SENIOR PROJECT

MARK J. SANITATE

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SENIOR RESEARCH PROJECT

INNOVATIVE RESEARCH CONDUCTED AT THE CENTER FOR RESEARCH AND DEVELOPMENT AT SINAI HOSPITOL OF DETROIT MICHIGAN.

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FACULTY ADVISOR: RANDALL VANCE O.D.

This senior project is one which was constructed at an Ophthalmic Research Department which is making diagnostic advancements in the areas of ocular health and prevention of disease. It was done to inform the reader of the promising technology occurring in the areas of early detection and prevention of disease. Information was gathered through the research efforts of Joseph Rosenshein, Ph.D, whose work and documents have contributed to the content of this paper.

All following information and research were obtained from the Center for Ophthalmic Research and Development.

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The two areas of research observed at the C.O.R.D. which will be reported on are:

1) **Increased Glaucoma Diagnostic Sensitivity through Discriminant Analysis of Multiple Tests Results**
2) **The Scanning Laser Ophthalmoscope as a New Diagnostic Tool**

Although there is other research being conducted at the C.O.R.D. the two topics mentioned are being worked on with full force and have been the two principle research projects in the last year.

INCREASED GLAUCOMA DIAGNOSTIC SENSITIVITY THROUGH DISCRIMINANT ANALYSIS OF MULTIPLE TEST RESULTS

Principal Investigator: JOSEPH ROSENSHEIN, Ph.D

Development of techniques and procedures of these tests have been occurring for approximately one year and no data concerning glaucomatous patients have been collected at this clinic to date.

Glaucoma is characterized by the presence of optic atrophy with the progressive loss of functioning retinal ganglion cells. It is assumed that sensitive measures of retinal ganglion cell activity could be used to assess levels of optic atrophy associated with glaucoma. Previous studies listed at the end of this paper, using psychophysical and electrophysical tests such as retinal layer perimetry, contrast sensitivity, color vision, increment threshold tests, flicker sensitivity, visual evoked potentials, and pattern electroretinagrams have shown that patients with glaucoma can be distinguished from a normal population. It should be noted that visual fields nor IOP measurements by themselves reflect early stages of glaucoma, although they are used in conjuntion with cup to disk ratios, physical appearance of optic disk and appearance of nerve fiber layer. It has been found that by the time a patient shows significant visual field defects, about 50% of the retinal ganglion cells have been damaged. Today, in order to avoid this it is necessary to treat elevated IOP's with the risk of significant side effects

and at a significant cost to the patient. The proposed research at the Center for Ophthalmic Research and Development is to investigate methods of detecting the onset and progression of the disease at earlier stages than that revealed by visual field measures or other single psychophysical or electro-physiological tests.

Tests selected for this study have been shown in previous research to effectively show retinal ganglion cell activity and therefore should permit earlier detection of the development of glaucoma. Early detection of patients not developing glaucoma will reduce the use of prophylactic medications along with their adverse side affects. More importantly, a battery of tests providing sensitive measures of retinal ganglion cell activity could be used to monitor effects of therapy in the earliest stages of glaucoma before the emergence of large scale ganglion cell damage and related visual field loss.

Forty glaucomatous and forty normal subjects will be tested when procedures are perfected. Normal patients will have one eye tested and glaucomatous patients will have both eyes tested. Eight non-invasive tests have been selected from preliminary research at the C.O.R.D. and from current research publications relating to the determination of retinal ganglion cell activity.

1.) Subjects will have their visual acuity maximized. Visual acuity will be measured by an automatic, computer controlled and generated graphics display using a forced

choice paradigm requiring the subject to move a joystick in the direction of a high contrast Snellen E against a white background. A similar test will be performed with the subject looking at a blue letter on the screen through a yellow adapting background light. Blue light is used because of the research data which shows that with glaucoma, blue color defects are seen before other color defects . (References may be found at the end of this paper.) Results are reported as a conventional Snellen fraction.

2.) Overall color vision will be determined by the use of the Farnsworth-Munsell 100 hue test. The test will use all four racks of a total of 85 caps. The results are reported as an error score which can be used to determine an axis of color confusion which may be associated with glaucoma.

3.) White contrast sensitivity will be measured by an automatic computer controlled graphics display using forced choice in which a stationary sinusoidal grating pattern appears at random at four different locations against a background of equiluminance on the screen. The results are reported as the contrast thresholds of detection for each of five spatial frequencies. Blue contrast sensitivity will be measured in a similar manner except that the subject will view a blue grating through a yellow adapting background. The blue luminance values will be calibrated by heterochromatic photometry against the known white values to compensate for any absorption of blue in the ocular media.

4.) Blue increment threshold sensitivity will be measured in a manner similar to the blue contrast sensitivity, except that the subject will be viewing a flashing blue spot of various intensities instead of a blue grating. The results are reported as the luminance thresholds for detection of the flashing spot in each of four quadrants as well as the overall average threshold.

5.) Visual field sensitivities will be measured using a standard automated perimeter (Octopus 2000). Reporting of the data will include the global indices of the visual field as well as a multi dimensional analysis (developed at C.O.R.D.) of the difference of the field from a normal field.

6.) Flicker visual evoked potentials (VEP) and EEG spectral response will be measured using a Tracor Nomad electrodiagnostic system. The subject will have three electrodes attached to the scalp and, with one eye occluded, view either a goggle with flashing light emitting diodes or a ganzfeld photic stimulator with a flickering strobe light. The frequency of the flickering light will be varied and the amplitude and latencies of the corresponding VEP and spectral response will be measured and reported for each of five different flicker frequencies.

7.) Pattern electroretinogram (PERG) and stimulus VEP measurements will be made using the same equipment as for the flicker VEP's described above. In addition to the scalp electrodes, the subject will be required to fixate for up to a minute on a

television monitor on which a checkerboard pattern will be flashing in counterphase reversal. The measurements will be reported as the amplitudes and latencies of the N1, P1 N2 points of the PERG's and PVEP's as a function of reversal frequency.

8.) Intraocular pressure will be measured using a standard slit lamp and Goldman applanation tonometer. The results will be reported as the pressure in millimeters of mercury.

At the end of testing each patient will be dilated and a photograph will be made for documentation.

Data obtained from the noninvasive testing procedures will be analysed using multivariant analysis. The objectives of the analysis applied to the test results are:

1.) To find a subset of the noninvasive tests that best reveals the difference amoung the two groups. (glaucomatous vs.normals)

2.) To determine a mathematical rule for predicting to which of the two groups an individual belongs, based on knowledge of the results of testing, only.

3.) To evaluate the performance of the discriminant function by determining the appropriate error rates. The error rates are the probabilities of misclassification using the discriminant function of a normal individual as glaucomatous, or a glaucomatous patient as being normal.

Once perfected this regimen of tests can be performed to measure retinal ganglion sensitivity levels so as to determine relative integrity of this cell layer and its relation to early detection of glaucoma.

THE SCANNING LASER OPHTHALMOSCOPE

The Scanning Laser Ophthalmoscope is a new ophthalmic instrument which has recently been developed. The Scanning Laser Ophthalmoscope (SLO) produces a high-quality television image of the retina using 1/1000th of the light needed for standard indirect opthalmoscopy. The SLO was first developed in this country by Robert H. Webb, George W. Hughes, and Oleg Pomerantzeff. Two generations of SLO reside with Dr. Webb and Co. at the Eye Research Institute of the Retina Foundation in Boston. Coopervision's prototype, based upon Webb and Co.'s work, resides at Sinai Hospital of Detroit, where it is being subject to further modification and design.

At this time the SLO is a large set-up which takes up an area of approximately 4ft by 7ft and is non-portable. The SLO basically consists of low power variable intensity Argon and Helium-Neon lasers which scan the patient's eye. The reflected energy of these lasers from the eye is received by photomultiplier tubes and converted to a color image on a monitor. The image quality is good despite the use of just two colors. All information can be stored or retrieved for review and comparison on videotape. The SLO also employs variable zooming magnification, a feature not available on standard retinal cameras.

There are 3 major characteristics which help prove the superiority of the SLO over the standard ophthalmoscope. First, since lasers are used to provide the illumination

of the eye, the coherency of the laser light enables the examiner to gain information about eyes which might not otherwise be viewable. Normal incoherent light is more subject to scatter than coherent light. With the SLO the laser beam is small and collimated on a specific portion of the retina and scatter is restricted. For patients with cataracts and other opacities in which a view of the fundus is difficult, the SLO is able to provide a good view of the retina to determine the health of the rest of the eye or the extent of a disease state.

Second, the SLO permits the use of lower light levels than with a standard ophthalmoscope or fundus camera. Since the scanning beam is introduced through a very small portion of the patient's pupil, the remaining area is available for light collection. Also the scanning nature of the laser system provides a greater safety factor since the intensity per spot per time is reduced.

When using fluorescein angiography, the present configuration of the SLO permits the investigator to record standard or oral angiography using 1/10 the dose needed when using a retinal camera. Either method reduces the risk of insult to the eye from the repeated flash intensity of a fundus camera and also allows continuous viewing via videotape recording. Oral fluorescein, which can be used more effectively with the SLO rather than with a fundus camera, permits the use of smaller doses of dye.

Third, the SLO has the ability to directly present visual stimuli to the eye at a chosen location. This allows the examiner to view different sections of the retina with pinpoint accuracy. This enables the examiner to also evaluate activity at different areas of the retina and also study fixation patterns. Previously the examiner was only able to assess visual function at different areas of the retina using interference, and the accuracy of previous measurement depended on the reliability of the patient to maintain fixation. The SLO permits simultaneous observation and recording of both the ocular fundus and the retinal image of the mapping stimulus.

One of the most interesting issues from this research department is the ability of the system to project any graphic material that can be displayed on a microcomputer monitor on to the retina. With this, it will be possible to conduct and incorporate the non-invasive tests which were discussed in Part 1 of this paper. The SLO also has the ability to perform retinal perimetry using mapping stimulus, and distortometry by placing an Amsler Grid on the suspect retina locus. The distortometry test provides simple, non-invasive information which allows the examiner to follow the progress of early macular disease before scotoma occurs. Complex dynamic stimuli can also be placed on the retina which may be particularly useful for maintaining attention during pediatric ophthalmoscopy. The SLO can also be used in the same extent that the Laser

Interferometer is used to predict visual acuity prior to surgery. The SLO enables accurate and precise acuity and field of vision evaluations by allowing the examiner to present the stimuli directly on and around the affected anatomical area in question.

Finally a comparison of the advantages and disadvantages of the SLO should be made.

ADVANTAGES: Lower light level, longer viewing time without risk to patient, coherent light, instant replay, real time recording and viewing, storage of images and data, ability to use fluorescein in 1/10 the dose with injection and better results orally. Also analysis of retinal function (such as acuity, visual field), presurgical prediction of acuity, and a good teaching tool.

DISADVANTAGES: The SLO is very expensive, it is not portable, it fills almost an entire room. The conventional ophthalmoscope is portable, rechargeable, hand held, and cost is less than 200.00 dollars.

In conclusion, it will be some time in the future before the SLO is seen on a routine basis even in large ophthalmological practices, but the possibilities displayed with such research developments are quite encouraging to the field of ocular health especially in regards to prevention and detection of disease.

PREVIOUS WORK PERFORMED

The motivation for developing the previous early glaucoma prevention tests has come from experimental results reported in the vision research literature as indicated below for each of the proposed tests:

1. Acuity and Glaucoma

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2. Color Vision and Glaucoma

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   Gunduz, K., Arden, G. B., et al, Color Vision Defects in Ocular Hypertension and Glaucoma, Arch. Ophthalmol., 106:929, 1988

   Sample, P.A., Boynton, R. M., Weinreb, R. N.:Isolating the Color Vision Loss in Primary Open-Angle Glaucoma, Amer. J. Ophthal. 106:686 1988

3. Contrast Sensitivity and Glaucoma

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4. Blue Increment Threshold Sensitivity and Glaucoma

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6 Flicker Visual Evoked Potentials and Glaucoma

Schmeisser, E. T., Smith, T. J.: Flicker VEP Frequency Response Curves in Glaucoma, Inves. Ophthalmol. and Vis. Sci. 29(Suppl.);239 1988

Grehn, F., Grusser , O.J., Stange, D.,: Effect of Short Term Intraocular Pressure Increase on Cat Retinal Ganglion Cell Activity, Behavioural Brain Research 14:109 1984

7. Pattern Electroretinogram and Glaucoma:

Trick, G. L., Bickler-Bluth, M., et al: Pattern Reversal Electroretinogram (PRERG) Abnormalities in Ocular Hypertension: Correlation with Glaucoma Risk Factors, Current Eye Research 7:201 1988

Weinstein, G. W., Arden, G. B., et al: The Pattern Electroretinogram (PERG) in Ocular Hypertension and Glaucoma, Arch Ophthalmol. 106:923 1988

Van Lith, G., Ringens, P., de Heer, L. J., Pattern Electroretinogram and Glaucoma, Dev. Ophthal., 9:133, 1984

Papst, N., Bopp, M., Schnaudigel, O.E., The Pattern Evoked Electroretinogram Associated with Elevated Intraocular Pressure, Graefes Arch. Clin. Exp. Ophthalmol., 222:34, 1984

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9. Intraocular Pressure and Glaucoma

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