the vessel interior than the lighter gray of the retinal background. The reader uses a cursor to mark the first vessel edge, and then draws the cursor across the vessel, enlarging the resulting circle until the edge of the circle coincides with the opposite vessel edge.

5.2.4 Measuring Branches of Larger Arterioles

For all arterioles with a caliber greater than or equal to 80u, the photograph reader measures the first available branches of that arteriole. The reader may move substantially beyond the usual measuring zone, Zone B, to measure the branches. Occasionally the vessel of interest may not bifurcate until after it leaves the area

photographed, in which case the branch measurement cannot be obtained. If the area of bifurcation is not photographed, or if photographic quality is impaired in the periphery, the grader may mark only that branch pair as ungradable and proceed with measurements for the remaining vessels. Ungradable branch pairs are marked with the value "-1" in the data set.

6.0 RECORDING DATA

After the grader has measured all the vessels of interest, and optionally reviewed the values obtained, the data are saved to a computer file under the subject identification number (for example, f102304.dat). The main data file consists of the following items: the number and caliber of each arteriole, the number and caliber of each vein, and the trunk number and branch calibers of each pair of arteriolar branches measured. An ancillary data file is created which identifies the identity and coordinate locations of all the vessels measured.

7.0 CALCULATION OF SUMMARY VARIABLES

For summarization of the data, completed measurement files are transferred to the ARIC database computer. Using a program developed within Paradox, the following variables are calculated:

1. CRAE (central retinal artery equivalent), using the Parr formula

$$W_c = (0.87 W_a^2 + 1.01 W_b^2 - 0.22 W_a W_b - 10.76)^{1/2}$$

in which W_c is the caliber of the trunk arteriole, W_a the caliber of the smaller branch, and W_b the caliber of the larger branch

2. Alternative CRAE, substituting branch measurements for trunk measurements of arterioles larger than x microns.

3. CRVE (central retinal vein equivalent) using the Wisconsin formula

$$W_c = (0.72 W_a^2 + 0.91 W_b^2 + 450.05)^{1/2}$$

in which W_c is the caliber of the trunk vein, W_a the caliber of the smaller branch, and W_b the caliber of the larger branch

4. A/V ratio (CRAE/CRVE)

5. Alternative A/V ratio (Alternative CRAE/CRVE)

Calculation of the central artery and vein equivalents is done using the Wisconsin simplified computational method, in which the measurements are successively combined pairwise according to the following algorithm rather by the pairing actually observed. Smallest measurement is combined with largest, next smallest with next largest, and so forth, with any remaining single measurement being folded into the next iteration, until a final result is obtained.

To produce the final data record for transmission to the Coordinating Center, the calculated variables are added to the record containing the numbered arteriolar, arteriolar branch, and vein measurements.

Exhibit 1
Retinal Image Processing - Overview of the Computer Interface

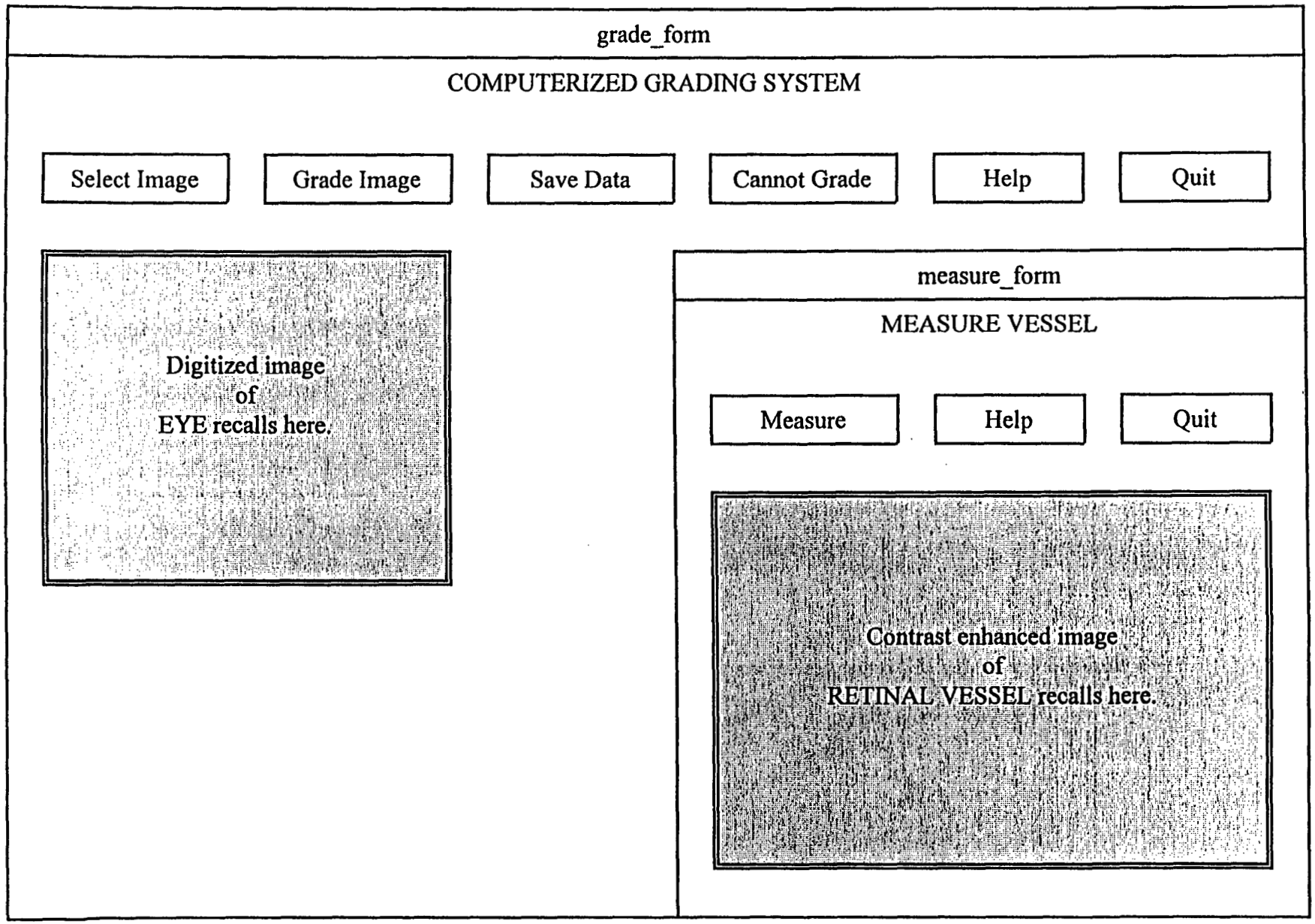

Exhibit 2
Retinal Image Processing - Recalling the Digitized Image

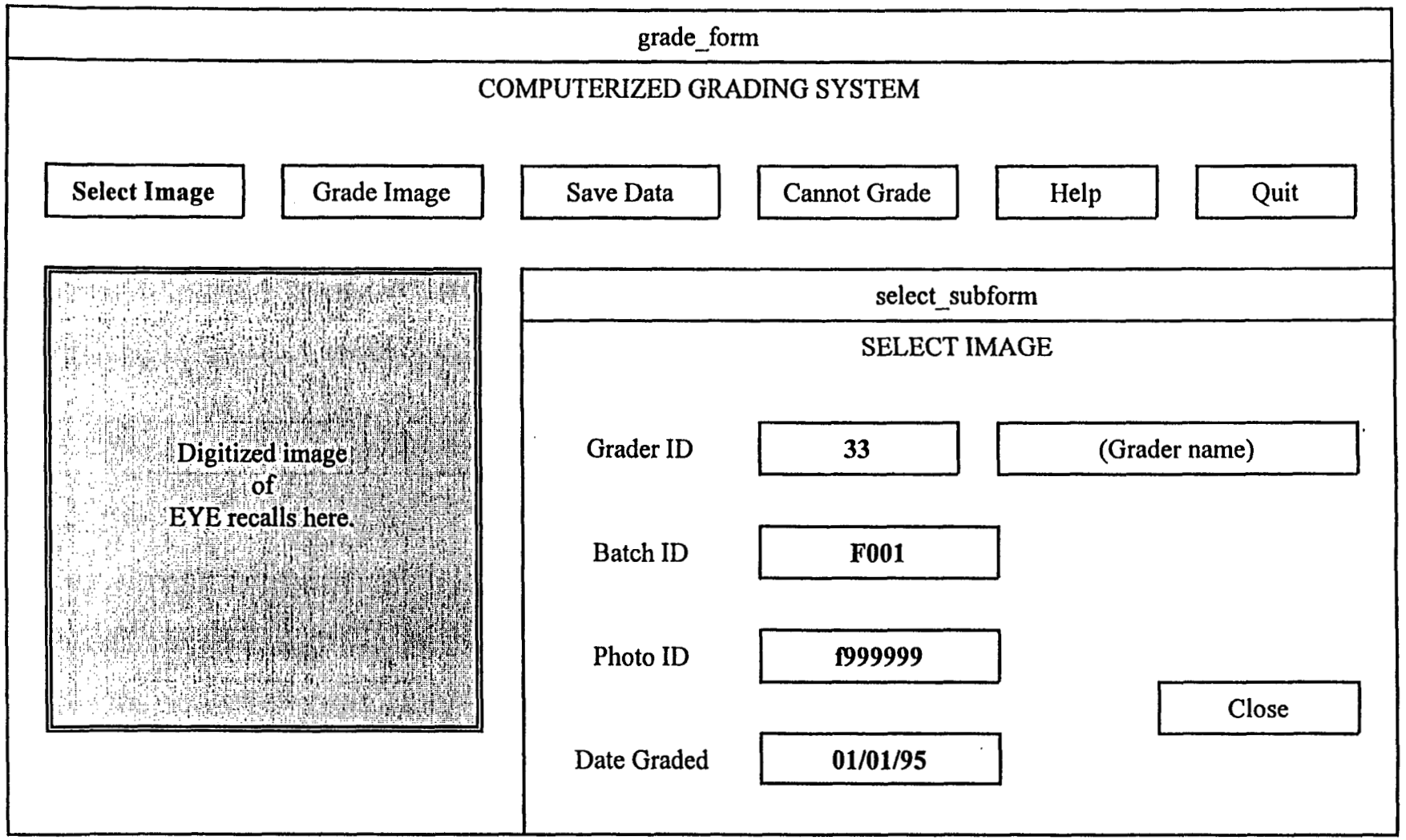

Exhibit 3A

Retinal Image Processing - Gridding the Retinal Image to Identify Zone B

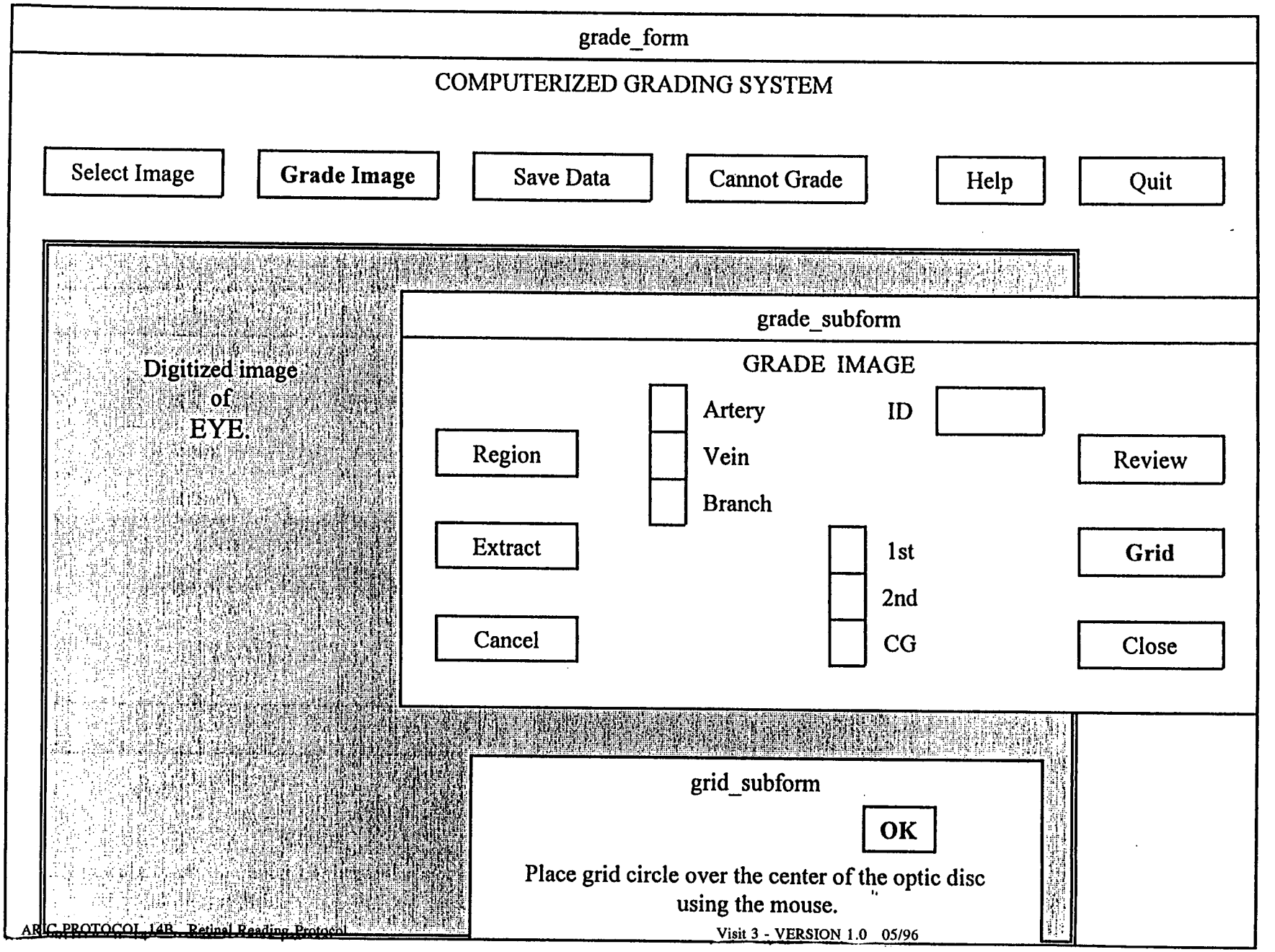

Exhibit 3B
Retinal Image Processing - Gridding the Retinal Image to Identify Zone B

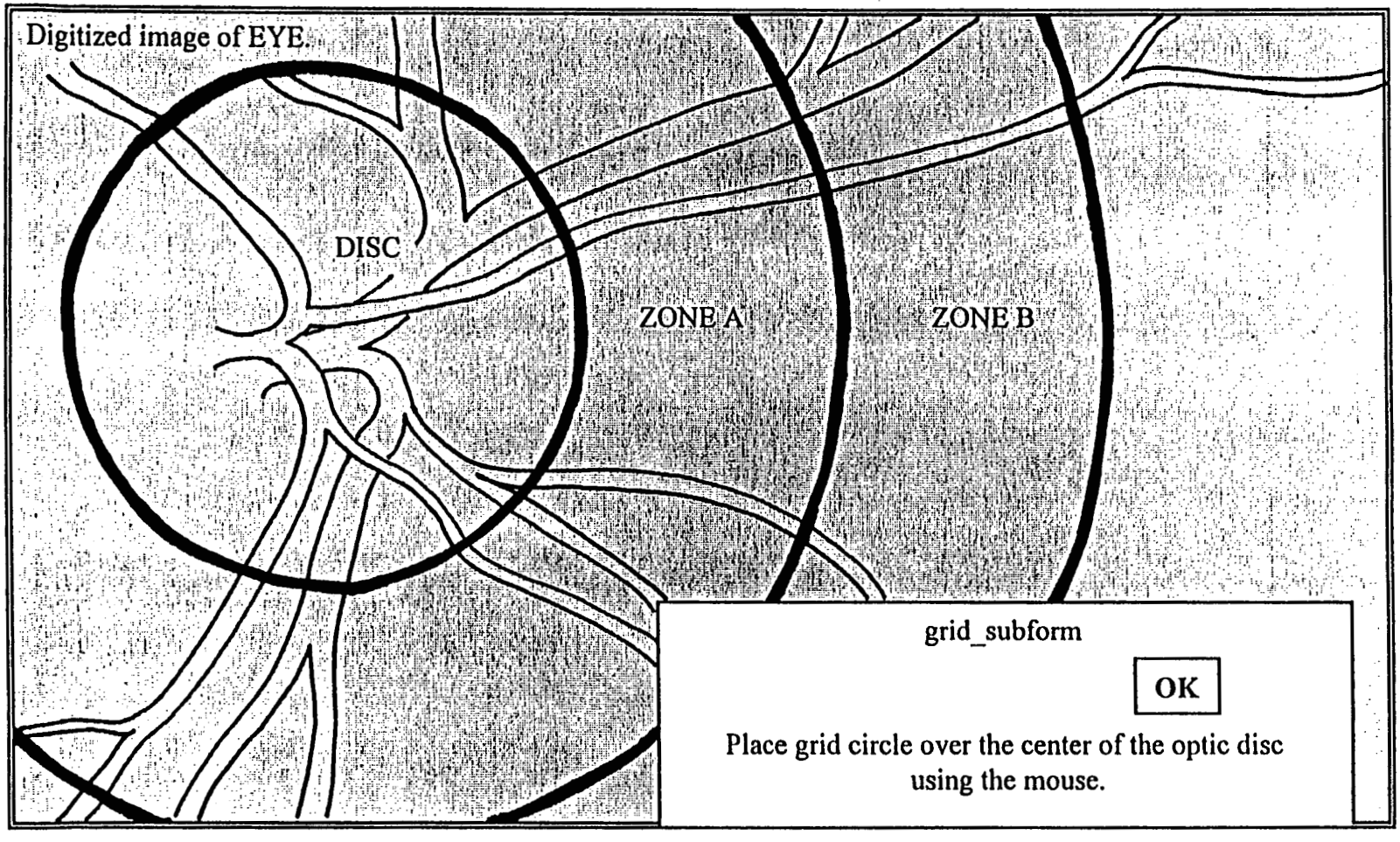

Exhibit 4A
Retinal Image Processing - Choosing Region of Vessel to Measure

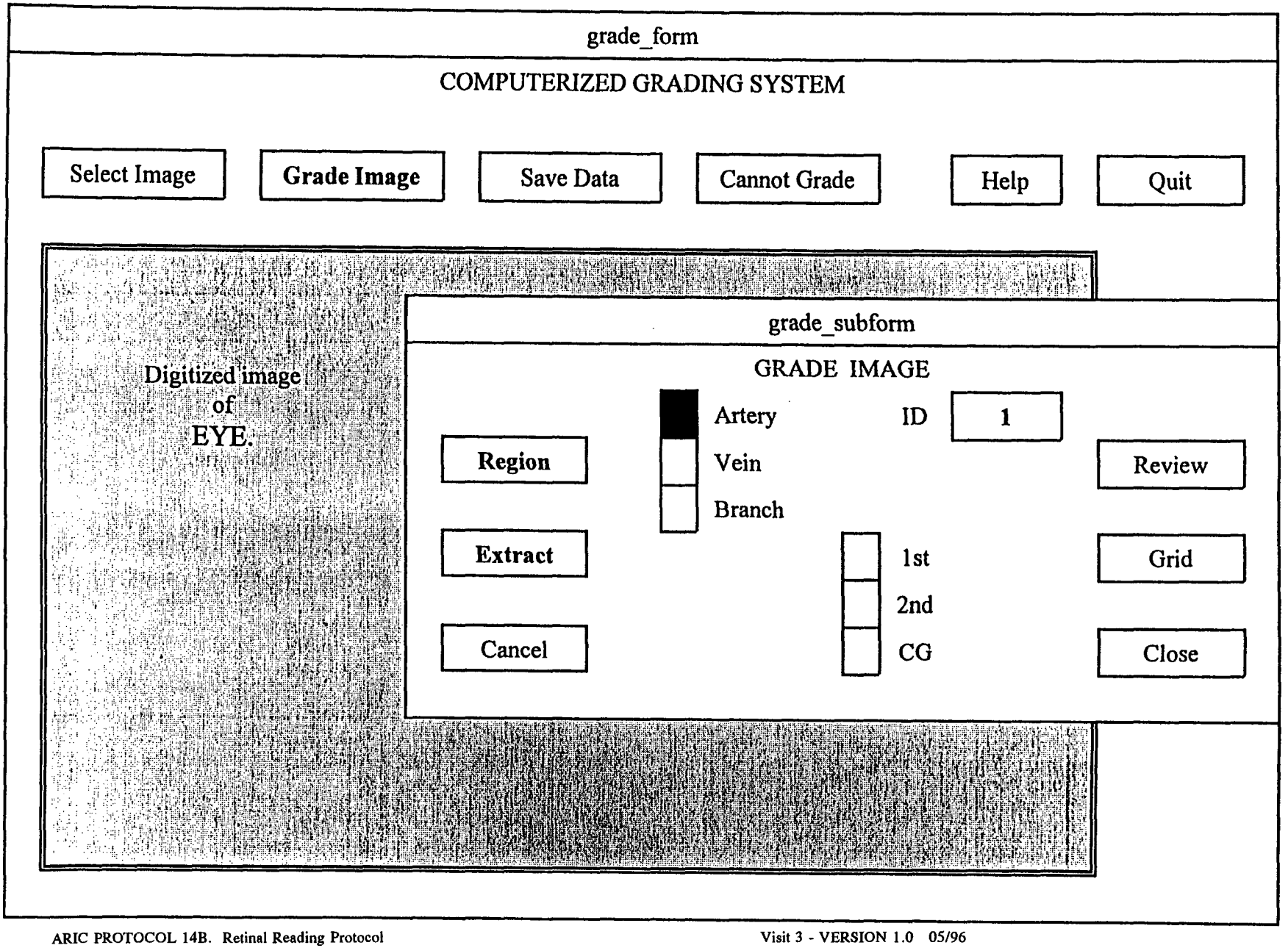

Exhibit 4B
Retinal Image Processing - Choosing Region of Vessel to Measure

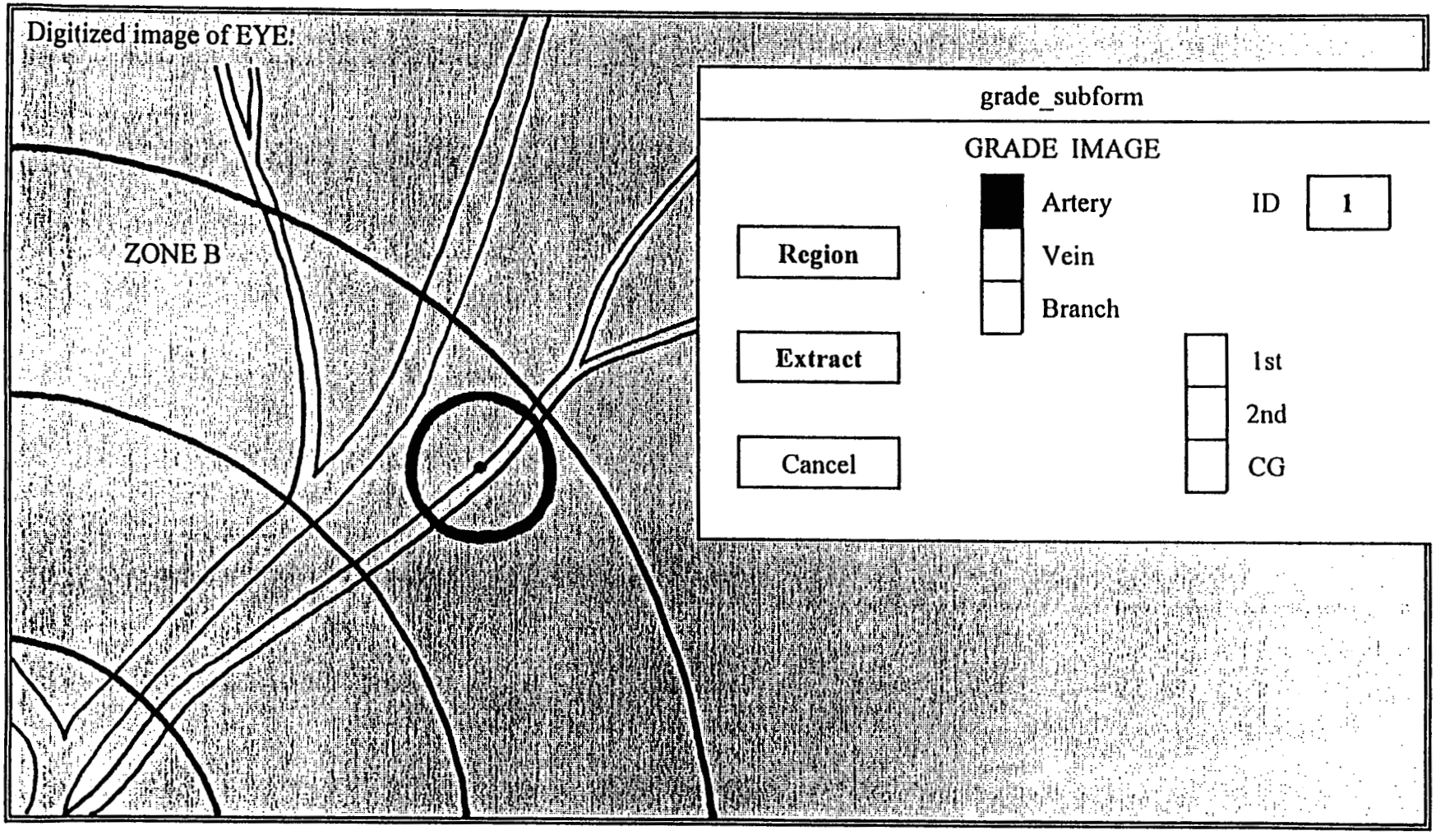

Exhibit 5A
Retinal Image Processing - Measuring Caliber of Retinal Vessel

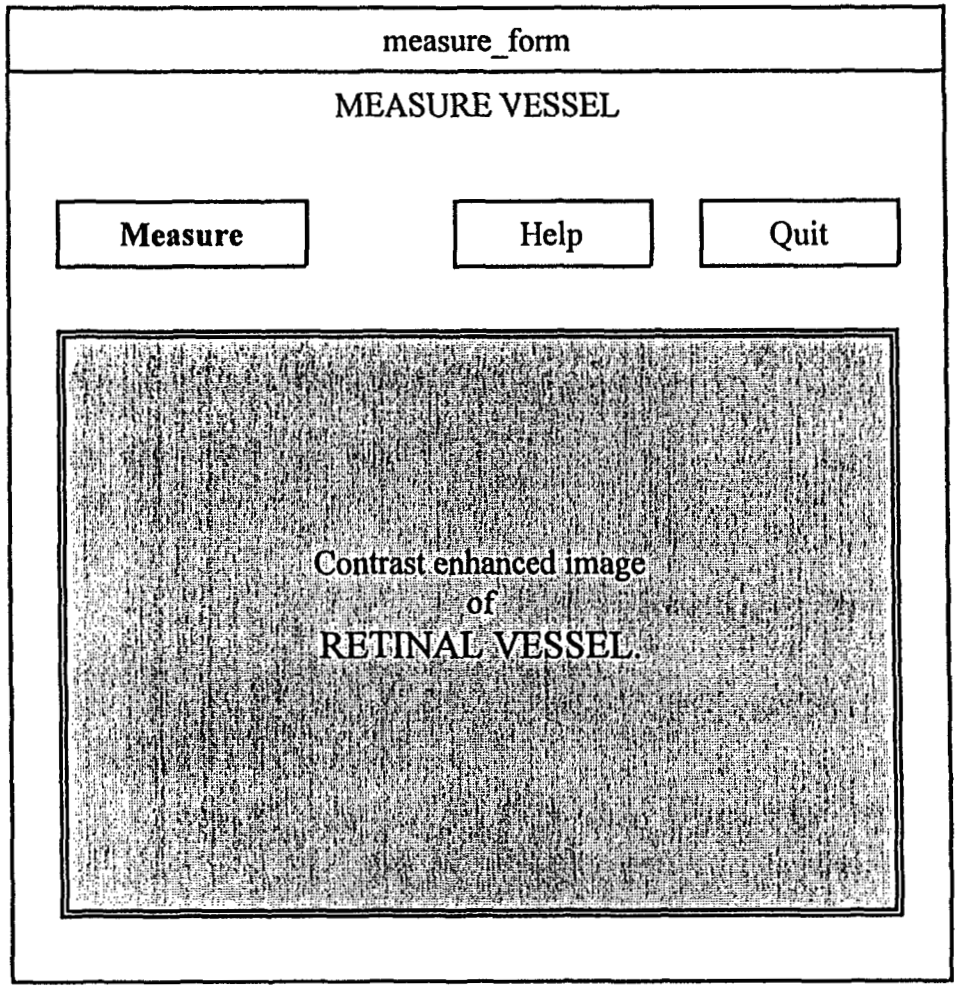

Exhibit 5B
Retinal Image Processing - Measuring Caliber of Retinal Vessel

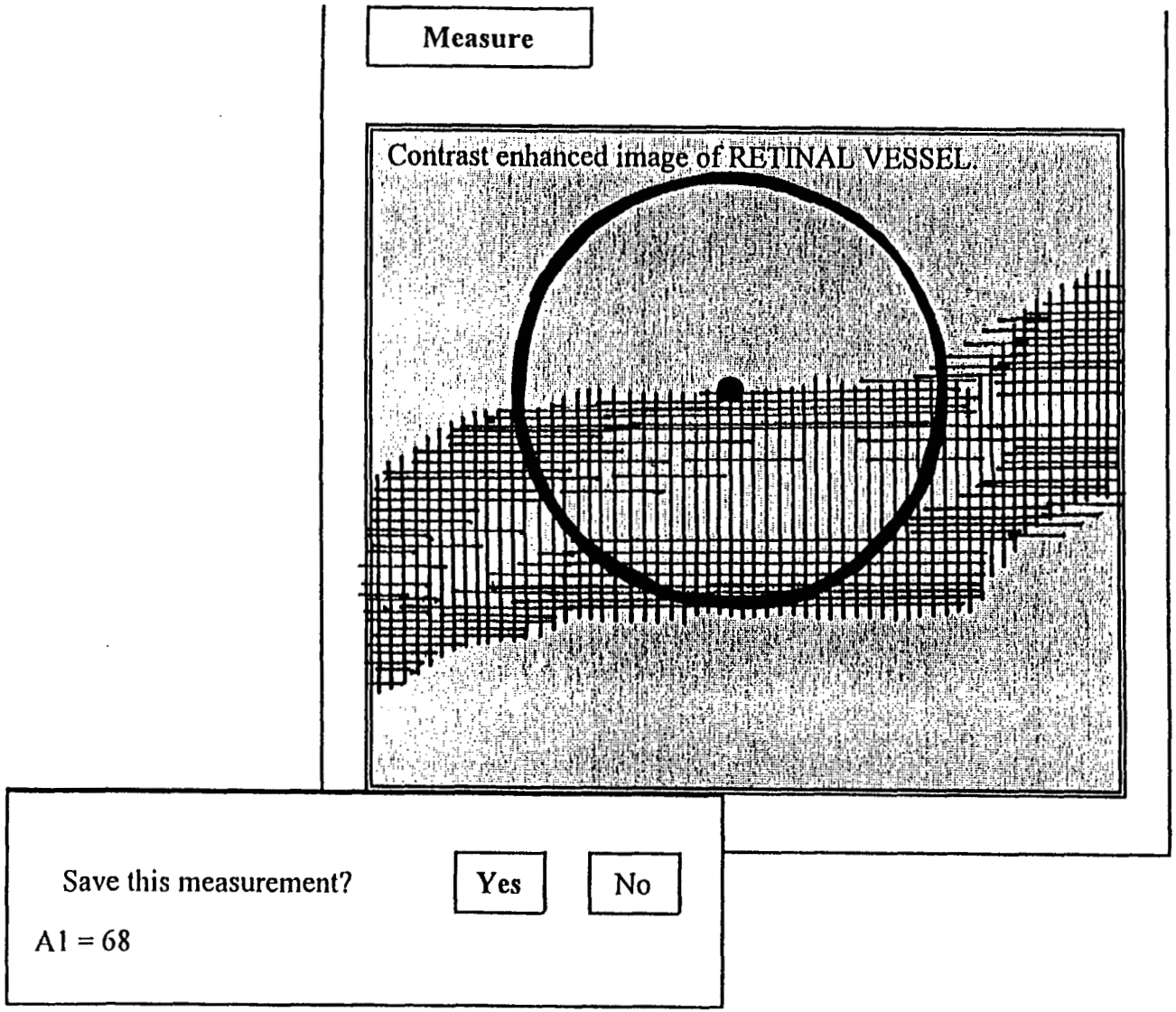

Exhibit 6
Retinal Image Processing - Sample Data Set

BATCH ID: F001
PARTICIPANT: F999999
GRADER: 33
DATE GRADED: 01/01/95

ARTERIES						VEINS	
	TRUNK	B1	B2		EQUIV		VEIN
A_1	68			B_1_AE	68	V_1	39
A_2	63			B_2_AE	63	V_2	109
A_3	91	96	78	B_3_AE	114	V_3	35
A_4	41			B_4_AE	41	V_4	42
A_5	83	55	68	B_5_AE	80	V_5	34
A_6	55			B_6_AE	55	V_6	110
A_7	35			B_7_AE	35	V_7	86
A_8	39			B_8_AE	39	V_8	90
A_9	63			B_9_AE	63	V_9	79
A_10	64			B_10_AE	64	V_10	68
A_11				B_11_AE		V_11	54
A_12				B_12_AE		V_12	90
A_13				B_13_AE		V_13	
A_14				B_14_AE		V_14	
A_15				B_15_AE		V_15	
A_16				B_16_AE		V_16	
A_17				B_17_AE		V_17	
A_18				B_18_AE		V_18	

CRAE_T: 152
CRAE_B: 162
CRVE: 198
AV_RATIO_T: 0.77
AV_RATIO_B: 0.82

Arteries requiring branch measurements: A_REQ_B: 2
Branch pairs measured: A_MEAS_B: 2
Proportion measured: A_B_RATIO: 1.00