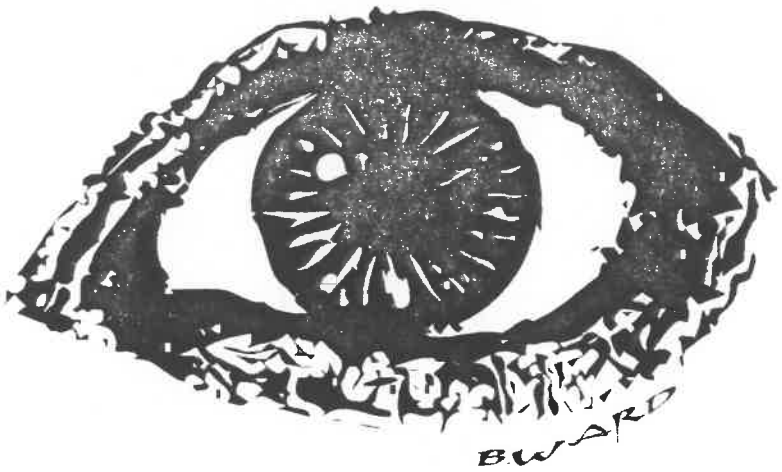

RESIDENT/FELLOW RESEARCH DAY

May 1, 1999

DEPARTMENT OF OPHTHALMOLOGY

THE UNIVERSITY OF IOWA COLLEGE OF MEDICINE

THE UNIVERSITY OF IOWA HOSPITALS & CLINICS

IOWA CITY, IOWA

Braley Conference Room
01136 Lower Level
Pomerantz Family Pavilion
8:00 - 1:00

RESIDENT/FELLOW RESEARCH DAY - 1999

DEPARTMENT OF OPHTHALMOLOGY

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PROFESSOR EMERITUS
G. Frank Judisch, M.D.
Sohan S. Hayreh, M.D., Ph.D., D.Sc.
Hansjoerg E. Kolder, M.D., Ph.D.
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Edward S. Perkins, M.D., Ph.D.
H. Stanley Thompson, M.D.

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PROFESSOR
Wallace L. M. Alward, M.D.
Robert Folberg, M.D.
James C. Folk, M.D.
Gregory S. Hageman, Ph.D.
Ronald V. Keech, M.D.
Jeffrey A. Nerad, M.D.
William E. Scott, M.D.
Edwin M. Stone, M.D., Ph.D.
John E. Sutphin, Jr., M.D.
Michael Wall, M.D.

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H. Culver Boldt, M.D.
Keith D. Carter, M.D
A. Timothy Johnson, M.D., Ph.D.
Randy H. Kardon, M.D., Ph.D.
Stephen R. Russell, M.D.

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FACULTY RESEARCH ADVISOR
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RESIDENT/FELLOW RESEARCH DAY - 1999

FELLOWS

CORNEA
Robert A. Oppenheim, M.D.

GLAUCOMA
Robert A. Honkanen, M.D.

NEURO-OPHTHALMOLOGY
Syndee J. Givre, M.D., Ph.D.

MOLECULAR BIOLOGY
Andrew J. Lotery, M.D.

OCULAR PATHOLOGY
Beata I. Rymgaylło-Jankowska, M.D.

OCULOPLASTICS
Lynette M. Watkins, M.D.

PEDIATRIC OPHTHALMOLOGY
Maria V. Barbe, M.D.
Kristie K. Shappell, M.D.

VITREORETINAL DISEASE
Mina M. Chung, M.D.
Alan J. Franklin, M.D., Ph.D.
Amin Kherani, M.D.
Raj K. Maturi, M.D.

RESIDENT/FELLOW RESEARCH DAY - 1999

ASSOCIATES

Dianna L. Bordewick, M.D.
Kean T. Oh, M.D.

THIRD-YEAR RESIDENTS

Edward M. Barnett, M.D., Ph.D.
Christian L. Hess, M.D.
Brian E. Nichols, M.D., Ph.D.
Richard C. Allen, M.D., Ph.D.
Susan M. Brown, M.D
Andrea Lusk, M.D.

SECOND-YEAR RESIDENTS

Annie Chang, M.D.
John R. Kinder, M.D.
Hunter T. Newsom, M.D.
Stacy L. Thompson, M.D.

FIRST-YEAR RESIDENTS

Zuleika M. Ghodsi, M.D.
Raghav R. Gupta, M.D.
Ekaterini C. Karatza, M.D.
Luis C. Omphroy, M.D.
Mark S. Wolken, M.D.

ORTHOPTIC STUDENT

Cindy Tribble

RESIDENT/FELLOW RESEARCH DAY

Saturday
May 1, 1999

SCHEDULE OF EVENTS

8:00 - 10:30	Presentations	1 - 10
10:30 - 11:00	Break	
11:00 – 1:00	Presentations	11 - 18
Morning Rounds	Presentations	19 - 24

RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

SATURDAY, May 1, 1999

8:00 **Dianna L. Bordewick, MD,** Dr. John Sutphin sponsor.....1
The Clinical Significance Of HLA (Human Leukocyte Antigen) Antibodies In High Risk Corneal Transplantation

8:15 **Stacy L. Thompson, MD,** Dr. Randy Kardon sponsor 2
Pupil Perimetry: The Stimulus-Response Function Of The Pupil Light Reflex Across The Visual Field

8:30 **Richard C. Allen, MD, PhD,** Dr. Edwin Stone sponsor.....3
Molecular Characterization And Ophthalmic Investigation Of Type 2A Von Hippel-Lindau (VHL) Disease

8:45 **Zuleika Ghodsi, MD,** Dr. Robert Folberg sponsor 4
Inflammatory Conjunctival Nevi

9:00 **Kristie K. Shappell, MD**, Drs. Edwin Stone & Gregory Hageman sponsors.....5
Retinopathy In The Koletsky Rat: The Effect Of Hypertension

9:15 **Lynnette M. Watkins, MD,** Drs. Keith Carter & Jeffrey Nerad sponsors 6
Metastatic Tumors Of The Extraocular Muscles

9:30 **Ekaterini C. Karatza, MD,** Drs. James Folk & Edwin Stone sponsosr.....7
Linkage Analysis Of Lattice Degeneration Of The Retina And Assessment Of Genetic Heterogenicity

9:45 **Robert A. Honkanen, MD,** Drs. Wallace Alward & Young Kwon, sponsors.....8
Clinical Features Of A Family With A Forkhead Transcription Factor (Fkhl7) Mutation.

10:00 **Andrew J. Lotery, MD,** Dr. Edwin Stone sponsor.....9
A Single Mutation Is Responsible For Malattia Leventinese (Autosomal Dominant Radial Drusen) And Doyne Honeycomb Retinal Dystrophy

10:15 **Mina M. Chung, MD,** Dr. Culver Boldt, ...10
Confocal Indocyanine Green (Icg) Angiography Of Atypical Choroidal Nevi: Evaluation Of Microcirculation Patterns

10:30 **BREAK**

11:00 **Sung-Pyo Hong, MD,** Drs. Wallace Alward, & Young Kwon sponsors,.....11
Correlation Of Visual Field Threshold Sensitivity And Peripapillary Nerve Fiber Layer Thickness As Measured By Scanning Laser Polarimetry

11:15 **Christian L. Hess MD,** Dr. Stephen Russell sponsor.....12
Peripheral Cryotherapy of Subfoveal Choroidal Neovascularization Associated with Age-Related Macular Degeneration

RESIDENT/FELLOW RESEARCH DAY
SCHEDULE OF EVENTS

SATURDAY, May 1, 1999

To Be Presented at Morning Rounds

The Clinical Significance Of HLA (Human Leukocyte Antigen) Antibodies In High Risk Corneal Transplantation

Bordewick D., Brown J., Mathers W., Sutphin J., Goeken N., Wollenzien J.

Purpose: This study was designed to investigate if the presence, or development of HLA specific antibodies are predictive of corneal graft rejection in high risk pateints. **Methods**: Fifty-one high risk patients were involved in this prospective study. A high risk cornea was defined as two or more quadrants of stromal vascularization (n=12) or previous graft failure (n=39). HLA antibodies were drawn at the following times: prior to penetrating keratoplasty (PK), aproximately one month, six months and one year following PK. Pateints were followed closely for graft failure or rejection. **Results**: HLA specific IgG was found in the serum of nine patients at baseline or during the first year following PK. The patients in this group experienced: two graft rejections (2/9) 15%, six failures (6/9) 67%, and one clear graft (1/9) 11%. HLA specific IgM was found in the serum of twelve patients. This group experienced: two rejections (2/12) 17%, six failures (6/12) 50%, and five clear grafts (5/12) 43%. Six patients demonstrated IgM at baseline or early following PK with subsequent conversion to IgG. The patients in this group all progressed to graft failure (6/6) 100%. Thirty-seven patients did not demonstrate antibodies at any point in the study. There was one graft failure and one rejection in this group. Thirty-five grafts remained clear (94%). **Conclusions**: Patients who did not demonstrate HLA specific antibody at any point in the study had excellent graft survival. Patients with pre-existing antibody, and those who developed antibody had a high rate of graft failure. Conversion from IgM to IgG appears to have a particularly poor prognosis for graft survival. HlA antibody studies may be clinically useful in predicting which corneal grafts are likely to fail and may help guide treatment decisions.

"Pupil Perimetry": The Stimulus-Response Function Of The Pupil Light Reflex Across The Visual Field

Stacy Thompson, M.D. and Randy Kardon, M.D., Ph.D.

Purpose: The purpose of this project was to understand how the pupil light reflex varies as a function of stimulus light intensity at different retinal locations. This information was used to estimate the number of pupil receptor "channels" and the sensitivity of these input channels across the retina. **Methods:** For this project, a computerized infrared pupillometer was used to record the timing and amplitude of the pupillary light reflex as a function of varying stimulus intensity at 10 different perimetric locations along the horizontal meridian in 9 normal subjects. Ten pupil light refexes were averaged for each of 8 stimulus intensities at each location.

Pupil responses were then plotted as log stimulus intensity on the "X" axis versus contraction amplitude on the "Y" axis to yield a "stimulus-response function" of the pupil light reflex. A Naka-Rushton nonlinear curve was fit to the response function at each location. The shape of the Naka-Rushton sigmoid curve can be defined by 3 parameters: "Rmax" which is the maximum contraction amplitude predicted (proportional to the number of receptive channels); "Log k" which is the intensity where 1/2 Rmax is reached (proportional to the sensitivity of each channel); and "n" which is the slope of the response function of the channel. These 3 parameters were then plotted across the horizontal meridian to compare the properties of the pupil light reflex channels in central and peripheral retinal locations. **Results:** The stimulus-response function of the pupil light reflex fit the Naka-Rushton function well at all retinal locations. The sensitivity (log k parameter) decreased as the stimulus light was moved from the fovea to the periphery of the retina. The most sensitive location was always the fovea, but the drop in sensitivity away from the fovea varied in different individuals. The density of pupil input channels (Rmax parameter) was also greatest at the fovea and decreased as the stimulus was moved to more peripheral retinal locations. At the fovea the slope of the function (n parameter) was more shallow. Therefore, the foveal location had a much different shape of response function compared to peripheral locations. The broad shallow slope of the foveal response function may imply that the pupillomotor input channels are organized differently at this location. **Conclusion:** This study has provided new information on the physiologic properties of the retinal input channels for the pupil light reflex. Characterizing the pupil response function using the Naka-Rushton equation can help us understand how the pupillary input channels are organized across the field with respect to sensitivity and density. The application of this technique to the study of damaged locations may allow us to better understand how disease causes damage in different retinal locations. This approach will allow us to characterize when disease is causing loss of channels (death of neurons) versus loss in sensitivity of the channel (dysfunction without neuronal death).

Molecular Characterization And Ophthalmic Investigation Of Type 2A Von Hippel-Lindau (VHL) Disease.

R.C. Allen, A.R. Webster, C.M. Taylor, J.L. Andorf, E.M. Stone. University of Iowa.

Purpose: Von Hippel-Lindau disease (VHL) is a dominantly inherited cancer syndrome causing susceptibility to ocular and central nervous system vascular tumors, renal carcinoma, and pheochromocytoma. At least three clinical/genetic subtypes of the disease have been recognized. The purpose of this study was to determine the molecular pathology as well as the prevalence and severity of ocular involvement in a family affected with VHL type 2A. **Methods:** A longitudinal clinical study and DNA analysis of 24 affected and at-risk VHL family members was performed. **Results:** VHL type 2A co-segregated in 14 affected patients with a T505C transition (Tyr98His) in exon 1 of the VHL gene. Two asymptomatic gene-carriers were subsequently identified. Seventy-five percent (12/16) of the gene-carriers had one or more ocular angiomas, being bilateral in 7/16. The mean number of ocular angiomas per gene-carrier was 3.3 (range 0-22). Six eyes in 16 gene-carriers had optic disc angiomas, 5/16 gene-carriers had lost vision due to angiomatosis. Two patients had NLP vision in at least one eye, both having presented at a relatively young age (<=20 years). The prevalence of cerebellar hemangioblastoma was 4/16, pheochromocytoma 11/16, and renal carcinoma 0/16. **Conclusions:** i) The patients with this mutation show a low susceptibility to renal carcinoma, and, when taken together with previously reported data for this specific mutation, is similar to the 'population risk' for sporadic renal disease. ii) The prevalence and severity of ocular angiomatosis in VHL type 2A does not significantly differ from the other subtypes of VHL. iii) This study exemplifies a) how a careful clinical assessment can increase the efficiency of mutation analysis, and b) how a precise molecular diagnosis can provide more accurate prognostic information for affected patients.

Inflammatory Conjunctival Nevi

Zuleika Ghodsi, M.D., Robert Folberg, M. D.

Purpose: Inflammatory conjunctival nevi are a prevalent problem for the Ophthalmologist. They are often misdiagnosed due to their appearance and rapid growth. The goal of this research project is to look at the epidemiology, clinical features, and pathology of inflammatory conjunctival nevi. **Methods**: A retrospective clinicopathological study of all specimens of conjunctival nevi examined between the years of 1987-1997 at the University of Iowa Ocular Pathology Laboratory will be performed. **Results:** 205 Conjunctival Nevi were biopsied between the years of 1987-1996. At this time, I am in the process of reviewing the clinical and pathologic reports for these cases. I will specifically be looking at the cases of inflammatory conjunctival nevi. There are no other results available at this time.

The results of this project will be combined with research being performed at the Department of Ophthalmology at the Hadassah-Hebrew University Medical School in Jerusalem, Israel.

Retinopathy In The Koletsky Rat: The Effect Of Hypertension

K.K. Shappell, W.G. Haynes, D. Morgan, J. Mitchell, E.M. Stone, G.S. Hageman, A.L. Mark

Purpose: The obese Koletsky rat is an inbred strain of spontaneous hypertensive rats. They are phenotypically obese, spontaneously hyperinsulinemic and hypertensive. Though others have proposed them as a model for non-insulin dependent diabetic retinopathy, pilot experiments demonstrated that the retinopathy was present in their lean counterparts. The lean Koletsky rat is used as a control animal as it does not exhibit hyperinsulinemia but is hypertensive. We proposed to show that the retinal degeneration observed in Koletsky rats is not secondary to hypertension. **Methods:** Male and female lean Koletsky rats and spontaneously hypertensive rats (SHR) were used as subjects. All animals were implanted with telemetry devices to allow for assessment of conscious blood pressure measurements. The animals were divided into three groups. The first was lean Koletsky rats given tap water, the second was SHR rats given tap water, and the third was SHR rats given tap water with variable concentrations of L-NAME (a nitric oxide synthase inhibitor). The L-NAME was titrated to keep the blood pressure of the SHR rats equivalent to the blood pressure which developed spontaneously in the Koletsky lean group. Animals were sacrificed at 5 months of age and eyes were harvested for light microscopic evaluation of the retina. **Results:** Loss of photoreceptor segments with preservation of the inner nuclear layer and beyond was evident on light microscopy in all Koletsky lean rats. No retinal abnormalities were noted in the SHR rats receiving tap water. In the SHR rats receiving L-NAME, one rat had abnormal appearing photoreceptors but all layers were intact and the remainder of the animals showed no evidence of outer retinal abnormalities. After a Bartlett's test for homogeneity of variances, a One-Way Analysis of Variance (ANOVA) was used to compare the mean arterial pressures (MAP) between groups. There was no statistically significant difference between the MAP of the SHR rats that received L-NAME and the Koletsky lean rats. There was a statistically significant difference between the MAP of SHR rats receiving L-NAME and those receiving tap water ($p<0.001$). Additionally, there was a statistically significant difference between the MAP of SHR rats receiving tap water and the Koletsky lean rats ($p<0.01$). **Conclusions:** The retinal degeneration present in the Koletsky rat is not secondary to hypertension. Our previous study showed it was not secondary to hyperinsulinemia associated with non-insulin dependent diabetes. The retinal degeneration is most likely autosomal recessive with the degeneration occuring between one week and five months. The next experiment will pursue the inheritance of the degeneration.

Metastatic Tumors of the Extraocular Muscles

Lynnette M. Watkins, MD, Keith D. Carter, MD, Jeffrey A. Nerad, MD

Purpose: To delineate the clinical prognostic value of metastatic tumor presentation to the extraocular muscles. This study will also highlight the types of tumor primaries that metastasize to the extraocular muscles, time of presentation of these metastases after diagnosis of primary tumor, and if concurrent metastases were present. This study will also discuss mean time to death after diagnosis of muscle metastases. **Methods**: The database of orbital oncology patients at the University of Iowa Hospitals and Clinics Department of Ophthalmology, Oculoplastics Division was reviewed in a retrospective fashion. Fourteen patients were identified as having orbital lesions present in one or more of the seven extraocular muscles by echographic or computed tomographic imaging. Identification of tumor metastases was completed after muscle biopsy via orbitotomy approach and histopathologic (and immunopathologic) examination. **Results:** Tumor primaries ranged from breast carcinoma (four patients), to rhabdomyosarcoma (two patients). Lymphoma, melanoma and undifferentiated sarcomas were also identified. Three of fourteen patients had involvement of multiple muscles. Of the fourteen patients who presented with neoplasms metastatic to the extraocular muscles, 11 (78%) were deceased. Mean time from tumor presentation to death was 10 months (range- 1- 40 months). Six of fourteen patients (43%) had other sites of metastatic disease present when the muscle metastases were diagnosed. These muscle metastases were the initial presentation of the disease in five of the fourteen patients (36%). **Conclusions:** Metastatic disease to the extraocular muscles portends a poor prognosis. Referral to a hematologist-oncologist for further work-up and palliative measures is indicated.

Linkage Analysis Of Lattice Degeneration Of The Retina And Assessment Of Genetic Heterogenicity

E.C. Karatza, MD, J.C. Folk, MD, E.M. Stone, MD, PhD

Background: Rhegmatogenous retinal detachment (RD) remains a significant cause of legal blindness and visual impairment throughout the world. Lattice degeneration of the retina is the most commonly recognized peripheral vitreoretinal abnormality known to predispose to rhegmatogenous RD. Approximately 30% of patients with retinal detachment also have lattice degeneration. A few studies suggest that a genetic predisposition may play a role in lattice degeneration. A subset of patients with familial retinal detachment associated with lattice degeneration appear to have an autosomal dominant inheritance pattern (1). However, the exact molecular mechanisms are not known, and consensus cannot be reached as to its mode of transmission. It is more likely to be a genetically heterogeneous disease based on reported prevalence data among first-degree relatives of patients with this condition (2). **Purpose:** To determine the chromosomal location of a gene responsible for lattice degeneration as a first step towards identification of a gene involved in this disease. **Materials & Methods: a) clinical evaluation:** We have obtained permission to perform this study from the Human Subjects Review Committee (Committee A) at UIHC. We will identify and invite large families with lattice degeneration for a dilated fundus examination and blood draw. **b) genotyping:** after obtaining informed consent, blood samples will be drawn and genomic DNA will be extracted using standard protocols (3) from members of 2-3 large families with the disease. Polymorphic DNA markers will be used for linkage analysis. **c) statistical analysis:** Linkage will be tested using the LOD score method (4). **Main outcomes:** We will determine the prevalence of lattice degeneration among first-degree relatives of the probands. The availability of phenotypic and genetic information from multiple family members will allow us to better characterize the likely mode of inheritance of lattice degeneration. Positional identification of the gene to a particular chromosomal region may eventually permit initiation of candidate gene testing for identification of the disease-causing gene(s) as well as characterization of point mutations. In the future, a combination of mutation analysis of specific genes and linkage analysis may enable the exact molecular cause of lattice degeneration to be determined. The eventual identification of specific disease-causing mutations, could improve the effectiveness of an ophthalmoscopic screening program for patients at risk as well as allow prophylactic treatment of patients at highest risk. **Conclusions:** Prevention of retinal detachment is a worthy goal of substantial benefit to both society and patients at risk. It is hoped that studies of the gene(s) involved in lattice degeneration of the retina will potentially enhance the pre-clinical diagnosis and effective management of affected individuals.

References:
1. Byer NE. (1978). Lattice degeneration of the retina. Survey Ophthalmol 23, 213
2. Murakami F, Ohba N. (1982) Genetics of lattice degeneration of the retina. Ophthalmologica 185, 136-140
3. Grimberg J., et al.(1989). A simple and efficient non-organic procedure for the isolation of genomic DNA from blood. Nucleic Acids Res. 17, 390
4. Morton NE. (1955). Sequential tests for the detection of linkage. Am J Hum Genetics 7, 277-318

Clinical Features Of A Family With A Forkhead Transcription Factor (Fkhl7)Mutation.

R.A. Honkanen, D. Nishimura, Y.H. Kwon, E.M. Stone, V. Sheffield, W.L.M.Alward, Department. of Ophthalmology and Visual Sciences, University of Iowa, Iowa City

Purpose: A number of developmental anterior segment disorders associated with glaucoma (GL) have been mapped to chromosome locus 6p25. Recently, mutations of the forkhead transcription factor gene (FKHL7) were shown to cause a spectrum of anterior segment anomalies. Until now, there has been no description in the literature of the spectrum of defects that can result from a single mutation in this gene. We clinically characterize the ocular and systemic manifestions that result from a single mutation of FKHL7. **Methods:** We obtained histories and clinical data on 26 members of a multigeneration family. Blood samples were obtained from 16 members and screened for the presence of FKHL7 mutations using an ARMS assay with confirmation of mutations by direct DNA sequencing. **Results:** A single mutation causing a T to C transition in FKHL7 was found in 6 members of the family. This mutation caused a change of a conserved amino acid at position 112 of the protein. Five of these six patients had clinical eye exams and all demonstrated anomalies of anterior segment. Patient II-3 had only a mild form of Axenfeld's anomaly (AA). There was a prominent Schwalbe's line (SL) with numerous small iris processes (IP). There was no iris hypoplasia (IH), GL, or systemic anomaly on exam. Patient III-1 had Rieger's Anomaly (RA) with a prominent SL, IP, and IH. The patient developed congenital GL, but had no systemic anomalies. Patient III-3 had Rieger's Syndrome (RS) with only minimal eye findings. There was a prominent SL with IP, but no IH or GL. The patient had hypodontia and mild maxillary hypoplasia. Patient IV-1 had Peter's anomaly at birth as well as findings consistent with AA. There is a prominent SLwith numerous broad IP. No GL, IH, or systemic anomalies were found. A cornealtransplant was performed with histopathology confirming central absence of Descemet's membrane and corneal endothelium. Patient IV-2 had RS. There was a prominent SL with IP but no IH or GL. The patient had abnormal dentition with mild microdontia. **Conclusions:** This report demonstrates how a single FKHL7 mutation can cause multiple abnormalities of varying severity in the anterior segment. Coexistent GL and systemic findings are also found with variable expression. To date, no prior description of ocularpathology due to a single mutation of the FKHL7 gene exists in the literature.

A Single Mutation Is Responsible For Malattia Leventinese (Autosomal Dominant Radial Drusen) And Doyne Honeycomb Retinal Dystrophy

Andrew J. Lotery, Kimberlie Vandenburgh, Val C. Sheffield, Edwin M. Stone

Purpose. To identify the genetic cause of Malattia Leventinese (ML) and Doyne's Honeycomb retinal dystrophy (DHRD) and assess the role of this gene in age related macular degeneration. **Methods.** Families with ML and DHRD were ascertained from Europe, America and Australia. Linkage analysis was used to narrow the critical gene interval for ML and DHRD and candidate genes within the interval were prioritized for mutation analysis by computer database analysis. Genomic organization of candidate genes was determined by a combination of long range pcr, vectorette pcr and direct BAC sequencing. Once intervening intronic sequence was established, candidate genes were screened for mutations by SSCP and direct DNA sequencing. **Results.** Haplotype sharing among families affected with the chromosome 2p-linked drusen phenotypes Malattia Leventinese and Doyne Honeycomb Retinal Dystrophy allowed narrowing of the critical gene interval. A specific gene was shown to map to the narrowest disease interval by STS content mapping. This gene was considered a good candidate on the basis of functional and expression data. Affected individuals from all 39 families with ML or DHRD included in this study were found to harbor a single mutation in this gene. This change was not present in 477 control individuals or in 494 patients with age-related macular degeneration. **Conclusions.** The genetic cause of ML and DHRD has been identified. This result ends a 100 years of debate on whether these two conditions are allelic variants of the same disorder. All cases of ML and DHRD are due to the same mutation and may be caused by a single founder effect. This work will aid in the development of an animal model for drusen, as well as in the identification of other macular degeneration genes.

Confocal Indocyanine Green (Icg) Angiography Of Atypical Choroidal Nevi: Evaluation Of Microcirculation Patterns

Mina M. Chung, M.D., H. Culver Boldt, M.D., Robert Folberg, M.D.

Purpose: The histopathologic presence of high risk choroidal microcirculation patterns in choroidal melanoma has been associated with an increased risk of mortality from metastatic disease. High risk patterns are present in the most aggressive melanomas, but they are not seen in relatively indolent melanomas or choroidal nevi. Imaging these patterns prior to enucleation may provide a non-invasive substitute for biopsy to establish the relative risk of metastatsis in patients. Recently, clinicopathologic correlation of microcirculatory patterns has been demontrated using confocal ICG angiography. We hypothesize that high risk microcirculatory patterns should not be present in atypical choroidal nevi which have been stable clinically, and therefore should not be detectable by confocal ICG imaging. **Methods**: 12 patients with choroidal nevi with atypical features such as diameter > 6 mm, elevation > 1 mm, irregular color, orange pigmentation, and subretinal fluid, were examined by indirect ophthalmoscopy, standardized echography and confocal ICG angiography. Visual acuity, lesion size, location, and clinical features, as well as internal reflectivity and vascularity, were recorded. **Results**: The mean follow-up time ws 26.5 months, with a range of 3 to 124 months. Confocal ICG angiography revealed high risk patterns in only 1 of 12 eyes. In this case, a small area of vascular loops was demonstrated in an amelanotic, 10 x 7 x 2 lesion which has been stable in size for 42 months. **Conclusions**: Confocal ICG angiography may be a useful, non-invasive way to identify high risk features of atypical melanocytic lesions of the choroid.

Correlation Of Visual Field Threshold Sensitivity And Peripapillary Nerve Fiber Layer Thickness As Measured By Scanning Laser Polarimetry

S. Hong, R.A. Honkanen, W.L.M. Alward, Y.H. Kwon, Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA

Purpose: To correlate visual field threshold sensitivity and peripapillary Nerve Fiber Layer Thickness (NFLT) as measured by a scanning laser polarimeter (GDx, Laser Diagnostic Technologies Inc., San Diego, CA). **Methods:** GDx was performed on 72 eyes of 43 patients with ocular hypertension, glaucoma suspicion, or glaucoma who visited the University Glaucoma Service during 11-12/97. From these, 54 eyes of 34 patients were chosen based on the criteria of 1) vision of □ 20/50, 2) absence of corneal disease, 3) reliable Humphrey visual fields performed within 6 months of the GDx measurement. We plotted Mean visual field Sensitivity (MS in dB) as a function of average peripapillary NFLT (Ellipse Average in μ) for the entire field, and superior and inferior hemifields. We also selected those with asymmetric hemifields (> 20% difference between superior and inferior hemifield MS, n=12) and correlated visual field asymmetry with that of the corresponding NFLT. **Results:** The visual field MS showed a non-linear relationship to the NFLT. The MS declined relatively little with decreasing NFLT until approximately 60μ; below 60μ, the MS declined rapidly. For those eyes with asymmetric hemifields, the asymmetry index of the MS (calculated as a proportion of one hemifield over the entire field MS) correlated positively with that of the corresponding NFLT ($r=0.55$). **Conclusions:** There is a non-linear relationship between visual field threshold sensitivity and peripapillary NFLT. The results suggest NFLT can decrease significantly before appreciable change in visual field threshold sensitivity occurs. For those with asymmetric hemifields, there is a positive correlation with corresponding NFLT asymmetry.

Peripheral Cryotherapy Of Subfoveal Choroidal Neovascularization Associated With Age-Related Macular Degeneration

Christian L. Hess, M.D., Stephen R. Russell, M.D.

Purpose: To determine whether cryopexy ablation of the equatorial/anterior choroid may ameliorate or suppress choroidal neovascularization (CNV) in age-related macular degeneration (AMD). **Methods:** Five individuals, 54 years of age or older, were prospectively identified who had subfoveal CNV deemed untreatable by the Macular Photocoagulation Study guidelines and had visual acuity in the affected eye of 20/64 or worse. Affected eyes were treated with 60 to 80 cryotherapy freezes in a scatter pattern throughout the equatorial and anterior fundus. Pre- and post-treatment evaluation included: MPS protocol refraction, fundus examination and photos, fluorescein angiography, Goldmann visual fields, and a subjective visual quality assessment (VFQ-25). Evaluation endpoints are to be assessed up to one year post-treatment. **Results:** Four of five individuals have completed at least 6 weeks of follow-up. Two of the five were noted to have iatrogenic pupillary mydriasis from the cryotherapy treatment. Treatment has been, otherwise, well tolerated. In two of three patients with 6 months of follow-up, visual acuity has remained stable (20/160→20/160 and 20/100→$20/125^{+2}$) and declined in one ($20/100^{-2}$→$20/320^{+1}$). In three patients, fluorescein angiography at 6 months demonstrated CNV with reduced hyperfluorescence but without change in size of the classic component. In 2 cases, the associated occult CNV component enlarged. **Conclusions:** In this pilot trial, no acute post-treatment exacerbation of the CNV leakage, CNV enlargement, or visual loss was noted. Given the frequency of post-treatment mydriasis and the lack of convincing anatomical or visual effect, we believe further enrollment in this protocol is not warranted. These preliminary data suggest cryotherapy ablation of the anterior and peripheral choroid, in the region of the equatorial choroidal watershed, does not ameliorate or suppress macular CNV in AMD.

Decision Management System For Analysis Of Cataract Extraction Surgery Outcomes

Brown SM, Oetting T

Purpose: To set up a decision management system to analyze outcomes of cataract extraction surgeries performed at the Iowa City Veteran's Administration Medical Center. **Method:** The project consists of two main phases: 1) system planning, design and implementation and 2) outcome analysis. System planning, design and implementation consists of system planning, information planning, database and query/report design, system development and testing, user procedures and system modification and maintenance. Outcome analysis includes but is not limited to: visual acuity outcomes over time, visual acuity outcomes versus surgery time, complication rates, refractive outcomes and patient's ability to perform specific tasks pre- and post-surgery. **Results:** To be presented. **Conclusions:** Pending. The system is to be used to assist in making decisions to improve quality of care and cost effectiveness.

Pigment Dispersion Syndrome (PDS): Inheritance And Associated Characteristics

A.L. Lusk, W.L.M. Alward

Purpose: The Pigment Dispersion Syndrome (PDS) predisposes affected individuals to Pigmentary Glaucoma (PG). The purpose of this study is to analyze numerous characteristics for this condition and evaluate the inheritance pattern. In the current literature, a small number of authors have attempted to characterize the inheritance pattern of PDS without complete success. At this time, no large-scale analysis has yet been attempted. The largest published study, *Archives of Ophthalmology, Vol. 115, March 1997,* investigated inheritance patterns in 54 members of 4 families, 28 of whom showed clinical evidence of PDS. **Method:** We evaluated patients, who have been diagnosed with PDS, and their first-degree family members. Evaluation included routine demographics, Krukenberg spindles (KS), iris color, transillumination defects (TID) and contour, refractive error (spherical equivalent and cylinder), keratometry (K), anterior chamber depth (ACD), lens thickness, axial eye length (AEL), angle pigment, Humphrey visual field mean defect (HVF MD) and corrected pattern standard deviation (HVF CPSD), and cup to disc ratios (C/D). We graded the presence of Krukenberg spindles on the following scale: 0 = none, 1 = few flecks, 2 = subtle spindles, 3 = dense spindle, and 4 = diffuse pigment. We also graded iris contour as follows: -2 = marked backbow, -1 = mild backbow, 0 = flat, 1 = mild convex, and 2 = marked convex. Patients on pilocarpine were documented as were patients status post peripheral iridectomy. We graded angle pigment on a scale of 0-4. When possible, pedigrees were constructed. Blood was obtained from all affected members as well as from unaffected members of large pedigrees. **Results:** To be presented.

Music Therapy: An Alternative Pain Management Technique For Panretinal Photocoagulation

Dr. Amin Kherani, MD, Dr. Stephen Russell, MD, Dr. Mina Chung, MD

Many patients tolerate panretinal photocoagulation (PRP) under topical anesthesia with varying levels of discomfort. The purpose of this study is to evaluate whether the application of an additional pain management technique, *auditory distraction*, may reduce subjective discomfort associated with PRP. Prior to treatment, the protocol and participation will be explained to each patient. Patients will then be randomized to one of two groups. Group 1 patients will receive PRP while listening to music of their choice. Group 2 patients will receive PRP without music. All patients will receive conventional topical anesthesia in the form of eye drops. Immediately following the PRP treatment, each patient will be asked to complete a survey addressing their pain, anxiety and comfort. This survey will attempt to quantify these subjective factors and these results will yield information regarding the effect of music on patient's pain during retinal photocoagulation.

Topographical Analysis Of Centration Following Excimer Laser Photorefractive Keratectomy: A Comparison Of The Orbscan And TMS Topograhy System.

T. Hunter Newsom, MD, John E. Sutphin, MD

Purpose: To evaluate the ablation centration after photorefractive keratectomy (PRK) for myopia using the Orbscan and TMS topography systems. Centration using each system will be compared and associated with preoperative refractive error, best corrected visual acuity (BCVA), best uncorrected visual acuity (BUVA), contrast sensitivity, and subjective complaints of glare or halos. A comparison using the Novatec and Summit excimer laser will also be done using the same parameters. **Methods:** Preoperative and postoperative corneal topography of all patients who underwent PRK at the University of Iowa were evaluated using the Orbscan and TMS systems. Each patient was identified as to which laser system was used (Summit or Novatec). The location of the center of ablation was assessed using the postoperative map as well as the preoperative and postoperative difference map. Ablation zone decentration was measured relative to the patients fixation and pupil center. **Results:** All the data from the Orbscan has been collected on all the patients who have undergone PRK using the Summit and Novatec excimer laser. We are currently obtaining the comparative centration data from the TMS.

The Clinical Significance Of "The Little Red Disc"

Annie Chang, James Corbett, Randy Kardon

Purpose: There are some patients who have been referred evaluation of anomalous appearing little red discs in the setting of a routine examination or in the setting of a specific complaint. This study will better characterize this finding and to evaluate the significance of little red discs and determine whether it is associated with poor vision, RAPD, color defects, or visual field abnormalities. **Methods:** The records and photographs of all patients with a diagnosis of little red discs or anomalous discs were examined. The criterion for selection were based on discs photographs with the following characteristics: 1) absence or very small cups 2) red appearing discs, and 3) small appearing discs in relation to vessel caliber and area. The disc-macula to disc diameter ratio will be determined if possible for better characterization of disc size. **Results:** The data is currently being compiled. The reasons for medical attention, the incidence of bilateral versus unilateral little red discs, the frequently distribution of visual acuity, and any correlation between visual field defects will be presented. **Conclusions:** to be presented

Long-Term Follow-Up Of Surgical Treatment Of Duane's Syndrome

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Purpose: To report the long-term results of a large series of patients undergoing treatment for Duane's Syndrome. **Methods:** We retrospectively reviewed charts for all patients with Duane's Syndrome undergoing strabismus surgery at the University of Iowa between August 1972 and November 1998. We identified those patients who were treated with appropriate horizontal muscle recession in order to relieve an abnormal head position (AHP) or a significant tropia in primary position. Quantity of recession varied with the angle of deviation in forced primary position, versions and ductions, and intraoperative forced ductions. Elimination of AHP was used as a criterion for success. **Results:** Sixty-two patients were treated with medial or lateral rectus recession depending on whether the patient was esotropic or exotropic in primary. Average follow-up was 3.7 years. Of those patients that had a pre-operative AHP, 61% achieved excellent post-op results (<=5° AHP) which increased to 93% when those with a post-op alignment of <=15° AHP were included. Only three patients went on to have a second procedure for noticeable residual AHP, two patients in the unilateral Type II group and one in the bilateral combined Type I and II group. **Conclusion:** Long-term success (good to excellent results) of recession of appropriate horizontal muscles was achieved in 93% of patients. This method offers a simple and effective surgical option for eliminating AHP and is our treatment of choice in patients with Duane's Syndrome.

Diagnosis Of Herpes Simplex Keratitis With The Polymerase Chain Reaction

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Objective: At present, the diagnosis of herpes simplex (HSV) keratitis is predominantly made on clinical findings, with viral culture and immunoassay used to detect atypical presentations. Several studies have shown the efficacy of using the polymerase chain reaction (PCR) to identify HSV DNA from tear samples in patients with epithelial disease. The objective of the study is to validate the use of HSV PCR on tear samples using an established assay and make this test available for clinical and research use. **Methods:** Tear samples will be collected from patients with HSV keratitis based on a typical appearance on clinical exam (dendrites, etc). When possible, viral culture will be obtained to confirm the diagnosis. Samples will undergo PCR for HSV using an established assay at the State Hygenic Lab. Samples will also be collected from patients with other viral (e.g. HZO), bacterial, fungal, protozoal, and non-infectious conditions affecting the corneal epithelium to asses specificity. Once a sufficient number of positive samples have been obtained to validate the test, it will be offered through the State Hygenic Lab. **Results:** Thus far only 10 samples have been run with additional samples currently being processed. Two samples from patients with clinically evident HSV keratitis have been positive, one with a postive culture to support the diagnosis. Eight other patient with other diagnoses, including resolved HSV keratitis were negative. Sample collection is ongoing. **Conclusion:** Based on a limited number of samples the HSV PCR assay shows good correlation with clinically diagnosed HSV keratitis and good specificity. Additional positive samples are needed to validate the assay for tear samples before it is offered as a test through the State Hygenic Lab. The expansion of the assay to other tissues (i.e. corneal scraping, vitreous, aqueous) and for the detection of viral RNA remains a future goal.

Carboxyamido-Triazole Is A Potent Inhibitor Of Retinal Neovascularization

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Introduction: Pathological ocular neovascularization leads to irreversible visual loss in many conditions such as age related macular degeneration, diabetic retinopathy, retinopathy of prematurity, and retinal vein occlusions. This study was performed to characterize the effects of an anti-metastatic and anti-angiogenic molecule, Carboxyamido-triazole (CAI), upon retinal neovascularization in a mouse model. **Methods:** Neonatal C57BL/6J mice were subjected to 75-85% oxygen from postnatal day 7 through 12 (PND 7 - 12), and then oxygen concentration was abruptly decreased to 21%, room air. CAI 100 mg/kg or vehicle control (PEG-400) was given daily on PND 14 - 16, and mice were then sacrificed on PND-17 for Group A. CAI 100 mg/kg or vehicle control (PEG-400) was given daily on PND 17 - 19, and mice were then sacrificed on PND-20 for Group B. Eyes were enucleated, fixed and subject to light microscopy. Some animals were perfused with fluorescein-dextran prior to enucleation. **Results:** A 91% inhibition of neovascular cell nuclei on light microscopy was observed for mice treated with CAI in Group A, $p < 0.0001$. Fluorescein-perfusion demonstrated a similar profound inhibition of neovascular fronds for CAI-treated mice in Group A. In Group B, a reduction of neovascular cell nuclei was observed on light microscopy for animals treated with CAI, and fluorescein perfusion suggested that CAI induced regression of neovascular fronds. Similar amounts of posterior retinal ischemia were observed in mice treated with either CAI or PEG-400 at both PND-17 and PND-20. **Conclusions:** CAI demonstrated potent angiogenic inhibition in this mouse hyperoxia model of retinal neovascularization. CAI almost completely abolished retinal neovascularization in Group A, and neovascular fronds appeared to involute after treatment with CAI in Group B. This data demonstrates that CAI can both inhibit the formation of abnormal neovascular structures, and cause previously formed neovascular fronds to regress.

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Functional Differences Between The Midbrain And Cortical Pupillary Light Reflex Pathway: Effect Of Stimulus Size

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Purpose: To differentiate two functional pathways of the pupil light reflex; the classical midbrain pathway and a cortical, postgeniculate pathway. It is hypothesized that the midbrain pathway is favored using larger sized light stimuli (20 degrees in diameter) and the cortical pathway is favored using smaller perimetric stimuli (4 degrees in diameter). **Methods:** Two groups of patients with homonymous field loss were studied; (1)patients with isolated postgeniculate damage and (2) patients with isolated pregeniculate damage to the optic tract . The pupillary contraction amplitude was measured as a function of stimulus intensity and size in the seeing and non-seeing hemifields using computerized infrared pupillometry. The decibel sensitivity difference between the seeing and non-seeing hemifields in each eye were calculated for the large and small sized stimuli in the pre and postgeniculate defects. **Results:** In postgeniculate damage, the smaller sized target revealed a greater pupil deficit between the seeing and non-seeing hemifields compared to the larger sized targets. The larger sized targets showed much less deficit between the seeing and non-seeing hemifields compared to the results in optic tract lesions. **Conclusion:** The cortical pathway for the pupil light reflex shows almost complete absence of the pupil light reflex when small, 4 degree diameter light stimuli are used. Larger stimuli (20 degree diameter) that are placed well within the area of visual field loss do not show nearly as much deficit as the same stimuli placed in a comparable area of field loss in patients with pregeniculate field loss due to an optic tract lesion. Pupil light reflexes from small sized stimuli seem to be mediated by the cortical pathway, whereas the midbrain pathway seems to have more influence on pupil light reflexes elicited by larger sized stimuli. This result may correspond to the receptive field size of neurons mediating the two pathways.

Sebaceous Cell Adenocarcinoma Of The Eye

John Kinder MD, Jeff Nerad MD, Keith Carter MD

Purpose: Sebaceous adenocarcinoma is a rare but potentially fatal epithelial tumor of the eyelid which is often misdiagnosed on initial presentation due to its similar appearance to other ocular disorders such as chalazion and blepharoconjunctivitis. If the tumor is diagnosed early, it can often be treated with local excision without the need for enucleation. This study will analyze the most common clinical features of sebaceous cell adenocarcinoma and determine the long term prognosis with regards to metastasis and mortality in relationship to type of treatment. **Methods:** The design of this study is a retrospective chart review. Inclusion criteria include all those patients with biopsy proven sebaceous carcinoma listed in the state Oncology Registry and treated here at the UIHC.

Microcirculatory Networks In Advanced Sebaceous Carcinoma

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Purpose: Microcirculatory networks have been identified in uveal, conjunctival and cutaneous melanoma, but have not been described previously in carcinomas. In advanced sebaceous carcinoma, large lobules of tumors may form that do not contain endothelial-lined blood vessels. This study was designed to determine if PAS-positive loops and networks form in advanced sebaceous carcinomas. **Methods:** Histologic sections of advanced sebaceous carcinoma were stained with hematoxylin-eosin, PAS without hematoxylin counterstaining, and for Factor VIII related antigen (FAR) and CD31. **Results:** In advanced sebaceous carcinoma, endothelial-lined blood vessels, positive for FAR and CD31 observed at the periphery of the tumor and in fibrous septa that divide the tumors into lobules. These endothelial lined vessels are not encountered within the lobules themselves. However, in advanced sebaceous carcinoma, we detected PAS-positive looping microcirculatory channels within the lobules. These channels consisted of tubules and sinusoids that were not lined by endothelial cells and which did not stain for either FAR or CD31. Some of these channels contained red blood cells, indicating a functional microcirculation to the interior of the tumor lobule. **Conclusions:** A patterned microcirculation identical to the loops and networks found in the uveal melanomas from patients at high risk for metastasis develops also in sebaceous carcinoma.

Rapamycin Inhibits Retinal Neovascularization

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Introduction: Ocular neovascularization is the final common pathway leading to visual loss in multiple ophthalmic disease processes. We examined the effects of Rapamycin, an recently developed analog of cyclosporin, on retinal neovascularization in a mouse model. Rapamycin is undergoing stage III clinical trials as a immunosuppressant in renal transplant recipients. Rapamycin is a potent inhibitor of cytokine and growth-factor-mediated cellular proliferation. Systemic Rapamycin prolonged corneal allograft survival and significantly reduced the incidence of neovascularization in a rat model of orthotopic allogenic penetrating keratoplasty. **Methods:** Neonatal mice were placed in 85% oxygen from postnatal day 7 through 12 and then returned to room air. Rapamycin 8 mg/kg or vehicle was given daily, or every other day, beginning day 14, and mice sacrificed on day 17 (Group A). A second cohort (Group B) received Rapamycin or vehicle daily (or on alternate days) beginning day 17. These mice were sacrificed on day 20. Eyes were immediately enucleated, fixed and examined under light microscopy. **Results:** Rapamycin treated mice exhibited a decrease in total number of neovascular cell nuclei (NCN) on light microscopy compared to control. 192 NCN/eye were present in control mice (n =2) while 54 NCN/eye (n=5) was present in the Rapamycin treated mice in Group A. In Group B, 173 NCN/eye (n=2) in the control group, and 64 NCN/eye (n=2) in the mice treated daily was observed. Mice treated with alternate day drug (n=2) had 128 NCN/eye. There was no significant change in mouse weight or behavior between the treated and control groups. **Conclusions:** In this pilot study, Rapamycin demonstrated a four fold inhibition of neovascular response. In Group B, Rapamycin appeared to cause a dose dependent involution of neovascular cell processes with treatment. This data indicates that Rapamycin has significant antiangiogenic properties with potentially low systemic toxicity for the treatment of neovascular diseases.

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