University of Wisconsin School of Medicine and Public Health

9th Annual
Medical Student Research Forum

January 18, 2011

PROGRAM and ABSTRACTS

Support for the 9th Annual Medical Student Research Forum is provided by The UW School of Medicine and Public Health Department of Academic Affairs and The Herman and Gwendolyn Shapiro Foundation
9th Annual Medical Student Research Forum

1:15 – 5:30 PM ■ TUESDAY, JANUARY 18, 2011
Health Sciences Learning Center

1:15-1:30 PM
1306 HSLC
Welcome
Robert N. Golden, MD
Dean and Vice Chancellor for Medical Affairs

1:30 PM
1306 HSLC
SHAPIRO GUEST LECTURE
The Legacy of Ivar Sandstrom and the Impact of UW Medical Students
Herbert Chen, MD, FACS
Professor of Surgery
UW School of Medicine and Public Health

Dr. Herbert Chen is a native of Marshfield, Wisconsin. He obtained his BS from Stanford University and graduated from Duke University School of Medicine Alpha Omega Alpha. Dr. Chen completed a general surgery residency followed by a surgical oncology and endocrinology fellowship at The Johns Hopkins Hospital.

Dr. Chen is currently Vice Chair of the Department of Surgery and Professor of Surgery and Biomedical Engineering at the University of Wisconsin. His other positions include Chief of Endocrine Surgery and Leader of the Endocrine Neuroendocrine Cancer Disease Group at the University of Wisconsin Carbone Cancer Center. He also serves as Chair of the SMPH Student Research Committee. His clinical interests include endocrine and neuroendocrine disease with a focus on minimally invasive endocrine surgery. His lab studies the role of Notch, rat-1, and GSK3 in neuroendocrine tumor proliferation and hormone production. He is a funded investigator with numerous NIH awards and training grants. Since joining the faculty, Dr. Chen has received several honors including the University of Wisconsin Medical Alumni Association Teaching award.

Dr. Chen has mentored a total of 83 faculty, post-doctoral fellows, residents, medical students, and undergraduates in his lab. He has published 259 original research and review articles and has edited 8 textbooks. He and his lab trainees have given more than 370 research presentations at regional, national, and international scientific meetings focusing on surgical education, endocrine surgery, and neuroendocrine cancers.

2:15 PM
1306, 1325, 1335 HSLC
Student Research Podium Presentations (Concurrent Sessions)

4:00-5:30 PM
HSLC Atrium
Poster Session and Reception

Listing of student oral and poster presentations and abstracts follow.
Abstracts are listed alphabetically by student last name.
Student Oral Presentations
Sessions run concurrently from 2:15 - 4:00 pm

**SESSION A**
Room 1306 HSCL
Faculty Facilitator: Herbert Chen, MD

**Qualitative Aspects of Treatment with Prolotherapy for Knee Osteoarthritis in a Multi-method Study**
STUDENT: Lane Benes, BS
MENTOR: David Rabago, MD
DEPARTMENT: SMPH Department of Family Medicine

**Role of Routine Axillary Ultrasound in the Pre-Operative Management of Patients with Breast Cancer**
STUDENT: Holly Caretta-Weyer, BS
MENTOR: Heather Neuman, MD, MS
DEPARTMENT: SMPH Department of Surgery

**Regulation of Ion Channel Activation Following Spinal Cord Injury**
STUDENT: Zach Clark, BS, MS
MENTOR: Daniel Resnick MD, MS
DEPARTMENT: SMPH Department of Neurological Surgery

**Inflammatory Profile of Vocal Fold Fibroblasts in Response to Cigarette Smoke Extract**
STUDENT: Adam Coughlin, BS
MENTOR: Susan Thibeault, PhD
DEPARTMENT: SMPH Department of Surgery

**Outcomes of Clostridium difficile Infection in Solid Organ Transplant Recipients at UW Hospital**
STUDENT: Trevor McKown, BS
MENTOR: Nasia Safdar, MD, MS
DEPARTMENT: SMPH Department of Medicine

**The Effect of Splenectomy on the Postoperative Complication Rate after Distal Pancreatectomy**
STUDENT: Angel F Matos, BS
MENTOR: Emily R Winslow, MD
DEPARTMENT: SMPH Department of Surgery

**Antiproliferative Effect of Chrysin on Anaplastic Thyroid Cancer**
STUDENT: TramAnh Phan, BS
MENTORS: Xiao-Min Yu, MD, PhD; Muthusamy Kunnimalaiyaan, PhD; Herbert Chen, MD, FACS
DEPARTMENT: SMPH Department of Surgery

**SESSION B**
Room 1335 HSLC
Faculty Facilitator: John Harting, PhD

**Wisconsin Stillbirth Services Program: A Multifactorial Approach to Stillbirth Analysis**
STUDENT: Beth VanderWielen, BS
MENTORS: Elizabeth McPherson, MD; Christina Zaleski, MD
DEPARTMENT: Medical Genetics Services, Marshfield Clinic

**Outcomes of Laparoscopic Gastric Bypass vs. Laparoscopic Adjustable Gastric Band Up to 5 Years Post-op**
STUDENT: Travis P. Schmidt, BS
MENTOR: Jon C. Gould, MD
DEPARTMENT: SMPH Department of Surgery

**Recurrent Hepatic Colorectal Metastases: Does the extent of Surgical intervention impact outcome?**
STUDENTS: Kathryn Zavala, BS
MENTOR: Sharon Weber, MD
DEPARTMENT: SMPH Department of Surgery

**Nitrous Oxide Exposure Inhibits CNS Regeneration In Vitro**
STUDENT: Krista Stewart, BA
MENTOR: Bermans J. Iskandar, MD
DEPARTMENT: SMPH Department of Neurological Surgery

**Savant Syndrome Registry: A Peek into Genius**
STUDENT: David Rebedew, BS
MENTOR: Darold Treffert, MD
DEPARTMENT: St. Agnes Hospital Department of Psychiatry

**Does Head and Neck Irradiation Increase the Chance of Multi-gland Disease in Patients with Hyperparathyroidism?**
STUDENTS: Monica Woll, BA
MENTOR: Herbert Chen, MD, FACS
DEPARTMENT: SMPH Department of Surgery
Theoretical Increase of Thyroid Cancer from Cervical Spine MDCT in Pediatric Trauma Patients

STUDENTS: Kelly R. Egan, MS
MENTOR: Paul A. Anderson, MD
DEPARTMENT: SMPH Department of Orthopedics and Rehabilitation

The Use of Advance Directives in Decision Making for High Risk Operations: Results of a National Survey of Surgeons

STUDENT: Andrew J. Redmann, BA, BS
MENTOR: Margaret L. Schwarze, MD, MPP
DEPARTMENT: SMPH Department of Surgery

Preoperative Functional Status Correlates with Some, but Not All, Postoperative Complications

STUDENT: Natalie Weisensel, BS
MENTOR: Gregory Kennedy, MD, PhD
DEPARTMENT: SMPH Department of Surgery

Mechanism of Action of a Novel Class of Antibiotics that Targets DNA Replication

STUDENT: Walker Shapiro, BA
MENTOR: James L. Keck, PhD
DEPARTMENT: SMPH Department of Biomolecular Chemistry

The Synergistic Effect of Pasireotide® and a Raf-1 Activating agent in Carcinoids

STUDENT: Yash Somnay, BS
MENTOR: Herbert Chen, MD, FACS
DEPARTMENT: SMPH Department of Surgery

A fMRI Study of Broca’s and Wernicke’s Language Lateralization in Vascular Lesion Patients

STUDENT: Nicole Korneder, BS
MENTOR: Vivek Prabhakaran, MD, PhD
DEPARTMENT: SMPH Department of Radiology

Does Cancer Have a Sense of Humor? The Use of Humor in Patients with Recurrent Ovarian Cancer

STUDENT: Margaret M. Rausch, BS
MENTOR: Stephen L. Rose, MD
DEPARTMENT: SMPH Department of Obstetrics and Gynecology
Effect of Altered Cadence on Knee Pain in Runners  
STUDENT: Erin AufderHeide, BA  
MENTOR: Bryan Heiderscheit, PhD, PT  
DEPARTMENT: Department of Orthopedics and Rehabilitation

The Impact of a Parent Child Preoperative Program in Perioperative Anxiety in Children  
STUDENT: John Awowale, BS  
MENTOR: Michael Kim, MD  
DEPARTMENT: Department of Pediatrics

Investigating the Relationship between Fetal Iron Deficiency and Asthma Development  
STUDENT: Mary E. Bacsik, BS  
MENTOR: Pamela J. Kling, MD  
DEPARTMENT: Department of Pediatrics

Impact of Vascular Lesions on Morbidity and Mortality: A Retrospective fmMRI Study  
STUDENT: Dovile Baniulis, BS  
MENTOR: Vivek Prabhakaran, MD, PhD  
DEPARTMENT: Department of Radiology

Flow Quantification with 4D Flow-Sensitive MRI: Validation in Patients with Congenital Heart Disease  
STUDENT: Christina Boncyk, BS  
MENTOR: Christopher Francois, MD  
DEPARTMENT: Department of Radiology

Efficacy of Training Pediatric Residents on an Early Literacy Promotion Intervention  
STUDENT: Stephanie Booms, BS  
MENTOR: Dipesh Navsaria, MPH, MSLIS, MD  
DEPARTMENT: Department of Pediatrics

Effectiveness of Training in Improving Star Excursion Balance Test Performance in Collegiate Athletes  
STUDENT: Nikki M. Burish, BS  
MENTOR: Alison Brooks, MD, MPH  
DEPARTMENT: Department of Orthopedics and Rehabilitation

Development of in vitro Blood Brain Barrier Model of CNS Dissemination of Mycobacterium Tuberculosis  
STUDENT: Emily Ciccone, MHS  
MENTORS: Zsuzsanna Fabry, PhD and Erika Heninger, PhD  
DEPARTMENT: Department of Pathology and Laboratory Medicine

Fine Needle Aspiration of the Thyroid: A Contemporary Experience of 3,981 Cases  
STUDENT: Nicholas Coorough, BS  
MENTOR: Herbert Chen, MD, FACS  
DEPARTMENT: Department of Surgery

Incidence of Bowel Obstruction after Restorative Proctocolectomy: Higher with Laparoscopic Approach?  
STUDENT: Scott Dolejs BS  
MENTOR: Charles Heise, MD  
DEPARTMENT: Department of Surgery

Adherence to Gait Analysis Recommendations Based on Surgeons’ Affiliation with the Gait Laboratory  
STUDENT: Koorosh J. Elihu, BA  
MENTOR: Tishya A. L. Wren, PhD  
DEPARTMENT: Department of Surgery, Children’s Hospital Los Angeles

Outcomes of C. difficile Infection in Intra-abdominal Solid Organ Transplant Recipients  
STUDENT: James Enser, BS  
MENTOR: Nasia Safdar, MD, MS  
DEPARTMENT: Department of Medicine

The Capacity of Aryl Hydrocarbon Receptor Ligands to Alter the Onset and Severity of EAE  
STUDENT: Lynn Frydrych, BS  
MENTOR: Joshua Mezrich, MD  
DEPARTMENT: Department of Surgery

The Novel Use of Glucose Measurements for Detecting Compartment Syndrome  
STUDENT: Andy Gerstner, BS  
MENTOR: Christopher Doro, MD  
DEPARTMENT: Department of Orthopedics and Rehabilitation

Identification of the Role of the Survivin Gene in Pancreatic Beta Cells  
STUDENT: David Halverson, BS  
MENTOR: Dawn Belt Davis, MD, PhD  
DEPARTMENT: Department of Medicine

Performance of Generic Health Related Quality of Life Instruments in Heart Failure Clinics  
STUDENT: Andrew J Henn, BS  
MENTOR: Nancy K. Sweitzer MD, PhD  
DEPARTMENT: Department of Medicine
Influence of Hamstring Muscle Activity on Pelvic and Lower Extremity Motion during Walking
STUDENT: Antonio Hernández, PhD
MENTOR: Darryl G. Thelen, PhD
DEPARTMENT: Department of Mechanical Engineering

Analysis of Language and Memory Lateralization by Functional MRI and WADA Test in Epilepsy and Effect of Gender on Postoperative Seizure Improvement
STUDENT: Nwe Linn Htet, BS
MENTOR: Vivek Prabhakaran, MD, PhD
DEPARTMENT: Department of Radiology

Utilizing Diffusion Tensor Imaging to Predict Post-Surgical Outcomes in Brain Tumor Patients
STUDENT: David Huss, BA
MENTOR: Aaron Field, MD, PhD
DEPARTMENT: Department of Radiology

Patient Preferences for Surgical or Percutaneous Intervention in Multi-Vessel Coronary Artery Disease
STUDENT: Jacqueline Israel, BA
MENTOR: Ryan Kipp, MD
DEPARTMENT: Department of Medicine

Acromioplasty in the State of Wisconsin from 2003-2009
STUDENT: Lina Jacques, BS, MS
MENTOR: Robert H. Above, MD, MA
DEPARTMENT: Department of Orthopedics and Rehabilitation

CT Measurement of Abdominal Fat Distribution to Predict the Metabolic Syndrome
STUDENT: Young Jee, BS
MENTOR: Perry J. Pickhardt, MD
DEPARTMENT: Department of Radiology

The Role of Autophagy in Melanoma Tumor Progression
STUDENT: DiDi Khatib, BA
MENTOR: Vijay Setaluri, PhD
DEPARTMENT: Department of Dermatology

Exploring the Role of Macrophage Clearance of Apoptotic Smooth Muscle Cells during AAA Inflammation
STUDENT: Christopher Kleefisch, BS
MENTOR: Bo Liu, PhD
DEPARTMENT: Department of Surgery

Bone Mineral Density Analysis from CT Colonography for Osteoporosis Screening
STUDENT: Travis Lauder, BS
MENTOR: Perry J. Pickhardt, MD
DEPARTMENT: Department of Radiology

HPRT Mutational Spectra in HPRT Mutant T cells in Human Melanoma
STUDENT: Eric Leiendecker, BS
MENTOR: Mark Albertini, MD
DEPARTMENT: Department of Medicine

Cerebral Blood Flow Response to Exercise and Hypoxia in Obesity
STUDENT: Lee A. Linstroth, BS
MENTOR: William G. Schrage, PhD
DEPARTMENT: Department of Kinesiology

PSA Doubling Time in Patients on Active Surveillance for Prostate Cancer
STUDENT: Andrew Livermore, BA
MENTOR: David Jarrard, MD
DEPARTMENT: Department of Urology

Are There Predictors of Malignancy in Patients with Multinodular Goiter?
STUDENT: Jie Luo, BS
MENTOR: Rebecca Sippel, MD, FACS
DEPARTMENT: Department of Surgery

Placement of Central Venous Catheters During Neutropenia- Should Our Institutional Practice Change?
STUDENT: Anita Mantha, MS
MENTOR: Neha Patel, MD
DEPARTMENT: Department of Pediatrics

Fasting and Post-prandial Spot Urine Calcium-to-creatinine Ratios Do Not Detect Hypercalciuria
STUDENT: Andrea N. Jones, BS
MENTOR: Karen E. Hansen, MD
DEPARTMENT: Department of Medicine
Is Thyroidectomy in Patients with Hashimoto’s Thyroiditis More Risky?

STUDENT: Catherine McManus, BS
MENTORS: Herbert Chen, MD, FACS; Rebecca Sippel, MD, FACS
DEPARTMENT: Department of Surgery

Assessment of Acoustoelastographic Analysis of In-Vivo Mechanical Properties of Soft Tissue

STUDENT: Max Michalski, MS
MENTORS: Michael Ryan, PhD, CPed; Bryan Heiderscheit, PT, PhD; Kenneth Lee, MD, MBA
DEPARTMENT: Department of Orthopedics and Rehabilitation

Dysmenorrhea in Women with Crohn’s Disease

STUDENT: Emilie Midtling, BA
MENTOR: Sumona Saha, MD
DEPARTMENT: Department of Medicine

Folate Mechanisms in Bone Regeneration: A Murine Model of Intervertebral Fusion

STUDENT: Arian Nasiri, BS
MENTOR: Paul Anderson, MD
DEPARTMENT: Department of Orthopaedics Surgery and Rehabilitation

Surgical Outcomes in the Treatment of Slipped Capital Femoral Epiphysis

STUDENT: Tuon, Nguyen, BS
MENTOR: Kenneth Noonan, MD
DEPARTMENT: Department of Orthopedics and Rehabilitation

Hip Arthroscopy in Children with Cerebral Palsy

STUDENT: Jeremiah R. Olson, BS, MA
MENTOR: James J. McCarthy, MD
DEPARTMENT: Department of Orthopedics and Rehabilitation

When Career and Life Collide: A Qualitative Study of the Medical Marriage

STUDENT: Kara Petrashek, BS
MENTORS: Carol Isaac PhD, PT; Molly Carnes, MD, MS
DEPARTMENT: University of Wisconsin Center for Women’s Health Research

Epidemiology of Cytomegalovirus Reactivation After Allogenic Hematopoietic Stem Cell Transplantation

STUDENT: Erica Pettke, MPH
MENTOR: Genovefa Papanicolaou, MD
DEPARTMENT: Memorial Sloan-Kettering Cancer Center, Infectious Diseases Service

Optimization of Tremor Assessment using the iPod

STUDENT: Heather Rusk, BA
MENTOR: Kari Sillay, MD
DEPARTMENT: Department of Neurological Surgery

Protein Kinase G as a Determinant of Behavior and a Potential Target of Dengue Virus Manipulation

STUDENT: Dean Sayre, BS
MENTOR: Robert Striker, MD, PhD
DEPARTMENT: Department of Medical Microbiology and Immunology

Mobile Markets: Education with Healthy, Affordable Food at the Neighborhood-level

STUDENT: Allison Schaus, BS
MENTOR: Paul Hunter MD
DEPARTMENT: UW Center for Urban Population Health

Assessing Environmental Risk Factors in Testicular Cancer, Undescended Testes and Hypospadias

STUDENT: Narek Shaverdian, BA
MENTOR: Margarett Shnorhavorian MD, MPH
DEPARTMENT: Seattle Children’s Hospital and University of Washington School of Medicine

Simvastatin’s Effect on CSF Neurofilament Light Chain in Adults at Risk for Alzheimer’s Disease

STUDENT: Malini Soundarrajan BS
MENTOR: Cynthia Carlsson, MD, MS
DEPARTMENT: Department of Medicine and Wisconsin Alzheimer’s Disease Research Center

When Career and Life Collide: A Qualitative Study of the Medical Marriage

STUDENT: Megan Steiner, BA
MENTORS: Carol Steiner, BA
DEPARTMENT: University of Wisconsin Center for Women’s Health Research

Calculating Intestinal Length and Mucosal Volume Using Computerized Tomography

STUDENT: Christopher Strouse, BS
MENTORS: Peter Nichol, MD, PhD
DEPARTMENT: Department of Surgery

Analysis and Isolation of PiG-A Variant T-Cells Using Flow Cytometry

STUDENT: Michael S Strupp, BS
MENTOR: Mark Albertini, MD
DEPARTMENT: Department of Medicine
Are Terminally Threaded Guide Pins from Cannulated Screw Systems Dangerous?
STUDENT: Jeffrey Swick, BS
MENTOR: James J McCarthy, MD
DEPARTMENT: Department of Orthopedics and Rehabilitation

An Assessment of Racial Disparity in Rates of Possible Risk Factors for H1N1-associated Hospitalization: Dane County, Wisconsin
STUDENT: Jessica Tischendorf, BS
MENTOR: Jonathon L. Temte, MD, PhD
DEPARTMENT: Department of Family Medicine

The Problem of Infant Mortality in Wisconsin: Roadblocks to Access and Quality?
STUDENT: Hanna Vanderloop, BS
MENTORS: Jonathan Jaffery, MD; Elizabeth Feder, PhD; Donna Friedsam, MPH
DEPARTMENT: UW Population Health Institute

Clinical Utility of fMRI in Surgical Planning for Patients with Intracranial Tumors
STUDENT: Siarhei Vysotski, BS
MENTOR: John S. Kuo, MD, PhD
DEPARTMENT: Departments of Radiology and Neurological Surgery

Using Phantom-less QTC to Determine Bone Mineral Density in the Thoracic Spine
STUDENT: Eric Wiesner, BS
MENTOR: Paul Anderson, MD
DEPARTMENT: Department of Orthopedics and Rehabilitation
Effect of Altered Cadence on Knee Pain in Runners

Authors: Erin AufderHeide, BA; Christa Wille; Elizabeth Chumanov, PhD; Bryan Heiderscheit, PhD, PT

Department: Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health
Mentor: Bryan Heiderscheit, PhD, PT
Support: Shapiro Summer Research Program, Department of Orthopedics and Rehabilitation, and the Wisconsin Hilldale Research Fellowship

BACKGROUND: Over half of recreational runners experience an injury each year, of which 42% are at the knee. Increasing step rate has been shown to decrease joint loading, but the implications of these findings have yet to be tested in runners with knee pain. The purpose of this study is to characterize how lower extremity kinematics and kinetics change in runners with clinically diagnosed knee pain and to determine if increasing running cadence will reduce pain (>30%) in those individuals.

METHODS: Thirty-two runners with clinically diagnosed knee pain are selected to participate in the study. Each subject runs on a force-instrumented treadmill, during which three-dimensional kinematics, kinetics, and muscle activities are recorded under five step rate conditions: -5%, -10%, preferred stride frequency, +5% and +10%. A digital metronome is used to assure cadence accuracy. Following each trial, subjects are asked to rate their level of perceived exertion (6-20 Borg Scale) and level of pain (0-10) using a visual analog scale. The knee extensor moment, energy absorbed, average pain during running, and RPE are compared between conditions using parametric (1-factor (cadence) repeated measures ANOVA) or non-parametric (Kruskal-Wallis) measures, as appropriate.

RESULTS: Both the energy absorbed at the knee and knee extensor moment decreased with increasing cadence. A stride frequency of +10% correlated to a 5% reduction in the knee extensor moment during loading response (p <0.05). The energy absorbed during the loading response decreased by 11% with a 5% increase in cadence and 12% with a 10% increase in cadence (p <0.05). Decreased RPE and level of pain correlated to the reduction in energy absorption during the loading response. As compared with healthy subjects, those with knee pain exhibited greater energy absorption at the knee joint and knee extensor moment at their preferred stride frequency.

CONCLUSIONS: Increasing cadence has the possibility to both expedite recovery from an existing injury and prevent future running-related injuries. Runners with knee pain exhibited both a reduction in pain and mechanic energy absorption with increased step frequency. Considering the high incidence of annual running-related injuries, altering cadence could play a crucial role in preventative healthcare.

The Impact of a Parent Child Preoperative Program in Perioperative Anxiety in Children

Authors: John Awowale, BS; Jennifer Mosher, MD; Michael Kim, MD

Department: Department of Pediatrics, University of Wisconsin School of Medicine and Public Health
Mentor: Michael Kim, MD
Support: Shapiro Summer Research Program and Department of Pediatrics

BACKGROUND: Surgery can be a highly anxiety provoking event for children which consists of injections, the trip to the OR, waking up in pain after surgery, not eating or drinking, and wearing the anesthesia mask. The aim of this study is to determine whether or not children who participate in a Parent Child Preparation Program (PCPP) prior to surgery experience less perioperative anxiety than those who do not.

METHODS: This will be a randomized blind clinical trial conducted at the American Family Children's Hospital (AFCH) in Children age 4-12 years with no prior surgeries or major medical conditions. Patients excluded include non-English speakers, developmentally delayed patients, or patients with anxiety disorders. Patients will be randomized to either complete a PCPP session prior to surgery or bypass it (control group). Families assigned to a PCPP session will go through a session lasting between 15-45 minutes that consists of a child life specialist presenting a pictorial preparation to the family containing pictures of each step during the surgical process. They will also take a tour of the surgical floor and children can practice using some of the instruments such as placing anesthesia masks on themselves, the specialist, or a doll. The day of surgery patient anxiety will be assessed using the modified Yale Preoperative Anxiety Scale (m-YPAS). The m-YPAS will be scored three times: in the waiting room, prior to departure for the OR and anesthesia induction. Parental anxiety will be assessed using the Spielberger State-Trait Anxiety Inventory self-evaluation questionnaire, which will be scored prior to surgery in the waiting room and post operatively. Two weeks following discharge a post hospital behavior questionnaire will be filled out over the phone to assess postoperative child anxiety. Desired sample size is 40 subjects in each group, this provides 80% power for determining the intervention effects between the study groups. The repeated mYPAS will be used to analyze the primary outcome measure of mYPAS, and t-test and chi square test will be used for demographic data.

FUTURE DIRECTIONS: Begin screening and consenting patients returning for the pre-surgery history and physical.
Investigating the Relationship between Fetal Iron Deficiency and Asthma Development

Authors: Mary E. Bacsik, BS; Theresa W. Guilbert, MD; Alyssa K. Phillips; Sharon E. Blohowiak; Pamela. J. Kling, MD

Department: Department of Pediatrics, Division of Neonatology, University of Wisconsin School of Medicine and Public Health,

Mentor: Pamela J. Kling, MD; Collaborator: Theresa W. Guilbert, MD

Support: Shapiro Summer Research Program; UW Cardiovascular Research Center Medical Student Fellowship; UW Medical Education and Research Committee; Wisconsin Partnership Collaborative Program; UW Institute for Clinical & Translational Research 1UL1RR026011 CTSA; Meriter Foundation; Thrasher Research Fund; NIH T32HD049302 Health Disparities Research Program.

BACKGROUND: Recurrent wheezing in infancy is a risk factor for asthma, the most prevalent chronic disease in U.S. children. Populations of children with asthma also exhibit a higher incidence of infantile iron deficiency (ID). The epidemiological association between lower plasma iron in cord blood and persistent wheezing in infancy may have biologic roots based on an iron dependence of T cell activation. Since eosinophilia (eosinophils ≥ 4% of total WBCs) at 6-12 months of age is a biomarker for recurrent wheezing in infancy, we hypothesized that poorer iron status at birth is directly correlated with eosinophilia at 6-12 months. Such a relationship would suggest a biological link between infantile ID and asthma.

METHODS: Newborns of at least 35 weeks gestational age with one or more risk factors for ID were recruited into a longitudinal study. Risk factors included: maternal ID, maternal diabetes, fetal overgrowth or undergrowth, mothers from ethnic minority groups, or those with lower socioeconomic status. Cord blood indices of storage iron (plasma ferritin), steady state erythrocyte (RBC) iron (ZnPP/H), and recent RBC iron (reticulocyte-enriched ZnPP/H) were measured. At 6-12 months, eosinophil % and absolute eosinophil counts were measured. Simple linear regression and unpaired t tests examined the relationship between eosinophil % and iron status at birth.

RESULTS: No linear relationship was found between either 6-12 month eosinophil % or absolute eosinophil count and any cord blood iron status index. Similarly, no difference was found in 6-12 month eosinophil % or absolute eosinophil count between infants in the highest and lowest cord blood plasma ferritin terciles. We found higher cord blood recent RBC iron (reticulocyte-enriched ZnPP/H) in those with eosinophilia versus those with a lower eosinophil % (p=0.048). The difference between recent RBC iron and steady state RBC iron (delta ZnPP) was significantly higher in those with eosinophilia versus those with lower eosinophil % (p=0.026).

CONCLUSIONS: Our findings suggest that late gestational ID may be associated with eosinophilia at 6-12 months, a biomarker for recurrent wheezing in infancy. There is need for further exploration of putative biological mechanisms between ID in infancy, childhood recurrent wheezing and asthma.

Impact of Vascular Lesions on Morbidity and Mortality: A Retrospective fMRI Study

Authors: Baniulis, D, BS. Korneder, N. Gallagher TA. Wood J. Kundu B. Utter A. Voss J. Nair VA. Field AS. Moritz C. Meyerand B. Prabhakaran V.

Department: Department of Radiology, University of Wisconsin School of Medicine and Public Health

Mentor: Vivek Prabhakaran, MD, PhD

Support: Shapiro Summer Research Program and Department of Radiology

PURPOSE: Motor and language deficits are particularly debilitating functional deficits and thus a major neurosurgical concern in the preoperative or postoperative setting of vascular lesion patients. The distance from vascular lesion to functioning cortex is a critical parameter for predicting deficits. This study examined the role of fMRI as a noninvasive method of preoperative planning for patients about to undergo resection of vascular brain lesions encroaching on areas of primary motor and language function. We tested the hypothesis that as the distance between areas of primary motor or language fMRI activation and vascular lesion edge decreases, patient morbidity will increase.

MATERIALS AND METHODS: Patients were selected from a growing database exceeding 400 patients (accumulated between 1999 and 2009) who underwent preoperative fMRI for various brain vascular lesions. Preoperative fMRI language and motor maps of 84 and 72 subjects respectively were reviewed retrospectively. Functional paradigms were tailored to vascular lesion location to elicit either primary motor or language activations. Distances from vascular lesion edge to edge and distances from vascular lesion edge to center of maximum primary motor or language fMRI activation (<1 cm, 1 – 2 cm, and >2 cm) were measured and correlated with pre- or postoperative morbidity information obtained from the electronic medical record. For enhancing vascular lesions, vascular lesion edge was considered the margin of enhancement. For non-enhancing vascular lesions, vascular lesion edge was estimated as the margin of its T2 or T2 FLAIR weighted signal abnormality. Morbidity information in terms of weakness and aphasia as well as mortality was examined. Statistical analysis was performed using chi-square test and multivariate ANOVA.

RESULTS: Preliminary data focused on a subset of patients n=72 (vascular lesions near motor area) and n= 84 (vascular lesions near language areas). A significant trend was found between distance from vascular lesion to motor activation and the existence of weakness/paresis (p= 0.06). A significant association was found between distance of the lesion from Wernicke's area alone and the presence of the deficit (p =0.03).

CONCLUSION: Distance between vascular lesion edge and areas of primary motor and language function may serve as predictors of motor and language deficits respectively.
Qualitative Aspects of Treatment with Prolotherapy for Knee Osteoarthritis in a Multi-method Study

Authors: Lane Benes, BS; Luke Fortney, MD; Andrew Slattengren, DO; Jessica Grettie, BS; Jeffrey Patterson, DO; David Rabago, MD

Department: Department of Family Medicine, University of Wisconsin School of Medicine and Public Health

Mentor: David Rabago, MD

Support: Family Medicine Summer Student Research and Clinical Assistantship Program

BACKGROUND: Prolotherapy is an injection-based treatment for chronic musculoskeletal pain consisting of an irritant solution injected on painful ligament and tendon attachments and in adjacent joint space. Objective results in the parent study suggest a 30-40% improvement in overall knee osteoarthritis (OA) related quality of life compared to baseline status. The qualitative response of patients receiving prolotherapy is not known. The objective is to assess the qualitative response of subjects who recently received prolotherapy for knee OA in a clinical trial.

METHODS: Twenty-two participants were randomly selected from three recent knee OA prolotherapy studies. We conducted semi-structured, in-depth telephone interviews. Transcribed responses were discussed by co-authors to identify major themes; disagreements were resolved by consensus.

RESULTS: Qualitative data reflected variability in subject outcomes; most had substantial symptom reduction and quality of life improvement. Four major themes emerged: most participants reported (1) improvement in pain and ability to perform activities of daily living; (2) safety; there were no long-term side effects; (3) pre-treatment counseling enhanced treatment adherence and optimism; (4) overall positive experience with prolotherapy. Three minor themes emerged: (1) confirmation of current prolotherapy practices; (2) functional improvement without pain reduction; (3) prolotherapy has the potential to prolong surgery.

CONCLUSION: For most, prolotherapy improves pain and functioning without side effects. Clear, complete description of the study rationale and procedures may enhance optimism and adherence to treatment appointment. Regardless of clinical outcome, subjects reported that they would recommend prolotherapy to others and receive it again in the future for this or other indications, suggesting an overall positive clinical experience. Participant reports confirm the current use of multiple treatment sessions and recommendation of post-treatment rest. Prolotherapy may be a worthwhile treatment to prolong the need for surgery.

Flow Quantification with 4D Flow-Sensitive MRI: Validation in Patients with Congenital Heart Disease

Authors: Christina Boncyk, BS; Alex Frydrychowicz, MD; Michael Loecher, BS; Elizabeth J. Nett, BS; Ben Landgraf, BS; Kevin Johnson, PhD; Oliver Weiben, PhD; Christopher Francois, MD

Department: Department of Radiology, University of Wisconsin School of Medicine and Public Health

Mentor: Christopher Francois, MD

Support: Shapiro Summer Research Program and Department of Radiology

BACKGROUND: Cardiac imaging is critical in patients with congenital heart disease (CHD) for delineating cardiovascular anatomy and cardiac function. The use of cardiac MRI in patients with CHD is limited by long examination times and the need for suspension of respiration during image acquisition. Time-resolved, 3D flow-sensitive PC MRI has the potential to simplify image acquisition and streamline the analysis of blood flow in patients with CHD.

METHODS: This prospective study enrolled twelve subjects (2F/10M, 20.2±23.6 years) with a varying types of CHD according to our IRB-approved and HIPAA-compliant protocol. Studies were performed on 1.5T and 3.0T scanners (GE Healthcare, Waukesha, WI). LV and RV stroke volumes (SV) were calculated from CINE 2D SSFP images analyzed on a dedicated cardiac workstation (ReportCard 2.0, GE Healthcare, Waukesha, WI). 2D PC through the AscA and MPA was used for flow quantification (CV Flow 3.3, MEDIS, Leiden, NL). 3D radially undersampled, time-resolved, 3D flow-sensitive PC MRI was performed using a previously described technique, PCVIPR (Vastly undersampled Isotropic Projection Reconstruction) [1,2]. Quantification of flow through the AscA and MPA from the PCVIPR datasets was performed on home built MatLab software (The Mathworks, Natwick, MA). 2D datasets generated from the PCVIPR data were in the same orientation as the 2D PC acquisitions. AscA and MPA flow with PCVIPR was compared to LVSV and RVSV, respectively, measured with 2D SSFP using linear regression and Bland-Altman analysis.

RESULTS: PCVIPR data was acquired in all subjects. AscA and MPA flow measured with PCVIPR had a strong correlation with LVSV (R2=0.912) and RVSV (R2 =0.719), respectively, measured with 2D SSFP. Bland-Altman analysis showed mean bias of 28.30 mL +/- 34.45 between PCVIPR and 2D SSFP for quantification of LVSV and mean bias of 1.27 mL +/- 31.43 when for the RVSV.

CONCLUSIONS: An initial comparison of flow quantification was obtained through the AscA and MPA using a 3D radially undersampled, time-resolved, 3D flow-sensitive MRI technique, PCVIPR. Flow values obtained with PCVIPR correlated well with the standard of reference for quantifying LV and RV stroke volumes, CINE 2D SSFP. Bland-Altman analysis showed a tendency for PCVIPR to underestimate stroke volumes relative to CINE 2D SSFP and 2D PC. Despite these limitations, results provide encouraging evidence that PCVIPR has the potential to quantify blood flow in complex CHD patients.
Efficacy of Training Pediatric Residents on an Early Literacy Promotion Intervention

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Support: Shapiro Summer Research Program and Department of Pediatrics

BACKGROUND: For two decades it has been shown that promoting early literacy in primary care clinics is important for early brain development and school readiness. In addition, it builds family togetherness and provides physicians with an effective, “organic” route for developmental surveillance during the health supervision visit. However, the education of pediatric residents on this methodology is largely informal and varies greatly between and even within different residency training programs. Furthermore, there has not been a formal study completed that measures the effectiveness of such training, despite the fact that these residents represent the immediate future of pediatrics.

METHODS: We created a de-identified survey for first-year pediatric residents to complete at orientation that assessed their knowledge, attitudes, and values regarding early literacy promotion. We also surveyed second- and third-year residents who have not received formal early literacy promotion training. We identified each survey with a specific code to allow for later matching. During first-year resident orientation, we delivered a training module on early literacy promotion interventions. All of the residents were surveyed again after four months to determine effectiveness of the training module, to compare trained versus not-trained residents, and to look for differences in surveys between residents who work at clinics where Reach Out and Read (ROR - a national program that promotes early literacy interventions in clinics) is in operation versus those at clinics where it is not.

RESULTS: Preliminary analysis of data from the initial survey demonstrates that first-year residents have relatively little exposure to early literacy promotion as 8 of 14 (57.1%) recall hearing about it in their medical school curriculum and only 4 of 14 (28.6%) have participated in ROR. The follow-up data shows greater understanding of the importance of early literacy promotion with the lack of books at some continuity clinics being the main barrier preventing residents from giving out books at well child checks. A detailed statistical analysis is in progress.

CONCLUSIONS: The training appears to have positive effects, but specific conclusions are forthcoming following a detailed statistical analysis. We are incorporating data from a second training site at Northwestern Feinberg School of Medicine to increase our sample size and also look for similarities and differences between the two sites.

Effectiveness of Training in Improving Star Excursion Balance Test Performance in Collegiate Athletes

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BACKGROUND: The relationship between balance and risk of lower extremity injury has been well established. The Star Excursion Balance Test (SEBT) is a functional screening tool used to assess dynamic stability and neuromuscular control. Several studies have utilized the SEBT to show that poor balance is a risk factor for lower extremity injury (Plisky et al 2006, McGuine et al 2000). The purpose of this study is to assess SEBT performance before and after pre-season conditioning to determine whether or not focused training sessions are needed to improve SEBT reach distances and reduce injury risk.

METHODS: Thirty-six male subjects were recruited from the UW Division I Men’s Hockey and Football teams. Leg length and foot size measurements were taken at the beginning of the first session. The athletes performed the SEBT on two days separated by 5-8 weeks. The athlete maintained a single leg stance on a force plate with hands on hips, then reached with the free limb as far as possible in the anterior, posteromedial, and posterolateral directions (Plisky et al 2006). The greatest of three trials for each reach direction was used for analysis of the reach distance in the respective direction. The greatest reach distance from each direction was summed in reference to the athlete’s leg length to yield a composite reach distance for analysis of the athletes’ overall performance on the test.

RESULTS: There was a significant decrease in anterior reach distance for both the right and left legs (p<0.05) but no anterior right/left reach distance difference (p>0.05). All other reaches: right leg posteromedial, both posterolateral and both composite reaches showed significant increases (p<0.05) in the second session.

CONCLUSIONS: All athletes were given a single leg stance on a force plate with hands on hips, then reached with the free limb as far as possible in the anterior, posteromedial, and posterolateral directions (Plisky et al 2006). The purpose of this study is to assess SEBT performance before and after pre-season conditioning to determine whether or not focused training sessions are needed to improve SEBT reach distances and reduce injury risk.

CONCLUSIONS: Although our definitive goal of this study is to associate balance measurements with risk of lower extremity injuries, we are currently unable to make these correlations due to the in-season status of the athletes. However, previous studies have shown that decreased normalized composite reach distances and greater anterior right/left reach distance difference predicted lower extremity injury (Plisky et al 2006). Our results demonstrate increases composite reaches and no anterior right/left reach distance difference following conventional training regimes with Division I Men’s Hockey and Football teams. These findings indicate that UW Athletic training programs for collegiate athletes are effective for improving balance and reducing lower extremity injury.
Role of Routine Axillary Ultrasound in the Pre-Operative Management of Patients with Breast Cancer

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Support: Shapiro Summer Research Program and Department of Surgery

BACKGROUND: Sentinel lymph node (SLN) biopsy is standard of care in establishing axillary status in breast cancer patients. However, preoperative axillary ultrasound combined with core needle biopsy may aid in surgical treatment decisions. The objective was to evaluate the impact of axillary ultrasound and core needle biopsy on breast cancer surgical decision-making.

METHODS: Breast cancer patients with clinically negative axilla who underwent axillary ultrasound from 9/2009-6/2010 (n=56) were identified. Charts were reviewed for demographic, treatment, and tumor characteristics. Lymph nodes were identified as suspicious for malignancy or benign and correlated with final pathology. Descriptive statistics were generated and sensitivity and positive predictive value for axillary ultrasound calculated.

RESULTS: Axillary ultrasound was abnormal in 36% (n=20), identified most frequently by cortical thickening (75%) and loss of fatty hilum (30%). Patients with suspicious ultrasounds (compared to benign) were younger (median age 59[28-80] vs. 66 [36-91], p=0.05), had larger tumors (1.9[0.4-8] vs. 1.1 [0.2-5.5], p=0.002), and higher scores on the SLN Metastases Nomogram (48%[10-84] vs. 21%[6-66], p=0.0002). Core biopsy was positive in 7/20; 6 patients proceeded directly to ALND and 1 to neoadjuvant therapy. Four patients were not amenable to biopsy; 2 had positive nodes at surgery.

Six of 36 (11%) patients with benign ultrasounds had positive SLNs. Retrospective review of these images did not identify suspicious nodes. Median SLN metastasis size was 0.4 cm and was the only positive node in most patients. A non-selected subset of patients with benign axillary ultrasounds (n=17) had SLN frozen section performed. SLN was positive in 4 (24%), leading to immediate ALND. Overall sensitivity of axillary ultrasound in detecting metastases was 63% with a positive predictive value of 50%.

CONCLUSIONS: Axillary ultrasound decreased SLN positivity to 17% (24-32% in the literature) and altered treatment planning in 13%, making axillary ultrasound a useful adjunct but not replacement to SLN biopsy. Additionally, axillary ultrasound does not preclude the utility of frozen section, as 24% of SLNs sent for frozen section had metastases identified. Based on current data, the routine use of axillary ultrasound in the pre-operative setting directly impacts clinical care and is warranted. Future research will focus on criteria used to select patients for pre-operative ultrasound to more cost-effectively identify patients at risk for positive nodes.

Development of in vitro Blood Brain Barrier Model of CNS Dissemination of Mycobacterium Tuberculosis

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Support: Shapiro Summer Research Program and the National Institutes of Health

BACKGROUND: Dissemination of Mycobacterium tuberculosis into the CNS is one of the most devastating clinical manifestations of tuberculosis (TB). However, there are currently no available animal models to study the pathogenesis of CNS TB. In this study, we attempted to define the mechanism of Mtb dissemination across the blood-brain barrier (BBB) by testing the “Trojan horse” hypothesis that Mtb-infected dendritic cells carry mycobacterium across the BBB. Deeper understanding of the mechanism of Mtb dissemination into the CNS may enable us to propose novel therapeutic strategies for CNS TB.

METHODS: Dendritic cells (DCs) were isolated from the bone marrow of mice genetically engineered to express Discosoma red (DsRed) fluorescent tracer protein in all cells and cultured for 10 days. Non-adherent cells were collected and re-plated once during maturation to exclude macrophages. To create the in vitro BBB, mouse brain capillary endothelial cells and astrocytes were plated on either side of a 6.5mm Transwell pure polyester membrane (0.4µm pores) and grown in 10% fetal bovine serum in DMEM media at 37°F for 5 days. On Day 5, a portion of the bone marrow-derived DCs were infected for 2 hours with human Mtb Δ6220, a green fluorescent protein-labeled strain, at a ratio of 2 bacilli/DC. 2.5x10^5 infected or naïve DsRed DCs in serum-free DMEM were then added to the top of the BBB and incubated at 37°F for 16 hours. The cells that migrated through to the bottom of the well were collected, counted and immunophenotyped using flow cytometry. The experiment was performed in duplicate.

RESULTS: Transepithelial electrical resistance (TEER) was measured at day 1 of BBB culture, day 5 prior to application of DCs, and day 6 post-harvest of migrated DCs. TEER increased by an average of 9.46 and 9.40 Ω·cm² on Plates 1 and 2 respectively between Day 1 and Day 5, verifying the formation of the BBB barrier. The average change in TEER after DC migration was higher in wells with naïve DCs as compared to infected DCs (2.82 Ω·cm² v. 1.38 Ω·cm²). The proportion of DCs that migrated was similar between infected and naïve DCs (Plate 1: 12% v. 11%, Plate 2: 5% v. 4%). Flow cytometry analysis revealed no difference in expression of CD80, CD40, or Ly6C on the DsRed+CD11c+CD11b+ infected and naïve DCs.

CONCLUSIONS: These data support the feasibility of generating an in vitro BBB using murine-derived cells and suggest that DCs can carry Mtb across the BBB.
Regulation of Ion Channel Activation Following Spinal Cord Injury

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BACKGROUND: Chronic neuropathic pain (NP) following spinal cord injury (SCI) is a clinical problem affecting up to 70% of SCI patients. The mechanisms underlying NP are not well understood, which has limited development of effective analgesics to treat NP. Previous work has established that the Na+/K+-Cl- cotransporter 1 (NKCC1) is upregulated following SCI. NKCC1 mediates Cl- ion influx and when upregulated can reverse the normal inhibitory action of the neurotransmitter GABA by altering the Cl- equilibrium potential. This represents a possible mechanism through which NP develops. The purpose of this study was to determine how NKCC1 is activated following SCI. The target of interest was the with-no-lysine(K)-1 (WNK1) kinase, which has been implicated in NKCC1 phosphorylation in previous studies.

METHODS: Spinal Cord Injury: Adult male Sprague-Dawley rats were anesthetized by inhalational anesthetic and laminectomies were performed at the T9 spinal level. Contusive SCI was induced at T9. Western Blotting: Monoclonal antibody against NKCC1 (T4; Developmental Studies Hybridoma Bank; Iowa City, IA), and anti-WNK1 polyclonal antibody (R&D Systems) were used for detection of NKCC1 and WNK1, respectively. Densitometric measurement of each protein band was performed with MetaMorph and Table Curve. Immunohistochemistry: Animals were sacrificed and perfused with 4% Paraformaldehyde. Spinal cords were harvested and coronal and axial sections (50 μm thick) were obtained from the injury epicenter. Sections were stained for phosphorylated WNK1 (p-WNK1) and cell nuclei, ToPro3. Antibodies pWNK1 Primary: pWNK1 R&D Systems 1:100 dilution. Secondary: Goat anti-rabbit Alexa Fluor 488 (Invitrogen) 1:200 dilution.

RESULTS: The active form of NKCC1 (phosphorylated) was upregulated following SCI consistent with previous work. Importantly, WNK1 levels were also upregulated following SCI in a time frame corresponding with NKCC1 activation. NKCC1 and WNK1 levels were increased as early as 1 day following SCI and remained elevated 7 days following injury.

CONCLUSIONS: The early expression of WNK1 following SCI may provide a crucial link between SCI and the development of neuropathic pain. By activating NKCC1, WNK1 may ultimately be responsible for alterations in ion homeostasis that contribute to inappropriate excitability of sensory neurons and NP. It remains to be determined where in the spinal cord WNK1 is expressed and how injury leads to its activation.

Fine Needle Aspiration of the Thyroid: A Contemporary Experience of 3,981 Cases

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Support: Shapiro Summer Research Program and Department of Surgery

INTRODUCTION: Fine needle aspiration (FNA) is an essential tool for the management of thyroid nodules. Recently, several national organizations have recommended FNA of all thyroid nodules >1 cm. With the increase use of imaging in the practice of medicine over the last decade, the number of incidentally discovered thyroid nodules is rising. Therefore, we analyzed our experience to determine if these changes in practice led to alterations in the population of patients undergoing FNA at our institution.

METHODS: Data were collected from 3,981 consecutive patients who underwent thyroid FNA at our institution between 2002 and 2009. Patients were divided in two groups: the early time period 2002-2005 (Group 1) and later time period 2006-2009 (Group 2). Data from the two groups were analyzed with ANOVA and Chi-squared tests (SPSS, Inc.). (Mean ± SE)

RESULTS: In comparing the groups, the number of FNAs performed in the later time period increased significantly by 250%. A significant increase in the number of FNAs per individual was not seen. Patients in the later time period (Group 2) were more likely to be female and were significantly older. With regard to FNA diagnoses, the number of benign FNAs increased while the percentage of cancerous and neoplastic FNAs decreased. There also appears to be an increase in the incidence of thyroiditis.

CONCLUSIONS: The use of thyroid FNA has markedly increased during this contemporary series. This rise in thyroid FNA appears to be due to biopsy of benign thyroid nodules. With time, more females and older patients have undergone FNA, possibly reflecting the increase use of imaging studies in this patient population.
**Inflammatory Profile of Vocal Fold Fibroblasts in Response to Cigarette Smoke Extract**

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Support: Department of Surgery NIH grant T32 DC009401

**BACKGROUND:** Tobacco smoke is the dominant risk for laryngeal squamous neoplasia and chronic laryngitis. The hallmark of many laryngeal diseases is the onset of mucosal inflammation, which can affect the critical functions of swallowing, breathing, coughing, and voice. While we currently have a limited understanding of how mucosal inflammation is manifested in response to cigarette smoke, we know that tissue-specific fibroblasts are able to mediate chronic inflammation of other tissues through the secretion of soluble cytokines and paracrine regulation. In Reinke’s edema of the vocal fold, lamina propria fibroblasts are the primary cell type exposed to the inflammation-induced edema associated with cigarette smoke exposure. Here we profile the cytokine response of human vocal fold fibroblasts to cigarette smoke exposure in vitro.

**METHODS:** Following accepted protocol of cigarette smoke extract (CSE) production, one Marlboro cigarette was combusted into a 30 mL syringe at a rate of 3 extractions/minute over 5 minutes. The smoke was bubbled into 10 mL of cell culture media. This CSE was neutralized to pH 7.4, filtered, adjusted to OD 1.0 (320nm) with a spectrophotometer and denoted 10% CSE. The control for CSE was air bubbled into the media. TNF-α (10 ng/mL) was used as a proinflammatory cytokine control. Immortalized human vocal fold fibroblasts (hVFF) were transiently treated for 3 hours with 0.5 and 1% CSE before being washed 2 times with 1x PBS and then returned to normal media for 24 hours. Trypan blue exclusion determined that cell death did not occur with CSE treatment. Cytokine levels of the media were assessed by the Bio-Rad Bio-Plex 200 assay reader.

**RESULTS:** CSE (1.0%) had a significant increase in VEGF levels compared to control, CSE (0.5%) and TNF-α. Although CSE (1.0%) exposure did show the trend of increasing IL-8 levels, this increase was not statistically significant. IL-1B, IL-12 and Eotaxin levels did not change.

**CONCLUSIONS:** Transient exposure of 1/10 of a combusted cigarette (CSE, 1.0%) showed the specific secretion of the angiogenesis regulatory cytokine VEGF relative to other treatments. Therefore, hVFFs could participate in the angiogenesis necessary for inflammation through the paracrine regulation of other tissues in the larynx. Lastly, since fibroblasts can mediate the inflammation associated with certain diseases, altering the immunomodulatory response of hVFFs could prevent diseases associated with mucosal inflammation of the larynx.

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**Incidence of Bowel Obstruction after Restorative Proctocolectomy: Higher with Laparoscopic Approach?**

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Support: Department of Surgery NIH T35 Short Term Training Grant DK062709-05

**BACKGROUND:** Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the gold standard surgical treatment for chronic ulcerative colitis. More recently, this procedure is being performed laparoscopically assisted. Post operatively, small bowel obstruction (SBO) is one of the more common associated complications. However, it is unknown whether the addition of a laparoscopic approach has changed this risk. This study aims to assess and compare the incidence of SBOs after both open and laparoscopic restorative proctocolectomy.

**METHODS:** All subjects that underwent restorative proctocolectomy from 1998-2008 were identified from the University of Wisconsin Colorectal Surgery Database. Medical records were reviewed for all cases of SBOs, confirmed by a combination of symptoms and radiological evidence. The incidence of SBO was subdivided into pre-ileostomy takedown, early post-ileostomy takedown (30 days post), and late post-ileostomy takedown (30 days to 1 year post). Several potential risk factors were also evaluated. Statistical analysis was performed utilizing Fisher’s exact (for incidence) or T-tests (for means). Significance was defines as P<0.05

**RESULTS:** A total of 290 open cases and 100 laparoscopic cases were identified during this time period. The laparoscopic group had a significantly lower BMI, decreased length of hospital stay, shorter time to takedown, lower % of males, fewer prior bowel resections, fewer prior other abdominal procedures, and longer operating room times. The differences between the groups were controlled for using a logistic regression. The overall incidence of SBO at 1 year post-ileostomy takedown was similar between groups (open n=42; 14.5% and laparoscopic n=16, 16%) (p=0.75). The time frame and severity, defined as SBOs requiring operation and number of recurrent SBOs, were similar between groups with the laparoscopic group trending towards SBOs occurring in the pre-takedown period. Significant risk factors for SBO include coronary artery disease, prior appendectomy, and postoperative ileus.

**CONCLUSIONS:** The burden of postoperative small bowel obstruction after restorative proctocolectomy is not changed with a laparoscopic approach. Most cases occur in the early post-operative period.
**Theoretical Increase of Thyroid Cancer from Cervical Spine MDCT in Pediatric Trauma Patients**

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**BACKGROUND:** There has been a dramatic increase in the number of multi-detector computed tomography (MDCT) scans performed each year in the United States. The risk and clinical justification for many of these procedures is under question. The purpose of this study is to determine the amount of radiation absorbed by the thyroid from a CT of the cervical spine compared to plain radiographs, and to calculate the theoretical thyroid cancer induction risk from these studies.

**METHODS:** A retrospective evaluation of a pediatric trauma database was performed at an academic, Level I trauma center. Inclusion criteria were: level I or II trauma patients, cervical spine imaging performed at our institution, and age <18 years. Amount of radiation absorbed by the thyroid from plain radiographs and CT of the cervical spine during clearance were calculated. ImpACT Patient Dosimetry Calculator was used to determine the absorbed dose to the thyroid from CT. Relative risk was determined by multiplying total amount of radiation (mGy) by sex-specific cancer-induction rates based on the 2006 Biological Effects on Ionizing Radiation VII report. Results were stratified by age and sex.

**RESULTS:** Six-hundred seventeen patients met the inclusion criteria, 224 receiving plain radiographs and 393 undergoing CT of the cervical spine. The average amount of radiation absorbed to the thyroid was 0.90 mGy (males) and 0.96 mGy (females) from plain radiographs and 63.6 mGy (males) and 64.2 mGy (females). The median excess relative risk of plain radiographs is 0.24% (males) and 0.51% (females) and for CT is 13.0% (males) and 25.0% (females). Young (0-6y) males and females have the highest ERR for one CT scan, 21.5% and 45.5% respectively, compared to the older two groups. Males 7-11 years had a 13.5% ERR and females 7-11 years a 29.7% ERR, while the adolescent male group (12-17y) had a 12.0% ERR and female adolescent group (12-17y) a 22.7% ERR.

**CONCLUSIONS:** Cervical spine CT results in a significantly higher dose of radiation to the thyroid than plain radiographs. Further, CT has a much greater potential to induce thyroid cancer, particularly in females and younger-aged patients. Additionally, there is a statistically significant difference in cancer induction rates between young children and teenagers of both genders with older patients being affected to a greater degree. These findings support the prudent development of protocols to minimize use of diagnostic CT in pediatric trauma patients.

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**Adherence to Gait Analysis Recommendations Based on Surgeons’ Affiliation with the Gait Laboratory**

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**BACKGROUND:** No studies have investigated how the effectiveness of gait analysis (GA) in influencing surgical treatments differs based on the relationship of the referring surgeon to the examining gait laboratory (gait lab). The current study examined differences in the adoption of GA recommendations among surgeons with varying degrees of affiliation with the examining gait lab. Our main hypothesis was that the influence of GA recommendations on surgical decisions would be greatest among referring surgeons most closely affiliated with the gait lab.

**METHODS:** This study examined retrospective data from children with cerebral palsy, ages 3-18 years, who underwent pre operative GA at our institution. Of 104 subjects, 37 were referred by surgeons directly affiliated with the gait lab (direct affiliation), 47 by surgeons practicing at the same institution but not directly affiliated with the gait lab (institutional affiliation), and 20 by surgeons not affiliated with the gait lab (no affiliation). Agreement among sources for each subject was defined as the ratio of the number of procedures recommended by both sources to the number of procedures recommended by either source. Procedures were counted separately for each side.

**RESULTS:** Surgeons affiliated with the gait lab (direct or institutional) had a higher average agreement between surgical treatments and GA recommendations than surgeons not affiliated with the gait lab. Furthermore, affiliation with the gait lab increased the likelihood that the surgeon would follow all of the GA recommendations for a patient. Surgeons in all groups frequently dropped procedures not recommended by GA, but were less likely to add procedures recommended by GA, with significantly fewer procedures being added by surgeons not affiliated with the gait lab (all P-values <0.001).

**CONCLUSIONS:** This study demonstrates that GA influences the surgical treatment plans of surgeons who are not affiliated with the examining gait lab, although the influence is stronger when the surgeons practice within the institution of the gait lab, and strongest when the surgeons are directly affiliated with the gait lab. Additional education could increase the degree to which outside physicians follow gait lab recommendations. Surgeons from an outside institution were least likely to add procedures recommended by GA, demonstrating that there may also be a limit to the influence of GA due to institutional differences and differences in individual surgeons’ practice patterns.
Outcomes of *C. difficile* Infection in Intra-abdominal Solid Organ Transplant Recipients

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**Support:** Shapiro Summer Research Program and Department of Medicine

**BACKGROUND:** Among recipients of intra-abdominal, solid organ transplants, diarrhea is a common problem and *Clostridium difficile* is an increasingly recognized pathogen. Knowledge of outcomes of *C. difficile* Infection (CDI) in SOT recipients is limited.

**METHODS:** We undertook a retrospective cohort study of all recipients of kidney and liver transplants diagnosed with CDI at a single center over a 13-year period. Data pertaining to all episodes of CDI were collected. Multivariate analysis using logistic regression was performed to determine independent predictors of clinical cure and 1-year mortality.

**RESULTS:** 106 kidney and 63 liver transplant recipients had 215 episodes of CDI. 80% of patients had a single episode and 16% had two episodes. There were 106 (62%) men and 64 (38%) women with a mean age of 55 (SD 10.93, range 25-75). Among all episodes, 48 patients (22%) had fever, 33 (15%) were hypothermic, 67 (31%) were hypotensive, and 37 (17%) were tachycardic. 11 (5%) were in the ICU. 14 (6.5%) were on vasopressors. Overall, 162 episodes (75%) were cured with 62 episodes (75%) in liver recipients and 100 episodes (76%) in kidney recipients. In 103 episodes (48%), patients were cured within 14 days. 13 patients (8%) died during hospitalization and 49 patients died within one year. No deaths were attributed to CDI. In multivariable analysis using death during hospitalization as the outcome, female gender was associated with a lower risk of death (OR 0.08, 95% CI 0.01-0.71), and hemodialysis, whether acute or chronic was associated with a higher risk of death (OR 9.09, 95% CI 2.5-33.3)

**CONCLUSION:** CDI in solid organ transplant recipients is associated with a 75% cure rate. Risk factors for death during hospitalization include male gender and hemodialysis.

The Capacity of Aryl Hydrocarbon Receptor Ligands to Alter the Onset and Severity of EAE

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**Support:** Department of Surgery NIH T35 Short Term Training Grant DK062709-05

**BACKGROUND:** The aryl hydrocarbon receptor (AHR), a cytosolic transcription factor characterized for binding the toxin 2,3,7,8-tetrachlorodibenzo-p-dioxin, is currently being investigated for a role in T cell differentiation. Previous studies have shown *in vitro* that the endogenous ligand 6-formylindolo[3,2-b]carbazole (FICZ) augments T helper 17 cells while the potential ligand kynurenine (Kyn), the first tryptophan derivative in the indoleamine 2,3-dioxygenase (IDO) pathway, promotes regulatory T cells (Tregs). These intriguing *in vitro* data led us to examine the AHR's *in vivo* role. We chose experimental autoimmune encephalomyelitis (EAE), a multiple sclerosis animal model, to investigate whether FICZ or Kyn modulate disease pathology in C57BL/6 (WT) and AHR null (Null) mice.

**METHODS:** We induced EAE using 100μg myelin oligodendrocyte glycoprotein peptide 35–55 (MOG). WT mice were separated into four groups: control, MOG immunization (MOG), MOG immunization containing FICZ (FICZ MOG), or MOG immunization with intraperitoneal Kyn injections (Kyn MOG). Null mice received either MOG or Kyn MOG. Mice were monitored daily for clinical disease scores: 0 - no symptoms; 1 - tail paralysis; 2 - hindlimb paresis; 3 - hindlimb paralysis; 4 - hindlimb and forelimb paralysis; 5 - moribund.

**RESULTS:** Compared to WT MOG, WT FICZ MOG had an increased mean clinical score and WT Kyn MOG intermittently delayed disease onset. There was no difference between Null MOG and Null Kyn MOG. Delayed disease onset was seen in Null mice compared to WT MOG. Flow cytometry of cervical lymph nodes during acute disease revealed an increase of Tregs in WT Kyn MOG (10.7%) compared to controls (8%) while a decrease was seen in WT MOG (6.44%) and WT FICZ MOG (7.3%). Additionally, as determined by flow cytometric bead array analysis of supernatants, WT FICZ MOG spleen cells produced higher levels of IL-17, IFN-γ, and TNF-α during peak disease.

**CONCLUSION:** The AHR plays a role in EAE. Null mice demonstrate delayed onset of disease, alluding to the AHR's physiologic role in T cell differentiation. FICZ leads to aggravation of disease and increased IL-17 while Kyn can delay disease and leads to increased Tregs in WT mice. Kyn does not affect disease in Null mice but intermittently abrogates disease in WT mice alluding that IDO works via the AHR. This work will lead to a greater understanding of AHR ligands which could ultimately define novel therapeutic strategies in autoimmunity and organ transplantation.
The Novel Use of Glucose Measurements for Detecting Compartment Syndrome

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BACKGROUND: Compartment syndrome (CS) is a condition in which an injury to a muscle compartment in the body can swell to the point where venous pressure equals arterial inflow and renders the muscle ischemic. This has devastating outcomes if not treated promptly with an open procedure referred to as a fasciotomy, which involves surgically opening the compartments and skin. Currently, the methods for detecting a CS are antiquated and rely on pressure sensors. These have proved to be unreliable and give values that are difficult to interpret and unfortunately lead to unnecessary fasciotomies, which are highly morbid procedures. Our goal was to develop a new method to detect CS by measuring the glucose levels within the compartment, expecting them to decrease in the setting of a CS, providing a marker for who needs fasciotomies.

METHODS: Dogs were anesthetized and pressure and glucose monitors were inserted percutaneously into the two anterior lower leg compartments. One of the compartments then had saline pumped into it causing the venous pressure to rise, creating a CS. The pressure was maintained for 8 hours while the glucose levels were recorded. The glucose levels in the saline-injected leg (with a created CS) were compared to the non-injected leg to determine the usefulness of glucose levels in diagnosing a CS.

RESULTS: In the limited number of experiments that were able to be accomplished there was an observed trend of decreased glucose levels within the saline-injected leg almost immediately subsequent to the initiation of the CS in all cases. Although the reliability of the glucose monitors throughout the entirety of the experiment was questionable in some of cases, there were two trials that had more stable results. In these experiments there was an average drop in glucose to 32% of the original value within 30 minutes of the CS being created as compared to 93% in the control leg.

CONCLUSIONS: Monitoring glucose levels within the muscle compartment of a suspected CS may prove to be a useful diagnostic tool for determining the necessity for the performance of a fasciotomy. The glucose levels appear to drop off as the pressure builds within the compartment, essentially cutting off the delivery of necessary nutrients to the muscle, which could lead to muscle necrosis. With further studies, reliable data could be obtained to determine a specific level of glucose that must be breached to result in necrosis and thus the need for a fasciotomy.

Identification of the Role of the Survivin Gene in Pancreatic Beta Cells

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BACKGROUND: Diabetes is a disease that affects over 20 million people in the United States. Both type 1 and type 2 diabetes result from reduced functional beta cell mass in the pancreas. In type 2 diabetes, there is an increased requirement for beta cells due to peripheral insulin resistance, and this demand cannot be met. Survivin has been identified as a gene that plays an important role in both beta cell proliferation, through the regulation of mitosis, and in the prevention of apoptosis. Using transgenic mice overexpressing survivin, the purpose of these experiments is to determine whether survivin overexpression is sufficient to correct the beta cell deficit in a mouse model of type 2 diabetes. We propose that increased expression of survivin will increase beta cell proliferation, and it may also decrease beta cell apoptosis. Overall, this will lead to increased beta cell mass.

METHODS: Experiments were to be conducted on obese mice that overexpress the survivin gene in beta cells (RIP-survivin transgenic mice) and compared to control obese mice that are known to develop hyperglycemia by 6-10 weeks of age. Based on our hypothesis, the RIP-survivin mice should exhibit improved insulin secretion and reduced glucose levels due to improved beta cell function, despite ongoing insulin resistance. To accomplish this comparison, 4 basic procedures were performed: Blood draws via a retro-orbital bleed to determine fasting glucose and insulin levels; Glucose tolerance tests (GTT) and insulin tolerance tests (ITT) via administration of glucose or insulin as intra-peritoneal injections, followed by blood samples at specific intervals between 0-2 hours; ELISA to determine blood insulin levels; Glucose assays to determine blood glucose levels. Animals were genotyped using polymerase chain reaction (PCR) on tail snip DNA using transgene specific primers.

RESULTS: It was ultimately determined via PCR genotyping that the transgene for survivin had been inadvertently lost during outbreeding to a new strain. In preparation of the arrival of new transgenics, protocols were developed and tested on control obese mice to yield successful GTT’s, ITT’s, ELISA tests and glucose assays.

CONCLUSIONS: The survivin transgene was no longer present in animals from the diabetic strain due to genotyping errors during the breeding process. Glucose tolerance tests in obese control mice from this diabetic strain show significant hyperglycemia and reduced insulin secretion.
Performance of Generic Health Related Quality of Life Instruments in Heart Failure Clinics

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BACKGROUND: Increasingly, generic health related quality of life (HR-QoL) tools are used to measure clinical efficacy. We studied associations between HR-QoL scores and clinical outcomes in patients (pts) newly referred to tertiary heart failure (HF) clinics.

METHODS: Pts with symptomatic HF and ejection fraction < 40% were recruited from 3 HF clinics. Pts completed 5 generic HR-QoL surveys (Health Utilities Indexes Mark 2 (HUI2) and 3 (HUI3), EuroQol-5D (EQ-5D), Quality of Well Being Scale (QWB-SA), Short Form (SF-6D), and the disease-specific Minnesota Living with Heart Failure questionnaire (MLHF). Data were obtained at the 1st HF clinic visit (BL) and 6 months later. Clinical improvement was defined as improved self-reported dyspnea (0=None to 3=at rest) and NYHA class. Correlations between survey scores and change in dyspnea/ NYHA class were assessed.

RESULTS: 160 HF pts (108 men) completed the study. Mean dyspnea score improved (BL:1.44±1.0, 6 mo:0.45±0.8, p<.0001), as did NYHA class (BL: 2.7±0.8, 6 mo 2.2±0.8, p=0.0003). No significant change was seen in the HUI2/HUI3 or EQ-5D during followup. QWB-SA, SF-6D from SF-12v2 and SF-6D SF-36 scores changed significantly and were weakly correlated with change in dyspnea (R=.12, .03 and .09, respectively). MLHF was most strongly associated with clinical improvement (p=.001 for correlation with dyspnea score, R=.274). Pain, sensory and cognition domains performed less well in HF than physical functioning domains, when not focused on mobility, and vitality domains.

CONCLUSIONS: Generic HR-QoL instruments detect clinical change in HF pts less well than disease-specific instruments; some have no ability to detect significant clinical improvement. Domains included in surveys may be important. Our findings suggest that generic HR-QoL surveys do not always adequately assess quality of HF care.

Influence of Hamstring Muscle Activity on Pelvic and Lower Extremity Motion during Walking

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BACKGROUND: Crouch gait is characterized by excessive knee and hip flexion during the stance phase of walking. Tight hamstrings have been implicated, with treatments aimed at releasing hamstring tension. However, clinical outcomes remain inconsistent, with some patients exhibiting excessive anterior pelvic tilt. The purpose of this study was to clarify the contribution of the hamstring muscles to pelvic and lower extremity motion during gait.

METHODS: Nineteen healthy young adults performed four 90 s walking trials on an instrumented treadmill. Ground reaction forces were monitored and used to trigger a muscle stimulator at either terminal swing or early stance in random gait cycles. The stimulator delivered a 90 ms pulse train to the right hamstrings via surface electrodes. Whole body kinematics and lower extremity EMG activities were recorded. These data were used to determine the onset and specificity of the stimulation, and pelvis, hip, knee, and ankle angles. Induced motion was defined as the change in joint angles between non-stimulated and stimulated strides, measured at 100 ms intervals following the stimulation (t-tests, p ≤ 0.05).

RESULTS: Electrical stimulation of the hamstrings significantly increased knee flexion (~3o) and hip extension (~1o) during stance. Hamstring activity also generated greater pelvic tilt and dorsiflexion (~2o each). The directions and magnitudes of induced joint motion were similar whether the hamstrings were stimulated during late swing or starting at heel contact. Induced motions were greatest at 300 ms after the stimulation onset, with trajectories returning to normative values at ~500 ms.

CONCLUSIONS: Electrical stimulation of the hamstring muscles induced significant changes in lower extremity posture during stance. The greatest effect was enhanced knee flexion, contradicting prior modeling studies which suggested that the hamstrings have greater influence at the hip, and may induce knee extension. The results also demonstrated that hamstring activity induces posterior pelvic tilt, hip extension and ankle dorsiflexion. Hence, releasing hamstring tension may reduce knee and ankle flexion, but could result in excessive hip flexion and anterior pelvic tilt if over-lengthened. We conclude that the relative influence of hamstring activity on individual joint angles may contribute to the adverse outcomes that are sometimes seen clinically, and should be considered when planning crouch gait treatments.
Analysis of Language and Memory Lateralization by Functional MRI and WADA Test in Epilepsy and Effect of Gender on Postoperative Seizure Improvement

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BACKGROUND: The intracarotid sodium amobarbital procedure (ISAP or WADA test) lateralizes cerebral functions to the cerebral hemispheres preoperatively. Functional magnetic resonance imaging (fMRI) is increasingly used to analyze preoperative language lateralization. In this study, concordance of fMRI with WADA was examined in patients with medically intractable seizures. The relationship of the distance between the epileptic focus to functional activation area with patients’ post-operative deficits in language is also analyzed.

METHODS: This study includes 17 patients with preoperative fMRI and WADA (n=17 for language tests, n=9 for memory, age range: 12-49). The images were analyzed using established fMRI paradigms for language and memory (Moritz/Haughton 2003). Activation of Broca’s and Wernicke’s areas were measured in three dimensions. A threshold-dependent lateralization index (LI) was calculated for language areas: LI = [(L-R)/(L+R)] * 0.5. LI>0.25 is considered left-hemisphere dominant, 0.25< LI < -0.25 considered bilateral, and LI<-0.25 considered right dominant. An experienced technologist’s interpretation of memory lateralization was utilized for analysis. Standard neuropsychiatry WADA test procedures were used for comparison. The shortest distance between a language area to the border of surgical focus (LAD) was measured (<10mm, 10-20mm, or >20mm) and compared with postoperative language deficits. The effect of gender on postoperative seizure improvement was also analyzed. Improvement (binary decision) was based on postoperative neurologic assessment at 6 months and/or reduction in seizure medication dose at 6 months. Chi square tests, Fisher’s exact test, ANOVA, and Student’s t-test were performed for statistical analysis.

RESULTS: Concordance between fMRI and WADA is 82.4% (p=0.88) for language dominance and 66% (p=0.64) for memory. No correlation was found between LAD and post-op language or memory deficit (p-value= 0.46 for language; p=0.37 for memory). Females demonstrated increased postoperative seizure improvement (Fisher’s p-value= 0.009; female=12; male=7). Gender groups had no significant difference in terms of age, handedness, preoperative seizure types, or location of surgical focus.

CONCLUSIONS: Language concordance between fMRI and WADA is similar to that reported in prior studies. Targets for future studies include further examination of the concordance of fMRI with WADA for memory paradigms and further correlation of LAD with language / memory deficits. However, this study clearly demonstrates fMRI as a useful preoperative adjunct to WADA for language lateralization in patients with medically intractable seizures.

Utilizing Diffusion Tensor Imaging to Predict Post-Surgical Outcomes in Brain Tumor Patients

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BACKGROUND: The use of Diffusion Tensor Imaging (DTI) in pre-surgical planning is rapidly growing. DTI utilizes magnetic resonance to detect the diffusion of water and the brain’s white matter structure. This information enables surgeons to be more confident in their resection margins and plan their approach to minimize damage to key fiber tracts including the corticospinal tract (motor), cingulum, and the superior longitudinal fasciculus. While studies have demonstrated better outcomes when surgeons utilized DTI information for surgical planning, our focus is on examining how tumor characteristics, as measured by DTI, affected patient outcomes.

METHODS: Our study examined patients who received a pre-operative DTI and underwent a primary or metastatic brain tumor resection at UW-Madison or Madison VA hospital. The unprocessed DTIs were obtained incidentally during fMRI sessions and played no role in the patients’ pre-surgical plans. As of publication, 32 patients have been processed, with 12 female and 20 male participants. The identification and processing of additional patients is still underway. Of those completed, fractional anisotropy (FA) maps were computed. Tumor location and its distance to the cingulum, corticospinal tract and superior longitudinal fasciculus were measured. Initial morbidity and mortality relied on a previous study that examined the impact of tumor location based on fMRI1. Mortality information was updated through the use of government death indexes.

CONCLUSIONS: This research remains a work in progress. Previous studies indicate that additional patients are required to have sufficient projected power (20-30 more subjects for a total of 50-60). Several technical factors have made this research project problematic. The research focus on mortality required the use of older DTI studies (2002-2008). During that period, DTI remained a new technique and the parameters of the scans changed frequently. For example, early scans utilized as few as 13 gradient directions, while currently 26 gradients are used resulting in greater fidelity. Standardizing the scans and computing the DTI FA maps took considerable effort. As research progresses, new data will be compared to the previous results obtained in the fMRI study1.
Patient Preferences for Surgical or Percutaneous Intervention in Multi-Vessel Coronary Artery Disease

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BACKGROUND: Physicians alter clinical practice based on results from interventional trials that use major adverse cardiovascular events (MACE) as a grouped endpoint. Recently, the SYNTAX Trial investigated revascularization of multi-vessel coronary artery disease (mv-CAD) with coronary artery bypass graft surgery (CABG) or multi-vessel percutaneous intervention with drug-eluting stents (mv-PCI) utilizing a MACE endpoint of death, stroke, myocardial infarction and repeat procedure. Investigators imply that each part of a MACE endpoint is viewed equally when designing trials and drawing conclusions. However, patients may reach different conclusions. We hypothesize that patients and physicians do not value the risks comprising the MACE endpoint equally.

METHODS: Thirty-one cardiac care physicians and 550 patients with known or suspected CAD were presented with a hypothetical scenario detailing revascularization for mv-CAD. Based on the results of the SYNTAX Trial, subjects were given risks of death, stroke, and need for second revascularization procedure (3%, 2%, and 5%, respectively) within one year of surgical bypass. Subjects were then given varying levels of risk of death (2%, 4% or 6%), stroke (1% or 2%) and need for second revascularization procedure (7%, 11%, 15% or 17%) within one year of mv-PCI. They were instructed to choose stent or bypass based on the presented risks.

RESULTS: Subjects preferred mv-PCI to CABG across all risk values and placed the greatest weight on risk of death. When the risk of death for mv-PCI was double that for CABG, a majority of subjects preferred mv-PCI over CABG (p<0.0001). Similarly, when the risk of repeat procedure for mv-PCI was more than three times the risk quoted for CABG, half of the subjects preferred mv-PCI over CABG (p<0.0001). Compared with subjects, clinicians were less accepting of increased risk with mv-PCI in order to avoid CABG revascularization.

CONCLUSIONS: Patients with known or suspected coronary artery disease do not value the individual components of the MACE endpoint equally. Additionally, patients favor mv-PCI over CABG revascularization even when quoted risks of death and repeat procedure that far exceed those quoted for CABG. There is a significant discrepancy between patient and physician acceptance of risk for undergoing revascularization. This needs to be recognized when counseling patients on revascularization methods for mv-CAD.

Acromioplasty in the State of Wisconsin from 2003-2009

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BACKGROUND: Anterior acromioplasty is a very common surgical procedure originally described by Charles Neer for impingement of the rotator cuff beneath the coracoacromial arch. It has become one of the more commonly performed operations. It is unclear if it is being performed for indications other than those originally described. The purpose of this study is to gain an understanding of the indications currently used for the application of this procedure.

METHODS: We searched a public state-wide database in Wisconsin from 2003-2009 for the procedure codes for open and arthroscopic acromioplasty. The data retrieved included number of procedures, patient age, sex, and corresponding primary diagnosis codes. We stratified the data according to age and sex and determined the primary diagnosis codes associated with this procedure for each group.

RESULTS: A total of 21,689 acromioplasties were performed (12,814 male: 8,875 female). The age of patients ranged from one to 91 years with a mean age of 48.9 years (male: 47.96 and female: 50.29). Approximately twenty-three percent of the patients were under the age of 40; 12.5% were 19 years old or younger. The majority of patients had expected diagnoses of Shoulder Region Disorder, Rotator Cuff Syndrome, Rotator Cuff Sprain and Rotator Cuff Rupture. There were however, a large percentage of diagnoses inconsistent with the original indications for the procedure including SLAP tear (6.59%), dislocation (1.27%) and adhesive capsulitis (2.03%).

CONCLUSIONS: These data are concerning. The benefit of acromioplasty is unclear for SLAP tears unless there is concomitant sub-acromial impingement. It has no clear role in the treatment of instability and can potentially lead to more adhesions in adhesive capsulitis. If performed in the presence of an irreparable rotator cuff tear, it can lead to anterior superior escape. There are also unclear indications in younger patients who likely have not developed bony acromial changes. Acromioplasty is a beneficial operation in appropriate patients. Further study needs to be directed at clarifying the indications for this procedure.
CT Measurement of Abdominal Fat Distribution to Predict the Metabolic Syndrome

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BACKGROUND: The metabolic syndrome is a cluster of risk factors associated with cardiovascular events, stroke, and type II diabetes mellitus. Distribution of abdominal fat, particularly visceral fat, has been shown to be a useful indicator for metabolic syndrome. Previous studies have focused on specific ethnic populations, oftentimes with a limited number of volunteers. The purpose of this study was to assess subcutaneous fat area (SFA), visceral fat area (VFA), visceral fat percentage (VF%), and other CT-based measurements in association with the metabolic syndrome in a predominantly Caucasian population.

METHODS: Standard SFA, VFA, and VF% measurements were obtained at the umbilical level from CT colonography studies in 474 consecutive asymptomatic adults using a dedicated software application (Fat Assessment Tool, EBW 4.5, Philips). Noncontrast liver attenuation was also recorded. Diagnosis of the metabolic syndrome was based on the 2005 International Diabetes Foundation (IDF) criteria, which incorporates abdominal obesity, glucose intolerance, hypertension, and dyslipidemia. Uni- and multivariate gender-specific analyses were performed.

RESULTS: The ROC area under the curve (AUC) for SFA was 0.865 (95% CI: 0.823-0.899) in men and 0.762 (0.711-0.806) in women. AUC for VFA was 0.887 (0.848-0.918) in women and 0.830 (0.784-0.867) in women. AUC for VF% was 0.527 (0.472-0.581) in men and 0.820 (0.774-0.859) in women. SFA threshold value of 204.7 cm² in men yielded a sensitivity and specificity of 80.3% and 84.5%, respectively. VFA threshold value of 71.5 cm² in women yielded a sensitivity and specificity of 83.7% and 80.7%, respectively. The best multivariate models did not significantly improve performance over SFA in men and VFA in women alone.

CONCLUSIONS: SFA alone was better than either VFA or VF% for predicting metabolic syndrome in men, whereas VFA was the best single predictor in women. These simple CT measures may have prognostic importance and could be reported prospectively.

The Effect of Ankle Braces on Injury Rates on High School Football Players

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BACKGROUND: Ankle injuries are the most common injury that occurs in young active individuals. It is widely accepted by many adolescent athletes and their coaches that wearing external supports (ankle braces) on their feet and ankles will reduce the chance they will sustain an ankle injury while participating in sports. However, there is no evidence that routinely wearing ankle braces will actually reduce the likelihood that these injuries will occur. The goal of this study was to determine whether using external ankle supports reduces the number of ankle injuries or increases the number of other injuries that occur in adolescent (high school) football players.

METHODS: This was a randomized controlled trial that utilized cluster (school) randomization. High school participation required that intervention be randomized at the high school level; therefore cluster randomization was necessary. Schools were placed into the intervention and control groups with a block by two design based on a schedule provided by the statistician. Schools who agreed to take part in this study were assigned to the intervention (use ankle braces) or control group (no ankle braces provided). Each subject who enrolled from an intervention school was provided and fitted with two (right and left) ankle braces and asked to use them throughout the season. Subjects who enrolled from a control school practiced and played as they normally do. Subjects were enrolled and followed on an intent-to-treat basis. The subjects who withdrew had their drop out date recorded and the number of exposures up to that point was recorded for the analysis.

RESULTS: Data is currently being compiled and almost complete. Statistical analysis will then be performed. Ankle injury rates will be summarized as both the percentage of athletes injured as well as injuries per athlete exposure. Ankle sprain rates will be estimated using the methods of Kaplan and Meier survival analysis and compared between the intervention and control group using a log-rank test. The Cox Proportional Hazards model will be used utilized to examine the relationship between ankle sprains and several independent variables (intervention, gender, previous injury history, etc.).

CONCLUSIONS: Once data has been collected and statistical analysis completed, effectiveness of ankle braces and injury rates in high school football players will be assessed. This could influence future use of ankle braces in high school football.
Fasting and Post-prandial Spot Urine Calcium-to-creatinine Ratios Do Not Detect Hypercalciuria

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BACKGROUND: Clinicians diagnose hypercalciuria using a 24-hour urine calcium (24HUC) or a spot urine-calcium-to-creatinine ratio (SUCCR) specimen. The SUCCR is considered to be interchangeable with the 24HUC, as studies show a high correlation coefficient between them. However, Bland-Altman analysis should be used before replacing one test with another, as correlation coefficients only measure the strength of relationship, not agreement, between two tests. We systematically compared fasting and post-prandial SUCCR measurements to 24HUC measurements using Bland-Altman analysis.

METHODS: 21 postmenopausal women aged 58 ± 7 years came to the research ward for three 24-hour inpatient stays. At each visit, subjects provided fasting morning and postprandial spot urine specimens, along with a carefully timed 24-hour urine collection under supervision of highly trained research nurses.

RESULTS: Amongst 61 paired specimens, the fasting SUCCR underestimated the 24HUC (Bland Altman bias -71 mg/24-hour), with a sensitivity and specificity for diagnosing hypercalciuria of 0% and 98% respectively. The post-prandial SUCCR overestimated the 24HUC (Bland Altman bias +61 mg/24-hour), with a sensitivity and specificity of 77% and 61% respectively. The average of fasting and post-prandial SUCCR measurements had a lower Bland Altman bias of -3 mg/24-hour but demonstrated a sensitivity and specificity of only 42% and 78% respectively.

CONCLUSIONS: The SUCCR performs poorly compared to the 24HUC. The fasting SUCCR systematically underestimates 24HUC and the post-prandial SUCCR systematically overestimates 24HUC. The average SUCCR demonstrates low sensitivity and specificity for hypercalciuria. Clinicians must continue using the 24HUC to diagnose hypercalciuria in post-menopausal women.

The Role of Autophagy in Melanoma Tumor Progression

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BACKGROUND: Autophagy, a pathway by which cells degrade their organelles, is a survival mechanism activated during nutrient starvation. Autophagy is regulated by mammalian target of rapamycin (mTOR) signaling pathway. Rapamycin, a drug that binds to and inhibits mTOR, activates autophagy, and sustained inhibition of mTOR, can induce cell death. The role of autophagy in cancer is controversial. Autophagy may promote tumor growth by eliminating some cells during nutrient deprivation to give cancer a new pool of nutrients. However, in some cases, autophagy inhibits tumor growth. The purpose of this study was to better understand autophagy and its regulation by mTOR in normal melanocytes and melanoma.

METHODS: Cultures of primary normal human neonatal melanocytes, primary melanoma, and metastatic melanoma cells were used. Cell proliferation and survival after treatment with rapamycin or MAP kinase inhibitor U0126 was measured using MTT assays. Data were analyzed using a one-way ANOVA. For mTOR protein expression, cultured cells were lysed and protein was estimated using a BCA protein assay kit. The proteins were separated by SDS-PAGE and transferred to a Polyscreen membrane. The membranes were blocked with 5% non-fat dry milk and incubated with primary antibodies [anti-mTOR and p-mTOR (Ser2448)] overnight at 4°C and an appropriate HRP-conjugated secondary antibody. β-actin controlled for protein loading variability.

RESULTS: First, we assessed if there was a differential sensitivity to rapamycin between melanocytes isolated from Caucasian, African American, and Asian neonatal foreskin. Over the concentration range tested, we did not find any difference in response to rapamycin among different melanocytes. When melanocytes, primary melanoma, and metastatic melanoma cells were exposed to varying concentrations of rapamycin, melanocytes appeared to be more sensitive to rapamycin than melanoma cells. Next, we tested melanoma cells with wild type or mutated BRAF to determine if there was a differential sensitivity to rapamycin. The cells overexpressing mBRAF were more sensitive to rapamycin than the control cells. Furthermore, rapamycin and U0126 synergistically inhibited the growth of BRAF mutant melanoma cells.

CONCLUSIONS: Our data suggest that activation of survival pathways known to be active in melanoma cells also makes them resistant to autophagic cell death. Thus, additional research on the role of the mTOR pathway in melanoma survival and proliferation is warranted.
Exploring the Role of Macrophage Clearance of Apoptotic Smooth Muscle Cells during AAA Inflammation

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BACKGROUND: Abdominal aortic aneurysm (AAA) is a degenerative disorder of aortic wall connective tissue with a high prevalence (0.5-3.2%) in the US general population. It is known that aneurysm is associated with inflammation and proteolytic degradation of the vascular wall. Our recent studies suggest that apoptosis of vascular smooth muscle cells (VSMCs) contributes to aneurysm formation at least in part through stimulation of the pro-inflammatory signaling pathways. This led us to hypothesize that insufficient clearance of apoptotic SMCs, necrosysmal tissues leads to secondary necrosis and subsequent production of pro-inflammatory cytokines. The goal of my summer research is to establish methods that allow us to examine clearance of apoptotic SMCs in experimental models of aneurysm.

METHODS: In vitro phagocytosis assay provides a means of evaluating the ability of macrophages to engulf apoptotic cells under a variety of environmental conditions. VSMCs were labeled with Vybrant DIO (Invitrogen). RAW 264.7, monocytes (ATCC) were labeled with PKH26 dye (Sigma). Apoptosis was induced in starved VSMCs with 400μM H2O2. The engulfment assay was performed with a VSMC suspension added to adhered RAWs for 4 hours at 37°C. Efficiency of cell labeling and engulfment was assessed via FLOW cytometry using BD FACSCalibur.

RESULTS: VSMCs and RAWs were successfully labeled with Vybrant DIO and PKH26 dyes, respectively, with efficiencies for both close to 100%. Preliminary results of the engulfment assay demonstrated ~16% more engulfed cells of apoptosis-induced VSMCs compared to control VSMCs.

CONCLUSIONS: The results of this research helped establish lab protocols/techniques that will provide for the continuation of testing our hypothesis. Basic protocols were developed for labeling both VSMCs and RAWs. Preliminary data was collected on the efficiency and consistency of an *in vitro* phagocytosis assay. Using this assay, we can then proceed to test whether the clearance of apoptotic VSMCs is compromised in conditions known to foster aneurysm development.

A fMRI Study of Broca's and Wernicke's Language Lateralization in Vascular Lesion Patients

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BACKGROUND: The language centers of the brain are plastic and can be influenced by many factors such as vascular lesions, tumors, resections, etc. We focused on age, gender, handedness, lesion location, type of lesion, and lesion volume as a few factors that may cause relateralization of the language areas. Proximity of the lesion to language cortexes is also significant. This study analyzed the correlation between the lesion-to-language center distance and the changes in language lateralization from the left hemisphere to the right hemisphere.

METHODS: From a database of 450 fMRI patients seen over the past 15 years, we narrowed the population down to patients who were scanned between 2001-2010, were over the age of 18, were not post-operative, had arteriovenous malformations (AVMs, N=42) or cavernous angiomas (N=23), and were right-handed (N=67, 38 females). Left hemisphere lesions were identified in 46 patients. Using BOLD fMRI, functional changes in language centers were mapped during simple exercises such as alphabet word generation, antonym word generation, and text reading tasks. The lateralization index, a measure of the degree of lateralization to the right or left hemisphere, was calculated from fMRI measurements of activated volume using the formula (L-R)/(L+R).

RESULTS: The distance from the lesion to the center and to the periphery of Wernicke’s area was significantly associated with language lateralization (p=0.0264, p=0.0015). Smaller lesion-to-language center distances correlated with increased language lateralization to the right hemisphere. Distance from the lesion to the center and to the periphery of Broca’s area was not statistically associated with right-sided lateralization. No other associations were seen with age, gender, lesion type, lesion volume, or lobe location.

CONCLUSIONS: This study suggests that AVM and cavernoma vascular lesions may partially shift left hemisphere language responsibilities to homologous areas in the right hemisphere, especially in cases with increased proximity of the lesion to the language center.
Bone Mineral Density Analysis from CT Colonography for Osteoporosis Screening

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BACKGROUND: Osteoporosis is a major public health issue that confers up to 50% of women and 20% of men risk for osteoporosis-related fracture. The current standard for bone mineral density (BMD) screening is DXA but quantitative CT (QCT) has also shown utility although issues of expense and radiation prevent frequent use. New programs allow BMD assessment on more routine CT scans such as CT colonography (CTC). Because CTC is already being performed for colorectal cancer screening, the data from imaging can be applied without any additional radiation exposure. The purpose here is to evaluate the performance of L-spine BMD assessment from CTC of both QCT and simple ROI.

METHODS: Inclusion criteria: CTC and DXA screen within 60 days, between Apr 2004 and Dec 2008 and with a DXA T-score reported for L-spine and/or hip. According to standards osteoporosis defined as T-score of -2.5 or less and osteopenia defined as T-score between -1.0 and -2.4. Supine and prone CTC acquisitions were evaluated and both 1.25 and 5mm slice thickness studies were evaluated and compared. The QCT technique at T12-L5 levels used sagittal MPR with the angle plane parallel with end plate. The T12-L5 BMD were recorded for supine and n=45 prone for a precision subset. Simple ROI utilized non-angled trabecular ROI at each T12-L5 level with a standard bone window and mean attenuation recorded.

RESULTS: Results showed that both lumbar QCT and simple ROI effectively measure BMD relative to the DXA reference. The following thresholds were set: QCT BMD threshold of 90 g/cm3 had 100% sensitivity for osteoporosis, 86.7% below threshold had low BMD, 49.6% above threshold had normal BMD. Simple L1 threshold of 160 HU is 100% sensitive for osteoporosis, 83.1% below 160 HU had low BMD and 56.7% above 160 HU had normal BMD. Simple T12-L5 threshold of 145 HU had 100% sensitivity for osteoporosis, 83.6% below 145 had low BMD and 52.5% above 145 had normal BMD.

CONCLUSIONS: Both lumbar QCT and simple ROI methods are effective for assessing BMD relative to the DXA reference standard. High sensitivity for osteoporosis (~100%), it effectively excludes osteoporosis in a substantial subset, precluding the need for DXA, Can identify osteoporotic fractures in false-negative DXA and Supine prone measurement precision was better for ROI method than phantomless QCT. A 2100 pt cohort is being evaluated applying these results to all abdominal CT studies to determine if the results are generalizable.

HPRT Mutational Spectra in HPRT Mutant T Cells in Human Melanoma

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BACKGROUND: Immunogenic antigens on melanoma can elicit clonal T cell expansion. It is widely recognized that rapid clonal expansion renders T cells susceptible to somatic mutation. Because mutation occurs preferentially in dividing populations, an assay was used to select for T cells containing a specific in vivo mutation to enrich for T cells with clonal expansion. The frequency of HPRT gene mutations (HPRT-) is higher in melanoma patients compared to healthy individuals, possibly the result of excessive clonal expansion by these T cells. Therefore, selection of T cells with HPRT mutations should enrich for T cells that were part of this expansion to melanoma.

METHODS: Peripheral blood mononuclear cells (PBMC) were obtained from two melanoma patients with metastatic disease. Single cell derived T cell isolates (SCD-T) were expanded using the HPRT clonal assay. Total RNA and genomic DNA were isolated. After performing RT-PCR and sequencing, the sequence of the variable region was compared to the sequences from the other isolates from the same patient to find SCD-T that shared variable region sequences. The isolates with readable T cell receptor (TCR) sequence also had RT-PCR followed by sequencing of their HPRT locus. These HPRT sequences were analyzed and compared to the wild type HPRT sequence to identify and quantify the mutations found in the mutant HPRT RNA.

RESULTS: Analysis of 54 samples from patient 5, and 44 samples from patient 11, revealed unique TCR expression by all SCD-T. When the HPRT locus was analyzed for patient 5, it was found to include a mix of exclusions (11), inclusions (1), inclusion/exclusion (2), and point mutations (20 of which 3 were nonsense). Patient 11 also showed a mix of mutations in the HPRT region with exclusions (13), inclusions (3), inclusion/exclusion (1), and point mutations (18 of which 1 was nonsense). Interestingly, in patient 11 it was found that of the exclusions, five were exclusions of exon 6.

CONCLUSIONS: In vivo expanded T cell clones were not identified in these 2 patients. The finding of different HPRT mutational changes and different TCR gene rearrangements in mutant isolates from the same individual define independent mutational events arising in different post-thymic T cell clones. Study of HPRT gene mutations in TCR-defined HPRT- T cell isolates from melanoma patients provides a probe to assess mechanistic questions in melanoma patients.
Cerebral Blood Flow Response to Exercise and Hypoxia in Obesity

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BACKGROUND: Cerebral blood flow (CBF) has-classically
been thought to remain nearly constant under a variety
of stressors such as orthostatic hypotension, increased
metabolism, and hypertension. However, during dynamic
exercise, CBF increases up to 20% due to an integrated
response of at least four signaling systems: metabolic,
myogenic, neural and endothelial responses. The CBF
response to increased blood CO2 or decreased blood O2 are
thought to be mediated via endothelial-dependent dilation
(EDD) mechanisms. Normal EDD is also vital for regulation of
thrombosis. Since obese individuals are at increased risk of
ischemic stroke, it is also reasonable to propose that impaired
EDD may be a key factor in stroke prevalence. The goal of this
study is to test whether the CBF response to exercise, hypoxia
and hypercapnia is altered in obese adults. These studies may
improve our understanding of the role of altered cerebral EDD
in this important clinical population. We hypothesize that obese
adults will exhibit impaired CBF during exercise, hypoxia, and
hypercapnia compared to lean adults.

METHODS: CBF is determined using a Doppler ultrasound
to measure blood velocity in the middle cerebral artery during
three experimental conditions: hypercapnia, hypoxia, and
exercise. To achieve hypercapnia, subjects will breathe
repeatedly from a bag containing 45% O2, 3% CO2 and
balance N2. We monitor the rise in end-tidal CO2 until it
reaches 10 mmHg above normal resting levels (~40 mmHg)
The response from three trials will be averaged. Subjects will
be made hypoxic by breathing using a mouthpiece delivering a
mixture of 10-15% O2, 0.5-1% CO2, and balance N2. The CO2
is adjusted to maintain eucapnic levels similar to rest. The O2
is adjusted to lower arterial oxygen saturation (SaO2) to 90% saturation (~15% O2) and 80% saturation (~10% O2). Finally,
subjects will exercise at VO2 = 1 L O2/min for five minutes.

RESULTS: Preliminary results show a decrease in the CBF
response in obese individuals in all three experimental
conditions compared to lean individuals. At this point, data
corresponds to two lean subjects and one obese subject. CBF
increased by 65% from baseline in response to hypercapnia
in lean individuals, compared to only a 19% increase in the
obese individual. In response to hypoxia, lean individuals
increase CBF 11% from baseline at SPO2 90% and 35% from
baseline in at SPO2 80%. The obese individual decreases
CBF by 2% from baseline at SPO2 90% and increases by 2%
from baseline at SPO2 80%. In response to cycling exercise,
CBF velocity increases 52% from baseline in lean individuals,
compared to a 2% increase in the obese individual.

CONCLUSIONS: Preliminary data suggests that obese
subjects display diminished CBF responses to hypoxia,
hypercapnia and exercise when compared with lean individuals.

PSA Doubling Time in Patients on Active Surveillance for Prostate Cancer

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BACKGROUND: Given both the high likelihood of untoward side effects with prostate cancer treatments and the slow-growing nature of many such cancers, certain men with positive biopsies opt to forego immediate treatment in favor of Active Surveillance. In this paradigm, patients who are candidates for treatment and whose cancers are below the treatment threshold in several categories (e.g., tumor grade, tumor volume) are monitored closely before definitive action is taken. The goal of this study was to determine whether PSA doubling time (PSA-DT), the time it takes for the initial PSA value to double, is an accurate predictor of tumor volume (an important intervention criterion) in patients on active surveillance.

METHODS: The goal of this retrospective chart review was
the creation of a database, including all PSA values and
biopsy results, for prostate cancer patients not considering immediate treatment. Patients were divided into the study group, consisting of those on active surveillance with initial PSA levels below 10 ng/ml, 1 or 2 cores of tissue involved on biopsy, and less than 5% total tissue involvement, or the control group, patients with larger volume tumors who were not candidates for treatment, due either to advanced age or significant comorbidities. For patients with three values over at least 18 months, PSA-DT was calculated using the equation
PSA(t) = PSA(initial) * em, where t is time after the initial PSA
reading and m is a rate variable proportional to PSA-DT. PSA
measurements performed during androgen blocking therapy
were not included.

RESULTS: For the control group (n=15), the average age
was 81, the average initial PSA was 8.7, the average tumor
volume was 14%, and the average PSA-DT was 51.9 months
(standard deviation 38). For the experimental group (n=23),
the average age was 66, the average initial PSA was 5.5, the
average tumor volume was 2%, and the average PSA-DT was
108.7 months (standard deviation 96).

CONCLUSIONS: Compared to the control group, the
men on active surveillance had lower tumor volumes and
correspondingly longer PSA-DT. However, there was much
variation within both groups, as evidenced by the large standard
deviations. Though these preliminary results suggest that tumor
volume is inversely proportional to PSA-DT, more patient data
must be included before firm conclusions can be drawn.
Are There Predictors of Malignancy in Patients with Multinodular Goiter?

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BACKGROUND: Historically multinodular goiters (MNG) have been thought to be benign condition with a low risk of associated malignancy. However recent data has suggested that the incidence of cancer in MNG is similar to that of solitary thyroid nodules. Pre-operative diagnosis of malignancy is usually done through fine-needle aspiration (FNA). However, FNA has low predictive value in MNG, and the presence of multiple nodules can make it difficult to adequately evaluate the entire thyroid. Therefore, the purpose of this retrospective study is to identify risk factors for malignancy in patients with MNG.

METHODS: 1791 consecutive patients underwent thyroid surgery at a single academic institution between May 1994 and December 2009. 838 patients had a MNG, which we defined as 2 or more nodules on pre-operative ultrasound, and were considered to be the study population. The medical records of these patients were reviewed and then analyzed with statistical software (SPSS, Inc.).

RESULTS: A final pathologic diagnosis of malignancy was found in 260 of 838 (31%) of MNG patients. The cancer was in the largest nodule in only 37% (n=95) of cases. Of the 260 patients with malignancy, 113 (44%) had a focus of cancer <1 cm. Pre-operative FNA was performed on 204 patients with malignancy on final pathology, and malignancy was suspected or confirmed by FNA in only 60% (n=123). Of the 137 cancers not recognized pre-operatively, 61 (45%) were >1 cm in size. Risk factors for malignancy were younger age and male gender. Patients with malignant nodules also had a smaller number of lesions, smaller glands, and fewer nodules than those patients with benign findings on pathology.

CONCLUSION: Malignancy was present in nearly a third of patients with a MNG undergoing surgical intervention. Malignancy was usually not in the largest nodule, and was only identified pre-operatively in 60% of patients. Risk factors for malignancy included male gender, younger age, fewer nodules, smaller gland weight, and smaller nodule size. The low predictive value of FNA in our population suggests the need for a more comprehensive evaluation of patients with MNG including a risk factor analysis and FNA of more than just the dominant nodule.

Placement of Central Venous Catheters During Neutropenia- Should Our Institutional Practice Change?

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BACKGROUND: While integral to the management of pediatric oncology patients, central venous catheters (CVC) are at high risk for developing infectious and mechanical complications. These risks are generally increased when CVC are placed during neutropenia. This study assessed early line complications in leukemic children with and without neutropenia. We intended to identify risk factors that lead to premature line removal and to develop guidelines for the type and timing of line placement.

METHODS: A retrospective chart review over a 10-year period was conducted in children aged 0-21 years with a diagnosis of B-ALL, T-ALL, or AML who had a long-term CVC placed before beginning chemotherapy. Data regarding demographics, line type, maximum temperature 24 hours prior to placement, date and type of catheter related complication, use of pre-operative antibiotics, and blood counts were reviewed through 42 days of line placement. Patients within a given diagnosis were subcategorized based on their ANC at diagnosis; category I: patients with ANC less than 0.5 x 10^9/L and category II: patients with ANC greater than 0.5 x 10^9/L. CVC related complications were compared within these subgroups. Line failure indicated a complication that required removal.

RESULTS: 42 of the 123 CVC placed in patients with leukemia (18 AML, 41 high risk B-ALL, 1 infant B-ALL, 55 standard risk B-ALL and 8 T-ALL) developed either an infectious complication (33, 26.83%) or a mechanical complication (9; 7.32%). 8 (6.50%) lines were removed due to infectious complications with slightly fewer line failures associated with category I (4; 6.45%) compared to category II (4; 6.56%). While in general this is not a significant difference, when broken down by category, a low ANC increased risk substantially for line removal in the high risk B-ALL group which showed an 11.76% (2 of the 17) line failure for a low ANC and a 4.2% (1 of the 24) line failure for a high ANC. Non-port catheters had a slightly higher failure rate at 7.02% (4 of the 57) compared to port catheters that had a 6.15% (4 of the 65) failure rate.

CONCLUSION: Although prior studies have shown that line placement during neutropenia increases risk of line failure, our study did not show a major difference. However, high risk B-ALL patients who have lines placed while neutropenic do have an approximately two times higher risk of line failure. Finally, there appears to be more risk of line failure in non-port catheters.
The Effect of Splenectomy on the Postoperative Complication Rate after Distal Pancreatectomy

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BACKGROUND: Cross-segmental imaging technology has resulted in significant advances in patient care, but it is also responsible for a substantial increase in the incidental detection of pancreatic lesions. Current limitations in the capacity to differentiate among benign and premalignant tumor have created the impetus to minimize operative intervention. Laparoscopic techniques have been developed that allow for spleen preserving distal resection of the pancreas with the aim of preserving the bodies’ ability to combat encapsulated bacteria. However, the magnitude of the increase in the lifetime risk of infection has only indirectly been estimated. On the other hand, the short-term complications of pancreatic surgery are well understood. The purpose of this comprehensive review is to examine the total complication rates, fistula rate, and infectious complication rate, at thirty days post-intervention of patients undergoing splenectomy during distal pancreatic resection.

METHODS: Studies considered report outcomes of adult patients undergoing distal pancreatectomy as the primary procedure. Only studies that explicitly describe the treatment of the spleen were considered. Primary outcome: postoperative complication rate at 30 days postoperative. Systemic search using Google Scholar, Cochrane Central Registry of Controlled Trials and NCBI National Library of Medicine was conducted independently be both authors. The searched used was: “Distal pancreatectomy OR Left pancreatectomy OR pancreatosplenectomy OR spleen-preserving distal pancreatectomy”. Relevant full text studies on human from 1980-2010 were downloaded to myNCBI and the titles and abstracts were searched for consideration. Candidate reports were obtained and subjected to inclusion and exclusion criteria. The references of these candidate reports were manually cross-searched twice by both authors.

RESULTS: To ensure that the broadest, most inclusive search was carried out, we decided to independently repeat the initial methodology of the review. The subsequent analysis of the already compiled data will be carried out once this revision step has been concluded.

CONCLUSIONS: Due to the variety of additional procedures carried concomitantly in many of the included reports, the analysis of the data might dictate the necessity of separating the findings into multiple subsets. This speaks to the interventional latitude given to the intervening physician when performing one of these procedures.

Outcomes of Clostridium difficile Infection in Solid Organ Transplant Recipients at UW Hospital

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BACKGROUND: Solid organ transplant recipients are at high risk for developing Clostridium difficile infection (CDI), a diarrheal illness associated with hospitalization and exposure to antibiotics. However, few studies have examined the outcomes of CDI in this patient population. The goal of this study was to identify prognostic indicators and outcomes of CDI in a cohort of solid-organ transplant recipients.

METHODS: Retrospective case-control study, with preliminary results from the case arm. The UNOS organ transplant database was used to identify all patients who received a liver or kidney transplant at UW Hospital between 1994 and 2008 that had a recorded episode of CDI at any time after the transplant date. 215 episodes among 169 patients (106 kidney recipients and 63 liver recipients) were included in the analysis. Patient medical records were examined for multiple variables, including comorbidities, antibiotic use, symptoms at presentation, treatment received, need for ICU care, in-hospital and 1-year mortality. The data was analyzed by multivariate logistic regression.

RESULTS: Clinical Presentation: 22% of episodes presented with fever, 15% with hypothermia, 31% with hypotension, and 17% with tachycardia. 22% of episodes presented with none of these findings.

Outcomes: 75% of episodes were cured (defined as resolution of symptoms without need for retreatment), and 48% of episodes were cured within 14 days of the start of treatment. There were no patient deaths directly attributable to CDI. 13 patients died while hospitalized and 49 patients died within one year of an episode of CDI.

Prognostic Indicators: Female sex was associated with a lower risk of death during hospitalization (OR 0.08, 95% CI 0.01-0.71). Acute or chronic hemodialysis was associated with a higher risk of death during hospitalization (OR 9.1, 95% CI 2.5-33.3).

CONCLUSIONS: Contrary to our expectations, in this study no patient deaths were attributable to CDI, and all-purpose in-hospital mortality in this population was comparable to that reported from previous studies examining CDI in the general inpatient population. Thus, it appears that solid organ transplant recipients may not have worse outcomes from CDI despite their immunocompromised state. We found that presenting symptoms such as fever and hypotension were insensitive for CDI in this population, underscoring the need for a high index of suspicion for CDI in any transplant recipient with new-onset diarrhea.
Is Thyroidectomy in Patients with Hashimoto’s Thyroiditis More Risky?

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BACKGROUND: Hashimoto’s thyroiditis (HT) is an organ –specific autoimmune disease characterized by production of antibodies such as anti-thyroperoxidase (TPO), which leads to destruction of the thyroid gland and a decrease in normal thyroid function. Thyroidectomy is performed when the patient presents with symptoms or when potential neoplastic degeneration occurs; however, surgery can be difficult due to the dense inflammatory process around the gland. We hypothesized that patients with HT may have a higher rate of complications following thyroid surgery.

METHODS: We identified 1791 consecutive patients who underwent thyroidectomy from May 1994 to December 2009. Patients with HT (n=311) were compared to without HT (n=1480) with regard to outcomes with ANOVA and Chi-squared (SPSS, Inc.).

RESULTS: Patients with HT were significantly younger (47 v. 49, p=0.034) and more likely to be female (89% v. 76%, p=0.0001). There was no significant difference between the two groups in the rate of malignancy. However, patients undergoing thyroidectomy with HT had a significantly higher post-operative complication rate. Specifically, the rates of overall complications (14.1% v. 8.8%, p=0.004), transient complications (10.3% v. 6.8%, p=0.03), and permanent complications (2.6% v. 0.8%, p=0.007) were all increased in HT patients.

CONCLUSION: Patients with HT had a higher rate of complications after thyroidectomy when compared to patients without HT. Therefore, careful consideration must be taken prior to pursuing operative treatment in patients with HT including providing adequate informed consent regarding the increased risks of surgery.

Assessment of Acoustoelastographic Analysis of In Vivo Mechanical Properties of Soft Tissue

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BACKGROUND: Acoustoelastography (AE) is a method that determines the mechanical properties of a tissue via the propagation of sound waves emitted and received by an ultrasound (US) transducer. Previous work on excised tendons has demonstrated AE’s capability to discriminate changes in the elastic properties of soft tissue (Frisch, Kobayashi et al. 2008). However, the reliability of the clinical, in vivo protocol and subsequent AE post-processing has yet to be tested. The purpose of the study was to evaluate intra- and inter-rater reliability of AE used to compute in vivo stiffness of the plantar fascia ligament, and Achilles, common lateral elbow extensor and infrapatellar tendons.

METHODS: Dynamic ultrasound images were captured bilaterally on the plantar fascia ligament, and Achilles, common lateral elbow extensor and infrapatellar tendons of 20 healthy subjects, using a linear array 5-12MHz ultrasound transducer longitudinally. The relevant joint for each tissue site was actively moved through a range of motion while recording a US cine-image. Cine-Images were then processed using software specifically designed for AE analysis (Eccosoft, Madison, WI). US imaging of all tissue sites was performed by both raters and was repeated 24 hours later with order determined by randomization. Both the intra- and inter-rater reliability was calculated for all outcome variables.

RESULTS: Analysis of the relative stiffness of the left Achilles tendon at a strain of 0.005 (0.5%) in trials with a peak strain of greater than 0.01 (1%) had statistically significant intra-rater reliability for both raters (rater 1: ICC=.904, p<0.05; 95% C.I. = 0.126-0.994; rater 2: ICC=.618, p< 0.05; 95% C.I. = -0.082-0.910). There was significant day 2 inter-rater reliability, and a trend for day 1 inter-rater reliability (day 2: ICC=.648, p<0.05; 95% C.I. = -0.033-0.918 and day 1: ICC=.583, p<0.1; 95% C.I. = -0.306-0.929, respectively). Analysis of the cine-images of the plantar fascia ligament, and Achilles, common lateral elbow extensor and infrapatellar tendons is currently in progress.

CONCLUSIONS: Preliminary analysis from this investigation report good to excellent intra-rater and good inter-rater reliability of a clinically relevant protocol for acquiring AE data. Future studies should be conducted to determine the reliability of AE in an in vivo comparison of healthy and diseased tendons and ligaments.
Dysmenorrhea in Women with Crohn’s Disease

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BACKGROUND: Crohn’s disease (CD) is a chronic relapsing, remitting inflammatory disease of the GI tract. The cause of CD is unknown but presumed multi-factorial. Patients with CD experience abdominal pain, cramping, bloating, fatigue, diarrhea, and weight loss. The symptomology of CD can be difficult to differentiate from dysmenorrhea (painful menstruation) leading to mismanagement. This study attempts to determine whether dysmenorrhea is more prevalent and severe in women with CD than women without, and to examine whether women with dysmenorrhea and CD have higher disease activity and lower QOL.

METHODS: A case-control study of menstruating women with CD compared to healthy age-matched controls. Cases were recruited in GI and controls were recruited in IM or WH at UWHC. Consent subjects completed written study materials following their appointments. Parameters examined included demographics, CD history and activity, general QOL, IBD-specific QOL, and menstrual distress symptoms. Data collected were analyzed to 1) Determine the prevalence of dysmenorrhea and menstrual symptoms in cases, 2) Compare the prevalence and severity of dysmenorrhea in cases and controls, 3) Determine the relationship between dysmenorrhea and CD activity scores, and 4) Determine the relationship between dysmenorrhea and QOL in cases.

RESULTS: Cases and controls reported comparable demographics, excluding student status (more controls were students, p=0.04). Substance use, co-morbidities, and surgeries were comparable between groups. Cases were most likely to have disease of the ileum or colon and most were found to be in remission. Cases and controls had comparable QOL. Dysmenorrhea was not found to be more prevalent or severe cases than controls (p=0.44). Cases with dysmenorrhea reported pain less than cases without dysmenorrhea (p=0.03).

CONCLUSIONS: More recruitment is needed for statistical analysis of our hypotheses. The early finding that cases with dysmenorrhea reported pain less frequently than cases without dysmenorrhea may suggest a higher pain tolerance in this group. This may be due to experiencing abdominal pain more frequently, resulting in a higher pain threshold.

Folate Mechanisms in Bone Regeneration: A Murine Model of Intervertebral Fusion

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BACKGROUND: The role of folic acid in promotion of prenatal growth and differentiation of Central Nervous System (CNS) and lessening the likelihood of Neural Tube Defects (NTDs) are well known. Recent research has also shown that folate is likely an effective growth and differentiation promoter in the adult nervous system and other tissues such as bone. Clinically, patients who are on folate inhibitors, such as methotrexate, exhibit delayed postoperative healing and similarly delayed healing has been observed in animal models given methotrexate. The purpose of this study is to determine if administration of folic acid can enhance repair and regeneration of bone tissue.

METHODS: Wild mice underwent lumbar fusion based on an established model proposed by Raj et al, 2007. Four groups were administered variable doses of folate both pre (3 days) and 10 days postoperatively (sham (ddH2O), 40 micrograms/kg, 80 micrograms/kg, 400 micrograms/kg). At 3 weeks postoperatively, mice were sacrificed and tissues were analyzed for bone growth and fusion using radiographs.

RESULTS: All mice showed evidence of intervertebral fusion by radiography, regardless of folate dosage. A trend toward increased bone formation and fusion mass coalescence was noted in experimental subjects as compared to control subjects, but this difference could not be quantified.

CONCLUSIONS: It appears that our model of intervertebral fusion in murine species is valid and repeatable. Although no significant difference was seen between groups, future studies using quantitative CT scanning and histopathology for analysis could reveal differences.
Surgical Outcomes in the Treatment of Slipped Capital Femoral Epiphysis

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BACKGROUND: Slipped Capital Femoral Epiphysis (SCFE) is a disorder affecting children and adolescents. It is a multifactorial disorder that is characterized by the slipping of the femoral head posteriorly and inferiorly relative to the femoral neck. SCFE requires accurate diagnosis and prompt intervention to prevent complications such as avascular necrosis (AVN) and early childhood arthritis. The current treatment of choice is in-situ fixation using cannulated screws (screws with hollow shafts). Fixation prevents further slippage and allows for stabilization of the femoral head, physal closure and relief of symptoms. Although fixation in-situ is the treatment of choice, it is still not clear if a single cannulated screw will produce a better outcome than using two cannulated screws. In this study, a retrospective analysis will be performed on patients who have had the procedure to compare the outcome of in-situ stabilization with one screw versus two screws.

METHODS: A list of patients with SCFE that had in-situ fixation in the last 20 years was generated from the UW Health Link. Patients with complicating conditions such as endocrinopathy, kidney transplant, Down syndrome were excluded from the study. Medical records of remaining patients were reviewed and pre- and post-procedure radiographs were analyzed. Collected data included types of injuries, details of the pinning procedures, hip angles, and other joint data, both immediately following injury/procedure and upon follow-up. A statistical analysis will occur following completion of data collection.

RESULT: The study is currently still in progress. A finalized list of patients who meet the study’s criteria is completed. Data collection has started for patients with sufficient data. However, the majority of the patients’ records are incomplete and these patients need to be contacted for follow-up. Letters have been mailed to all patients with insufficient data requesting them to schedule a follow-up appointment.

CONCLUSION: A major obstacle of the study is locating all patients who were lost to follow-up. The next step is to call these patients and ask them to return for a follow-up appointment. This step is pending IRB approval. Sufficient follow-up is needed to produce significant statistical meaning.

Hip Arthroscopy in Children with Cerebral Palsy

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BACKGROUND: The use of arthroscopy for the treatment of various pediatric conditions continues to increase, but there is currently no literature that addresses its use on the hip of children with cerebral palsy. Children with cerebral palsy frequently suffer from subluxation of the hip and poor bone density and thus make such arthroscopies more technically demanding.

METHODS: We considered a retrospective case series of 4 patients under the age of 21 with cerebral palsy who underwent an arthroscopy to evaluate the condition of the cartilage of the hip. The mean age at the time of surgery was 15.3 years (range 9-20). One was female and three were male. The mean follow up time was 18 months (7-30 months). Chart and radiographic reviews were used to assess patients’ demographics, radiographic clinical results, surgical technique and follow-up information.

RESULTS: In all cases the articular cartilage could be evaluated, but distraction was more difficult. In three of the four cases, the articular cartilage was felt to be acceptable and successful hip reconstructions were performed, one in conjunction with the hip arthroscopy and two in a staged fashion. The other patient went on to undergo a total hip replacement. There were no complications and all patients were self-reported as pain-free at their final follow-up.

CONCLUSION: Hip arthroscopy in the pediatric patient with cerebral palsy provides a safe and effective way to accurately assess intra-articular conditions and also provides distinct advantages over MRI and MRI arthograms.
When Career and Life Collide: A Qualitative Study of the Medical Marriage

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Mentors: Carol Isaac PhD, PT; Molly Carnes, MD, MS

Support: Shapiro Summer Research Program and Department of Medicine

BACKGROUND: With the growing number of female physicians, there are fewer traditional medical marriages made up of a male physician and a stay-at-home wife (AAMC, 2008-2009; Levinson, 2004). The “two-career family” is a more frequent occurrence for both male and female physicians’ families and dual-doctor marriages continue to rise (Papanek, 1973; Sobecks, 1999; Woodward, 2005). As more women enter the physician workforce and the number of two-career families increases, the effects of a physician’s demanding career on his or her spouse are of interest. This qualitative study explores the current medical marriage from the perspective of the spouses of internal medicine residents and faculty at one academic medical center.

METHODS: Semi-structured, in-depth interviews with the spouses of 6 faculty and 5 residents of the Department of Medicine at the University of Wisconsin who were participants in a previous study of careers in medicine. Questions covered topics of balance, career choices and support networks. A grounded theory approach facilitated the analysis of common themes between groups, within groups and as a cohort.

RESULTS: Participants were grouped into three main categories based on whether they had a career, a “job”, or were also physicians. When looking at statements coded as positive or negative comments, it was found that the highest percentage of positive comments were made by the dual-physician families (61% positive: 39% negative) followed by dual career couples (48% positive: 52% negative) and the job-physician couples (0% positive: 100% negative). Emerging themes from the interviews include the challenges of being married to a physician, anger against the medical education and healthcare systems, how meaningful work creates a sense of self, the degree of spousal support, and how close the families are to achieving their ideal life.

CONCLUSIONS: This exploratory study looks at physician marriages from the spouse’s perspective. As women enter the traditional male physician role, their male spouses frequently assume the traditional female social role, violating gender norms; however, spouses that were more satisfied with their career (including stay-at-home fathers) exhibited less negativity in the text.

Epidemiology of Cytomegalovirus Reactivation After Allogenic Hematopoietic Stem Cell Transplantation

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BACKGROUND: Cytomegalovirus (CMV) is a frequent and serious complication of allogeneic HSCT. We studied the epidemiology of CMV reactivation in our cohort of adult and pediatric patients that received allogenic-HSCT at MSKCC from 2004-2008.

METHODS: Retrospective study of 293 adult and pediatric CMV seropositive patients who underwent first allogeneic HSCT at MSKCC from January of 2004 through December of 2008. CMV infection was monitored by the pp65 antigenemia assay (CMV Ag). Simple logistic regression models were used to examine the relationship between CMV reactivation and transplant variables. Variables with a P value of ≤0.3 were included in the multivariate models. Analyses were performed using SAS version 9.0.

RESULTS: 148 (51%) patients had CMV reactivation. Transient low grade CMV viremia accounted for 23% of episodes. 40% of patients who received myeloablative conditioning developed clinically significant early CMV reactivation. In univariate analysis, HLA mismatch, acuteGVHD and CMV positive donor were associated with CMV reactivation. In multivariate analysis, cord blood or peripheral blood graft, T-cell depletion, HLA mismatch and aGVHD were significant.

CONCLUSIONS: The overall rate of CMV reactivation among CMV seropositive recipients was 50%. Approx 23% of CMV reactivation episodes were transient. Among patients who received myeloablative conditioning the rate of clinically significant CMV reactivation was 40%. In multivariate analyses, cord or peripheral blood graft, HLA mismatched donors, T-cell depletion and acute GVHD were associated with CMV reactivation.
**Antiproliferative Effect of Chrysin on Anaplastic Thyroid Cancer**

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**BACKGROUND:** Anaplastic thyroid cancer (ATC) is an undifferentiated, fast growing malignancy, for which there are no effective therapies. Though ATCs only make up less than 2% of thyroid cancer cases, they represent over half of the thyroid cancer related deaths. Chrysin, a natural flavonoid, has recently been reported as a potential anti-cancer agent. However, the effect of this compound on ATC cells is not known. Thus, in this study, we evaluated antiproliferative nature of Chrysin in ATC cells as well as the possible underlying mechanisms.

**METHODS:** The human HTH7 and KAT18 were derived from patients with ATC. These cells were treated with Chrysin (25-50 μM) or DMSO control for up to 6 days. Cell proliferation was measured every 2 days using MTT assay. Western blot analysis for total Akt and phospho-Akt (ser473) was performed to investigate the effects of Chrysin on ATC. Quantitative real-time PCR (qPCR) was performed to measure Notch pathway downstream effector, Hes-1. A CBF-1-luciferase assay was done to validate the functional activation of Notch pathway in Chrysin treated ATC cells. In addition, Western Blot for total Akt and phospho-Akt (ser473) was performed to investigate the role of PI3K/Akt pathway.

**RESULTS:** Chrysin inhibited proliferation of HTH7 and KAT18 in a dose and time dependent manner. A significant increase of cleaved caspase-3, and cleaved PARP was shown in HTH7 and KAT18 treated with increasing concentration of Chrysin while a decrease of cyclin D1 and Mcl-1 was also observed. Furthermore, Chrysin-treated HTH7 cells showed a dose-dependent induction of Notch1, Notch2, Notch3, and Hes-1 mRNA levels. The similar up-regulation of Notch family genes was shown in KAT18 cells except for Notch3. The increase in luciferase activity in Chrysin treated ATC cells validated the activation of Notch pathway. In addition, treating ATC cells with Chrysin inhibited Akt phosphorylation.

**CONCLUSIONS:** Chrysin has antiproliferative effects on ATC cells by inducing apoptosis. The inhibition of ATC cell growth is associated with the activation Notch pathway and/or the inhibition of PI3K/Akt pathway. Thus, the natural flavonoid Chrysin warrants further clinical investigation as a new potential drug against ATC.

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**Does Cancer Have a Sense of Humor? The Use of Humor in Patients with Recurrent Ovarian Cancer**

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Support: Shapiro Summer Research Program and Department of Obstetrics and Gynecology

**BACKGROUND:** The use of humor in the care of patients with cancer has been shown to lessen anxiety and discomfort, enhance immune system function, and improve responses to physical stress. However, the timing and setting for employing humor by physicians or other caregivers can be perceived differently depending on the patient and the context. Little is known about the use and perception of humor in this population. The objective was to assess the use of humor by caregivers as perceived by women with recurrent ovarian cancer.

**METHODS:** Structured patient interviews with women being treated for recurrent ovarian cancer were conducted for this qualitative study using a pre-planned, open-ended questionnaire and allowed for additional patient discussion. Consecutive interviews were performed until the saturation point, the point at which no new information was being observed from further interviews. Transcripts of the interviews were then analyzed using the phenomenological method as described by Colaizzi. Significant statements were identified from each transcript. Meanings were formulated from these statements. The formulated meanings were then clustered into themes common to participants. These themes were then integrated into an in-depth description of the phenomenon.

**RESULTS:** Seventeen patients were accrued prior to reaching saturation. 82% of patients reported using humor to cope with cancer, and 76% felt that humor helped to alleviate anxiety. The use of humor by physicians and nurses was perceived as appropriate and positive 100% of the time. A relationship with a physician was often felt necessary prior to the use of humor. Humor was often perceived as comments referring to a caregiver’s life outside of medicine. These comments strengthened the bond patients felt with their caregivers. In addition, 81% of patients identified waiting times during visits and treatments as anxiety-provoking, and the time when a humorous distraction would be most helpful.

**CONCLUSIONS:** This study revealed that humor is an often used coping mechanism for women with recurrent ovarian cancer, and helps alleviate anxiety. The use of humor by physicians was found to be universally perceived as appropriate and positive. These findings reveal the role that humor plays in the lives of recurrent ovarian cancer patients, and have served as the basis for a future trial to study the effects of a humorous intervention on anxiety during the waiting periods that accompany chemotherapy visits.
Savant Syndrome Registry: A Peek into Genius

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BACKGROUND: Savant syndrome is a rare but remarkable condition in which persons with developmental disabilities or other CNS injury or illness have some striking “islands of genius” that stand in stark contrast to overall limitations. Since it was first described in 1887, reports of savant syndrome have been largely anecdotal or studies with a very small number of subjects. The purpose of this project was to make a formal registry of congenital and acquired savants from around the world categorized by ability, disability, gender, age, educational level, geographical location and a number of other variables. It is the first such registry world-wide and will serve as an invaluable resource for detailed studies on savant.

METHODS: Subjects for the current study were chosen based upon existing mail and email inquiries, face-to-face interactions, and media articles (N=367) about savants. Identification characteristics were gleaned from the aforementioned items and entered into Microsoft Excel for analysis purposes. Emails were not solicited rather all the emails received were inquiries from these individuals seeking guidance and/or information. Emails and media articles were screened for information including name, date of birth, gender, address, form of delivery (if available), race, ethnicity, schooling type, level of education, occupation (if applicable), whether the savantism was acquired or congenital, cause of the savantism if acquired, age of onset of savant abilities, disabilities, abilities, IQ, work-up, treatment, progress, family history of disease/abilities, history including if they have had training in their ability, and parental education level and occupation.

RESULTS: The savant syndrome registry has shown there are savants in over twenty countries across the world. Over 319 savants are listed in the registry and have a range of principle abilities and disabilities. There appears to be a relationship between autistic spectrum disorders and savant syndrome. Furthermore, the majority of savants are congenital savants.

CONCLUSIONS: This study has shown that previously hypothesized prevalences of savant syndrome are indeed very close to what the true population is. Moreover, this study has shown the diversity of abilities, disabilities, and backgrounds savants come from.

The Use of Advance Directives in Decision Making for High Risk Operations: Results of a National Survey of Surgeons

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BACKGROUND: Little is known regarding surgeons’ use of advance directives (ADs) and their willingness to operate on high-risk patients with directives limiting postoperative care.

METHODS: To explore the relationship between ADs and surgical decision making, we mailed a self-administered survey to 2100 randomly selected vascular, neurovascular and cardiovascular surgeons. Survey items were developed based on a qualitative study about surgeons’ attitudes and practices concerning ADs. Stepwise logistic regression was used to determine the relationship between participant characteristics and two outcomes: (1) how often surgeons discuss ADs preoperatively, and (2) how ADs limiting postoperative life-supporting therapy (LST) influence the decision to operate.

RESULTS: We received 912 responses. Around half of respondents sometimes (35%) or always (19%) discussed ADs prior to surgery, with older surgeons more likely than younger physicians to do so (OR=1.64, p=0.002). More than three-fourths of respondents sometimes (43%) or always (39%) discussed patient preferences to limit postoperative care during the process of informed consent. Surgeons frequently invited family members to be present for preoperative discussions involving patient preferences in the event of a poor outcome (40% sometimes, 33% always). Despite this attention to patient preferences, surgeons reported experiencing conflict with patient’s family members (61% sometimes or always) regarding goals of care for postoperative patients. Although surgeons rated ADs as the least important patient factor for operative decision making relative to other factors (eg: anticipated post-operative quality of life), 54% of surgeons reported they declined to operate on patients with advance directives limiting postoperative LST. Compared to surgeons from either vascular (OR=1.73, p<0.001) or neurosurgery (OR=2.76, p<0.001), cardiothoracic surgeons were more likely to refuse to operate electively on patients with ADs.

CONCLUSIONS: Although surgeons discuss patient preferences for postoperative care with patients and their families, most rely on informal conversations rather than formal ADs. Regardless of the nature of this preoperative discussion, conflict regarding goals of care often occurs postoperatively. Surgeons may also be less likely to perform elective operations on patients who have ADs limiting LST.
Optimization of Tremor Assessment using the iPod

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BACKGROUND: Tremor, a debilitating symptom common in neurological diseases including Parkinson's, is currently measured by the standard Unified Parkinson's Disease Rating Scale (UPDRS). With this, tremor is rated as mild, moderate, severe, or incapacitating by clinicians based upon motor tasks, which can cause subjectivity and rater variability. Deep Brain Stimulation surgical therapy (DBS), in which implanted electrodes stimulate areas of the thalamus and reduce symptoms, is a common treatment for refractive tremor symptoms. This study aims to analyze the precision and variability of tremor rating in the upper extremities with a newly developed application for the iPod based on motor tasks from the UPDRS in comparison to the standard clinician rating in the setting of DBS.

METHODS: To analyze a broad range of tremor severity, 10 non-DBS subjects with tremor symptoms and 10 DBS subjects will complete UPDRS upper extremity motor tasks 3 times during 3 visits. DBS subjects will be tested with stimulation on and off to measure baseline and with the treatment. The tasks will be rated by clinicians, the application with the iPod strapped to the patients' hands, and combined. The scores from 3 different trained clinicians and the iPod, as well as scores for each repetition will be compared.

RESULTS: As the study was only recently IRB approved, pending results will address rating precision and variability between raters.

CONCLUSIONS: We hypothesize that there will be less variability between raters and rating sessions with the iPod application and that the iPod will provide a more precise rating of tremor severity. The application will also be improved based upon user-satisfaction and by increasing the capabilities of the application. Once the validity is known, the application will also be used to compare the location of electrode placement in DBS and the level of symptomatic relief with the aim improve the therapy. As the application is mobile and user-friendly, and used with widely available technology, the goal is to integrate the technology into clinical practice, as well as in patients' daily lives to improve disease management.

Protein Kinase G as a Determinant of Behavior and a Potential Target of Dengue Virus Manipulation

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Support: Shapiro Summer Research Program and Howard Hughes Fellowship 133-133FD51 A534265

BACKGROUND: Dengue virus (DEN) is an important human pathogen that relies on Aedes mosquitoes for efficient transmission to human hosts. Studies of viral-host molecular interactions recently demonstrated that a number of serine/threonine residues of the DEN protein NS5 are phosphorylated during infection of mammalian cells. These phosphorylation events were determined to be due to the virally-driven autophosphorylation and activation of a cellular cGMP-dependent kinase termed protein kinase G (PKG). The phosphorylation state of DEN NS5 in mosquito cells is unknown; however, PKG is expressed in insect species, including Aedes mosquitoes. Interestingly, increased PKG activity has been implicated in the regulation of foraging behavior in several insects. Evidence suggests that enhanced activation of PKG in Drosophila, honey bees, and some beetles results in changes in behavior with the insect traveling greater distances in the search of food. Preliminary studies in Aedes mosquitoes are consistent with these observations; pharmacological activation of PKG in these animals has drastic effects on animal flying behavior. The goal of this project was to explore the interaction between Aedes PKG and DEN NS5 in vitro, serving as one of the first steps in the investigation of the hypothesis that dengue viruses modify the behavior of their vectors by activating PKG to enhance the insect's drive to travel in search of food.

METHODS: Aedes PKG cDNA obtained from a tissue lysate was inserted into the pQE-30 bacterial expression plasmid, resulting in an expression vector containing Aedes PKG with a 6x His tag. Purified Aedes PKG was then to be incubated with DEN NS5, cGMP, and [γ-32P]ATP in an in vitro kinase assay to determine the phosphorylation states of both Aedes PKG and DEN NS5.

RESULTS: Aedes PKG was inserted into the vector successfully, as determined by sequence comparison with GenBank sequence XM_0011663347.1. Purification of the construct proved to be more problematic and at present has not yet been completed.

CONCLUSIONS: The generation of an Aedes PKG expression plasmid provides an important tool for further studies of the molecular interaction between dengue virus and its invertebrate vector. Should the assay outlined above demonstrate the proposed interaction between Aedes PKG and DEN NS5, future utilizations of this construct include outlining the residues of DEN NS5 phosphorylated and comparing the level of Aedes PKG activity to that of humans.
Mobile Markets: Education with Healthy, Affordable Food at the Neighborhood-level

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Support: Ira and Ineva Reilly Baldwin Wisconsin Idea Endowment grant and Shapiro Summer Research Program

BACKGROUND: This project aims to increase the consumption of nutritious food in the lower-socioeconomic status (SES) zip codes of Milwaukee which claim some of the highest levels of obesity and chronic disease associated with poor diets in Wisconsin. In these lower SES neighborhoods, 34% of residents experience obesity, levels worse than either the US or the rest of Wisconsin (Milwaukee Health Report), and 66% of residents in these same neighborhoods experience inadequate fruit and vegetable consumption, higher than Milwaukee as a whole (Milwaukee Health Report).

These same neighborhoods contain “food deserts” where grocery stores are absent and access to affordable and nutritious foods is limited. SHARE Wisconsin has recently established a Mobile Market (MM) program to increase access in these neighborhoods. The MM program partners with 12 non-profit community-based service organizations (CBOs) to provide monthly on-site access to healthy and affordable food within the target communities. However, solely increasing access to affordable and healthy food has not changed eating habits in these neighborhoods.

METHODS: Community-based, engaging, and culturally appropriate education about nutrition and food preparation is needed to promote and support behavior change. A community advisory board (CAB), consisting of one CBO member and one customer representative, guides the development of this project from the community’s perspective. A technical advisory board (TAB), consisting of faculty, professionals, and students working in nutrition and population health from UWSMPH, UWM and the UW Extension, assists in linking current knowledge and evidence in nutrition education programming to both the development and evaluation of a community-based intervention.

To obtain a baseline measure of consumption and to better assess MM customers’ educational preferences, a questionnaire was developed for administration at MM sites. The survey will inform the CAB and TAB about knowledge, attitudes and behaviors as they relate to food selection, preparation and consumption.

RESULTS: Questionnaire administration is currently ongoing. Questionnaire data will inform both the CAB and TAB in developing or adapting a community-based nutrition education intervention and social marketing plan.

CONCLUSION: We plan to reach 500 MM participants at a minimum of 4 sites by providing evidence-based, community-engaged nutrition education. This education will improve knowledge and attitudes about nutrition and increase healthy food purchases among people in low SES areas of Milwaukee.

Outcomes of Laparoscopic Gastric Bypass vs. Laparoscopic Adjustable Gastric Band Up to 5 Years Post-op

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BACKGROUND: Laparoscopic gastric bypass (LGBP) and the laparoscopic adjustable gastric band (LAGB) are two procedures commonly performed to treat morbid obesity and associated medical conditions. Patients who elect to pursue LGBP may be different from those who choose to undergo LAGB. Outcomes and risks may differ between procedures. We sought to compare patient demographics and evaluate the outcomes following LGBP and LAGB out to 5 years post-op in a Bariatric Surgery Center of Excellence.

METHODS: A retrospective analysis was performed on prospectively maintained data collected for patients to undergo LGBP and LAGB at a single bariatric surgery program between January 2005 and January 2010. Patient demographics, weight loss outcomes, and complications were evaluated.

RESULTS: LGBP was performed in 313 patients and LAGB in 193. Patients did not differ with regards to sex (LGBP 82% female, LAGB 79% female, p=0.10) or age (47.7 +/- 11.7 years LGBP (18-71) vs. 47.1 +/- 12.3 years LAGB (19-72), p=0.56). Patients who elected to pursue LGBP did have a higher initial BMI than those who opted for LAGB (49.3 +/- 7.6 kg/m2 (35.2-79.0) LGBP vs. 45.7 +/- 7.0 kg/m2 (34.4-70.0) LAGB, p<0.001). LAGB patients were offered the option of ‘same day’ discharge, and 107 (55%) met criteria and were successfully discharged. Length of stay and the 30-day readmission rate and early major complication rates were significantly higher in LGBP. Weight loss was greater for LGBP at all study intervals (63.2%, 65.1%, and 64.2% EWL LGBP (p=0.001) vs. 32.5%, 32.3%, 36.7% EWL LAGB (p=0.001) at 1, 2, and 3 years post-op). Weight loss failure was defined as less than 20% EWL (excess weight loss) at 2 or 3 years post-op. Weight loss failures were more common at both 2 years (0% LGBP vs. 9% LAGB [n=17]) and 3 years (0% LGBP vs. 4% LAGB [n=7]; p<0.001) for LAGB.

CONCLUSIONS: Patients who choose to undergo LGBP have a higher initial BMI than those who elect for LAGB. LGBP is associated with significantly fewer weight loss failures and greater EWL at all intervals evaluated. This should be balanced against the fact that LGBP is associated with higher complication and readmission rates. Reoperation rates are greater in LAGB patients, mostly related to late band slippage. Both procedures have a role in contemporary bariatric surgical practices. Patients should be informed of the pros and the cons of each procedure when choosing a bariatric operation.
Mechanism of Action of a Novel Class of Antibiotics that Targets DNA Replication

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Support: Shapiro Summer Research Program and Investigator grant NIH GM068061

BACKGROUND: Microbial protein-protein interactions are attractive targets for developing new antibiotics. One such target is bacterial single-stranded DNA-binding protein (SSB), whose interactions with DNA replication and repair enzymes are critical for bacterial cell viability. SSB binds to these enzymes via interactions with its unstructured C-terminal tail. This protein binding element is well conserved across bacterial SSBs, but different from the analogous elements in eukaryotes, making agents that disrupt SSB/proteins complexes excellent potential antibacterial drugs. Dr. Keck's Lab identified several small molecules that interrupt the interaction between E. coli SSB and several of its protein partners, including Exonuclease I (ExoI). Though these compounds were shown to be antibacterial, derivatives with improved solubility failed to inhibit bacterial growth. Two experiments were performed. (1) The derivative compounds were tested for their ability to inhibit SSB binding to ExoI in a purified in vitro system to determine whether the modified compounds retained their inhibitory properties. (2) The ability of the compounds to inhibit bacterial DNA replication in vivo was tested.

METHODS: (1) Inhibition of SSB-ExoI binding by derivative compounds: A fluorescein-labeled peptide consisting of the C-terminal 10 residues of SSB was combined with ExoI purified from E. coli and titrated with the derivative compounds. Fluorescence polarization was used to assess binding of the peptide to ExoI. (2) Inhibition of DNA replication: E. coli was grown in the presence of the inhibitory compounds and DNA synthesis was monitored by measuring the incorporation of [3H]dTTP.

RESULTS: (1) Some of the derivative compounds disrupted Exo binding to the SSB C-terminal peptide. Other derivatives showed no inhibition. This information will be used in subsequent development of new derivatives. (2) Bacteria grown in the presence of the original compounds showed decreased incorporation of tritiated dTTP consistent with their inhibiting DNA replication directly.

CONCLUSIONS: (1) Further study is needed to determine why the derivative compounds all fail to inhibit bacterial growth despite the fact that several of the compounds appear to disrupt SSB binding to ExoI. (2) Decreased incorporation of tritiated dTTP in the presence of the original compounds suggests that these molecules do inhibit bacterial DNA synthesis.

Assessing Environmental Risk Factors in Testicular Cancer, Undescended Testes and Hypospadias

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BACKGROUND: Multiple studies have reported an increase in the prevalence of diseases of the male genitourinary system within the last three decades. Although there is strong evidence and a need to further evaluate genetic risk factors for testicular germ cell tumors (TGCTs), hypospadias and undescended testes, there is building evidence that environmental risk factors play a role in the susceptibility of these diseases as well. The testicular dysgenesis syndrome theory proposes that testicular germ cell tumors, undescended testes, and hypospadias have a common etiology. Evidence to support this theory is sparse. We seek to examine whether suspected risk factors involved with undescended testes and hypospadias are associated with TGCTs to evaluate the testicular dysgenesis syndrome theory.

METHODS: The development of the genitourinary system is greatly influenced by hormones, especially during key developmental points and therefore environmental exposures that could affect the hormonal milieu may be playing a role in the increased prevalence of these diseases. We will access environmental risks through a questionnaire developed for mothers of sons with hypospadias, undescended testes and/or TGCTs inquiring into factors relating to pregnancy, fertility, occupational and dietary exposures and drug, alcohol and supplement use.

RESULTS: This research is in progress.

CONCLUSIONS: Although several risk factors have been identified and evaluated, small study populations have limited this area of research. By investigating these risk factors in a combined population of hypospadias, undescended testes and TGCTs patients not only can these risk factors be investigated within a larger population, but new insights into the proposed theory that relates these diseases, the testicular dysgenesis syndrome, can be gained.
The Synergistic Effect of Pasireotide® and a Raf-1 Activating agent in Carcinoids

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Support: Shapiro Summer Research Program and Department of Surgery

BACKGROUND: Somatostatin analogs are the mainstay treatment for controlling tumor proliferation and hormone secretion in carcinoid patients. The new somatostatin analog Pasireotide (SOM230) may be more potent given its broader receptor spectrum and elevated binding affinity. Data suggest that ERK1/2 phosphorylation potentiates the anti-tumor effect of somatostatin analogs in carcinoids. Also, ERK1/2 phosphorylation by Raf-1 activating agents reduces biomarker expression in carcinoids. Thus, Raf-1/MEK/ERK1/2 pathway activating drugs may synergize with somatostatin analogs like SOM230. We investigate the effects of SOM230 in combination with Teriflunomide (TFN), a Raf-1 activator, in a human carcinoid cell line.

METHODS: Human GI carcinoid cells (BON) were incubated in TFN (0-100µM), SOM230 (0-10µM) or both, for 96 hours. Methylthiazolyldiphenyl-tetrazolium bromide (MTT) rapid colorimetric assay measured cell growth. Western blotting was performed for human achaete-scute complex-like 1 (ASCL1), Chromogranin A (CgA), and pro-apoptotic markers. Combination indices (CI) were derived from the Chou-Talalay method using CompuSyn ® software. Quantity One software v. 4.6.3 (Bio-Rad) generated densitometric values.

RESULTS: Combination treatment with SOM230 and TFN reduced cell growth beyond the additive effect of either drug alone. Combination indices < 1, thus verifying synergy between both drugs. Treatment with up to 50µM TFN reduced both ASCL1 and CgA expression dose-dependently by up to 50%. SOM230 alone minimally affected biomarker expression. Addition of low dose SOM230 following TFN inhibited ASCL1 and CgA levels beyond the sum inhibitory effect of either drug alone. Combination of 0.5µM SOM230 and 50µM TFN reduced ASCL1 and CgA levels by 95% and 66% respectively, compared to controls. Combination treatment increased levels of phosphorylated ERK1/2, cleaved PARP and caspase-3, and reduced levels of total caspase-3, X-linked inhibitor of apoptosis (XIAP), survivin and Mcl-1, beyond the additive effect of either drug alone.

CONCLUSIONS: Combined SOM230 and TFN treatment in BON carcinoid cells synergistically inhibits cell growth and biomarker expression via the induction of apoptosis. Elevated Raf-1 activity may underlie the anti-tumor effect consequent of synergy. Combination therapy may benefit carcinoid patients who respond poorly to high toxicity. As each drug has been evaluated independently in clinical trials, combinatorial drug trials are warranted.

Simvastatin’s Effect on CSF Neurofilament Light Chain in Adults at Risk for Alzheimer’s Disease

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BACKGROUND: Midlife vascular risk factors increase the risk of developing Alzheimer’s disease (AD) later in life. In animal models, statins decrease amyloid-β levels in the brain and cerebral spinal fluid (CSF) and may potentially alter AD pathology. Since pathological changes occur decades prior to clinical manifestation, statin therapy during midlife may be most beneficial in preventing AD onset. CSF biomarkers have significant potential for use in predicting preclinical AD. The role of CSF neurofilament light chain (NF-L) and the impact of statins on this novel biomarker are largely unknown. The goal of this study was to investigate the effect of simvastatin CSF NF-L level among cognitively healthy adults with increased risk for AD.

METHODS: In a 9-month, double-blind, randomized, controlled study of 100 asymptomatic middle-aged adults with a parental AD history, we evaluated the effect of 80 mg simvastatin vs. placebo on CSF NF-L and the association between this biomarker and other CSF biomarkers and cognition.

RESULTS: Twenty percent of participants (n = 100, age 53.4 ± 7.9, 70% women, 38% APOE4 positive) had a CSF NF-L level above the 125 ng/L detection limit. Logistic regression models indicated that treatment did not affect the number of participants with a detectable CSF NF-L level at month 9 (p = 0.468). Among those with detectable baseline NF-L, no significant correlations were found between CSF NF-L and other CSF biomarkers (p > 0.100). Spearman rank order correlation showed marginally significant positive correlations to mental control score (p = 0.056) and working memory (p = 0.057). Linear mixed effects analyses indicated that NF-L is a marginally significant predictor for delayed recall (p = 0.059) and working memory (p = 0.067), and a significant predictor for mental control (p = 0.043). Subjects above the detection limit of CSF NF-L were older (p < 0.001) and had lower processing speed at baseline (p = 0.046). CSF NF-L showed positive correlation with hs-CRP (p = 0.007).

CONCLUSION: In this cohort of asymptomatic adults at risk for AD, 9-month treatment with simvastatin did not affect CSF NF-L levels. Those with increased CSF NF-L levels showed worse functioning in mental control and processing speed. CSF NF-L levels did not correlate with other CSF biomarkers. Given the small number of participants with detectable CSF NF-L in this study, larger trials are needed to evaluate the role of CSF NF-L as a preclinical biomarker for AD.
When Career and Life Collide: A Qualitative Study of the Medical Marriage

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Department: University of Wisconsin Center for Women’s Health Research

Mentors: Carol Isaac PhD, PT; Molly Carnes, MD, MS

Support: Shapiro Summer Research Program and Department of Medicine

BACKGROUND: With the growing number of female physicians, there are fewer traditional medical marriages made up of a male physician and a stay-at-home wife (AAMC, 2008-2009; Levinson, 2004). The “two-career family” is a more frequent occurrence for both male and female physicians’ families and dual-doctor marriages continue to rise (Papanek, 1973; Sobecks, 1999; Woodward, 2005). As more women enter the physician workforce and the number of two-career families increases, the effects of a physician’s demanding career on his or her spouse are of interest. This qualitative study explores the current medical marriage from the perspective of the spouses of internal medicine residents and faculty at one academic medical center.

METHODS: Semi-structured, in-depth interviews with the spouses of 6 faculty and 5 residents of the Department of Medicine at the University of Wisconsin who were participants in a previous study of careers in medicine. Questions covered topics of balance, career choices and support networks. A grounded theory approach facilitated the analysis of common themes between groups, within groups and as a cohort.

RESULTS: Participants were grouped into three main categories based on whether they had a career, a “job”, or were also physicians. When looking at statements coded as positive or negative comments, it was found that the highest percentage of positive comments were made by the dual-physician families (61% positive: 39% negative) followed by dual career couples (48% positive: 52% negative) and the job-physician couples (0% positive: 100% negative). Emerging themes from the interviews include the challenges of being married to a physician, anger against the medical education and healthcare systems, how meaningful work creates a sense of self, the degree of spousal support, and how close the families are to achieving their ideal life.

CONCLUSIONS: This exploratory study looks at physician marriages from the spouse’s perspective. As women enter the traditional male physician role, their male spouses frequently assume the traditional female social role, violating gender norms; however, spouses that were more satisfied with their career (including stay-at-home fathers) exhibited less negativity in the text.

Nitrous Oxide Exposure Inhibits CNS Regeneration In Vitro

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Support: Shapiro Summer Research Program and American Association of Neurological Surgeons Medical Student Summer Fellowship

INTRODUCTION: Nitrous oxide (N2O) is a commonly used anesthetic and its mechanism of action involves folate inhibition. We have shown that folate supplementation enhances CNS regeneration and functional recovery from spinal cord and brain injury. N2O reverses the beneficial effects of folate in vivo. To determine whether this effect of N2O is neuronal or glial, we investigated the effects of in vivo N2O exposure on axonal growth in culture.

METHODS: Sprague-Dawley rats were subjected to dorsal column transection after one or more exposures to N2O. The lumbar DRGs were removed 3 days after surgery and cultured. Cells were fixed and stained at timepoints 13-72hrs after removal. Axonal elongation was assessed blindly and statistically analyzed.

RESULTS: Single and multiple doses of N2O significantly inhibit the ability of CNS neurons to extend axons compared to untreated controls (p<0.05). This deleterious effect is evident almost immediately, with no axonal regeneration at 13 hours, and is long-lasting, with a 4-fold decrease in axonal regeneration between N2O-treated and untreated neurons at 72 hours.

CONCLUSIONS: By isolating exposed neurons from environmental variables, it is clear that N2O decreases the neuron’s intrinsic capacity to regenerate. Any negative consequences of N2O should be thoroughly examined because it is commonly used. Due to potential inhibition of CNS regeneration, N2O may be unsafe to use in surgery on the brain and spinal cord. Injurious effects of anesthesia have received significant attention recently. In this study, we report the first example of a mechanism by which such injury occurs.
Calculating Intestinal Length and Mucosal Volume Using Computerized Tomography

Authors: Christopher Strouse, BS; Paul Milewski, PhD; Denise Ney, PhD; Jamie Weichert, PhD; Kim Maurer; Peter Nichol, MD, PhD

Mentor: Peter Nichol, MD, PhD

Department: Department of Surgery, University of Wisconsin School of Medicine and Public Health

Support: Department of Surgery NIH T35 Short Term Training Grant DK062709-05

BACKGROUND: Short bowel syndrome (SBS) is a disorder characterized by the loss of intestinal length and surface area, resulting in malabsorption. Some patients can regenerate some absorptive capacity (AC) and failure to identify these patients results in their reliance on total parenteral nutrition (TPN) with serious implications. TPN costs $150,000/yr, and the 2 and 5 year survivals for patients on TPN are 86% and 49% respectively.

A patient’s AC at the onset of SBS is predictive of their potential for absorptive growth, however there are no convenient and reliable ways to assess a patient’s AC. A convenient, cost-effective, and non-invasive way to determine a patient’s AC would be of great value in optimizing management in these patients.

We set out to develop a way to determine a patient’s AC by calculating intestinal surface area from contrasted CT scan images. We developed a mathematical algorithm and set out to validate it using a rat model.

METHODS: Algorithm: We developed an algorithm to calculate intestinal mural surface area from consecutive transverse CT images using MATLAB software. Areas of intestinal mucosa are identified, and summed across all slices to give the total volume. Summating the interface between the mucosa and lumen across all slices yields the inner intestinal surface area.

ANIMALS: IACUC approval for these studies was obtained from the University of Wisconsin SMPH (J.W. protocol # m02169). To verify our algorithm, we performed CTs on 6 juvenile rats averaging 211g. The rats were anesthetized with isoflurane and a 25 gauge IV was placed in the tail vein. A dose of 1 ml of enteral contrast was given orally and a 0.1 ml dose of IV contrast was given. A CT was performed (0.62 mm slice thickness). Animals were then sacrificed via decapitation and intestines were harvested and measured.

RESULTS: A total of 6 rats underwent CT imaging and intestinal weight measurement. The average intestinal mucosal wet weight was 3.11g (s = 0.6). Image resolution was inadequate for analysis with our algorithm. Oral administration of contrast failed to illuminate the whole small intestine, and IV administration of contrast did not produce reliable results.

CONCLUSIONS: We were unable to validate our algorithm in the rat. This animal model presented several challenges. They included difficulty administering sufficient quantity of contrast quickly, inadequate resolution of the human CT scanner, and incomplete perfusion of the mucosa by contrast.

Analysis and Isolation of PIG-A Variant T-Cells Using Flow Cytometry

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Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health; Ann’s Hope Foundation; and the Gretchen and Andrew Dawes Melanoma Research Fund

BACKGROUND: The phosphatidylinositol glycan class A (PIG-A) gene is involved in a key step in the formation of glycosylphosphatidylinositol (GPI) anchor biosynthesis, with non-functional PIG-A mutations resulting in absent GPI expression. This surface protein provides an easily analyzable indicator of cellular mutations. Activated T cells are undergoing many replication cycles and are more susceptible to mutations. We hypothesize that in vivo somatic cell mutant T cells from melanoma patients are predictive biomarkers for anti-melanoma immunity. Currently the lab uses the hypoxanthine guanine phosphoribosyltransferase (HPRT) system to identify anti-melanoma T cells. This HPRT analysis is time consuming and labor intensive, and there is need for more than a single system to detect and characterize somatic cell gene mutations in humans as probes for fundamental biological processes. The purpose of this study was to identify PIG-A variant T cells for molecular and functional analyses.

METHODS: Flow cytometry analysis was performed on multiple normal and patient PBMC, staining for the expression of GPI as well as other CD surface antigens using LSR II cytometer. Fluorescently labeled aerolysin (FLAER), a modified bacterial toxin, was obtained to analyze the GPI expression. Mouse anti-human fluorescently labeled antibodies were used to stain other surface antigens.

RESULTS: A staining protocol using CD14,19,3, VIVid, TCR, and FLAER showed reproducible and well marked separation in FLAER negative (FLAER−) populations. The median fluorescence intensity for the negative populations in both the kit and FLAER groups had values below 170. However the positive populations in the kit had values around 2000, while the FLAER group was over 12,000, demonstrating superior population separation using FLAER as compared to the kit. Using the SORP BD FACS Aria sorter, FLAER – samples were able to be collected and using an expansion protocol 1.65 x 106 cells were expanded and cryopreserved for subsequent analysis.

CONCLUSIONS: FLAER staining protocol repeatedly produced more consistent and better-defined PIG-A variant results than both the CD48/55 and kit protocols. Isolated PIG-A variant cells will now be confirmed as PIG-A mutant T cells with a growth assay using pro-aerolysin that binds the GPI protein and lyases the cell. Subsequent studies will proceed with functional and molecular studies of PIG-A variant T cells to determine if they are enriched for anti-melanoma T cells.
Are Terminally Threaded Guide Pins from Cannulated Screw Systems Dangerous?

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Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

BACKGROUND: Threaded and smooth pins are often used in orthopedic surgery. Although uncommon, injury to the soft tissues can and do occur, including nerve or vessel injury from aberrant pin placement. Currently, there is little data to assess how the soft tissue structures are injured and what the relative risks are for threaded pins versus smooth guide pins. The purpose of this study was to compare the risk of nerve injury from threaded pins versus smooth guide pins due to: 1) past point-drilling of the pin, or 2) entanglement of the pin with soft tissue.

METHODS: Past-point drilling was tested by a blindfolded participant drilling a 1.6 mm guide pin (terminally threaded or smooth) through a porcine femur until they felt they had drilled through the second cortex. The distance over-drilled was measured in mm. 20 trials were randomly completed, 10 with each pin type. Entanglement of soft tissue was tested by placing the terminal portion of the guide pin on the nerve. Two drilling positions were tested: 1) drilling at 90° and 2) parallel to the nerve. The drill was run for 1 second and assessed for entanglement and magnitude of entanglement (measured in mm of nerve wrapped by the pin). 60 trials were completed, 15 with each pin type, and in each of the 2 positions.

RESULTS: The average past-point drilling depths were 4.6 and 16.9 mm for the smooth and threaded pins, respectively (p<0.05). The mean nerve overwrapping was 0.45 and 4.7 mm, for the smooth and threaded pins, respectively (p<0.05), drilled at 90° and 0.15 and 0.92 mm respectively (p<0.05) in the parallel position. In 13 of 60 trials with the smooth pin and 50 of 60 trials with the threaded pin, wrapping was observed (p<0.05).

CONCLUSION: This study demonstrates that it is difficult to determine by feel when the threaded pin has drilled through the second cortex of the bone, in contrast to the smooth pin. Furthermore, soft tissue entanglement is more likely and to a greater magnitude with threaded pins than with smooth pins.

An Assessment of Racial Disparity in Rates of Possible Risk Factors for H1N1-associated Hospitalization: Dane County, Wisconsin

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Support: Department of Family Medicine Summer Student Research and Clinical Assistantship Program

BACKGROUND: Investigation completed by the Dane County-City of Madison Department of Public Health in the Spring of 2010 revealed a nine-fold disparity in crude hospitalization rates for H1N1 influenza between black and non-Hispanic whites in Dane County (104.6 per 100,000 for black vs. 15.3 per 100,000 for non-Hispanic white)—three times the disparity observed for the state of Wisconsin. This study examines prevalence of risk factors associated with H1N1 hospitalization in clinical populations in Dane County and any racial differences in these prevalences.

METHODS: This study is a retrospective, cross-sectional study of the prevalence of potential risk factors for H1N1 hospitalization in Dane county. From the University of Wisconsin-Department of Family Medicine (UW-DFM) clinical data warehouse, de-identified patient records segregated by age, race and ethnicity for all unique individuals with a visit to a Dane County UW-DFM clinic from January 2008 to December 2009 were acquired and sorted into four primary demographic groups: black children (0-17 years) and adults, and white children and adults. Counts and prevalence (cases/1000) of the following potential risk factors for H1N1 hospitalization were observed: malignant neoplasms, diabetes mellitus, hemoglobinopathies, neurological disease, heart disease, chronic lung disease, asthma, renal disease, pregnancy, tobacco exposure and obesity.

RESULTS: Preliminary assessment suggests significant disparities between black and non-Hispanic white Dane County residents in the prevalence of diabetes mellitus, hemoglobinopathies, chronic lung disease, renal disease, pregnancy, tobacco exposure, and obesity (rate ratios greater than 2.0, black v. non-Hispanic white). Further data analysis is pending.

CONCLUSIONS: The differences between black and non-Hispanic whites for prevalence of risk factors for H1N1 hospitalization explain part of the disproportionate hospitalization rates. Additional investigation into severity of illness may further explain the disparity in hospitalization rates in Dane County. A chart review is planned to assess additional features of demographics of the hospitalized population and course of illness.
The Problem of Infant Mortality in Wisconsin: Roadblocks to Access and Quality?

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Mentors: Jonathan Jaffery, MD; Elizabeth Feder, PhD; Donna Friedsam, MPH
Support: Shapiro Summer Research Program

BACKGROUND: Wisconsin has a significant problem regarding the racial disparity in infant mortality rates. The disparities exist despite Wisconsin's extensive coverage for expecting mothers and infants of low income through BadgerCare and the enhanced pregnancy benefits of the Medicaid PNCC program. A study in 2008, showed that PNCC in Wisconsin has a positive effect on birth outcomes and its effects increase with intensity of service. Women enrolled in PNCC had fewer preterm babies, low weight babies and babies who had to be transferred to NICU's. The 2006 DHS Evaluation of PNCC suggested there is great variation among the counties in successfully enrolling and caring for their target population. This project will explore components of the referral to enrollment process such as who is making the referrals, marketing of the program, follow up by PNCC Care Coordination Providers, care capacity, and coordination of care to see if they offer clues to the differential enrollment rates in different areas.

METHODS: Using PNCC enrollment data from the DHS and 2001 PNNC data, all Wisconsin counties were ranked to determine which counties are most and least successful at enrolling and providing care to their target populations. An online survey with follow up via email and phone will be conducted to try to obtain a survey response of 50%. Follow up interviews will then be conducted to willing respondents. Comparisons will be drawn from surveys and/or interviews with specific PNCC providers and general demographic data.

RESULTS: This study is still in progress.

CONCLUSIONS: The results of this study could provide suggestions on how to increase enrollment of a population at high risk for poor birth outcomes in a program that is thought to improve birth outcomes in Wisconsin.

Wisconsin Stillbirth Services Program: A Multifactorial Approach to Stillbirth Analysis

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BACKGROUND: Stillbirth accounts annually for about 26,000 deaths within the United States. Among over 30 classification systems in use [Reddy et al., 2009], most identify a discrete cause in less than half of the analyzed stillbirths. Fetal causes, which are the focus of many etiologic studies, are identifiable in only about 25% of stillbirths in developed nations [Pauli and Reiser, 1994, Wapner and Lewis, 2002]. We analyzed 416 of the most recent (2004-2010) Wisconsin Stillbirth Service Program (WiSSP) cases from a multifactorial approach.

METHODS: Data including pregnancy and family history, clinical examination, photographs, radiographs, autopsy, placental pathology, and laboratory data collected from birthing hospitals was evaluated centrally to identify causal (sufficient to independently explain fetal demise) and non-causal abnormalities which were classified into fetal, maternal, and placental categories. Summary letters were sent to referring physicians and counseling was offered to all families.

RESULTS: In 70% of cases a cause sufficient to independently explain the demise was identified including 40% placental, 21.5% fetal, and 12.7% maternal. Results for stillbirths and second trimester miscarriages did not differ significantly. In 95% of cases at least one cause or non-causal abnormality was recognizable and in two thirds of cases, more than one cause or non-causal abnormality was identified. In cases with maternal cause, the placenta was virtually always abnormal. Both placentas (59%) and fetuses (38%) were frequently smaller than expected for gestational age. Previous miscarriage and/or stillbirth was a risk factor for future losses with 35% of previous pregnancies ending in fetal demise.

CONCLUSIONS: A multifactorial approach to stillbirth investigation allows for an underlying cause to be determined in the majority of cases. Non-causal abnormalities are found in the majority of cases regardless of primary cause. Despite more complete investigation in near term stillbirths, causes are more readily identified in earlier losses. Recommendations include complete evaluation of all second and third trimester losses with special attention to placental pathology and thorough investigation for multiple causes or abnormalities whether or not a primary cause is initially recognized. Improved understanding of the causes of late miscarriage and stillbirth may contribute to management of pregnancies at risk and eventually to prevention of stillbirth.
Clinical Utility of fMRI in Surgical Planning for Patients with Intracranial Tumors

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Support: Shapiro Summer Research Program, Department of Neurological Surgery and Department of Radiology

BACKGROUND: Functional magnetic resonance imaging (fMRI) is a non-invasive technique used to identify eloquent cortical structures by examining the differences in blood oxygen level dependent (BOLD) response during task performance and at rest. This technique was originally used in a basic science setting, but has become prominent as a clinical tool in recent years. Studies have shown that fMRI activation patterns, as measured by the BOLD response, are consistent with the cortical responses seen during intraoperative brain mapping (Roux et al, 2000). However, preoperative fMRI scanning is still not a universal practice, and the protocols used for fMRI procedures are not uniform between institutions. It is clear that there is a need for more research in this area to better characterize the true clinical utility of fMRI, especially in its use as an adjunct in surgical planning. This is particularly important in determining the extent to which fMRI can be used as a predictive model of surgical morbidity and mortality.

METHODS: 1727 adult patients undergoing resection of an intracranial mass between 2001 and 2009 at the University of Wisconsin Hospital & Clinics were identified in a retrospective fashion by review of the case logs from the Department of Neurosurgery. Of the original 1727 patients, 278 patients were included in the study. Inclusion criteria were pathological diagnosis of glial or metastatic tumor, supratentorial cortical location, and first-time diagnosis of intracranial mass. Exclusion criteria included all tumors not of glial or metastatic origin, sellar, infratentorial, ventricular or subcortical location, and/or recurrent tumor. All available data in UWHC’s electronic medical record was reviewed. In addition to all pertinent demographic data, information regarding patient outcome with particular attention to motor, language, sensory and visual function, was recorded: Preoperative, immediate postoperative, 3 and 6 month postoperative date was gathered. A Glasgow outcome score was assigned to each patient based on the authors’ interpretation of the patient's functional status at 6 months. Out of 278 patients, 160 patients didn’t receive preoperative fMRI and 118 patients received preoperative fMRI.

RESULTS: The data is currently undergoing final steps of editing before statistical evaluation.

CONCLUSIONS: Our null hypothesis is that fMRI doesn’t improve patient’s outcomes. After the data will be analyzed, the following outcomes can emerge: fMRI influence patient’s morbidity/mortality, fMRI doesn’t influence patient’s morbidity/mortality. Implications of the results will help determine role of fMRI in clinical diagnostic and presurgery assessment of patients with intracranial tumors.

Preoperative Functional Status Correlates with Some, but not All, Postoperative Complications

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Support: Shapiro Summer Research Program and Department of Surgery

BACKGROUND: Premorbid functional status and disability have been previously correlated with poor patient outcomes including increased mortality, hospitalization stay, and health care costs. However, there is limited data available on its effect for postoperative complications. We hypothesize that a partial or total dependent preoperative functional status will correlate with an increase in post-operative complication incidence.

METHODS: Data from patients undergoing elective resection for colon cancer were obtained from the American College of Surgeons National Surgical Quality Improvement Program database from the years 2005 through 2008. Explanatory variables included demographic, laboratory, preoperative, and operative variables; outcome variables included 30-day rate of complications, 30-day mortality rate, and 30-day reoperation rate. Univariate analysis was performed to determine the association of pre-operative functional status and post-operative complication incidences. Each statistically significant complication from the univariate analysis was then compared to the explanatory variables using multivariate logistic regression analysis.

RESULTS: A total of 3,547 patients met the inclusion criteria with 399 patients (11%) classified as totally dependent and 533 patients (15%) classified as partially dependent. Patients classified as functionally independent had significantly lower co-morbidities and more favorable laboratory variables. Fourteen of the 20 postoperative complications were found to be significantly correlated with preoperative functional status in the univariate analysis. Of those 14 complications, only six complications were independently associated with partial or total dependent functional status using logistic regression: requiring a ventilator for more than 48 hours (OR: 2.0; 3.3), septic shock (OR: 1.9; 1.1 N.S.), pneumonia (OR: 2.3; 2.5), urinary tract infection (OR: 2.1; 1.5 N.S.), re-intubation (OR: 1.5; 1.1 N.S.), and coma (OR: 3.4; 4.9). Additionally, return to the operating room was found to be significant in multivariate but not univariate analysis.

CONCLUSION: In a national population of patients undergoing elective resection for colon cancer, preoperative functional status was found to correlate with specific postoperative complications. Functional status may be an indicator for patients at risk for some but not all postoperative complications following elective resection.
Using Phantom-less QTC to Determine Bone Mineral Density in the Thoracic Spine

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Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

BACKGROUND: Osteoporosis and other metabolic bone diseases can significantly affect bone mineral density (BMD) and the success of implants used in orthopedic surgery. Measurement of BMD is traditionally accomplished by dual photon x-ray absorptiometry (DEXA) scans of the lumbar spine. However, the advancement of CT scans have provided another possible means of measuring BMD. Phantom-less bone mineral density (PLBMD) systems are easily integrated into the CT workflow for non-dedicated Quantitative CT (QCT) bone mineral density (BMDP) systems that are used in orthopedic surgery. The purpose of this study was to determine if BMD as reported by the PLBMD program developed by Philips (BMDP) correlated with BMD as reported by lumbar DEXA scan (BMDD) for both lumbar and thoracic QCTs. Secondarily, it was our goal to establish a baseline normal distribution of BMDP in the thoracic spine for use in the development of thoracic t-scores.

METHODS: In the comparison of BMDD to BMDP, 38 and 29 subjects were identified for the analysis in the lumbar and thoracic spines respectively. All patients had undergone DEXA and CT studies within one year. Normative Hounsfield unit (HU) data was generated for the thoracic spine with CT examinations performed on 80 consecutive trauma patients; stratified by age and gender. Additionally, 316 female subjects aged 20-29 were identified to establish a baseline, normal distribution of BMD utilizing CT scans for the development of t-scores in the thoracic spine.

RESULTS: Correlations were found between BMDD and BMDP for both lumbar (p<0.0001) and thoracic QCT (p<0.01). Establishment of normal, baseline BMDP values in the thoracic spine is ongoing.

CONCLUSIONS: Regional bone mineral density as measured by the Philips PLBMD system correlates with bone mineral density as measured by DEXA for both lumbar and thoracic spine. This data suggests that PLBMD programs could be used in the assessment of regional BMD in the lumbar and thoracic spines with no additional cost or radiation to the patient. With the eventual establishment of a normal, baseline distribution of thoracic BMD it will be possible to quantitatively measure patients’ bone mineral density in terms of t-scores. This has the potential to aid in fracture prediction, diagnosis of osteoporosis, and predicting the stability of metal implants for surgical decision making in the thoracic spine.

Does Head and Neck Irradiation Increase the Chance of Multi-gland Disease in Patients with Hyperparathyroidism?

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Mentor: Herbert Chen, MD, FACS

Support: Shapiro Summer Research Program and Department of Surgery

BACKGROUND: Exposure to low dose therapeutic radiation, whether used to treat lymphoma, breast cancer, or other benign conditions such as acne, is thought to cause an increased risk for thyroid and parathyroid neoplasia. Therefore, in this study, we investigated whether patients with a history of head/neck irradiation and hyperparathyroidism (HPT) had a higher incidence of multi-gland disease.

METHODS: Between November 2000 and May 2010, 1428 patients with HPT underwent parathyroidectomy at the University of Wisconsin. Of these cases, 39 patients (2.7%) had a history of radiation exposure (RADR). These 39 cases were compared to the 1389 cases with no prior radiation exposure (NO RADR).

RESULTS: There was no significant difference in gender or age between the groups. While most laboratory values were similar, pre-op parathyroid hormone levels were higher in the NO RADR patients compared to the RADR groups (97 ±7 vs. 106 ±8 pg/ml, p = 0.001). Interestingly, the resected parathyroid glands were significantly smaller in the RADR compared to the no RADR group (511 ±70 vs. 790 ±37 mg, p = 0.001). The surgical cure rates were high and identical between the groups (97% vs. 97%, p = 0.926). There was no difference in the recurrence rate (p = 0.392). Contrary to common belief, RADR patients did not have a significantly higher incidence of multi-gland disease (p=0.774). Of the 39 RADR patients, 12 (31%) had multi-gland disease whereas 398 of the 1389 (28%) of the NO RADR patients had multi gland disease.

CONCLUSIONS: Surgical outcomes are excellent in patients with a prior history of radiation and HPT undergoing parathyroidectomy. Previous radiation exposure does not increase the likelihood of multi-gland disease in patients with HPT.
Recurrent Hepatic Colorectal Metastases: Does the Extent of Surgical Intervention Impact Outcome?

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Mentor: Sharon Weber, MD

Support: Department of Surgery NIH T35 Short Term Training Grant DK062709-05

BACKGROUND: Surgical treatment of recurrent hepatic colorectal (CR) metastases has been shown to be safe and effective, with median survival of 30-40 months. We sought to examine the effect of the extent of surgical intervention on outcome in patients with recurrent hepatic CR metastases, as this has not been well studied.

METHODS: Patients with recurrent hepatic CR metastases were identified from a prospective database and records were retrospectively reviewed. Patient outcome was analyzed according to the extent of surgical intervention: anatomical resection, nonanatomical (wedge) resection, intra-operative ablation, and noncurative interventions. Demographic data, tumor characteristics, recurrence-free survival (RFS), and overall survival (OS) were analyzed.

RESULTS: Between 1989 and 2009, 77 patients with recurrent hepatic CR metastases were identified. Of the 40 patients treated with curative intent, the following procedures were utilized: 20 ablations, 16 anatomical resections, and 4 non-anatomical resections. Thirty-seven patients were treated noncuratively. OS was improved in patients undergoing surgical intervention compared to nonsurgical treatment (p<0.001, Table 1). In addition, both RFS and OS were prolonged after anatomical resection compared to non-anatomical resection or ablation.

CONCLUSIONS: In patients with recurrent hepatic CR metastases, both overall survival and recurrence-free survival was improved in patients undergoing anatomical resection compared to other interventions. When possible, patients with recurrent CR metastases should be treated by anatomically-based hepatic resection.
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