THE ABRIDGED AOS THESIS: A 50-YEAR SURVEY

By **Kirk R. Wilhelmus MD PhD***

Purpose: To determine the prevalence, chronology, and characteristics of AOS theses that were published elsewhere besides the Transactions.

Methods: After tabulating 408 theses published in the Transactions from 1954 to 2003, I searched six electronic databases for analogous reports by the same author based on title and abstract. After copying these articles, I compared the design, data, text, and figures with the original thesis to create a list of abridged theses for analysis.

Results: After excluding 14 (3%) reports that appeared elsewhere before the Society's annual meeting, this bibliometric survey found 157 (38%) theses that led to 192 subsequent publications in 46 different periodicals and one book.. Ophthalmology journals published 92% of these papers, and 56% appeared in four higher-impact eye journals that published twice as fast as other periodicals ($P < 0.0001$). Only 41 (26%) abridged theses appeared between the annual meeting and the publication of the Transactions, and the initial abridgement was published a median 1.2 (interquartile range, 0.7—1.7) years after the meeting. Ninety-two (59%) initial papers had one or more coauthors, and 22 (14%) by-lined a first author other than the thesis writer. The requisite AOS annotation was footnoted by 99 (63%) initial articles, 38 (24%) cited the original thesis in the bibliography, and 42 (27%) did neither. On average, the cumulative length of subsequent articles was 30% shorter than the original thesis.

Conclusion: Collateral publication of an abridged AOS thesis commonly occurred in the mainstream ophthalmic literature, often after publication of the full thesis and occasionally without cross reference.

CLINICOPATHOLOGIC CORRELATIONS OF WOUND STRENGTH AND TRANSPARENCY IN HUMAN DONOR CORNEAS AFTER LASER IN SITU KERATOMILEUSIS (LASIK)

By **Hans E. Grossniklaus MD***, Daniel G. Dawson MD, Ingo Schmack MD, **George O. Waring II MD**, Henry F. Edelhauser PhD

Purpose: To correlate the histologic, immunofluorescent staining, and ultrastructural findings with wound strength and transparency after LASIK.

Methods: One hundred thirty corneas from 68 human donors with a prior history of LASIK (range=1 month-7 years postop) were received from eye banks. The corneas were selected for gross examination only, haze analysis by confocal microscopy, or tensile wound strength testing. All specimens were then processed for routine histology, immunofluorescent staining and/or transmission electron microscopy (TEM).

Results: Histologic, immunfluorescent staining, and TEM showed that the wound margin contained an ~9μm thick, ~50-70μm long hypercellular fibrotic stromal scar composed of a dense, irregular network of normal diameter collagen fibrils and normal-size fibril bond proteoglycans, frequently interspersed keratocytes, and occasional myofibroblasts. The remaining regions of the wound (paracentral and central) contained an ~5μm thick hypocellular primitive stromal scar predominantly composed of abnormally large proteoglycans with scattered loose networks of small diameter collagen fibrils and occasional interspersed keratocytes. The tensile wound strength and haze tests showed that the hypercellular wound margin was stronger (average 28% normal tensile strength) and more hazy (average 30% more haze than normal) than the remaining hypocellular wound (average 2.5% normal tensile strength, transparent). All LASIK specimens had random Bowman's layer undulations present on the flap surface and focal areas of epithelial thickening from basal cell hypertrophy; epithelial hyperplasia was commonly present only over the wound margin.

Conclusion: The corneal stroma heals after LASIK surgery by actively producing two variants of scars over the first 6 months after surgery. The majority of the lamellar wound is composed of a transparent, weak, hypocellular, primitive scar, whereas the flap wound margin contains a stronger, hazy, hypercellular fibrotic scar. Bowman's layer undulations and the epithelial cell modifications appear to be secondary tissue adjustments that occur within the first few months after surgery.

PROGNOSTIC FACTORS FOR VISUAL FIELD PROGRESSION IN THE ADVANCED GLAUCOMA INTERVENTION STUDY: A RECURSIVE PARTITIONING ANALYSIS

By **Joseph Caprioli MD***, Kouros Nouri Mahdavi MD, and Federico Badala MD

Purpose: To identify risk factors at time to failure for visual field (VF) progression in a prospective, randomized, glaucoma treatment trial.

Methods: Five hundred five eyes (401 patients) from the Advanced Glaucoma Intervention Study (AGIS) with ≥7 VF exams and ≥3 years of follow-up were recruited. Sequential pointwise linear regression analysis (PLR) was used to evaluate VF status annually. Visual field progression was considered to have occurred when threshold sensitivity in ≥2 test locations within a Glaucoma Hemifield Test cluster declined at a rate ≥1.0 dB/year with $p< 0.01$. Time to visual field progression was defined as time of first progression

confirmed in one subsequent PLR analysis and at the end of follow-up. Recursive partitioning analysis was used to determine prognostic factors for VF progression.

Results: Four prognostic groups were identified based on mean number of glaucoma medications and long-term IOP fluctuation. Eyes on ≤1 medication with IOP range/visit <1.3 mmHg had the lowest progression rate with Progression Rate Ratio (PR) =0.5. Eyes on two medications had a moderate risk of VF progression (PR=1.5). Eyes on one medication with IOP range/visit ≥1.3 mmHg demonstrated higher risk (PR=2.2). Eyes on >2 medications were most likely to show VF progression (PR=4.2). A larger number of medications was significantly associated with higher mean IOP and higher IOP fluctuation (Spearman's r =0.31 and 0.30 respectively; p<0.001).

Conclusion: A larger number of glaucoma medications and higher IOP fluctuation were associated with VFprogression.

COMBINED POSITRON EMISSION TOMOGRAPHY / COMPUTED TOMOGRAPHY FOR EVALUATION OF PRESUMED CHOROIDAL METASTASES

By Mark J. Donaldson MBS*, **Jose S. Pulido MD MPH**, Brian P. Mullan MD, David J. Inwards MD, Herb Cantrill MD, Max R. Johnson MD, Min-Kyu Han MD, Leonid Skorrin Jr DO, Tom Link CRA

Background: Choroidal metastases are the most common ocular malignancy and are the first sign of systemic malignancy in approximately one third of patients. Of patients with no previous diagnosis of cancer, a complete oncologic evaluation fails to find the primary lesion in approximately 50% of cases. Newer imaging modalities such as combined PET/CT may improve the yield of the systemic workup.

Methods: Consecutive patients presenting with presumed choroidal metastases were evaluated with whole body combined PET/CT scanning.

Results: Four patients presenting with choroidal metastases as the first sign of systemic malignancy were evaluated. In all four cases, PET/CT demonstrated the ocular lesion, and the primary malignancy which was confirmed by tissue biopsy. False negative results were seen in two cases of cerebral metastases. PET/CT demonstrated lesions not visible on CT or MRI in two cases.

Conclusion: Combined PET/CT is a useful addition to the work-up of patients with choroidal metastases. It provides the opportunity to detect lesions not visible with other imaging modalities and the ability to image patients with contraindications to MRI. It is essential to correlate PET images with clinical information and the results of other imaging modalities and tissue biopsy remains the gold standard in the diagnosis of malignancy. False positives and negatives can occur with PET/CT, and further research is needed before this promising technology becomes a routine part of the evaluation of patients with choroidal metastases.

NITRATE AND AMINO ACIDS LEVELS IN THE VITREOUS OF POLIFERATIVE DIABETIC RETINOPATHY AND THEIR POSSIBLE ROLE IN THE PATHOPHYSIOLOGY OF THE DISEASE

By Scott A. Shippy PhD*, **Jose S. Pulido MD MPH**, Leyi Gao, Miao- Jen Lu, Colin A McCannel MD, R. Mark Hatfield MD, and Robert Dundervill II MD

Purpose: To compare the levels of nitrates and amino acids in the vitreous of patients undergoing vitrectomy for proliferative diabetic retinopathy (PDR) compared to those undergoing vitrectomy for macular hole (MH) or epiretinal membrane (ERM).

Methods: Nanoliter capillary electrophoresis (NCE) as previously described by us was used with a detection level of 100nM for glutamate and other amino acids and 1.3 microM for nitrate. 100 microL of pure vitreous taken at the time of vitrectomy was assayed with NCE. Results from PDR-derived samples were compared by t-test to those for MH or ERM.

Results: Mean Nitrate levels in the vitreous of 24 eyes with MH/ERM was 17.0(+/-5.0) microM while it was 45.0(+/-22.1)microM in the vitreous of 17 eyes with PDR (p<0.0001). A statistically significant difference (p<0.05) was seen in glutamate levels, 3.9(+/-3.2) microM MH/ERM (n=23) versus 8.1(+/-6.6) microM PDR (n=13) and arginine levels with 28.6(+/-15.5) microM for MH/ERM (n=14) and 56.3(+/-

42.4) microM for PDR (n=9). The levels of gamma-aminobutyric acid (GABA) were trending different with MH/ERM: 19.8(+/-12.7) microM (n=12) versus PDR: 33.8(+/-14.4) microM.

Conclusion: Nitrate, glutamate and arginine are significantly elevated in the vitreous of patients with PDR. Nitrate is a stable metabolite of nitric oxide that is associated with capillary dilatation and this may be a pathophysiological reason for vessel dilation in PDR patients. Arginine is the molecular source for nitric oxide and the increased arginine may reflect an upregulation of the nitric oxide system. The transmitters glutamate and GABA may also be agents in the pathophysiology of PDR.

CONGENITAL CATARACTS, A NEW FINDING IN WOLFRAM SYNDROME

By Rebecca Baird Mets and **Marilyn Baird Mets MD***

Purpose: To report a new finding, congenital cataracts, in Wolfram Syndrome, an autosomal recessive disorder also known by the eponym, DIDMOAD (Diabetes Insipidis, Diabetes Mellitus, Optic Atrophy and Deafness)

Methods: Observational case series, describing two siblings followed over 17 years, one of whom presented with congenital cataracts at age one month. Genetic testing was carried out in the lab of Marci M. Lesperance, MD for the Wolfram's gene WFS1 on both patients and their parents. The systemic findings, clinical course, and genetic findings were reviewed.

Results: Further workup by us revealed deafness in the presenting sibling, (proband). Cataracts were noted in the older sibling who was already known to be deaf. The proband was diagnosed with diabetes mellitus at age 4 1/2 years and the sibling at age 8 years. Optic atrophy was seen at ages 5 1/2 and 8 years respectively. Genetic testing showed two different changes in the nucleotide sequence in exon 8 in both patients. These mutations have been associated with Wolfram Syndrome in previous studies. In addition, DNA from both parents showed that each had one of the mutations.

Conclusion: The molecular basis for Wolfram Syndrome was confirmed in these two siblings. The proband presented with congenital cataracts. Therefore, Wolfram syndrome should be considered in the differential diagnosis of congenital cataracts.

DOES TITRATION OF MITOMYCIN C INFLUENCE TRABECULECTOMY OUTCOME?

By Susan J. Lee MD, Augusto Paranhos MD, and **M. Bruce Shields MD***

Purpose: To evaluate the benefit of titrating the concentration and exposure time of mitomycin C (MMC) as an adjunct to trabeculectomy.

Methods: Retrospective review of 155 eyes of 155 consecutive glaucoma patients undergoing trabeculectomy with titration of concentration and exposure time of MMC, based on patient's risk factors for surgical failure. After minimum follow-up of 6 months, patients were divided into success (intraocular pressure 7-17 mmHg), hypertension (>17 mmHg) and hypotony (<7 mmHg) groups, which were compared with regard to MMC protocol and patient variables. A review of the literature was also conducted on reports of trabeculectomy and MMC with and without titration.

Results: There was no significant differences between the three outcome groups and MMC protocol ($p>0.05$). The only significant patient variable was older age in the hypotony group ($p=0.009$). The literature is conflicting regarding the value of titrating MMC as an adjunct in trabeculectomy.

Conclusion: The outcome of trabeculectomy with adjunctive MMC appears to represent a complex interaction of patient and surgical variables. While there is some support for a benefit of titrating MMC according to individual patient variables, there is inadequate evidence at the present time to claim superiority for any MMC protocol, with or without titration.

Disclosure: Dr. Shields is a consultant for Becton Dickinson and GMP Companies.

TRICHOTILLOMANIA: AN OPHTHALMOLOGIST 'S VIEWPOINT

By **Allan J. Flach MD***

Purpose: Trichotillomania is the irresistible urge to pull one's hair, eyebrows or eyelashes often resulting in alopecia or madarosis. Six new cases of trichotillomania are reviewed with the goal of evaluating the potential role of the ophthalmologist in the diagnosis and treatment of patients with this unusual disorder.

Methods: Six cases of trichotillomania are reviewed and compared to those reported in the literature. Special attention is given to the differential diagnoses, associated psychiatric states and the individual differences these patients exhibit when they present to various subspecialties in medicine.

Results: Five of six patients were women (ages 12 to 50 years) who had characteristic missing and broken lashes along the lid margin of all four eyelids in the absence of other signs of disease. In addition, two patients had eyebrow involvement. The eyelash plucking occurred over a 2 to 25 year period. Only three patients were aware of the activity. Associated psychiatric states included chronic depression, obsessive compulsive disorder, delusional state and feeling stressed.

Conclusion: This is the largest series of patients with trichotillomania reported in the ophthalmic literature. The differential diagnosis for madarosis and alopecia is extensive. The ophthalmologist can be of great assistance in confirming the correct diagnosis and in the subsequent management of these patients.

THE CLINICAL PERFORMANCE AND ADVERSE EVENTS OF HIGH DK SILICONE HYDROGEL CONTACT LENSES WORN CONTINUOUSLY (CW) FOR UP TO 30 DAYS IN CLINICAL PRACTICE SETTING IN THE UNITED STATES

By **Peter C. Donshik MD***, Sally M. Dillehay OD EdD, Bill Long BS, Joesph T. Barr OD MS, Peter Bergenske OD, Glenda Secor OD, John Yoakum OD

Purpose: A 3 year trial was initiated to evaluate the performance and adverse events of lotrafilcon A (N&D) lenses in practice setting.

Methods: 19 sites dispensed 317 patients (634 eyes) to wear N&D. Clinical and subjective data were obtained at baseline and 1-12 month intervals over 3 years. The biomicroscopic signs and subjective symptoms of contact lens wearers who were fitted into high Dk/t N&D CW lenses or low Dk/t 2 week replacement daily wear (DW) were compared. Adverse events reported with N&D during the trial are summarized and compared to previous reports.

Results: Through 36 months, the N&D cohort showed improvement in limbal redness, conjunctival redness, and corneal neovascularization. Seven of 10 biomicroscopy signs continued to improve. For the DW cohort, papillary conjunctivitis, corneal staining, and limbal redness increased through 36 months. No biomicroscopy signs improved throughout the trial. Improvement in patient symptoms in the N&D cohort through 36 months occurred for dryness, redness, photophobia, tearing, lens awareness and blurred vision. The DW cohort reported worsening in dryness, blurred vision, and redness. Total lens-related adverse events for N&D in year 1 were reported for 19 eyes (3.0%), in year 2 for 11 eyes (1.7%) and in year 3 for 7 eyes (1.1%).

Conclusion: Improvements in corneal health and patient symptoms were seen with lotrafilcon A through 36 months. Results from this trial show that while adverse and inflammatory events can occur among silicone hydrogel CW patients, they are low and may be lower in practice than previously reported.

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* Presenter
Bold type indicate AOS member.