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Western Regional Meeting Abstracts

WAFMR, WSCI, WAP and WSPR
Joint Plenary Session II
1:45 PM
Thursday, January 28, 2010

Session: Plenary Session
1
STUDIES OF THE FREQUENCY OF ASSISTED REPRODUCTIVE TECHNOLOGY BIRTHS AND TWINNING IN PRADER-WILLI SYNDROME
J. Gold, C. Ruth, V. Kimonis University of California, Irvine, Orange, CA.
Purpose of Study: To determine the association between ART and Prader-Willi Syndrome (PWS) by evaluating the frequencies of ART-births in three distinct molecular groups, compared with ART-births in the USA. To evaluate the natural frequency of twinning with and without ART in the PWS group.
Methods Used: Data was collected from surveys administered by:
1) The Prader-Willi Syndrome Association of the USA (PWSAUS)
2) The sponsored Rare Diseases Clinical Research Network (RDRCN)
3) Review of medical records from PWS patients seen by the Genetics Division at UCIMC
Summary of Results: Total number of PWS patients was 1,888. Total frequency of ART was 2.3% (44/1,888), 95% confidence interval (CI) 1.62%-2.98%. There was no statistical significant difference in the frequency of ART-conceived PWS patients. chi squared = 1.024 df p = 0.599. However the difference in frequencies of the genetic subtypes in the ART-conceived patients and naturally conceived patients was statistically significant (p = 0.019). By comparison ART conceived patients were more likely to have UPD and imprinting center defects. This study also demonstrated that there was no increased frequency of natural twinning without ART in the PWS population above the U.S. population.
Conclusions: Studies have concluded that the effects of ART procedures may be restricted to imprinting disorders in which the maternal allele is hypermethylated or in which an imprinting defect accounts for a significant proportion of affected cases. This study shows a significant increase in UPD in PWS from ART-births suggesting an association with ART and UPD. At this time, the mechanisms causing this association have not been fully established. Growth factor genes are implicated in the growth disturbance of the fetus and the placenta. Certainly advanced maternal age is a cause of increased risk for trisomy. One of the mechanisms for maternal disomy is trisomic rescue. Women of increased age have a higher occurrence of maternal uniparental disomy and also have a higher likelihood of pursuing ART.

Session: Plenary Session
2
LIMB REGENERATION IN NORMAL AND OLIGOZEUGODACTYLY CHICKS
RO. Woods1, CU. Pira1, JF. Fallon2, KC. Oberg1
1 Loma Linda University, Loma Linda, CA and 2 University of Wisconsin, Madison, WI.
Purpose of Study: The application of fibroblast growth factor 2 (Fgf2) to amputated chick wing buds at Hamburger and Hamilton stage 23 (HH23) up-regulates Sonic hedgehog (Shh) and induces limb regeneration; however, at a slightly later stage (HH25) application of Fgf2 neither up-regulates Shh nor induces limb regeneration. Preliminary studies suggest that simultaneous application of Shh with Fgf2 at HH25 restores regeneration. Therefore, we hypothesized that Shh plays an important role in regeneration competence, promoting proliferation, in addition to its well-established role in anterior-posterior patterning.
Methods Used: We tested our hypothesis using a mutant chick—oligozeugodactyl (ozd)—that lacks limb-specific Shh expression. Following amputation (distal 500 µm) of the right limb bud at HH23, we applied Fgf-soaked heparin-acrylile beads at the posterior margin of the limb stump. Phosphate buffered saline (PBS) soaked beads were used for controls. The embryos were incubated for 6 additional days and harvested for skeletal analysis. The embryos were fixed in 3% trichloracetic acid, cartilage stained with Alcian green and the soft tissues cleared with methyl salicylate. The extent of regeneration in the amputated limb was determined by comparison with PBS bead experimental controls. A further comparison was made between the extent of regeneration in ozd limbs that lack Shh and wild type (wt) limbs, which up-regulate Shh.
Summary of Results: We found that Fgf application regenerated 22% (N = 3) of the missing limb (stylopod and radius) in ozd mutant chicks and 51% (N = 9) in wt chicks. Furthermore, 100% of the wt chicks regenerated the stylopod (compared to 33% of the mutants), regenerated a portion of the missing ulna, and 66% displayed some form of digital growth. No regeneration was seen with PBS-soaked bead implants controls.
Conclusions: This study suggests that the presence of Shh enhances proliferation and regeneration. More data are needed to validate these findings; in addition, studies are needed to determine what role ectopic Shh may play in the Fgf-induced regeneration of ozd chicks.

Session: Plenary Session
3
SMOKING REDUCES SURFACTANT PROTEIN D AND PHOSPHOLIPID IN LAVAGE FROM SMOKERS WITH AND WITHOUT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
JM. More1,2, D. Voelker1, ED. Chan1, RP. Bowler1 National Jewish Health, Denver, CO and 2 Stanford University, Stanford, CA.
Purpose of Study: Surfactant protein D (SP-D) and other collectins; in particular, SP-D, a member of the collectin family of proteins, participates in innate immune processes of the lung. Although SP-D is predominantly in lung lining fluid, there are no reports of SP-D and phospholipids in the bronchoalveolar lavage fluid (BALF) of COPD patients. Thus, in this study, we hypothesized that COPD patients would have lower BALF SP-D levels compared to healthy smoking and non-smoking controls.
Methods Used: To test our hypothesis we measured BALF SP-D levels in 110 volunteers (46 smokers and 64 never smokers) using an enzyme-linked immunosorbent assay (ELISA). BALF SP-D was corrected for lavage dilution using urea blood/BALF concentration. BALF phospholipid content was also measured. A diagnosis of COPD was made by post-bronchodilatory spirometry using forced expiratory volume at one second divided by forced vital capacity (FEV1/FVC).
Summary of Results: BALF SP-D (urea corrected) was found to be lowest in current smokers (12.8 µg/mL ± 11.0 µg/mL), higher in former smokers (25.2 µg/mL ± 13.7 µg/mL), and highest in never smokers (52.4 µg/mL ± 7.2 µg/mL; P < 0.008). BALF SP-D was lower in COPD subjects (19.1 µg/mL ± 12.9 µg/mL) compared to healthy nonsmokers (51.8 µg/mL ± 7.2 µg/mL) but higher compared to healthy smokers (16.0 µg/mL ± 11.8 µg/mL; P < 0.012). Among smokers, there was a correlation between BALF SP-D and FEV1/FVC ratio (P < 0.016), but not percent-predicted FEV1. There were no correlations between BALF SP-D and age, sex, or pack years in smokers or non-smokers. Recovered BALF phospholipids were also lowest in current smokers (6.5 nmol ± 1.5 nmol), higher in former smokers (13.2 nmol ± 2.0 nmol), and highest in never smokers (14.9 nmol ± 1.1 nmol; P < 0.0001). Among all study groups, the ratio of SP-D to phospholipids in BALF remained relatively constant.
Conclusions: These data suggest that smoking and particularly current smoking are associated with lower recovered phospholipid and SP-D levels in lung lining fluid. Lower amounts of phospholipids, SP-D and other collectins may explain more rapid progression of disease and increased incidence
Session: Plenary Session 4
EXOGENOUS DIHYDROTESTOSTERONE DOES NOT INCREASE INTRAPROSTATIC DIHYDROTESTOSTERONE CONCENTRATIONS IN HEALTHY MEN: IMPLICATIONS FOR MALE HORMONAL THERAPIES
ST. Page1, DW. Lin2, E. Mostaghel3, B. March1, J. Wright2, JK. Amory1.
AM. Matsumoto1,2, University of Washington, Seattle, WA; University of Washington, Seattle, WA and VA Puget Sound Health Care System, Seattle, WA.

Purpose of Study: Since the prostate is an androgen-sensitive organ, concern exists that androgen replacement might adversely impact prostate health in older men. The predominant circulating androgen in men is testosterone (T) but within the prostate dihydrotestosterone (DHT) predominates due to the high level of expression of the enzyme 5a-reductase which converts T to DHT. 5a-reductase inhibitors, which lower intraprostatic DHT, have been shown to lower the risk of prostate cancer; therefore, hormonal replacement strategies that do not increase intraprostatic DHT might be desirable. We hypothesized that exogenous DHT, by providing negative feedback to the pituitary and thus suppressing gonadotropin and T production, might paradoxically lower intraprostatic DHT and androgen-action within the prostate.

Methods Used: 27 healthy men ages 35-55 were randomly assigned to receive either daily transdermal DHT gel or placebo gel for 4 weeks. Blood was obtained bi-weekly throughout the study. Prostate volume was measured at baseline, on Day 28 when a prostate biopsy was obtained, and on Day 56. DHT and T concentrations were measured by liquid chromatography-tandem mass spectrometry. Androgen-regulated gene expression was compared using laser-capture microdissection and microarrays on frozen biopsy specimens.

Summary of Results: Serum DHT increased nearly seven-fold during treatment (baseline DHT 0.98 ± 0.28; Day 28 6.99 ± 1.18 ng/ml) and was significantly different than the placebo group at Day 28 (P < 0.001). Serum T concomitantly decreased in the DHT-treated group compared to baseline and placebo treatment (P < 0.05). Preliminary analyses demonstrate that intraprostatic DHT concentrations on Day 28 were different in the two groups (DHT: 8.44 ± 3.25, Placebo: 8.30 ± 2.70 ng/g). Prostate volume, serum PSA, and androgen-regulated gene expression were not different between groups.

Conclusions: Increases in serum DHT do not increase intraprostatic levels of DHT and were not associated with increases in PSA, prostate volume, or androgen-regulated gene expression in men. DHT gel might have utility as part of an androgen replacement regimen for men.

WAFCM, WSCI, WAP, WSPR, WSMRF
Student Subspecialty Award Poster Session
6:00 PM Thursday, January 28, 2010

Session: Student Subspecialty Award Poster Session 5
THE PREVALENCE OF ELBOW FLEXION CONTRACTURE IN CHILDREN WITH BRACHIAL PLEXUS BIRTH PALSY
LC. Shefler1,2, A. Bagley3, MA. James1,2, University of California, Davis, Sacramento, CA; Shriners Hospital for Children, Northern California, Sacramento, CA and University of California, Davis, Sacramento, CA.

Purpose of Study: Elbow flexion contracture is a well-known complication of brachial plexus birth palsy (BPBP) that adversely affects function and appearance. The prevalence of elbow flexion contracture in this population is not known, nor is it understood whether BPBP severity is associated with elbow flexion contracture severity.

Methods Used: A retrospective chart review of 319 patients with brachial plexus birth palsy who were seen between 1991 and 2009 was performed to identify patients who developed elbow flexion contracture. BPBP severity was classified according to Narakas (type I: C5/6 palsy; type II: C5/6/7 palsy and type III: global palsy).

Summary of Results: Elbow flexion contracture was present in 166 of 319 (52%) children with BPBP. Divided into age subgroups of 0-4 years (n = 123), 5-11 years (n = 126) and 12-20 years (n = 70), 25%, 60% and 84% of children had documented elbow flexion contractures, respectively. The median age of onset of elbow flexion contracture was 4.8 years. Elbow flexion contracture was present in 49% of patients with Narakas type I BPBP, 55% with type II and 60% with type III.

Conclusions: The prevalence of elbow flexion contracture in children with BPBP may be greater than clinicians perceive and increases with patient age and severity of BPBP. Because elbow flexion contracture has a negative impact on upper extremity function and appearance, future research should address the etiology and treatment strategies of elbow flexion contractures in children with BPBP.

Session: Student Subspecialty Award Poster Session 6
RATE OF HEAD CIRCUMFERENCE GROWTH IN INFANTS AT-RISK FOR AUTISM: A POSSIBLE CLINICAL MARKER
O. Jensen1, S. Webb2, J. Munson3, University of Washington School of Medicine, Seattle, WA and University of Washington Autism Center, Seattle, WA.

Purpose of Study: There is evidence that Autism Spectrum Disorders (ASD) correlate with an increase in head growth during early childhood. Further, head circumference (HC) has been shown to predict symptom development in children with ASD, and may thus provide information about a child’s prognosis and/or predict responses to intervention (Elder et al, 2007). HC growth rate could prove to be a useful clinical marker for ASD because measurement of HC is a part of a normal well-child exam. This study examined the relationship between rate of HC growth early in life and the later development of ASD symptoms.

Methods Used: Data on Occipitofrontal (OFC) head circumference, height and weight was taken from well child checks (WCC) from the University of Washington Autism Center Toddler Assessment Project (TAP). The sample consisted of 44 ASD kids from TAP and 52 controls from the Plagiocephaly Outcomes Project from Seattle Children’s Hospital. Z-scores were calculated based on CDC norms. WCC data was supplemented with measurements taken in the lab at the University of Washington. Subjects were excluded if less than 3 data points were available, if data was not available until at least 18 months, or if subjects were born before 32 weeks gestation. A total of 600 data points were collected across 96 subjects.

Summary of Results: Results were interpreted using a 2 slope mixed effects model comparing changes in OFC Z-scores between ASD and typical kids from 0 to 24 months. The slope for the ASD kids was significantly steeper than the average (0.092) during the first year of life (p = 0.000), and then leveling out very close to normal (0.004, p = 0.78) during the second year of life. The control group did not differ significantly as compared to the ASD sample during either the first or second year of life (p=0.12 = 0.83, p12-24 = 0.46). Both groups differed significantly from the CDC norms, however they were not statistically different from each other.

Conclusions: The mixed results from this study neither discount nor prove the hypothesis that children with ASD may show a patterned and atypical growth rate early in life. Further study is required to further evaluate the significance of a differing growth rate in kids with ASD, and the validity of comparing local samples to CDC norms.

Session: Student Subspecialty Award Poster Session 7
HIGH-DENSITY LIPOPROTEIN (HDL) MIMETIC PEPTIDES CAN RESTORE THE ANTI-INFLAMMATORY PROPERTIES OF HDL FROM PATIENTS WITH CORONARY ARTERY DISEASE
O. Elhoudarwaej, G. Hough, S. Harna, M. Garife, M. Navab David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Plasma levels of high-density lipoprotein (HDL) are known to inversely correlate with the incidence of coronary artery disease (CAD). The protective function of HDL is attributed to its role in reverse cholesterol transport from peripheral tissues for elimination, preventing lipid oxidation and inhibiting the formation of inflammatory molecules. Under inflammatory conditions, however, HDL can lose its beneficial properties and become pro-inflammatory.

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Methods Used: In the current study, we used plasma from 13 CAD patients and 10 healthy controls to determine if treatment with HDL mimetic peptides L-4F, apoJ[113-122] or the tetrapeptide FREL would lower the HDL inflammatory index (HII). We used a bioassay in which normal low-density lipoprotein (LDL) from healthy controls was added to human aortic endothelial cultures to determine the extent of lipid oxidation in LDL and the resulting induction of monocyte chemotactic protein 1 (MCP-1).

Summary of Results: In the absence of HDL, the cells oxidized the lipids in LDL, which stimulated the cells to produce MCP-1. In the presence of normal HDL, the extent of LDL oxidation and thus MCP-1 production was reduced. HDL from CAD patients, however, had a high HII and actually amplified LDL oxidation. Treatment of both patient plasma and control plasma with mimetic peptides resulted in patient HDL preventing LDL oxidation and MCP-1 induction (i.e. resulted in HDL with low HII).

Conclusions: HDL mimetic peptides can restore the anti-inflammatory properties of HDL from patients with CAD, suggesting a potential therapeutic benefit using these mimetic peptides.

Session: Student Subspeciality Award Poster Session
8 DEPRESSION IN PREMEDICAL UNDERGRADUATES
DZ. Fang UC San Diego School of Medicine, San Diego, CA.

Purpose of Study: Medical students and physicians are exposed to unique pressures that render them vulnerable to increased rates of depression, an illness which can impair quality of life and predispose to numerous medical and psychiatric sequelae. These same types of pressures also plague premedical undergraduates who work long hours to become competitive for medical school admission. However, far less is known about their risk for depression.

Do the seeds of depression faced by medical students and physicians begin in medical school, or can they be traced back to premedical training? We attempt to answer this question by assessing the severity of depressive symptoms in premedical students compared to other undergraduates.

Methods Used: We invited all undergraduate biology majors at UC San Diego to participate in a web-based survey. Subjects were also recruited through Experimetrix, a UC San Diego psychology research recruitment program. The survey consisted of demographic and clinical based questions such as gender, ethnicity, age, major, graduation date, premedical status, perceived financial strain, and past, current, and family history of major depression. We used the Patient Health Questionnaire (PHQ-9) to assess depressive severity.

Summary of Results: 647 premedical and 1495 non-premedical undergraduates completed the questionnaire. Premedical students were more likely to meet symptomatic criteria for major depression and exhibit greater depression severity than non-premedical students despite no differences in past or family histories of major depression. Female premedical students exhibited greater depression severity than female non-premedical students and males. Hispanic premedical students, in particular, had higher rates of depression than other premedical students and Hispanic non-premedical students. Finally, we found a substantial discrepancy between the number of students with major depression based on PHQ-9 criteria and the number actually carrying a clinical diagnosis of major depression.

Conclusions: These findings underscore the importance of recognizing the unique strains and mental health consequences of a premedical curriculum, especially for women and certain minority ethnic populations. Further research must be done with the intention of identifying opportunities for prevention and early intervention which may provide significant public health payoffs in the long run.

Session: Student Subspeciality Award Poster Session
10 TESTOSTERONE REDUCES NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) OF HYPOGONADISM
L. Nikolaenko1, M. Diaz-Arjona1, S. Laureli1, C. Wang1, Y. Lu1, S. French2, R. Swerdloff3 1Harbor-UCLA Med Ctr, LA Biomed Res Inst, Torrance, CA and 2Harbor-UCLA Med Ctr, Torrance, CA.

Purpose of Study: NAFLD is the leading cause of hepatic steatosis and is associated with obesity, diabetes and Metabolic Syndrome (Met S). Androgen deficiency is a risk factor for diabetes and Met S, but its role in hepatic dysfunction has not been well studied. We established a rat model of hepatic steatosis to investigate the effects of testosterone (T) on the pathogenesis of NAFLD.

Methods Used: Male rats were randomly placed into four groups: castrated rats on high-fat diet (HFD), castrated rats with T replacement on HFD, intact rats on HFD, and intact rats on regular chow diet (RCD). The RCD provided 71% energy from fat; RCD provided 16% of energy from fat. The rats were fed ad libitum for 15 weeks. DEXA scan was performed to evaluate body fat composition and weight. Serum and tissues were analyzed.

Summary of Results: Serum T level was undetectable in castrated rats, and T replacement led to higher serum T levels than in intact rats. Castrated rats on HFD gained less body weight than those on a low-fat diet was higher than T-treated rats on HFD or the intact rats on RCD. Liver enzymes and serum cholesterol were also higher in the T-deficient rats as compared to rats of the other groups (Table 1). Liver histopathology revealed a severe micro- and macrovesicular steatosis.

Table 1: Serum T, body composition, liver enzymes and lipid profile

Parameter (Group) | Serum testosterone (ng/dl, median) | T cell (median) | Fat (median) | Glucose (median) | ALAT (median) | AST (median) | Cholesterol (mg/dl, median) | HDL (mg/dl, median) | Triglyceride (mg/dl, median) |
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<tr>
<td>Castrated</td>
<td>4.98 (1.92, 6.52)</td>
<td>15 (12, 20)</td>
<td>26 (20, 30)</td>
<td>49 (37, 57)</td>
<td>74 (70, 78)</td>
<td>16 (13, 19)</td>
<td>66 (49, 74)</td>
<td>132 (125, 135)</td>
<td>30 (25, 35)</td>
</tr>
<tr>
<td>Castrated + T (HFD)</td>
<td>4.89 (1.92, 6.52)</td>
<td>15 (12, 20)</td>
<td>26 (20, 30)</td>
<td>49 (37, 57)</td>
<td>74 (70, 78)</td>
<td>16 (13, 19)</td>
<td>66 (49, 74)</td>
<td>132 (125, 135)</td>
<td>30 (25, 35)</td>
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* Median ± SEM; **Geometric mean (95% confidence interval)
macroversicular accumulation of fat in hepatocytes with multiple inflammatory foci of castrated rats fed HFD. However, hepatocytes of the T-treated and intact rats on HFD demonstrated only a mild to moderate microvesicular steatosis.

**Conclusions:** The degree of hepatic micro- and macrovesicular steatosis and hepatic inflammation were considerably greater in rats with undetectable serum T than in the other groups. T treatment of castrated rats on HFD reduced hepatic steatosis. This study demonstrates that T plays a protective role in fat accumulation and NAFLD development and that androgen deficiency contributes to the severity of hepatic steatosis.

Session: Student Subspecialty Award Poster Session

11

**A SYSTEMATIC REVIEW COMPARING IMMUNOPROPHYLAXIS REGIMENS AFTER LIVER TRANSPLANTATION WITH HEPATITIS B CORRE ANTIBODY POSITIVE DONORS**

B. Waterman, A. Chi, S. Saab UCLA, Los Angeles, CA.

**Purpose of Study:** Orthotopic liver transplant recipients without Hepatitis B (HBV) infection who receive liver grafts from HBV Core Antibody (HbcAb) positive, HBV surface antigen (HbsAg) negative donors have an increased risk of developing de novo HBV infection. We compared the two most common prophylactic regimens - lamivudine (LAM) monotherapy and LAM + Hepatitis B Immunoglobulin (HBIG) combination therapy - to determine the relative efficacies of these two protocols in preventing de novo HBV infection.

**Methods Used:** A comprehensive search of the Cochrane Database of Systematic Reviews, MEDLINE (1966–2009) was conducted. Eligible studies included OLT recipients who received HBCaAb(+) liver grafts and were treated prophylactically with either LAM monotherapy or HBCaAb + LAM combination therapy. Patients were excluded if the donor or recipient was HBCaAb(+) or HBV DNA(+) at time of liver transplantation.

**Summary of Results:** 13 studies were identified as meeting eligibility criteria. Data for all relevant patients within these studies was abstracted and incidence of de novo HBV infection, mortality, and mortality due to de novo HBV infection were assessed. Incidence of de novo HBV infection in patients receiving LAM-only prophylaxis was 2.7% (n = 73) compared with 3.6% (n = 110) in patients receiving HBIG + LAM combination therapy. Risk of developing de novo HBV infection based on pre-transplant recipient HBV serology in each treatment group could not be calculated due to incomplete data and the limited number of de novo HBV infection cases in the series reviewed.

**Conclusions:** Published studies have not shown HBIG + LAM therapy to be more effective than LAM-only treatment. Nucleoside analogue monotherapy should therefore be considered when treating HBV(+)-patients who have received liver allografts from HBCaAb(+) donors.

Number of HBV Recurrences Grouped by Recipient Pre-Transplant Serologies and Post-Transplant Prophylaxis Regimens

<table>
<thead>
<tr>
<th>Recipient Serology</th>
<th>Post-Transplant Prophylaxis</th>
<th>LAM Alone</th>
<th>LAM + HBIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBCaAb</td>
<td>Total Number</td>
<td>No. HBV Recurrence</td>
<td>Total Number</td>
</tr>
<tr>
<td>+</td>
<td>23</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>25</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>-</td>
<td>17</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>-</td>
<td>18</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>2 (2.7%)</td>
<td>110</td>
</tr>
</tbody>
</table>

Session: Student Subspecialty Award Poster Session

13

**LIVER IGF-1 mRNA EXPRESSION IS DECREASED BY MECHANICAL VENTILATION OF PRETERM LAMBS**

CA. Blair, C. Amundsen, D. Metcalfe, MJ. McCoy, B. Beck, A. Whitworth, A. Smith, J. Alvord, L. Dong, MJ. Dahl, L. Joss-Moore, L. Moyer-Mileur, DM. Null, BA. Yoder, RH. Lane, RA. McKnight, K. Albertine University of Utah, Salt Lake City, UT.

**Purpose of Study:** Neonatal chronic lung disease (CLD) is associated with poor postnatal growth. Growth is modulated by insulin-like growth factor-1 (IGF-1). Because serum concentration of IGF-1 is low in preterm infants with CLD and the liver is a source of IGF-1 in the serum, we measured IGF-1 and IGF-1 binding protein 3 (IGF-1 BP3) mRNA expression in the liver of chronically ventilated preterm lambs. We also measured signal transducers and activators of transcription 5b (STAT5b) because IGF-1 expression is regulated by STAT5b.

**Methods Used:** Total RNA was isolated from liver tissue of PT lambs managed by MV for 21d, PT lambs managed by nasal CPAP (n = 4) compared to PT lambs managed with nasal CPAP. We assessed liver IGF-1 expression in the 21d MV group. Although not significantly different, IGF-1 BP3 mRNA expression was ~50% lower in the 21d MV group. STAT5b mRNA expression was unaffected by ventilation mode at 21d. These different expression in mRNA and protein abundance in the liver were partially mirrored at 3d of ventilation, although the differences were not statistically significant.

**Conclusion:** Ventilation mode affects liver expression of IGF-1 and its upstream mediator, STAT5b. Specifically, MV for 21d decreases liver IGF-1 mRNA expression and STAT5b protein abundance compared to nasal CPAP as the positive gold-standard because alveolar formation is nearly normal when preterm lambs are managed by nasal CPAP. We speculate that low IGF-1 and STAT5b in the liver of PT lambs managed by MV contributes to poor growth postnatally that is characteristic of neonatal CLD.
Adipose Tissue Adiponectin Receptor-2 (AdipR-2) mRNA Levels in Neonatal Stress in Rat Pups

K. Gulliver, S. Haley, J. Thomson, B. Barrett, RH. Lane, L. Moyer-Mileur
University of Utah, Salt Lake City, UT.

Purpose of Study: Elevated glucocorticoid (GC) levels in early life are linked to obesity in later life. Massage therapy lowers GC and may lessen obesity risk by modulating the adipose gene expression. We hypothesized that molecular events that arise from DMT would decrease GC and alter adipose tissue leptin and adiponectin mRNA levels in neonatal stressed rat pups.

Methods Used: Timed pregnant S-D rats were delivered at term, litters culled to 10 pups (5 M, 5 F) and randomized to: neonatal stress (NS; 60 min of maternal separation + injection + hypoxia/hyperoxia; n = 40); NS + developmental massage therapy (DMT; NS = 10 min of DMT; n = 40), or Control (C; 60 min of maternal separation, n = 40). Treatments were given daily on D5–D9 and litters were cross-fostered D5–D20. DMT consisted of 5 min of tactile stimulation followed by 5 min of range of motion to fore- and hind-limbs. Weight gain was similar during and post-intervention (D14, and D21), body composition (D21) by dual energy x-ray absorptiometry, D21 serum levels by ELISA for GC, leptin, adiponectin, and D21 RNA levels of GC receptor (GR), adiponectin receptor (AdipR-1 and R-2), and leptin receptor (OB-R) in subcutaneous (SQ) and retroperitoneal (RP) adipose depots. Results are presented relative to C values.

Summary of Results: Weight gain was similar during and post-intervention. D21 relative body fat (%) was lower in NS females (65.2 ± 9.0%) and DMT males (88.5 ± 9.8%) (p < 0.01). Serum leptin levels were lower in NS females (43.8 ± 15.7%), DMT males (37.2 ± 10.2%), and NS females (71.3 ± 11.2%) (p < 0.01). SQ assay tissue GR mRNA was lower in NS males (68.4 ± 13.6%) compared to DMT (111.5 ± 25.8%) or C (p < 0.01); SQ adipR-2 mRNA was lower in NS females (85.1 ± 30.7%) versus DMT females (145.6 ± 27.1%) (p < 0.05). In males, RP adipR-2 mRNA was lower in NS (70.9 ± 19.9%) versus DMT pups (104.0 ± 24.9%) (p < 0.01).

Conclusions: DMT during neonatal stress modulates mRNA levels of adipose genes involved in GR signaling. In adults, obesity is associated with lower adipR-1 and R-2 mRNA expression. Although neonatal stress did not increase adiposity at D21, adipR-2 gene expression was decreased in a depot and sex-specific manner. Study of the long-term effect of neonatal stress and DMT on adiposity and adipose tissue gene expression is warranted.
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PLASMA REGULATES MONOCYTE PROGRAMMED DEATH LIGAND-1 EXPRESSION IN JUVENILE LUPUS

J. Kuo1, J. Ous2, A. Stevens2,3

1University of Washington School of Medicine, Seattle, WA; 2Seattle Children’s Research Institute, Seattle, WA and 3University of Washington, Seattle, WA.

Purpose of Study: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibodies and deficient phagocytic activity by monocytes (Mo). The course of SLE alternates between the flare, or active state, and the remission, or inactive state. The flare state of SLE has been correlated with loss of Programmed Death Ligand-1 (PD-L1) expression on Mo. PD-L1 is a critical regulator of the immune response. It controls effector T lymphocytes to maintain immune tolerance and protect tissues from immune-mediated damage. Dysfunctions of the PD-L1 pathway have been reported in various autoimmune diseases, including SLE, rheumatoid arthritis, and Grave’s disease. We hypothesized that plasma from SLE patients contains soluble factors that regulate PD-L1 expression in Mo.

Methods Used: 9 patients aged 8 to 17 were studied, along with 4 age-matched healthy controls. Peripheral blood mononuclear cells (PBMC) were incubated for 2 days with plasma obtained from either healthy donors or SLE patients. The expression level of PD-L1 on Mo was assayed by four-color flow cytometry. Cytokines were assayed in plasma samples and PBMC culture supernatants by Luminex cytokine assay.

Summary of Results: An average of 61% of Mo from SLE patients in flare expressed PD-L1 compared to 71% of Mo from healthy donors. Plasma from healthy donors induced PD-L1 expression in SLE Mo, but not in SLE plasma. Plasma from SLE patients with active disease (p < 0.05) and spleen did not downregulate PD-L1 expression in healthy Mo. We detected decreased levels of TNF-α in SLE PBMC culture supernatants compared to healthy PBMC. Blocking TNF-α in healthy plasma with a specific monoclonal antibody inhibited PD-L1 upregulation in SLE Mo.

Conclusions: Lupus flare plasma does not contain factors that can inhibit PD-L1 induction in Mo. In contrast, the plasma of lupus patients in a flare state is missing soluble factors that are required for PD-L1 expression. Mo TNF-α is a soluble inducer of PD-L1 expression in Mo and may be a key regulator in lupus. Further understanding of the mechanism of PD-L1 dysregulation in SLE could lead to new treatments and clinical assays to develop more specific treatments for SLE patients.

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IDENTIFICATION OF TWO NOVEL SECRETED PROTEINS INVOLVED IN TRICHOMONAS VAGINALIS PATHOGENESIS

O. Twu1, N. de Miguel2, J. Wohlschlegel1, P. Johnson2

1UCLA-David Geffen School of Medicine, Los Angeles, CA; 2UCLA-Geffen School of Medicine, Los Angeles, CA.

Purpose of Study: Trichomonas vaginalis is the cause of the most common non-viral sexually transmitted infection worldwide. Because T. vaginalis is an obligate extracellular pathogen, adherence to epithelial cells is critical for parasite survival, infection, and cytopathogenicity. Despite the importance of surface proteins in parasite adherence, there has been no systematic investigation of them for this parasite. This project compares the membrane proteome of six strains; three that are highly adherent to vaginal epithelial cells and three that are non-adherent.

Methods Used: The surface proteins of the parasite were biotinylated followed by protein purification on a streptavidin resin and relative quantification of corresponding tryptic peptides by mass spectrometry. Specific proteins identified were analyzed by BLAST analyses. The subcellular localization of the proteins expressed in the parasite was determined by IF and secretion and gain of function assays were performed.

Summary of Results: Of the 438 proteins identified, two were significantly differentially expressed between adherent and non-adherent strains. Genome analysis of these two hypothetical proteins revealed a family of about a hundred proteins but only these two were differentially expressed, suggesting a possible role in pathogenesis. Although no clear homology with previously described proteins was detected, BLAST search hits include biofilm-adhesion like proteins and a Candida adhesion protein. By IF, both proteins exhibited Golgi and punctate vesicle-like staining inside the cell, indicating they could be secreted. Western blot analysis of parasite culture supernatant confirmed secretion of both proteins and validated their presence in the proteome analysis.

Conclusions: Identification of these two proteins into a non-adherent strain may increase attachment to vaginal epithelial cells three fold. These data indicate that the two proteins identified in this study play a role in adhesion and may participate in pathogenesis. Further research into this family of proteins may provide new insights into the host-pathogen interactions of T. vaginalis infections.

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MATERNAL SEPARATION IN THE NEONATAL PERIOD DECREASES ADIPOSE GR AND 11βHSD MRNA IN THE ADULT RAT

J. Wiedmeyer1, L. Jess-Moore1, N. Li2, Y. Wang1, M. Hale1, J. Neu2, R. Lanel1

1University of Utah, Salt Lake City, UT and 2University of Florida, Gainesville, FL.

Purpose of Study: Early post-natal nutrition effects the development of adult onset obesity and metabolic disease. Infants hospitalized in the NICU encounter maternal separation and formula feeding. We have formerly shown that maternal separation and post-natal nutritional content alters adipose tissue gene expression in the juvenile rat; specifically the glucocorticoid receptor (GR) and the steroid activating reductase 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). Steroid signaling is an important component in the development of adult adipose dysregulation and the long term effect of maternal separation and postnatal diet on adipose tissue gene expression is unknown. We hypothesize neonatal maternal separation will decrease 11βHSD1 and GR mRNA levels in the adipose tissue of the rat at day 300 of life.

Methods Used: Mother fed (MF) pups were compared to those receiving one of three rat milk substitutes for 6 days via a gastrostomy tube. The three isocaloric formulas contained either standard rat milk substitute (RMS), 150% Protein (RMS-PRO) or 150% Carbohydrate (RMS-CHO). 11βHSD1 and GR mRNA levels in subcutaneous adipose tissue from day 300 male and female adult rats were analyzed to determine the effect of maternal separation and postnatal diet on precursors of adiposity.

Summary of Results: Maternal separation significantly reduced GR transcript levels in the RMS group in subcutaneous adipose tissue in male adult rats (25.8% ± 7.0%) whereas supplemented milk substitute offset decreased levels in GR transcript levels only. 11βHSD1 levels were significantly decreased regardless of diet (RMS 23.9% ± 8.6%; RMS-PRO 37.1% ± 17.6%; RMS-CHO 41.3% ± 14.2%). No differences in female mRNA levels were detected.

Conclusions: Maternal separation decreases GR and 11βHSD1 mRNA levels in the adipose tissue of the adult male rat. While increased postnatal protein dampens the effect of maternal separation on GR mRNA, 11βHSD1 mRNA effects are independent of postnatal diet. Males and females are differentially affected. We speculate that mRNA changes observed will be
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ANALYSIS OF GENETIC VARIATION WITHIN FOXE1 AND RISK FOR OROFACIAL CLEFTS
NI. Mohammed1, DM. Iovannisci1, B. Lin1, K. Schultz1, E. Lammer1, G. Shaw2, A. Lidral2, CHORI, Oakland, CA; 1Stanford University, Palo Alto, CA and 2University of Iowa, Iowa City, IA.
Purpose of Study: A previous genome wide linkage scan discovered a novel locus for cleft lip with or without cleft palate at 9q22-q33. To identify a gene of interest within this region, Moreno et al. used a frequentative and complementary fine mapping strategy. They initially identified several candidate genes (PTCH, FOXE1, FG03, TGFBR1, ZNF189, and GABABR2) and screened them for alterations, revealing 24 new variants. Additional localized hybridization studies on mouse tissues samples taken during the formation of the palate showed FOXE1 expression in the epithelia of the fusing palatal processes. Significant SNP and haplotype association signals (p = 1.45E-08) clustered near FOXE1, indicating that it is a major gene for cleft lip and/or palate.
Methods Used: DNA samples have been obtained from a population-based sample of 1,386 newborns from three counties in California from 1999–2004. Of these samples 523 are DNA samples from babies born with cleft lip and/or palate, and cleft palate alone (cases) and 863 controls (normal babies born without any defect). The method for SNP genotyping is based on the Sequenom MassARRAY platform. We genotyped these infants for 22 SNPs within and around FOXE1 by designing two novel multiplex assays that allowed us to simultaneously genotype all SNPs.
Summary of Results: We have genotyped 75% of our samples. Among those whose genotypic distributions of controls met Hardy-Weinberg expectation, five FOXE1 SNPs indicated significant statistical associations with risk for cleft lip and/or cleft palate (p < 0.05).
Conclusions: Our preliminary results support the findings of Moreno et al. that genotype distributions of the FOXE1 polymorphisms are different between the case and control population, and some FOXE1 SNPs also show associations with cleft palate alone.

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22
THE VASODILATORY EFFECTS OF SURFACTANT ON LUNG AND SYSTEMIC ARTERIES
DI. Hunt1, M. Chang1, QK. Blood1, TA. Merrit1, SM. Wilson2, AB. Blood1,2
1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA.
Purpose of Study: Surfactant administration to premature infants can cause hypotension which increases the risk of adverse events such as compromised cerebral blood flow. This study tested the hypothesis that two commonly prescribed animal-derived surfactants have direct vasodilatory properties mediated by nitric oxide synthase and cyclooxygenase activity.
Methods Used: 4th generation pulmonary arteries or the superficial femoral artery were isolated from fetal sheep at 140 days gestation. The experimental procedure was the same for both arteries. Arteries were mounted on a wire myograph in Krebs solution at 37 C. Serotonin (pulmonary arteries) or nitroprusside (femoral arteries) were added to the vessels caliper as a control. The role of NOS or cyclooxygenase were assessed by adding diclofenac blocked the vasodilatation of Curosurf, but did not affect Survanta, suggesting that Curosurf’s mechanism involves both NOS and cyclooxygenase activation, but that neither pathway is involved with Survanta-mediated vasodilation. The vasodilating effects of Curosurf, but did not affect Survanta, suggesting that Curosurf’s mechanism involves both NOS and cyclooxygenase activation, but that neither pathway is involved with Survanta-mediated vasodilation. The vasoactive properties of surfactants appear more potent in pulmonary compared to systemic arteries. Future research will examine the properties of synthetic surfactants as well as the vasoactive properties of various surfactant components.

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RAB26 FUNCTIONS IN THE RENAL EPITHELIAL PRIMARY CILIUM
BR. Peterson, H. Ward, A. Wandinger-Ness The University of New Mexico School of Medicine, Albuquerque, NM.
Purpose of Study: Primary cilia are specialized sensory structures that allow cells to mediate downstream signals in response to their extracellular environment. Inherited diseases including autosomal dominant retinitis pigmentosa, Bardet-Biedl syndrome, and polycystic kidney disease are manifestations of dysfunctional primary cilia. Rab proteins are regulators of membrane trafficking and intracellular signaling, with demonstrated roles of Rab8 and Rab11 in the transport of proteins to the primary cilium. Rab26 is abundant in renal tubule cells where its function is not known. Therefore, we tested if Rab26 localizes to renal primary cilia and plays a role in ciliogenesis and ciliary function.
Methods Used: Stable Madin-Darby Canine Kidney (MDCK) cell lines with tet-inducible systems were generated to over-express wild type or dominant negative forms of Rab26. Cells were labeled with antibodies specific for Rab26 and acetylated alpha tubulin and secondary fluorescent antibodies and imaged using confocal microscopy. The average length of primary cilia and the percentages of cells expressing primary cilium between the cell lines were compared at 5 days post-confluence. Ciliary tracheal sections were labeled with antibodies specific to Rab26 and evaluated using transmission electron microscopy. Immunoprecipitation and immunoblotting assays were used to elucidate protein-protein interactions.
Summary of Results: Rab26 was visualized in the primary cilium using both confocal and electron microscopy of human and canine renal epithelial cells and canine tracheal sections, respectively. MDCK cell lines induced to over-express wild-type Rab26 demonstrated a significantly increased percentage of cells expressing primary cilium when compared to uninduced cell lines. MDCK cells expressing a dominant negative form of Rab26 showed an altered ciliary phenotype. Endogenous Rab26 coimmunoprecipitated with polycystin-1.
Conclusions: Rab26 localizes to the primary cilium in MDCK cells. Over-expression of Rab26 leads to increased expression of primary cilium in MDCK cells, indicating a potential role in ciliogenesis. Given a known role of Rab26 in cellular transport and the interaction of Rab26 and polycystin-1, we speculate that Rab26 may be involved in targeting key regulatory proteins, including polycystin-1, to the primary cilium in renal epithelial cells.

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24
MECHANISMS UNDERLYING ASTROCYTOSIS FOLLOWING SCATIC NERVE INJURY
Y. Liu, M. Xu, C. Chavkin University of Washington, Seattle, WA.
Purpose of Study: Neuropathic pain is a widespread debilitating condition that has been challenging to treat. Partial sciatic nerve ligation (pSNL) in mice is a commonly used model for studying chronic pain, performed by tightly ligating approximately one-third to one-half the diameter of the nerve. Previous research has shown that pSNL results in dynorphin-dependent kappa opioid receptor activation, which subsequently leads to astrocyte proliferation in the ipsilateral dorsal horn of the spinal cord. Induction of neuropathic pain is linked to this astrocytic focus; however, the underlying cellular processes are unclear. The goal of this study is to investigate the role of p38 mitogen-activated protein kinases (MAPKs) in mediating neuropathic pain.
Methods Used: Our experiments used GFAP-CreERT2/p38Δlox/Δlox conditional knockout (CKO) mice, which selectively excised p38α in astrocytes following tamoxifen administration. 4 wild type (WT) and 4 CKO mice were given intraperitoneal tamoxifen injections once daily for 7 days. On day 5 of injections, all mice were anesthetized with pentobarbital, and
Session: Student Subspecialty Award Poster Session
25
HSP-70 LEVELS DECLINE IN DECEASED CRITICALLY ILL PATIENTS, RISE IN ALIVE CRITICALLY ILL PATIENTS FOLLOWING ADMISSION TO THE ICU
AG. Edwards, PE. Wischmeyer University of Colorado School of Medicine, Aurora, CO.
Purpose of Study: Heat Shock Protein 70 (HSP70) is a vital stress response protein key to cellular response/survival from illness and injury. Increased HSP70 levels have been shown in experimental models to reduce myocardial and lung injury, as well as improve clinical outcome in experimental sepsis. Very limited clinical data has revealed enhanced plasma HSP70 (pHSP70) expression may be associated with improved clinical outcome. We tested the hypothesis that elevated pHSP70 expression at ICU admission would correlate with reduction of 28 day ICU patient mortality. Second, we hypothesized ICU survival would correlate positively with increasing levels of pHSP70 relative to admissions levels.
Methods Used: 73 critically ill patients had blood collected at multiple timepoints for pHSP70 (ICU Day 0–7). Patients were from a non-selected subgroup obtained from a total of 200 patients enrolled in a prospective observational ICU trial. Plasma analyzed for HSP70 using Mesoscale technology (Mesoscale Discovery, Inc.). Data then correlated to 28 day ICU-survival. Initial statistics via t-test.
Summary of Results: Patients alive 28 days post-ICU admit showed increasing pHSP70 levels over time relative to baseline admission pHSP70 (115.85% of baseline), whereas patients who expired showed a decrease in pHSP70 levels over time relative to baseline admissions levels (88.84% of baseline, p = 0.05). Additionally, patients who expired had higher mean admission pHSP70 (92.89 ng/ml) vs. patients alive at 28 days post-ICU admit, (44.68 ng/ml p = 0.05).
Conclusions: Our data reveal ICU patients who survived to day 28 post-ICU admit have lower baseline (admission) levels of pHSP70, and showed increasing pHSP70 over time. This suggests therapeutic enhancement of pHSP70 levels improve ICU survival. Further, elevated baseline pHSP70 levels may serve as predictor of ICU mortality.

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POLYMETHYL METHACRYLATE PARTICLES INHIBIT HUMAN MESENCHYAL STEM CELL DIFFERENTIATION INTO OSTEOBLASTS
R. Chiu, RL. Smith, S. Goodman Stanford University Medical School, Stanford, CA.
Purpose of Study: Orthopedic wear debris generated from total joint replacements causes osteolysis and implant loosening in part by stimulating osteoclast activity and impairing the function of osteoblastic lineage cells. Previously, we have shown that particles of polymethylmethacrylate (PMMA) bone cement inhibit the osteogenic differentiation of murine primary marrow stromal cells and MC3T3-E1 osteoprogenitors with respect to proliferation, alkaline phosphatase production, and mineralization. We hypothesized that the inhibitory effects of PMMA particles are also observed with human mesenchymal stem cells (hMSCs) with respect to the aforementioned parameters.
Methods Used: Primary bone marrow-derived hMSCs were obtained from Lonza (Walkersville, MD). These cells were positively selected for mesenchymal markers CD105, 166, 29, and 44, and negatively selected for hematopoietic markers CD14, 34, and 45. hMSCs were induced to differentiate into osteoblasts in osteogenic medium containing dexamethasone (0.1 μM), ascorbic acid (50 μg/mL), and β-glycerophosphate (10 mM) and treated with PMMA particles at doses of 0.000, 0.075, 0.150, and 0.300% v/v on this first day (day 0) of osteogenic differentiation. hMSC proliferation, alkaline phosphatase production (protein quantity, mRNA expression, and cell surface expression), and collagen type 1 mRNA expression were assessed during the first 8–10 days of osteogenic culture. Mineralization was assessed by quantifying calcium content in extracellular matrix on the fourth week of osteogenesis.
Summary of Results: hMSCs exposed to PMMA particles showed significant dose-dependent reductions in proliferation and type 1 collagen expression throughout the entire culture period. Alkaline phosphatase protein quantity, mRNA expression, and cell surface expression were also significantly reduced in a dose-dependent fashion. Matrix mineralization was significantly reduced as indicated by decreased matrix calcium content.
Conclusions: This study has shown that PMMA particles inhibit the osteogenic differentiation of hMSCs. This study along with our previous research shows that exposure of osteogenic lineage cells, including osteoblasts, osteoprogenitors, and mesenchymal stem cells, to wear debris particles compromises bone formation in the prosthetic bed.

Behavior and Development Concurrent Session
8:30 AM
Friday, January 29, 2010
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COGNITIVE AND SOCIAL DEFICITS IN CHRONIC NEONATAL HYPOXIA
W. Lan1, SR. Mayoral2, AA. Penn1 Stanford University, Palo Alto, CA and Stanford University, Palo Alto, CA.
Purpose of Study: Cognitive and social deficits are common long-term sequelae of premature birth. Using a chronic neonatal hypoxia model of prematurity birth, we previously demonstrated sex-specific hippocampal volume loss in mice pups. This study investigates what long-term cognitive and social deficits are observed in this model, whether sex-specific differences are seen and whether deficits are correlated with differences in regional brain volumes.
Methods Used: On postnatal day 3 (P3), C57BL/6 dams and pups were placed in a hypoxia chamber (FiO2 = 0.1) until P11. Control litters remained in normoxia (FiO2 = 0.21). After P11, both groups were raised in normoxia. Behavioral testing began at 6 weeks of age and consisted of standardized cognitive testing (open field, fear conditioning, Morris water maze), non-interventional cognitive testing (Intelligence) and social testing (3-chamber social behavior, modified 5-trial social memory). After behavioral studies were completed, mouse brains were harvested for volumetric analysis using unbiased stereology.
Summary of Results: Mice exposed to chronic hypoxia (n = 26) had impaired performance in fear conditioning and Morris water maze, particularly females (n = 13) when compared to their normoxic peers (n = 13). In contrast, hypoxic males (n = 7) showed a tendency towards decreased exploration and delayed reversal of place learning compared to normoxic peers (n = 8) in the Intelllicage. Both hypoxic males (n = 7) and females (n = 6) showed impaired cued punishment learning in the Intelllicage compared to normoxic peers. Neonatal hypoxia impaired social memory in older male mice (n = 14) without changing social exploration. There was no difference in overall activity level between the groups. No regional brain volume differences were seen between the groups.

Conclusions: Cognitive and social deficits are seen in mice that have recovered from chronic neonatal hypoxia. Both males and females show prolonged deficits on tests requiring hippocampal function, with sex-specific differences detected in individual behavioral tests. No significant regional brain volume differences were observed by 12 weeks of age to account for behavioral differences. Further study of both neonatal and adult brains with immunohistochemistry is needed to detect subtle differences that might account for these behavioral differences.

Session: Behavior and Development
28 MEDICAL AND DEVELOPMENTAL FEATURES OF TETRASOMY X AND PENTASOMY X SYNDROME
N. Ayari, A. Berge, A. Reynolds, N. Tartaglia University of Colorado Denver, Aurora, CO.

Purpose of Study: Tetrasomy and Pentasomy X syndromes are rare disorders affecting 1:50,000 to 1:200,000 females. Less than 50 patients have been described, and features of the syndromes are still not well characterized. Here we describe medical and developmental features of 17 new patients with Tetrasomy X (n = 13) and Pentasomy X (n = 4).

Methods Used: Patients were recruited for a study on health and development in sex chromosome aneuploidy. The study visit included review of medical records, medical and developmental history, physical examination, developmental or cognitive assessment, adaptive functioning (ABAS-II), and behavioral questionnaires (BASC).

Summary of Results: Subjects ranged from 2 to 24 years (mean 9.25). Mean age of diagnosis was 1.9 years, with ascertainment due to developmental delays and/or dysmorphic features in all cases. Median height SDS was −0.6 (−1.9 to +2.1) in Tetrasomy X and −1.0 (−3.5 to −0.8) in Pentasomy X. The most common medical features included congenital heart malformations (6/17), strabismus (5/17), hip dysplasia (4/17), constipation (14/17), radioulnar synostosis (7/17), dental problems (11/17), and hospitalizations for pneumonia (7/17). Common physical examination findings included hypotonia (16/17), pes planus (8/17), plagiocephaly (7/17), hypertelorism (8/17), epicanthal folds (8/17), and clinodactyly (9/17). Early developmental delays in speech and motor skills were present in all patients. Cognitive testing in Tetrasomy X (n = 8) showed a mean FSIQ of 69 (Range 50–80). Other participants were too young for cognitive assessment or unable to complete testing. Mean adaptive functioning composite scores were 64 for Tetrasomy X and 55 for Pentasomy X, with strengths in socialization and weaknesses in communication and daily living skills. Mean T-scores on the BASC were elevated in the areas of withdrawal and attention problems.

Conclusions: Tetrasomy and Pentasomy X syndromes are associated with characteristic medical and physical features. Developmental delays and cognitive deficits are universal, however the mean FSIQ in our patients with Tetrasomy X is higher than previously reported. Adaptive functioning is more impaired in Pentasomy X compared to Tetrasomy X. These results provide additional background needed to develop treatment recommendations for these patients.

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29 ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS WITH SEX CHROMOSOME ANEUPLOIDY
N. Tartaglia, N. Ayari, C. Hutaff-Lee University of Colorado Denver School of Medicine, Aurora, CO.

Purpose of Study: ADHD symptoms including attention problems, distractibility, hyperactivity, and impulsivity are frequently reported in children and adolescents with sex chromosome aneuploidy (SCA). The purpose of this study is to characterize the rates and subtypes of ADHD in 4 SCA subgroups (XXY, XXXX, XXYY, XXXY), and to investigate psychological and medical features associated with ADHD diagnoses in individuals with SCA.

Methods Used: Participants were recruited to participate in a study on health and development in sex chromosome aneuploidy. 150 subjects age 6–20 participated in the study including 45 XXY, 30 XXXY, 52 XXYY, and 23 XXX. Study participants completed a cognitive assessment, and medical/ psychological history. Parents and teachers completed standardized questionnaires containing the DSM-IV criteria for ADHD (SNAP-IV or Conners). Adaptive functioning was assessed by the ABAS-II or Vineland-2. Significance for statistical comparisons was set at p < 0.05.

Summary of Results: In this sample, 36% of males with XXY, 76% of males with XY, 73% of males with XXY, and 39% of females with XXX met DSM-IV criteria for a diagnosis of ADHD. The ADHD-Predominantly Inattentive subtype was more common in children with XXY and XXX, while the ADHD-Combined subtype was more common in XY and XXYY. There were no significant differences between timing of ascertainment (prenatal vs. postnatal), verbal or nonverbal cognitive scores, or parental education between groups with and without ADHD. However, subjects with ADHD had significantly lower adaptive functioning skills and a significantly higher rate of co-morbid psychological disorders compared to those without ADHD.

Conclusions: Overall, 54% of children and adolescents with SCA in this study met criteria for ADHD. These findings support a recommendation that all children and adolescents with SCA be screened for ADHD. Rates of ADHD were higher in males with XXY and XXXY, and these groups were also more likely to show symptoms of hyperactivity and impulsivity. ADHD is associated with lower adaptive functioning and psychological comorbidities. Future studies of neuropsychological abnormalities underlying the clinical ADHD symptoms and interventions are needed for this group of patients.
and influences primary care providers to pursue appropriate medical surveillance. Parents report feeling satisfied with the clinic experience. Tools obtained from the visit help them advocate for their child.

Session: Behavior and Development

**31**
THE EFFECTS OF DEFENSE MECHANISMS ON SELF ESTEEM AND FAMILY DYNAMICS IN OVERWEIGHT CHILDREN

B. Creel1, WN. Evans1,2, GA. Mayman1,2, H. Restrepo1,2 1Children’s Heart Center Nevada, Las Vegas, NV and 2University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: To examine the influence of defense mechanisms on self-esteem and family dynamics in overweight children who participated in a 12-week medically supervised and psychologically monitored weight management program.

Methods Used: The study was conducted from 01-2007 to 05-2008. The study population was 309 families with children aged 9–17 years, with body mass index (BMI) ≥90th percentile, who attended our 12-week risk factor reduction and psychological support program. Children with diagnosed psychiatric disorders were excluded. Parents/proxy caregivers and their children were pre- and post-tested by completing the Child Health Questionnaire and interviewed/evaluated by the psychologist at 4 week intervals.

Summary of Results: Mean age of 309 participant children was 12.5 ± 1.9 years (range 9 – 17 years), mean BMI Z-score was 2.24 ± 0.32 (range 1.36 – 2.96), with 50% of males and race distribution of 58% Hispanic, 23% Caucasian, 7% African-American, and 12% other races. Denial and projection defense mechanisms were observed to be practiced by parents whose obese children had low self-esteem and poor family dynamics. Table summarizes results pre and post intervention.

Conclusions: Parents with obese children may share ineffectual defensive patterns which are responsible for their child’s low self-esteem and for poor family dynamics. Re-assessing and then re-structuring parents’ maladaptive defense mechanisms may help children strengthen their own defenses and provide them a sense of empowerment in changing to healthier eating habits.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Program</th>
<th>Post-Program</th>
<th>Norm</th>
<th>Pre-Program</th>
<th>Post-Program</th>
<th>Norm</th>
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<tr>
<td>Self-Esteem</td>
<td>73.7 ± 19.7</td>
<td>79.4 ± 19.2*</td>
<td>80.1</td>
<td>70.8 ± 21.3</td>
<td>75.3 ± 20.0*</td>
<td>79.8</td>
</tr>
<tr>
<td>Family Activity</td>
<td>58.3 ± 27.4</td>
<td>63.3 ± 28.6</td>
<td>71.5</td>
<td>74.7 ± 25.8</td>
<td>79.9 ± 23.0*</td>
<td>89.7</td>
</tr>
<tr>
<td>Family Cohesion</td>
<td>60.1 ± 50.5</td>
<td>68.6 ± 32.2*</td>
<td>61.3</td>
<td>64.7 ± 26.9</td>
<td>69.2 ± 26.2*</td>
<td>72.3</td>
</tr>
</tbody>
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* Pre vs. post program p < 0.001 + Pre vs. post program p < 0.01

Session: Behavior and Development

**32**
ASSESSING THE FEASIBILITY OF A UNIVERSAL SUICIDE SCREEN IN A NON-PSYCHIATRIC EMERGENCY DEPARTMENT

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Purpose of Study: Suicide attempts and ideation represent about 0.6% of emergency department (ED) visits, with a doubling of rates between 1992 and 1999. Yet, when patients are queried, research suggests that suicidal ideation rates may be much higher, between 3 and 11%. Despite the substantial prevalence of suicidal ideation, few EDs currently implement routine, systematic screening of patients for suicidality. This study is investigating the feasibility of screening every ED patient (excluding those with a primary medical health complaint or those who are incapacitated). We employed a five-item, yes/no patient safety questionnaire that incorporated elements from the Patient Health Questionnaire and the Columbia Suicide Severity Rating Scale. The first two items assess depression and anhedonia, while the last three items address passive and active suicidal ideation and lifetime suicide attempts. We will assess whether this tool effectively elucidates those with high risk suicidal thoughts. It will also address the burden on the hospital ED staff once a suicidal patient has been identified.

Methods Used: Methods: For 3 8-hour shifts and 3 8-hour shifts, research staff will consent and screen every patient who is placed in an ED room. Subjects must be 18–89 years old and English speaking. Subjects cannot have a primary psychiatric complaint and must be alert to consent (cannot be incapacitated or medically unable to participate). Those answering “yes” to passive/active suicidal ideation questions (regardless of lifetime attempt or current depression status) will be additionally queried by a hospital mental health staff or physician.

Summary of Results: Results: Of 219 subjects consented and screened, 9 were positive for high suicide risk and, of those individuals, most answered “yes” to multiple questions. The average screen administration length was 3.3 min.

Conclusions: Conclusion: These findings demonstrate the five-item patient safety screen is an efficient tool for consistent suicide screening. Because of the extensive consenting procedure, we suspect that the prevalence rate of suicidal ideation was artificially low. Also, given the small sample size and number of positive screens, we could not assess the positive predictive value of the last three questions. However, we believe this is an efficient screening tool for the ED.

Session: Behavior and Development

**33**
UTILIZATION OF COMPLIMENTARY AND ALTERNATIVE MEDICINE IN PRESCHOOL AGED CHILDREN WITH AUTISM SPECTRUM DISORDER AND DEVELOPMENTAL DELAY

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Purpose of Study: To compare the utilization of CAM and conventional services in children with ASD to children with DD. Service utilization was examined in both groups with regard to parental education and ethnicity.

Methods Used: Participants were enrolled in the CHARGE Study, a population-based case-control study of 2 to 5 year olds with ASD, DD and children from the general population. Included in this analysis were 332 children with ASD confirmed by ADOS and ADI-R and 78 children with confirmed DD. Developmental and adaptive functioning were assessed by the MSEL and VABS. Demographic, medical and treatment information was ascertained from California birth records, telephone interview and medical assessments and questionnaires at clinic visit. Logistic regression models adjusted for child’s age, sex and parental education were performed to examine the frequency of services and treatments in children with ASD and DD.

Summary of Results: CAM usage was more common in children whose parents had a college degree (44% vs. 25%), regardless of group (OR 2.3, 95% CI 1.5, 3.6). After adjusting for education, Hispanics were not significantly more likely to use CAM than White non Hispanics (OR 0.71, 95% CI 0.43, 1.19). Utilization of any CAM treatment was not statistically different in ASD (38%) vs. DD (27%), (OR 1.5, 95% CI 0.86, 2.69). CAM therapies more commonly received in children with ASD included dietary intervention (OR 3.0, 95% CI 1.7, 4.9) and vitamin supplements (OR 3.0, 95% CI 1.3, 9.1). Cetation and antifungals were only observed in the ASD group. Children with ASD were significantly more likely to receive social skills, behavior modification and sensory integration services. Children with DD were significantly more likely to utilize physical therapy, nursing, vision and nutrition services.

Conclusions: Overall, CAM usage is similar in ASD and DD. Parental education was correlated with increased utilization of CAM in both groups. When corrected for parental education, CAM usage was not significantly different by ethnicity. Frequency of specific CAM and conventional services and treatments differ in ASD and DD.

Session: Behavior and Development

**34**
RATE OF HEAD CIRCUMFERENCE GROWTH IN INFANTS AT-RISK FOR AUTISM: A POSSIBLE CLINICAL MARKER

G. Jensen1, S. Webb2, J. Marsan3 1University of Washington School of Medicine, Seattle, WA and 2University of Washington Autism Center, Seattle, WA.

Purpose of Study: There is evidence that Autism Spectrum Disorders (ASD) correlate with an increase in head growth during early childhood. Further, head circumference (HC) has been shown to predict symptom development in children with ASD, and may thus provide information about a child’s prognosis and/or predict responses to intervention (Elder et al, 2007). HC growth rate could prove to be a useful clinical marker for ASD because measurement of HC is a part of a normal well-child exam. This study...
examined the relationship between rate of HC growth early in life and the later development of ASD symptoms.

**Methods Used:** Data on Occipitofrontal (OFC) head circumference, height and weight was taken from well child checks (WCC) from the University of Washington Autism Center Toddler Assessment Project (TAP). The sample consisted of 44 ASD kids from TAP and 52 controls from the Plagiocephaly Outcomes Project from Seattle Children’s Hospital. Z-scores were calculated based on CDC norms. WCC data was supplemented with measurements taken in the lab at the University of Washington. Subjects were excluded if less than 3 data points were available, if data was not available until at least 18 months, or if subjects were born before 32 weeks gestation. A total of 600 data points were collected across 96 subjects.

**Summary of Results:** Results were interpreted using a 2 slope mixed effects model comparing changes in OFC Z-scores between ASD and typical kids from 0 to 24 months. The slope for the ASD kids was significantly steeper than the average (0.092) during the first year of life (p = 0.000), and then leveling out very close to normal (0.004, p = 0.78) during the second year of life. The control group did not differ significantly as compared to the ASD sample during either the first or second year of life (p=12 = 0.83, p12–24 = 0.46). Both groups differed significantly from the CDC norms, however, the rates statistically different from each other.

**Conclusions:** The mixed results from this study neither discount nor prove the hypothesis that children with ASD may show a patterned and atypical growth rate early in life. Further study is required to further evaluate the significance of a differing growth rate in kids with ASD, and the validity of comparing local samples to CDC norms.

**Session:** Behavior and Development

**35 CERVICOFACIAL VENOUS MALFORMATION AND AUTISTIC SPECTRUM DISORDER IN A PATIENT WITH KABUKI SYNDROME**

J. Lemay1, M. Hicks1, M. Innes2, A. Kirton1

1ACH/ Uof Calgary, Calgary, AB, Canada and 2ACH/Uof Calgary, Calgary, NF, Canada.

**Case Report:** Kabuki Syndrome (KS) is a constellation of features of unknown etiology characterized by a specific facial phenotype, development-delay, and intellectual disability. Autistic features have been described in two case reports of KS without the use of gold standard tests such as the Autism Diagnostic Interview - Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). No association of KS and cervicofacial venous malformation, which is a rare condition, has been reported yet.

A male patient diagnosed at 4 months of age with KS was referred to a developmental clinic at 4 years of age with behaviour, speech, motor and adaptive concerns, impairment with social interactions and presence of stereotyped behaviors. A complete developmental assessment using validated and standardized tests as well as imaging studies were done.

Low cognitive abilities (1st percentile) were measured on the Mullen Scales of Early Learning. On the Adaptive Behaviour Assessment System (ABAS-II), his General Adaptive Functioning score was in the Extremely Low range (0.2nd percentile). Severe expressive, intelligibility and phonological delays (under 1st percentile) and moderate receptive impairments were seen on the Preschool Language Scale-IV. After the assessment with the ADOS Module I and the ADI-R, a diagnosis of ASD, best described as autistic disorder, was provided. On the Peabody Developmental Motor Scales-II, results indicated severe fine and motor gross delays. Interestingly on cerebral MRI/MRV imaging studies, sinus pericranii was found and later confirmed by cerebral angiography.

We describe a unique case of a patient with Kabuki Syndrome, Autistic Disorder and cervicofacial venous malformation. Several candidate genes have been described separately for autistic spectrum disorders and venous malformations but none for Kabuki Syndrome. We speculate a single underlining genetic etiology may lead to the specific features seen in this patient.

**Conclusions:** Women’s justification of IPV is related to their current and past experiences with violence and their sense of personal autonomy.

**Session:** Behavior and Development

**36 JUSTIFYING PHYSICAL VIOLENCE AGAINST MEN AND WOMEN: A STUDY OF FEMALE INTIMATE PARTNER VIOLENCE VICTIMS IN MALAWI**

SE. Medeiros1,2, K. Dalal3, R. Mohammadi3, S. Bazargan-Hejazi3

1Charles Drew University, Los Angeles, CA; 2David Geffen School of Medicine at UCLA, Los Angeles, CA; 3Karolinska Institute, Stockholm, Sweden and 4Linkoping University, Institute for Medicine & Health Sciences, Linkoping, Sweden.

**Purpose of Study:** Intimate partner violence (IPV) is a global public health and human rights problem that cuts across age, religion, ethnicity and culture. In southern Africa, high rates of IPV are common and associated with consequences spanning physical and emotional health, family dynamics and economic losses. Much research has been devoted to identifying risk and eliciting factors of IPV while a few studies focused specifically on attitudes of female victims of IPV, specifically women’s attitudes towards violence against women. This cross-sectional study examines attitudes of female IPV victims in Malawi with respect to physical violence against both women and men.

**Methods Used:** Data was collected as part of the 2004 Malawi Demographic and Health Survey (MDHS). Over 8,000 women, ages 15-49 years, from rural and urban households, responded to a comprehensive questionnaire covering demographic and health issues, including physical, emotional and sexual violence. Along with demographic variables, data collected included exposure to IPV, attitudes toward wife beating (WB) and husband beating (HB), history of parental physical violence, and autonomy in domestic decision-making.

**Summary of Results:** Among the 8290 respondents, 14%(1033) reported emotional violence, 25%(1647) less severe violence, 2.9%(230) severe violence, and 15%(1102) sexual violence. Women justified HB for a behavioral problem (19%), refusing sex (9.3%) or having sex with another woman (25%), and justified WB for a behavioral problem (28%), refusing sex (17%) or going out without permission (17%). Responses differed depending on type and severity of IPV, with victims more likely to non-victims to justify violence (22%;16%); family history of IPV, with women whose fathers beat their mothers more likely to justify violence (20%;16%); and autonomy, with women with no say more likely to justify violence than those with full or partial say (18%;17%;13%).

**Conclusions:** Women’s justification of IPV is related to their current and past experiences with violence and their sense of personal autonomy.
Cardiovascular I
Concurrent Session
8:30 AM
Friday, January 29, 2010

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38
ASYMPTOMATIC POSITIVE CMV SEROLOGY IS ASSOCIATED WITH INCREASED RISK FOR THE DEVELOPMENT OF CARDIAC ALLOGRAFT VASCULOPATHY (CAV) AFTER HEART TRANSPLANTATION
S. Davis, M. Hamilton, J. Kobashigawa
David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: In heart transplant patients, cytomegalovirus (CMV) infection may be characterized by high fever, malaise, and gastrointestinal symptoms. It is also associated with an increased risk of subsequent development of cardiac allograft vasculopathy (CAV). However, some heart transplant patients will develop serologic evidence of de novo CMV infection without symptoms. It is unclear whether these patients, who do not exhibit clinical symptoms and who are not treated, are also at risk for the subsequent development of CAV.

Methods Used: Between 1994 and 2008, we evaluated 740 heart transplant patients and assessed them for CMV infection in the absence of symptoms in the first year post transplant. There were 16 asymptomatic patients who had newly detected CMV serology including: 1) immunoglobulin switch from CMV IgG to IgM; 2) detection of new onset IgM CMV antibodies; or 3) detection of CMV viremia by PCR. These patients were followed for subsequent 5 years for the development of CAV by angiography and compared to group of asymptomatic CMV patients (n = 23) and a control group of patients without CMV infection (n = 701). 5-year actuarial survival was also assessed.

Summary of Results: This asymptomatic CMV positive serology group was found to have a significantly lower freedom from CAV at 5 years after transplant compared to the control group (50% vs. 81%, p = 0.002) but similar to the asymptomatic CMV group (50% vs. 69%, p = ns). 5-year survival was significantly lower in the asymptomatic CMV group (69% vs. 87%, p = 0.02) and the symptomatic CMV group (65% vs. 87%, p < 0.001) compared to the control group.

Conclusions: Asymptomatic CMV infection that is not treated confers an increased risk of subsequent CAV. Further study into the beneficial effects of antiviral therapy for these patients is warranted.

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39
C4D OR C3D POSITIVITY IN HEART TRANSPLANT BIOPSIES IS NOT A MARKER FOR POOR OUTCOME
M. Share, M. Hamilton, J. Kobashigawa
David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Antibody-mediated rejection (AMR) in heart transplant patients has been associated with poor outcome. The diagnosis of AMR is mostly dependent on endomyocardial biopsy histology. More recently, staining for complement fragments, C4d and C3d in the presence of endothelial swelling, intravascular macrophages have been suggested to be representative of AMR. However, the meaning of C4d or C3d alone in heart biopsy samples has been questioned.

Methods Used: Between June 2001 and May 2008, we reviewed 5490 biopsies in 361 patients to assess the outcome of any first year heart biopsy positive for C4d and/or positive for C3d without concomitant cellular rejection or AMR. We assessed 5-year actuarial survival, freedom from cardiac allograft vasculopathy (CAV, angiographic stenosis >30%), and freedom from non-fatal major adverse cardiac events (NF-MACE, myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, new onset peripheral vascular disease).

Summary of Results: 113/361 (31%) patients were found to have at least 1 biopsy in the first year post transplant positive for C4d and/or C3d alone without concomitant cellular or AMR. The patients with these biopsies did not receive anti-rejection therapy. These patients were compared to 210 patients without C4d and/or C3d who served as controls. There was no significant difference in 5-year actuarial survival (89% vs. 92%, p = 0.31), 5-year actuarial freedom from CAV (84% vs. 86%, p = 0.55), and 5-year actuarial freedom from NF-MACE (96% vs. 93%, 0.35) between the 2 groups. In addition, there was no significant difference in 1-year freedom from any-treated rejection (97% vs. 98%, p = 0.70). Further breakdown in C4d or C3d presentation including focal, multifocal, and diffuse histology revealed no difference in outcomes.

Conclusions: The presence of C4d and/or C3d alone without cellular or AMR in heart transplant biopsies appears benign and is not associated with poor clinical outcome for these heart transplant patients.

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40
ACCOMMODATION AFTER HEART TRANSPLANTATION
M. Kawano, M. Hamilton, J. Kobashigawa
David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: The presence of donor-specific antibodies (DSA) is associated with poor outcome after heart transplantation. The term accommodation applies to the heart transplant patient where DSA is detected w/o heart biopsy AMR changes but with normal cardiac function. With accommodation, the allograft acquires resistance to injury and does not allow the DSA to damage the donor heart function. We sought to confirm the presence of accommodation by reviewing the short- and long-term outcome of stable heart transplant recipients with DSA.

Methods Used: Between 2000 and 2009, 261 patients had DSA detected in the first year after heart transplantation. 222/261 (84%) patients had evidence for accommodation with normal cardiac function and were not treated. 2 of these accommodation patients had AMR findings in at least one first year biopsy but with normal cardiac function and were not treated. The remaining 39 patients had DSA with cardiac dysfunction which required treatment. These patients were compared to a contemporaneous control group of 91 heart transplant patients without DSA. These 3 groups were assessed for 5-year actuarial survival, freedom from cardiac allograft vasculopathy (CAV, angiographic stenosis >30%), and freedom from non-fatal major adverse cardiac events (NF-MACE, myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, new onset peripheral vascular disease).

Summary of Results: The Accommodation Group (DSA with normal cardiac function) had comparable 5-year actuarial survival, freedom from CAV, and NF-MACE, compared to the control group (table). Patients with DSA and cardiac dysfunction had a significantly lower 5-year actuarial freedom from CAV compared to the Accommodation and Control groups (66% vs. 83% and 75% respectively; p = 0.02). There was no difference in outcomes within the accommodation group between those patients with or without AMR biopsy findings.

Conclusions: Patients with accommodation (DSA with normal cardiac function) in the first year after heart transplantation have comparable long-term outcome compared to patients without DSA, suggesting that accommodation does exist. Further study is needed to assess the impact of DSA characteristics (ie titers) that might explain this phenomenon.

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41
LONG-TERM OUTCOMES OF PRIMARY GRAFT DYSFUNCTION IN CARDIAC TRANSPLANTATION
S. Wong, S. Wong, M. Kawano, R. Shemin, M. Kwon
David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Early injury is associated with the long-term development of coronary allograft vasculopathy (CAV) in cardiac transplantation. CAV is a major complication following adult heart transplantation and is associated with decreased long-term survival. We examined whether adult heart transplant recipients incurring primary graft dysfunction (PGD) were more susceptible to the development of CAV than their non-PGD counterparts.

Methods Used: We performed a retrospective review on 857 patients undergoing heart transplantation between January 1994 and December 2008. Primary graft dysfunction was defined by the need for extracorporeal
membrane oxygenation implementation, open-chest, or intra-aortic balloon pump placement within 72 hours of transplantation. CAV was defined by ≥50% atherosclerosis in any vessel. Allograft survival was defined by patient death or need for re-transplantation.

Summary of Results: 42 patients with PGD were identified. 12 (28.6%) PGD patients died and 2 (4.8%) required re-transplantation within the 30-day post operative period, compared to 19 (2.3%) mortalities and 0 (0%) re-transplants in the non-PGD control group. Of surviving patients, only 2 (7.1%) of the PGD patients developed CAV, versus 15 (19.7%) in the non-PGD group. The two PGD developing CAV did so at 0.79 and 1.95 years, compared to the control group developing CAV 4.4 ± 3.3 years post transplantation. When comparing 1- and 5-year allograft survival, the PGD group had worse outcomes than the control group, with 55% vs. 89% survival at 1-year and 45% vs. 79% survival at 5-years post transplantation.

Conclusions: PGD is associated with higher 30-day mortality and lower 1- and 5-year allograft survival rates. However surviving patients do not show increased tendency towards CAV development.

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42 HIGH-DENSITY LIPOPROTEIN (HDL) MIMETIC PEPTIDES CAN RESTORE THE ANTI-INFLAMMATORY PROPERTIES OF HDL FROM PATIENTS WITH CORONARY ARTERY DISEASE

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David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: In large populations, HDL-cholesterol levels are inversely related to the risk of atherosclerotic clinical events; however, in an individual, the predictive value of an HDL-cholesterol level is far from perfect.

Summary of Results: We observed that while the HDL from the wild type mice prevented LDL oxidation and MCP-1 induction (HDL inflammatory index = 0.51, p= 0.002 for LDL+HDL vs LDL alone), HDL from apoE deficient mice increased the level of oxidation of LDL and induction of MCP-1 (HDL inflammatory Index = 1.39. p= 0.012).

Conclusions: conclusion: ApoE deficiency induced-inflammation and susceptibility to coronary atherosclerosis is accompanied by loss of HDL protective capacity.

Session: Cardiovascular I

43 A NOVEL ROLE FOR HEPARIN-BINDING EPIDERMAL-LIKE GROWTH FACTOR IN EARLY ATHEROSCLEROSIS

B. Kim1, S. Lee2, J. Berliner3,4
David Geffen School of Medicine at UCLA, Los Angeles, CA. 1 David Geffen School of Medicine at UCLA, Los Angeles, CA and 4 David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: By inducing inflammatory changes in endothelial cells and macrophages, oxidized 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (OX-PAPC) has been demonstrated to be central to early atherosclerosis. While previous signaling pathways have been described, they cannot fully explain the effect of OX-PAPC. From gene expression analyses, we hypothesized that OX-PAPC induces metalloproteinases to cleave the proform of heparin-binding epidermal growth factor (HB-EGF) to its soluble form, activating the epidermal growth factor receptor (EGFR) and inducing the release of inflammatory cytokines.

Methods Used: Human Aortic Endothelial Cells (HAEC) were cultured in VEC™ MCDB-131A media with 100U/mL penicillin and 100ug/mL streptomycin at 37 C. HAEC were: (1) treated with OX-PAPC derived by air exposure of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids), (2) transfected with small interfering RNA (siRNA) from Qiagen or IDT and porated with Lipofectamine 2000™ (Invitrogen), or (3) treated with human recombinant HB-EGF. To assay gene expression: RNA and cDNA were prepared by RNA extraction kit (Bio-Rad) and iScriptTM cDNA synthesis kit (Bio-Rad). SYBR® Green reaction reagent and Roche PCR amplification system performed Q-RTPCR (normalized by GAPDH expression). To assay pro- or mature HB-EGF, cell membranes were fractionated and visualized by Western Blot (4-20% gradient Tris-HCl gel, PVDF membranes, Enhanced Chemiluminescence Plus (Amersham) to develop, VersaDoc System (Bio-Rad) to image, and Quantity One® to calculate band density.

Summary of Results: HB-EGF siRNA transfection reduced interleukin-8 (IL-8) release with Ox-PAPC treatment by ~60%. Conversely, at 1 hour, treatment with human recombinant HB-EGF (50 ng/ml) yielded a ~60% increase. Further, at 1 hour, Ox-PAPC treatment increased the ratio of activated-EGFR to total-EGFR by ~50%. Finally, Ox-PAPC treatment appeared to increase the release of HB-EGF on Western Blot at 4 hours.

Conclusions: These data strongly suggest a novel role for HB-EGF and EGFR in OX-PAPC-mediated inflammation and hence atherosclerosis.

Session: Cardiovascular I

45 ALTERNATANT PROTEIN DEPRIVATION: DEVELOPMENTAL PROGRAMMING OF THE RENIN ANGIOTENSIN SYSTEM IN HEART

E. Kim, R. Goyal, L.D. Longo
Loma Linda University, Loma Linda, CA.

Purpose of Study: Understanding the mechanisms of hypertension (HTN) is important, as heart disease and stroke are the most common causes of death in the US. Epidemiologic studies demonstrate that maternal low protein diet (MLPD) results in an increased incidence of HTN in the offspring. Studies also suggest that the HTN is due to the changes in the renin-angiotensin system (RAS), a pathway that regulates blood pressure and water balance. Furthermore, evidence suggests that a local RAS exists in various tissues and organs including heart. Therefore, we tested the hypothesis that MLPD results in alterations in the cardiac RAS, which can lead to the developmental programming of HTN in the male offspring.

Methods Used: We conducted the studies in FVB/J mice. Normal and low protein diet (50% protein restricted, isocaloric) were administered seven days before mating, and were continued throughout pregnancy. Non-invasive

The inflammatory index for LDL alone (LLI) was set at 1. Normal HDL reduces the oxidation of LDL and thus the inflammatory index will be below this reference value.
tail-cuff method was used to measure blood pressure, in-cell western immunoblot for protein analysis and real-time PCR to examine mRNA expression.

Summary of Results: Our results demonstrate a significant increase in blood pressure starting at 16 weeks of age in the male offspring from MLPD group, as compared to control. Statistical analysis of mRNA and protein levels of heart showed that at 3 weeks of age, there was no change in mRNA and protein expression. However, at 32 weeks of age, we observed a significant increase in the mRNA levels of angiotensin I-converting enzyme (ACE1), angiotensin II-converting enzyme (ACE2), and angiotensin receptor 1 (AT1) in heart as a consequence of 50% maternal low protein diet (MLPD). Furthermore, at 32 weeks of age, there was significant increase in angiotensinogen (AGT) and ACE1 protein expression and decrease in AT1 as a consequence of 50% MLPD.

Conclusions: Maternal protein deprivation of the mouse fetus results in developmental programming of HTN later in life. Results also indicate a significant increase in various components of the cardiac RAS at 32 weeks of age. Of interest, expression of the cardiac RAS was normal at 3 weeks of age. Further studies are needed to discover the possible cause of increase in the expression of the RAS genes (e.g., gene regulation) at an older age, which may lead to the development of HTN.

Session: Cardiovascular I
46 QUANTITATIVE CONTRACTILE CHARACTERISTICS OF HUMAN EMBRYONIC AND INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCTYES
S. Lundy1,2, M. Regnier1,2, M. Laflamme2,3 1University of Washington, Seattle, WA; 2University of Washington, Seattle, WA and 3University of Washington, Seattle, WA.

Purpose of Study: Recent work has demonstrated the therapeutic potential of cardiac cell transplantation following myocardial infarction. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) show particular therapeutic potential due to their ability to contract and couple with host myocardium, but ethical concerns and clinical limitations of immunologic rejection still pose significant challenges to widespread clinical adoption. The human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) is a promising cell type generated from autologous fibroblasts and re-differentiated into beating cardiomyocytes, thus potentially alleviating many shortcomings of hESC-CMs. Before these cells can be tested in an in vivo model of myocardial infarction, however, their contractile characteristics must first be quantitatively evaluated.

Methods Used: We have recently successfully differentiated iMR90 fetal fibroblast-derived hiPSCs and H7 hiESCs into beating cardiomyocytes using serial treatment with activin-A and BMP-4. To assess contractility, we quantitatively measured single cell contractions of hESC-CMs and hiPSC-CMs using optical videomicroscopy and calcium imaging.

Summary of Results: Preliminary results suggest that hESC-CMs and hiPSC-CMs exhibit similar spatiotemporal contraction kinetics, including time to peak contraction, time to 50% relaxation, contraction velocity, and maximum magnitude of contraction. Furthermore, both types of stem cell-derived cardiomyocytes exhibit a dose-dependent chronotropic response to beta adrenergic stimulation. Finally, both hESC-CMs and hiPSC-CMs demonstrate similar calcium transients as measured with the ratiometric calcium indicator fura-2.

Conclusions: In summary, hESC-CMs and hiPSC-CMs appear to develop similar single cell characteristics and may provide a viable alternative cell source for future therapeutic approaches involving cardiomyocyte transplantation.

Session: Cardiovascular I
47 DONOR TO RECIPIENT HEIGHT MATCH IN ADDITION TO WEIGHT MATCH IS IMPORTANT FOR GOOD OUTCOME AFTER HEART TRANSPLANTATION
A. Moradzadeh, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Most commonly, size matching of donor hearts is based on donor/recipient weight ratios. There are many cases however, where the donor is either too tall or too short with the weight being acceptable. The aim of the current study was to determine if height mismatch affects outcome after heart transplantation.

Methods Used: Between 1994 and 2009, we assessed 327 patients transplanted at our institution. To exclude the influence of donor/recipient weight differences, all patients in this study had donor/recipient weight ratios between 0.9 and 1.1. The heights of the donor and recipient were divided into 3 groups: Group A (donor/recipient height ratio <0.9, N = 12); Group B (donor/recipient height ratio >0.9 and <1.1, N = 297); Group C (donor/recipient height ratio >1.1, N = 18). 5-year actuarial survival, freedom from cardiac allograft vasculopathy (CAV, angiographic stenosis >30%), and non-fatal major adverse cardiac events (NF-MACE, myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, new onset peripheral vascular disease) were measured.

Summary of Results: Group C had a significantly lower 5-year actuarial survival compared to Group B (50%, vs. 78% p = 0.001). Causes of death in Group C included rejection (n = 3), CAV (n = 4), and multiple organ system failure (n = 2). Group A exhibited a trend toward a lower 5-year actuarial survival compared to Group B (58% vs. 78%, p = 0.09). 5-Year actuarial freedom from CAV and freedom from NF-MACE were found to be similar between all 3 groups. There was no effect of donor/recipient height on primary graft failure or rejection in the first year after transplantation. The percent of donor/recipient gender mismatch was the same in all 3 groups.

Conclusions: Donor to recipient height mismatch, especially donor/recipient height ratio >1.1 (with comparable weight ratio) is associated with decreased 5-year survival after heart transplantation. Further study to confirm this finding with a larger cohort of patients is warranted.
Session: Community Health
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TELEMEDICINE TO DETECT DIABETIC RETINOPATHY IN AMERICAN INDIAN/ALASKA NATIVES AND OTHER ETHNICITIES
SL. Mamsberger1,2,3, TM. McClure1, KA. Wooten1, TM. Becker4,5 1Legacy Health System, Portland, OR; 2Oregon Health & Science University, Portland, OR; 3Veteran’s Administration Hospital, Portland, OR; 4Oregon Health & Science University, Portland, OR; 5Hunter Health Clinic, Wichita, KS and 6Northwest Portland Area Indian Health Board, Portland, OR.
Purpose of Study: To determine the level of diabetic retinopathy (DR), the need for ophthalmology referral, and proportion of progressive diabetic retinopathy in underserved rural and urban populations of American Indian/Alaska Natives (AI/AN) and other ethnicities using a telemedicine protocol.
Methods Used: We randomly selected diabetic patients to participate in a store-and-forward telemedicine program using non-mydriatic cameras (Camera group). We performed retinal photography at least once per year and used the International Diabetic Retinopathy scale to stage DR from Stage 1 (mild NPDR) to Stage 5 (proliferative DR).
Conclusion: Of those with images in the Camera group, DR worsened (>1 stage) in 3 participants (3.0%); DR improved (<1 stage) in 3 participants (1.3%); and stayed the same in 36 participants (16.1%).

Session: Community Health
50
HEARING HEALTH IN NORTHWEST AMERICAN INDIAN COMMUNITIES
WH. Martin1,2,3, WE. Lambert1,7, LD. Simpson8,7, Y. Shi2, SE. Grist5,6, N. Hildebrandt7,1, JR. Kennedy7,1, TM. Becker4,5 1Oregon Health & Science University, Portland, OR; 2Oregon Health & Science University, Portland, OR; 3Oregon Health & Science University, Portland, OR; 4Northwest Portland Area Indian Health Board, Portland, OR; 5Veterans Administration Medical Center, Portland, OR; 6Oregon Health & Science University, Portland, OR and 7Yukama Indian Health Center, Toppenish, WA.
Purpose of Study: Hearing loss is highly prevalent in American Indian/Alaska Native (AI/AN) communities. Losses can isolate members from the spoken aspects of culture. This study documented hearing health risk exposures and the results of rehabilitation intervention in NW tribal groups.
Methods Used: We performed hearing screening in rural and urban tribal collectives. We identified hearing losses, provided diagnoses, and when needed, provided hearing amplification devices (hearing aids and other devices). We tracked quality of life changes resulting from amplification over a 6-month period. We used questionnaires to identify potential risks from types of noise exposures.
Summary of Results: We screened 289 participants, of which, 134 (46.4%) required medical intervention and/or amplification. In the group fitted with hearing aids (n = 24), significant life improvement was noted when amplification was used. An additional 24 participants have completed evaluation and the results are being analyzed. Rural participants reported significantly higher noise exposures than did those from urban settings. Both settings had a high prevalence of potentially dangerous noise exposures.

Session: Community Health
51
DEVELOPING A COMMUNITY HYGIENE CLINIC IN SULTAN, WA
JJ. Kopa University of Washington, Seattle, WA.
Purpose of Study: In an attempt to combat elevated risk of disease associated with homelessness, this project sought to draw on resources already available in the community to regularly provide shower facilities for men and women currently living without a home in Sultan, WA.
Methods Used: Through contacts made at the Monroe city council and the Sea Mar clinic, several local organizations began a collaborative relationship to supply facilities, materials and staffing. Criteria for selecting collaborative partners included: an established commitment to community service, experience in working with Sultan’s homeless community, and experience in community leadership. An action plan was developed, implemented and evaluated.
Summary of Results: Volunteers of America, a national organization with a strong outreach network in Sultan, offered the monthly use of showers, towels, cleaning supplies and laundry facilities. They also helped to coordinate outreach to several local churches who volunteered to staff monthly clinics. Take the Next Step, a grassroots social services agency in Monroe, donated hygiene kits that included soap, shampoo and shaving supplies for use in between clinics. Crosswater Community Church joined several smaller church communities in providing volunteers to staff the clinic. In addition, the Sultan School District pledged assistance in staffing and shower facilities.
Conclusions: Through the collaborative efforts of several community organizations that were already working with Sultan’s homeless community, the hygiene clinic provides a necessary, sustainable service. In addition, it provides an organizational framework on which other services can be added, which may include more frequent showers, regular health screening, and meal sharing. In addition to providing a vital service to a vulnerable social group, the clinic allows the Sultan community, along with healthcare and social services to begin to forge bonds of trust with a small portion of their community that already subsists on the fringes of society.
on the CHA level of training and experience. This list was modified to target village OB patients, explaining the process and reasons for each test, and included counseling on abortion, adoption, and drug and alcohol cessation. The two one-page handouts were faxed to each clinic with an explanation of intent.

Conclusions: Community health aides are the first, and in some cases, only resource utilized by village OB patients before their delivery. Providing them with a quick reference to use with their OB patients may serve to improve village prenatal care and increase the comfort level of health aides. Offering the village women a guide to their own prenatal care may have the effect of increasing the knowledge base of the village women as a whole.

Session: Community Health
53 LIBBY AMPHIBOLE ASBESTOS EDUCATION IN THE MEDICAL COMMUNITY OF LIBBY, MONTANA
K. Kadling University of Washington, Seattle, WA.
Purpose of Study: Vermiculite was mined outside Libby, MT starting in the 1920s. A unique type of asbestos fiber (amphibole) contaminated the mine. Mining operations spread asbestos fibers in and around Libby for 70 years. Despite the mine closing in 1990, the illness burden continues to be staggering. Amphibole fibers have a severe and unusual pathophysiology compared to traditional asbestos, including the ability to cause disease from environmental exposure alone. This has only recently become recognized in the medical community. The purpose of this project was to help educate and remind primary care physicians about the basics of this awful and strange disease. Secondarily, the project served to bolster dialogue between the primary care clinics and the center for asbestos related disease (CARD) clinic regarding continuity of care and upcoming research projects.

Methods Used: Information sessions with Dr. Brad Black, director of the CARD clinic, regarding the perceived needs of the Libby medical team in terms of asbestos education served as a starting point. This was followed by gathering feedback from primary care physicians about what more they wanted to learn and a review of asbestos literature online. The project concluded as a presentation on background of the disease, unique aspects of pathophysiology compared to traditional asbestos, including the ability to cause disease from environmental exposure alone. This has only recently become recognized in the medical community. The purpose of this project was to help educate and remind primary care physicians about the basics of this awful and strange disease. Secondarily, the project served to bolster dialogue between the primary care clinics and the center for asbestos related disease (CARD) clinic regarding continuity of care and upcoming research projects.

Conclusions: In order to best care for the many patients in Libby who are afflicted with ARD, physicians need to understand and recognize the unique aspects of this disease. Continued physician education and open dialogue between the primary and specialty clinics is essential in best caring for these people. It also provides the benefit of enrolling patients in research groups to better understand how to more effectively recognize and treat ARD.

Session: Community Health
54 LATIN-AMERICAN IMMIGRANT MOTHERS’ EXPERIENCES WITH HEALTHCARE IN LOS ANGELES: A QUALITATIVE STUDY
Y. Castellon, K. VanderWall, A. Kuo David Geffen School of Medicine at UCLA, Los Angeles, CA.
Purpose of Study: In the past decade the Latino community has grown and become more diverse. Currently, the majority of medical literature focuses on the healthcare experiences of Mexican Americans, Puerto Ricans, and Cuban Americans. However, there has been an exponential growth of Central American immigrants. As such, there is a need for more research in this population in order to provide culturally-competent care. Our study examines the perspectives of a diverse group of Latin American immigrant women from Central America about their experiences with access to healthcare.

Methods Used: Participants were divided into four focus groups, each representing a different Latin American Country. Recruitment and focus group sessions took place at the South Central Family Health Center, a Federally Qualified Health Center in Los Angeles. Focus groups were conducted in Spanish by a volunteer moderator. Participants discussed ten open-ended questions during a one-hour session. A demographic questionnaire was completed. Focus group audio-recordings were translated and transcribed. Data were analyzed using triangulation approach among three members of the research team. Major themes across all groups were identified.

Summary of Results: Twenty-one participants completed the study. The 4 major themes identified were: prevention (50), traditional practices (60), disconnect with the U.S. healthcare system (100), and rationale for status of U.S. healthcare system for the undeserved (20). The third theme was further categorized: lack of respect by MD’s/Staff (33), financial limitations (18), preference for native system and medications (36), and recognition of limitations of U.S. system (13).

Conclusions: All groups prescribed to traditional healing practices from their native country. Participants demonstrated a strong preference for using these remedies prior to seeking medical care. They also expressed a preference for medications manufactured in Latin America. These practices were seldom discussed during the medical visit, disconnecting the patient from the medical encounter. Understanding within group-differences among the Latino population is important because ethnic differences exist. More studies incorporating the diverse experiences of these groups are needed in order to inform the delivery of culturally-competent care.

Session: Community Health
55 FALL PREVENTION EDUCATION FOR YAKAMA NATION ELDERS IN TOPPENISH, WA
DK. Duffield University of Washington School of Medicine, Seattle, WA.
Purpose of Study: Each year, 30% of the U.S. population over the age of 65 is injured by a fall. Although specific rates for falls in elderly American Indians are unavailable, it is known that American Indians experience 150% more unintentional injuries per capita than the total U.S. population. Additionally, falls add to the lower life expectancy of American Indians compared to the U.S. average. Thus, reducing the risk of falls in the elderly is key to keeping this vulnerable population healthy and living longer.

Methods Used: Medical providers at Yakama Indian Health Service (IHS) were solicited for their opinions on unmet health needs for elders. Fall prevention education came out of these conversations. A discussion with a program manager at the Yakama Nation Area Agency on Aging (AOA) confirmed this need. A literature review was conducted to determine effective and appropriate health education interventions for fall prevention programs. Those chosen were interventions that had been previously shown to reduce falls, required changes that were likely to be adopted by elders, and had little or no associated financial cost.

Summary of Results: A 30 minute health education discussion with approximately 40 community dwelling American Indian elders took place during a daily senior center lunch provided by the AOA. The discussion had three focal points: the importance of calcium and Vitamin D supplementation, light to moderate balance and strength exercise, and fall hazards around the home. Elders were engaged, answered questions about home hazards appropriately, and asked insightful questions. Elders were also sent home with a fall prevention brochure which included a home hazard check-list and set of exercises, in addition to a printed version of presented materials. This brochure is now available for reproduction and distribution by IHS and the AOA.

Conclusions: A key aspect of this community intervention was working with IHS and AOA not only to organize the event, but to gain the trust of the elders. Fall prevention education presented in this familiar, social environment was well received and understood by the attendees. Thus, multi-faceted interventions focusing on fall risks and easily adoptable changes by elders in a trusted environment seem mostly likely to succeed.

Session: Community Health
56 ASSESSING THE HEALTH NEEDS OF AFRICAN IMMIGRANTS IN CALIFORNIA
J. Ekwueme1,2, I. Chukwu1,2, A. Jo1 David Geffen School of Medicine at UCLA, Los Angeles, CA and 3Charles Drew University of Medicine and Science, Los Angeles, CA.
Purpose of Study: The number of foreign-born Africans in the United States has grown forty-fold since 1960 and over half of this growth occurred after 2000. Unfortunately, there is little data that focuses on the health and healthcare needs of this rapidly growing immigrant population. Although typically grouped with African Americans, they have many distinguishing characteristics. As such, their health status and needs may be different to that of African Americans, and interventions addressing this population may need unique tailoring. The goal of this project was to begin to understand about the health status and health needs of this population.

Methods Used: We utilized qualitative research methodology to obtain in-depth information on the general health status of this target population, focusing on the barriers to assessing adequate health services, and what the community believes would be most helpful health intervention in addressing their current health needs. We conducted three focus groups with 37 African immigrants from two Nigerian and one Ethiopian churches. All of the focus groups were audio taped and transcribed. Transcriptions and field notes were analyzed via editing method.

Summary of Results: From these focus groups we found that many are frustrated by the lack of adequate health information and difficulty in adhering to healthy behaviors (e.g., exercise, obtaining ethnic foods) and accessing quality health care. With regard to intervention preferences, the following were mentioned: a need to distinguish the African immigrant population from the African Americans; a need for cultural competency education for physicians treating African immigrants; a need for health education for the immigrant population about the American health systems as well as how to be healthy; a need to change health systems and policy to enhance health access for this Population.

Conclusions: Although limited by sample size and qualitative nature of this study, it was apparent that most of the participants were frustrated about their health and health care. They also voiced strong opinions about their health care needs. Our findings suggest a need for interventions to address health needs of this population.

Session: Community Health
57
FUELING INTEREST IN HEALTHCARE CAREERS: A WORKSHOP DESIGNED FOR THE TWIN FALLS, IDAHO MIGRANT SUMMER SCHOOL

K. Dove-Maguire University of Washington, Seattle, WA.

Purpose of Study: The American physician workforce does not currently reflect the diversity of the country. In Twin Falls, Idaho, this workforce homogeneity is accentuated. Students belonging to minority groups continue to be underrepresented in medical school graduates. Early educational exposure, learning opportunities, and positive role models have been shown to increase interest and influence career choice among students belonging to minority groups. A workshop on healthcare careers and anatomy was designed for fourth through sixth grade students at the Oregon Trail Elementary Migrant Summer School to increase underrepresented student interest in healthcare.

Methods Used: A review of professional literature indicated that most students have selected career paths by high school. Many interventions indicate that field-specific educational opportunities had a greater effect when implemented prior to high school. In addition, exposure to a female role model in a science career increased interest of female students considering a scientific career. Research into local community resources revealed the Migrant Summer School, a program designed to improve educational experiences for children of migrant workers. A workshop targeting fourth through sixth grade students was designed to increase student interest in healthcare careers.

Summary of Results: Two one-hour workshops were conducted which included information on healthcare careers and an anatomy lesson. Students listened to heart and lung sounds using stethoscopes, handled diagnostic kits, and used blood pressure cuffs. Basic pathology of the lungs and heart was listened to heart and lung sounds using stethoscopes, handled diagnostic kits, and used blood pressure cuffs. Basic pathology of the lungs and heart was...

Conclusions: Although limited by sample size and qualitative nature of this study, it was apparent that most of the participants were frustrated about their health and health care. They also voiced strong opinions about their health care needs. Our findings suggest a need for interventions to address health needs of this population.

Session: Community Health
59
SCIENCE TUTORING: PIPELINING AMERICAN INDIANS INTO THE HEALTHCARE FIELD

SM. Verlander University of Washington, Seattle, WA.

Purpose of Study: The Seattle Indian Health Board (SIHB) serves a diverse Native community in the Seattle metropolitan area and offers a bevvy of services, one of which is Youth Services. This program was initially established to help pipeline Native students into healthcare. Research demonstrates disparities in Native academic performance as well as medical school admissions. SIHB Youth Services’ is challenged to provide educational support to students failing science courses.

Methods Used: To address this challenge, a science study center and club was established in previously unused space at SIHB. Donations of books and supplies such as microscopes were solicited from the University of Washington, Cascade Cancer Center, and Fred Hutchinson Cancer Research Center. The science club meets weekly to explore a subject of the month, which can be in any number of scientific fields, including biology, health, and physics. SIHB staff have taken on the responsibility for ongoing club activities and curriculum. A review of the professional literature shows that similar social/educational approaches have been successful in urban and underserved communities.

Summary of Results: The science study center is now fully operational. The Youth Services staff at SIHB is committed to facilitating science club meetings while maintaining a positive and active learning environment. Currently, ten native students are actively enrolled in the science club.

Conclusions: This intervention follows in the footsteps of similar successful projects. It could result in an increase in Native students’ interest in science while helping to boost student science grades in the short term. Early educational success could lead to increases in Native Americans choosing healthcare professions in the long term. This can impact health positively by providing more culturally appropriate health care to the urban Native American Community and is hopefully a long-term solution.
Session: Community Health

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JOHNSON COUNTY INTERAGENCY SUMMER BICYCLE HELMET SAFETY INTERVENTION

G. Wallace
University of Washington School of Medicine, Seattle, WA.

Purpose of Study: The majority of bicycling youth in Johnson County do not wear helmets. This is not an isolated case; the 2007 Wyoming Youth Risk Behavior Survey reported 70% of Wyoming middle school bicycle riders did not wear helmets. Bicycle helmets are well known to be effective in preventing significant bicycle related injury. A countywide interagency intervention with Public Health, local Police Departments, and Johnson County Healthcare Center was initiated to promote bicycle helmet usage.

Methods Used: The author facilitated the creation of 120 free ice cream coupons and 60 free bicycle helmet coupons donated by local businesses and Johnson County Public Health. Coupons were given to Buffalo and Kaycee police chiefs who asked their officers to contact helmeted and non-helmeted bicycling youth and give them coupons for a free ice cream or free helmet, respectively. A newspaper article about the intervention and bicycle safety was written by the author and published in the Buffalo Bulletin. The author, police chief, and public health nurse were interviewed about the intervention on the local radio show "Sparks' radio show".

Summary of Results: The intervention began on 7/29/09. As of 9/10/09, 15 helmet coupons had been redeemed at Public Health in Buffalo and 9 in Kaycee. All coupons had been given out. The Buffalo Police Chief reports "certainly not less helmet usage, and more helmets if anything because we have given them away". Public Health has many reports of people receiving the coupons and that people are excited about them.

Conclusions: This intervention has been very successful overall. The police have received lots of compliments and report that kids and their officers have enjoyed the intervention. It is possible that more helmets than the 24 accounted for by redeemed coupons were given out by as a result of this intervention; Public Health reports an increase in helmets given out likely attributed to folks who heard about the program but had not received a coupon or that had received a coupon but did not bring it in. In addition to promoting helmet use and bicycle safety, the intervention provided a friendly interface for the police with the local youth while simultaneously supporting local businesses. The author is optimistic that this intervention has educated people about the importance of bicycle helmets and has increased bicycle helmet use in Johnson County.

Session: Community Health

61

SECOND HAND SMOKE EXPOSURE IN WYOMING - A MODEL FOR CHANGE

OB. Wells
University of Washington, Seattle, WA.

Purpose of Study: Attempts to regulate indoor smoking in Wyoming have failed several times at several levels of government. Public polling has shown that 90% of Jackson residents want smoke-free public places and 10% are opposed. However, all efforts to pass legislation have failed at the state, county and city levels. In response, The Teton County Public Health District was created and a smoke-free air rule was proposed. The rule was approved on 03/24/09 and was to take effect on 05/23/09. However, a lawsuit was filed by a group of business owners that prevented the rule from taking effect. On 03/24/09 and was to take effect on 05/23/09. However, a lawsuit was filed by a group of business owners that prevented the rule from taking effect. The purpose of this project was to raise awareness in the community concerning the need for smoke-free legislation, to educate locals on the detrimental effects of second-hand smoke exposure and to educate local business owners on the economic impact of smoking. The teton County Courts rule in favor of the smoke-free air rule, this will provide a model and establish precedence for other towns in Wyoming to regulate indoor smoking. This project raised awareness by assessing individual health risk due to second-hand smoke exposure in over 100 Jackson residents as well as educating locals concerning the need for local support of the Teton District Smoke-Free Air Rule.

Endocrinol

Concurrent Session

8:30 AM
Friday, January 29, 2010

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TUMOR INDUCED OSTEOIMALACIA WITH NO CLINICALLY APPARENT TUMOR

L.E. Aguirre, K. Colleran, P. Kasprzak
University of New Mexico Health Sciences Center School of Medicine, Albuquerque, NM.

Case Report: Tumor-induced osteomalacia (TIO) is a rare syndrome characterized by hypophosphatemia, decreased renal phosphate reabsorption, normal or low serum 1,25-dihydroxyvitamin-D concentration, myopathy, and osteomalacia. Fibroblast growth factor 23 (FGF23) is a phosphaturic protein overexpressed in tumors that cause TIO and is responsible for the manifestations of TIO. Patients typically present with a history of chronic bone pain, fractures, and proximal muscle weakness. We describe a 56-year-old male patient who presented with severe musculoskeletal pain for years and a history of multiple traumatic fractures. Initial osteoporosis work up in 2006 did not show any abnormalities but did not include a serum phosphorous level. The patient was started on oral bisphosphonate therapy. In 2009 he underwent another evaluation for secondary causes of osteoporosis. Work up only revealed subnormal plasma phosphate levels (1.2 mg/dl; normal range, 2.4–5), low levels of 1,25-dihydroxyvitamin-D levels (12 pg/ml; normal range, 15–75) and elevated serum alkaline phosphatase (472U/L; normal range, 20–145). Suspected TIO prompted testing for FGF-23 which was found to be elevated (310 RU/mL; normal range, 0–180). PET/CT showed no evidence of metastatic disease but numerous areas of increased activity in the skeleton. Bone scan revealed severe osteopenic changes. DXA showed worsening of bone mineral density. To date we have not identified an underlying malignancy. This case illustrates a case of phosphaturic wasting osteomalacia with elevated FGF-23 without clinically evident tumor.

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63

THE REGULATION OF THE SODIUM IODIDE SYMPORTER IN BREAST CANCER BY RETINOIC ACID

LL. Richter1, T. Koga1,2, G. Brent1,2
1University of New Mexico Health Sciences Center School of Medicine, Albuquerque, NM and 2V A Greater Los Angeles Health Care System, Los Angeles, CA.

Purpose of Study: The sodium iodide symporter (NIS) is exploited for radioidine imaging and treatment in thyroid cancer. NIS is expressed in 80% of breast cancers, suggesting an attractive potential treatment option for this cancer. Endogenous expression of NIS in breast cancer, however, is usually not sufficient for therapeutic use of radiodine. All-trans-retinoic acid (tRA) treatment increases NIS expression and radioidine uptake in MCF7 breast cancer cell xenografts in mice, but not in thyroid. Unfortunately, the high dose of tRA needed to achieve these levels of NIS limits its use. Elucidation of the mechanism by which tRA induces NIS may lead to alternative targets for upregulation of NIS expression, as well as insight into the role of tRA on breast cancer cell proliferation and differentiation. We have shown that PKG and p38 MAPK signaling pathways mediate the breast cancer-selective effect of tRA on NIS. Expression of a negative regulator of an oncogene RAP1...
TABLE 1. Serum T, body composition, liver enzymes and lipid profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum T (ng/mL)</th>
<th>Total T (ng/mL)</th>
<th>Fat mass (g/kg)</th>
<th>Lean mass (g/kg)</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>AST/ALT</th>
<th>ALP (U/L)</th>
<th>Glucose (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.2 (0.5)</td>
<td>13.2 (1.7)</td>
<td>20.4 (3.2)</td>
<td>45.6 (5.7)</td>
<td>39 (12)</td>
<td>9 (3)</td>
<td>0.39</td>
<td>130 (20)</td>
<td>80 (15)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>Castrated</td>
<td>0.6 (0.1)</td>
<td>1.1 (0.2)</td>
<td>24.5 (4.5)</td>
<td>30.5 (4.0)</td>
<td>90 (20)</td>
<td>15 (3)</td>
<td>1.5</td>
<td>150 (25)</td>
<td>90 (15)</td>
<td>55 (30)</td>
</tr>
</tbody>
</table>

*Mean ± SEM; **Geometric mean (95% confidence interval)

Session: Endocrinology I

65 TESTOSTERONE SUPPLEMENTATION REVERSES SARCOPENIA IN AGING THROUGH REGULATION OF MYOSTATIN, JNK, AKT, AND NOTCH SIGNALING PATHWAYS

EL. Kovacheva1, AP Sinha Hikim2, R. Shen1, L. Sinha-Hikim1 1Charles Drew University, Los Angeles, CA and 2David geffen School of Medicine, UCLA, LA Biomed, harbor-UCLA, Torrance, CA.

Purpose of Study: Aging in humans is characterized by loss of muscle mass (sarcopenia) and strength. Such age-related loss of muscle mass increases the risk of falls, fractures, and disability. Testosterone (T) supplementation increases muscle mass and strength in older men. Here, using a mouse model, we investigated the molecular mechanisms by which T prevents aging-associated sarcopenia.

Methods Used: Groups of 15 older (22 months old) mice received a single sc injection of gonadotropin releasing hormone antagonist every 2 weeks to suppress endogenous T production and were implanted subdermally under anesthesia with 0.5 or 1.0 cm3-filled implants for 2 months. Groups of 15 young (4 months old) and old (24 months old) mice were used as respective controls.

Summary of Results: Aged mice not receiving T treatment exhibited a significant (P < 0.05) increase in the rate of muscle cells apoptosis along with a correlative decrease (10.9%; P < 0.05) in the weight of gastrocnemius muscles when compared with young mice. These aged mice also showed a significant (P < 0.001) decrease in muscle fiber cross sectional area of both fast (23.5%) and slow (28.1%) fiber types. Importantly, such age-related changes were fully reversed by the higher dose (1-cm) of T treatment. T treatment effectively suppressed age-specific increases in oxidative stress, processed myosinat levels, activation of c-Jun NH2-terminal kinase, and cyclin-dependent kinase inhibitor p21. Furthermore, it restored aging-specific decreases in glucose-6-phosphate dehydrogenase levels, the first and rate limiting enzyme of the pentose phosphate pathway, phospho-Akt, and Notch signaling. These alterations were associated with satellite cell proliferation and differentiation as demonstrated by increased expression of PCNA and myogenin levels.

Conclusions: These results suggest that testosterone attenuates loss of muscle mass in aging by restoring the microenvironment through stimulation of cellular metabolism and pro-survival signaling together with the inhibition of cell-death pathway.

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66 DOWN REGULATION OF VITAMIN D RECEPTOR SIGNALING IN BREAST CANCER STEM-LIKE CELLS: IMPLICATIONS FOR THERAPEUTIC INTERVENTIONS

M. Braga1, M. Hewison2, S. Pervin3, R. Singh1,3 1Charles Drew University of Medicine and Science, Los Angeles, CA; 2UCLA, Los Angeles, CA and 3UCLA, Los Angeles, CA.

Purpose of Study: The expression of vitamin D receptor (VDR) is an important determinant in breast tumor’s response to vitamin D. The levels of VDR declines in late-stage poorly differentiated breast tumors and is absent in metastases. The purpose of this study is to investigate the VDR expression and differential response to vitamin D treatment in normal and breast cancer stem-like cells (BCSCs).

Methods Used: BCSCs were isolated from MCF-7 and SKBR-3 cell lines using mammosphere based assays and characterized by immunofluorescence, western blot and quantitative real-time PCR (qPCR) for the expression of various stem-cell surface markers. Cells were treated with various doses of 1,25 (OH)2 vitamin D (0–0.1μM) for 0–7 days. In some cases cells were simultaneously treated with 1μM DETA-NONOate. The average size and number of mammospheres were analyzed by quantitative image analysis. Apoptosis was measured by caspase assays. Cell cycle study was performed by FACS analysis.

Summary of Results: BCSCs isolated from MCF-7 and SKBR-3 expressed key stem cell markers Sox2, Oct-4, Klf4, C-Myc, and nanog. These cells were also characterized to CD44+, ESA+ and CD24+/absent expression. VDR protein and mRNA levels were down regulated in BCSCs isolated from MCF-7 and SKBR-3 cell lines, in sharp contrast to those from normal mammary epithelial cells. The protein levels of RXR-α, TGF-β1, and PAL-1 were significantly down regulated in these stem-like cells compared to normal mammary epithelial cells.
the cells grown on high attachment plates. The down-regulation of VDR in BCSCs was associated with induction of Snail (~2.2 fold) and down-regulation of e-cadherin (~68%). Vitamin D treatment inhibited the proliferation of MCF7- and SKBR3 cells in a dose-dependent manner, but BCSCs were resistant to this treatment. DETA-NONOate, a nitric oxide (NO)-donor was highly effective in combination with vitamin D in inhibiting BCSC proliferation.

**Conclusions:** Resistance of BCSCs to vitamin D treatment may be associated with down-regulation of VDR signaling. Using NO in combination with vitamin D may provide a therapeutic approach to effectively target breast cancer.

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**Session: Endocrinology I**

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**DUTASTERIDE REDUCES PROSTATE SPECIFIC ANTIGEN (PSA) IN HYPOGONADAL MEN WITH BENIGN PROSTATIC HYPERPLASIA UNDERGOING TESTOSTERONE (T) REPLACEMENT THERAPY**

L.A. Hirano, ST. Page, AM. Matsumoto 1,2 University of Washington, Seattle, WA and 3VA Puget Sound Health Care System, Seattle, WA.

**Purpose of Study:** Dutasteride inhibits both type 1 and 2 androgen receoptes in the prostate and may increase intraprostatic dihydrotestosterone (DHT). Exogenous DHT does not increase intraprostatic DHT might be desirable. We hypothesized that exogenous DHT, by providing negative feedback to the pituitary and thus suppressing gonadotropin and T production, might paradoxically lower intraprostatic DHT and androgen-action within the prostate.

**Methods Used:** 27 healthy men ages 35–55 were randomly assigned to receive either daily transdermal DHT gel or placebo gel for 4 weeks. Blood was obtained bi-weekly throughout the study. Prostate volume was measured at baseline, on Day 28 when a prostate biopsy was obtained, and on Day 56. DHT and T concentrations were measured by liquid chromatography-tandem mass spectrometry. Androgen-regulated gene expression was compared using laser-capture microdissection and microarrays on frozen biopsy specimens.

**Summary of Results:** Serum DHT increased nearly seven-fold during treatment (baseline DHT 0.98±0.28; Day 28 6.99±1.18 ng/ml) and was significantly different than the placebo group at Day 28 (P < 0.001). Serum T concomitantly decreased in the DHT-treated group compared to baseline and placebo treatment (P < 0.05). Preliminary analyses demonstrate that intraprostatic DHT concentrations on Day 28 were no different in the two groups (DHT: 8.44±3.25, Placebo: 8.30±2.70 ng/g). Prostate volume, serum PSA, and androgen-regulated gene expression were no different between groups.

**Conclusions:** Increases in serum DHT do not increase intraprostatic levels of DHT and were not associated with increases in PSA, prostate volume, or androgen-regulated gene expression in men. DHT gel might have utility as part of an androgen replacement regimen for men.

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**Session: Endocrinology I**

**69**

**IUGR INCREASES MRNA LEVELS OF RBP4 IN INSULIN RESISTANT RATS**

B. Burshears, Y. Wang, M. Hale, Q. Fu, X. Yu, C. Callaway, R. McKnight, L. Joss-Moore, R. Lane University of Utah, Salt Lake City, UT.

**Purpose of Study:** IUGR individuals are known to be at a higher risk for adult-onset metabolic disturbances, such as insulin resistance. Insulin resistance in humans has been associated with an increase in serum retinol binding protein 4 (RBP4). Furthermore, elevated levels of transthyretin (TTR), a protein that forms a complex with RBP4, has been related to over-nutrition. It is unknown what affect IUGR has on expression of RBP4 and TTR in liver, retroperitoneal adipose, and subcutaneous adipose tissues in a rat model of IUGR that has been previously characterized by insulin resistance and adiposity. We therefore hypothesized that IUGR would increase the expression of RBP4 and TTR in the rat liver, retroperitoneal, and subcutaneous adipose. We have previously demonstrated that retroperitoneal and subcutaneous adipose have different expression profiles.

**Methods Used:** IUGR was generated by bilateral uterine artery ligation on pregnant e19 rats. Using tissue from rat pup livers collected after c-section on e21.5, term = Day 0 (D0) and at D21, and subcutaneous and retroperitoneal adipose collected at D7, D21, and D60, mRNA was isolated, cDNA synthesized, and RT-PCR used to analyze RBP4 and TTR.

**Summary of Results:** IUGR males had decreases in RBP4 mRNA in D0 and D21 liver, D7 retroperitoneal and subcutaneous adipose, and D21 subcutaneous adipose. TTR mRNA levels were elevated in female D60 subcutaneous and retroperitoneal adipose tissues when compared to control male while males were not affected. Our most intriguing finding was that IUGR increased RBP4 mRNA levels in D60 retroperitoneal adipose tissue in males, but not females. Moreover, male D60 levels of RBP4 in subcutaneous adipose tissue were increased when compared to sham.

**Conclusions:** IUGR increased mRNA levels of RBP4 at D60 in gender and tissue specific manner. At this age, our IUGR rat model has insulin resistance, with males being more severely affected than females. These findings are intriguing and suggest that RBP4, at a minimum, could be a biomarker, and possible cause of insulin resistance based on transgenic studies in mice. It is known that, in our model of IUGR, the females have significant catch-up growth while males remain smaller in size (despite increased adiposity). We speculate that elevated levels of TTR at D60 in females correspond with long-term effects.

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**Session: Endocrinology I**

**70**

**VALIDATION OF A COMMERCIALLY AVAILABLE GROWTH HORMONE RELEASING HORMONE ANTIBODY FOR STUDYING RADIATION-INDUCED GROWTH HORMONE DEFICIENCY**

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**Purpose of Study:** Since the prostate is an androgen-sensitive organ, concern over the potential for prostate-related side effects with replacement therapy might adversely impact prostate health in older men. The predominant circulating androgen in men is testosterone (T) but within the prostate dihydrotestosterone (DHT) predominates due to the high level of expression of the enzyme 5α-reductase which converts T to DHT. 5α-reductase inhibitors, which lower intraprostatic DHT, have been shown to lower the risk of prostate cancer; therefore, hormonal replacement strategies that do not increase intraprostatic DHT might be desirable. We hypothesized that exogenous DHT, by providing negative feedback to the pituitary and thus suppressing gonadotropin and T production, might paradoxically lower intraprostatic DHT and androgen-action within the prostate.
Purpose of Study: Therapeutic cranial irradiation including the hypothalamic-pituitary axis (HPA) results in a variety of neuroendocrine disturbances, with growth hormone (GH), the first and most sensitive of the anterior pituitary hormones to be affected. Little is known about the cellular and molecular mechanisms of radiation damage to the hypothalamic-pituitary axis and how they interact. Immunohistochemical methods are among the most effective and economic for answering these important questions. However, a high-quality growth hormone-releasing hormone (GHRH) antibody for immunohistochemical staining has yet to be found. We tested the commercially available GHRH antibody (Advanced Targeting Systems, AB-16AP) to verify the use of this antibody for our research on the mechanisms of radiation induced GH deficiency.

Methods Used: To establish the validity of the antibody for staining GHRH-positive neurons, we compared the intensity of staining in the median eminence of 1-week-old prepubertal, and 6-week-old postpubertal rats using an Olympus Fluoview (FV1000) Scanning Confocal Microscope. The production of GHRH is known to increase during pubertal growth period. The brains of 1-week-old prepubertal and 6-week-old postpubertal male Sprague-Dawley rats were fresh-frozen. Frozen sections (30 micrometer) were cut by a cryostat and immunofluorescence GHRH staining was visualized by goat anti-rabbit IgG conjugated with Alexa fluor 488 (green), while nuclei were counterstained with propidium iodide (PI, red). In addition, IGF-I serum levels were tested by ELISA (R&D Systems).

Summary of Results: GHRH-positive staining was strongly localized to the median eminence, while no immunoreactivity was demonstrated in other brain regions. In 1-week-old rats, the GHRH-positive intensity in the median eminence averaged 11% of the PI intensity, whereas in 6-week-old rats it averaged 69%, thus increasing by 6-fold in post- vs. prepubertal rats. The IGF-I serum levels correlated well with the GHRH staining level in the median eminence.

Conclusions: The GHRH antibody AB-16AP is highly specific for rat GHRH and is, therefore, suitable for our research in radiation-induced GH deficiency.

Session: Endocrinology I

A 38 YEAR-OLD MALE WITH RECURRENT NEPHROLITHIASIS AND HYPERVITAMINOSIS D

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Case Report: A 38 year-old male with a history of recurrent nephrolithiasis, hypercalciuria, elevated vitamin D 1.25(OH)₂ levels, normal vitamin D 25(OH) levels, low PTH, and no history of calcium deposit ingestion was referred to the Endocrinology and Metabolism department. Past medical history was also significant for scoliosis requiring Harrington rod placement as a child. Consideration was given to a genetic mutation leading to increased renal calcium excretion but no evidence of vitamin D 1.25(OH)₂ synthesis or absorption. IGF-I serum levels correlated well with the GHRH staining level in the median eminence.

Conclusions: The GHRH antibody AB-16AP is highly specific for rat GHRH and is, therefore, suitable for our research in radiation-induced GH deficiency.

Session: Genetics

IDENTIFYING SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATED WITH AN INCREASED SUSCEPTIBILITY TO TYPE 2 DIABETES IN THE PIMA INDIAN POPULATION

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Purpose of Study: Type 2 diabetes mellitus, with its increasing prevalence both within the United States and globally, has become a major public health problem. The Pima Indians of Arizona suffer from the world’s highest prevalence of this disease. Although the underlying causes of type 2 diabetes include both environmental and lifestyle factors, studies have shown that genetics is also a major component. The purpose of this study was to determine whether the genes that contribute to type 2 diabetes in Caucasians also contribute to diabetes in Native Americans. Knowledge of the specific genes and metabolic pathways underlying this disease could facilitate the development of targeted treatment options.

Methods Used: Recent genome-wide association studies using single nucleotide polymorphisms (SNPs) identified six novel susceptibility loci for type 2 diabetes among individuals of European descent. These SNPs were genotyped in DNA from 1,329 diabetic and 1,700 non-diabetic full-heritage Pima Indians for replication studies. Genotyping was performed using the Applied Biosystems SNplex assay and statistical analysis performed using the SAS package (SAS Institute, Cary, NC).

Summary of Results: Among the SNPs analyzed, only rs664754 near the JAZF1 gene was associated with type 2 diabetes in Pima Indians (p = 0.03, OR = 1.20 with 95% CI 1.02–1.40). A 2-hour oral glucose tolerance test administered to non-diabetic test subjects revealed elevated glucose levels (239 mg/dl) among those homozygous for the risk allele compared with those heterozygous (124 mg/dl) and homozygous for the non-risk allele (111 mg/dl).

Conclusions: These findings suggest a possible involvement of JAZF1 in the etiology of type 2 diabetes in both Caucasians and Pima Indians. However, the other five genes associated with diabetes in Caucasians do not appear to contribute to this disease in Pima Indians suggesting that the genetic basis for diabetes is not the same across all ethnic groups. Therefore, treatment may need to be tailored to fit the specific pathophysiological needs of different ethnic groups rather than the universal approach that has traditionally been used.

Session: Genetics

CHROMOSOME 16p11.2 DELETION: EXPANSION OF THE PHENOTYPE TO INCLUDE DIAPHRAGMATIC HERNIA

J. Hogue, A. Slavotinek, M. Wat, D. Scott, K. Rauen 1University of California, San Francisco, San Francisco, CA and 2Baylor College of Medicine, Houston, TX.

Case Report: Congenital diaphragmatic hernia (CDH) is a common birth defect in which genetic factors play a significant role. Chromosome anomalies visible by G-banding have long been recognized as a cause of CDH. In contrast, submicroscopic deletions have only recently been shown to be an important cause of this sporadic birth defect. Submicroscopic deletions of chromosome 16p11.2, including a recurrently deleted region at 29.5-30.1 Mb, have been associated with autism and occur at an estimated frequency of ~1% of such patients. Recent reports have expanded the phenotype of the 16p11.2 deletion syndrome to include speech delay, mental retardation, and neuropsychiatric presentations. We describe two patients with CDH found to have de novo submicroscopic deletions of 16p11.2 by array comparative genomic hybridization (CGH). These patients allow us to broaden the phenotype and establish 16p11.2 deletions as a novel etiology for non-isolated CDH. Our first patient was a newborn boy with a left-sided, Bochdalek CDH born to non-consanguineous parents. His physical exam was notable for proximally placed, hypoplastic, and disarticulated thumbs bilaterally. He had severe respiratory
Session: Genetics

74 CANCER PREDISPOSITION SYNDROMES AND ARRAY COMPARATIVE GENOMIC HYBRIDIZATION: WHEN ONE ANSWER DOES NOT TELL THE WHOLE STORY
S. Ramanathan1, DJ. Michelson2, RD. Clark1 1Loma Linda University Children's Hospital, Loma Linda, CA and 2Loma Linda University Children's Hospital, Loma Linda, CA.

Purpose of Study: To illustrate the risks and potential errors associated with genetic counseling for a group of children with cancer predisposition syndromes and array comparative genomic hybridization (aCGH) anomalies and the lack of aCGH reporting standards in this setting.

Methods Used: Array comparative genomic hybridization testing (either BAC or oligo, performed in a commercial, CLIA-certified lab)

Summary of Results: We report 4 children with cancer syndromes and deletions detected on aCGH. In each child, the deleted interval included a gene known to be associated with a cancer predisposition syndrome but in 2 patients, who had BAC aCGH, this was discovered only after a diligent and time-consuming pursuit by clinical genetic staff. These four patients were originally referred for developmental delay/mental retardation (DD/MR) and birth defects in three and learning disabilities in one. Their diagnoses were Peutz-Jeghers syndrome (PJS, STK11), neurofibromatosis 2 (NF2, NF2), Gorlin syndrome (GS, PTCH1) and Li-Fraumeni syndrome (LFS, p53). The diagnoses of NF2 and PJS preceded the aCGH results, which explained unusual findings: cleft palate and MR in the former and learning disabilities diagnoses of NF2 and PJS preceded the aCGH results, which explained

Conclusions: Even as aCGH testing gains wide use, there are no agreed standards in the reporting and interpretation of abnormal/equivocal results. In our patients with long chain fatty acid oxidation severe hyperammonemia as initial presentation.

Session: Genetics

76 IMPlications of global H3K18ac patterns in oncogenic transformation
Y. Chan1, R. Ferrari2, S. Kurdistani1,2 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2UCLA, Los Angeles, CA.

Purpose of Study: Cancer cells display altered epigenetic patterns that affect the expression of oncopgenes and tumor suppressors and contribute to cancer development. One epigenetic alteration, decreased acetylation of histone 3 lysine 18 (H3K18ac), correlates with a more aggressive cancer phenotype and predicts poor prognosis. Interestingly, the adenovirus oncoprotein e1a causes global hypoacetylation of H3K18 which is necessary for cellular transformation, suggesting an important role for this modification. Understanding genome-wide patterns of H3K18ac may therefore help elucidate its role in cancer.

Methods Used: Chromatin immunoprecipitation (ChIP) using an antibody against H3K18ac was performed on G1 arrested contact-inhibited IMR90 fibroblasts. ChiPed DNA was ligated to specific primer adapters and sequenced via the Illumina sequencing platform. Next, sequences from cDNA libraries will be used to characterize the IMR90 transcriptome and help elucidate the role of H3K18ac in transcription regulation and its implications in oncogenesis.

Summary of Results: Preliminary sequencing results generated from the H3K18ac and H3K18ac ChiPed libraries reveal two distinct patterns of H3K18ac enrichment. H3K18ac was found at the transcription and termination start sites (TSS and TTS) of many genes. Furthermore, peaks of H3K18ac were associated with the exon side of exon-intron and intron-exon boundaries. Unbiased clustering algorithm (k-means) of all the annotated human genes for H3K18ac enrichment showed one subset of genes, consisting of mainly developmental genes, in which acetylation was significantly present at both the TSS and TTS. In a second set of genes involved in several other cellular processes, enrichment was restricted at the TSS.

Conclusions: H3K18ac enrichment at the TTS has been shown in other systems but never before characterized in human primary fibroblasts. Enrichment at boundaries between exons and introns could be important in regulating events of splicing. Moreover, distinct patterns of H3K18ac may play integral roles in regulating transcription with H3K18ac inducing transcription when present at both the TSS and TTS or poising a gene for later activation when restricted at the TSS. Further data on genomic expression may elucidate the significance of these patterns and how altering them may favor an oncogenic phenotype.

Session: Genetics

77 Severe hyperammonemia as initial presentation in patients with long chain fatty acid oxidation defects - considerations for initial treatment
A. Niemi, S. Hintz, GM. Enns Stanford, Stanford, CA.

Purpose of Study: The emergence of massively parallel DNA sequencing platforms has made resequencing an affordable approach to study genetic variation. However, whole genome resequencing remains too costly to apply in the study of genetic contributions to disease. Sequencing protein coding regions (‘exomes’) offers the potential to reduce costs while enriching for the discovery of disease-causing mutations. Molecular Inversion Probes (MIPs) generated from oligonucleotides released from programmable microarrays (Agilent) have been previously used to capture and amplify a fraction of human exons (50,000) in a single reaction. However the technique suffered from poor capture efficiency, and a labor-intensive gel-purification step.

In this project, we extended the capture capability to the entire human exome while also improving the ease-of-use and efficacy of the protocol. Methods Used: In order to test a streamlined protocol, MIPs were amplified and prepared from a pool of 385,000 oligonucleotides (Agilent) with and without a gel purification step. Regions of human genomic DNA were captured following previously published protocols, with changes made to probe, ligase, and polymerase concentrations used in the reaction. RT-PCR was used to initially assay the effects of the changes made to the capture efficiency. Samples were then sequenced on an Illumina GA-2 machine. 36 base-pair reads were then mapped back onto a database of targeted regions and the percentage of exome sequenced was determined.

Summary of Results: Gel and RT-PCR results indicated that a streamlined protocol produced successful capture, and that the changes made to the capture reaction improved efficacy of capture by ten-fold. A total of 16 million sequencing reads were mapped to 330,000 of the 385,000 targeted sites. In a final optimized protocol, 2.5 gigabases of sequence would result in the detectable capture of 90 percent of the human exome. This reflects a ten-fold improvement in percent of exome captured in one reaction.

Conclusions: We show that it is possible to use MIPs to capture a majority of human exons for next-generation massively parallel DNA sequencing, extending the domain of sequence-based studies on variation.
Purpose of Study: Although neonates with urea cycle defects (UCD) or organic acidaemias (OA) often present with critical elevations of ammonia (NH3), severe hyperammonemia has been encountered more rarely in long chain fatty acid oxidation defects (LCFAOD). Caloric support to promote anabolism is a mainstay of therapy, in addition to alternative pathway therapy and hemodialysis. However, patients with FAOD will not be able to utilize intravenous lipids; indeed, lipids may even worsen the clinical situation by promoting further accumulation of toxic metabolites. Because neonates with inherited errors of metabolism (IEM) and severe hyperammonemia are typically indistinguishable from each other based on physical exam, it would be useful to be able to differentiate FAOD from UCD and OA on presentation so that appropriate therapy can be provided in a timely fashion.

Methods Used: We retrospectively reviewed charts of patients who were treated for hyperammonemia during the neonatal period and were subsequently diagnosed with LCFAOD (n = 2) and compared the laboratory values at presentation to those obtained at presentation from patients with UCD (n = 11) or OA (n = 12). For statistical analyses Wilcoxon rank test was used.

Summary of Results: The mean NH3 at the time of presentation in patients with UCD was 1071 μM, in patients with OA 625 μM and in patients with LCFAOD defect 896 μM (NS, p = 0.2185). The mean BUN in patients with UCD was 6.5 (n = 7), in patients with OA 24 (n = 11), and in patients with LCFAOD defect 20.5 (n = 2) (p = 0.0753). The mean blood glucose in patients with UCD was 108 mg/dl (n = 8), in patients with OA 68 mg/dl (n = 11), and in patients with LCFAOD defect <20 mg/dl (unmeasurable) (n = 2) (p = 0.0466).

Conclusions: Neonates with LCFAOD may present with hyperammonemia that is indistinguishable from those with UCD or OA. In neonates with severe hyperammonemia the presence of low BUN point to UCD, whereas normal to high BUN in combination with severe hypoglycemia should alert physician to consider withholding intravenous lipids in the initial phases of therapy until diagnosis of fatty acid oxidation defect has been excluded.

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GLUTATHIONE DEFICIENCY IN METHYLMALONIC ACIDEDEMIA IS RESPONSIVE TO TREATMENT WITH N-ACETYL-CYSTEINE
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Purpose of Study: Methyhamonic aciduria (MMA), an autosomal recessive inborn error of metabolism, results from deficient activity of methylmalonyl-CoA mutase. This mitochondrial enzyme participates in the catabolism of valine, isoleucine, methionine and threonine and converts methylmalonyl-CoA to succinyl-CoA. Patients have severe disease with episodic metabolic decompensation and hyperammonemia, and are at risk for basal ganglia changes, pancreatitis and renal insufficiency. Treatment includes protein restriction with concurrent hydroxocobalamin supplementation. It is hypothesized that some of the clinical seqeulae result from mitochondrial dysfunction, supported by studies in a knock out mouse model of MMA. The antioxidant glutathione (GSH) protects against damage from reactive oxygen species that accumulate with mitochondrial dysfunction, a condition associated with GSH deficiency and corresponding elevations of 5-oxoproline. A 7-year-old with MMA, evidence of mitochondrial dysfunction, and 5-oxoprolineuria responded to ascorbate therapy; ascorbate may have acted as an alternative antioxidant to GSH in this case (Treue et al in 1996).

Methods Used: Retrospective chart review.

Summary of Results: Our patient was noted to have 5-oxoprolineuria and low blood GSH level as a neonate. Despite treatment with ascorbate, blood GSH remained low and 5-oxoprolineuria persisted. In addition, other markers of mitochondrial dysfunction, including lactate and TCA cycle intermediates, were abnormally elevated by urine organic acid analysis. Furthermore, cystine, a glutathione precursor, was abnormally low in plasma. The patient was started on N-acetylcysteine (NAC) with the rationale that cysteine is essential for GSH synthesis. Within one week, 5-oxoprolineuria was significantly improved and normalized within a month.

Conclusions: This case provides additional evidence that GSH deficiency and secondary mitochondrial dysfunction are features of organic acidaemias, such as MMA. Although NAC is best known for treatment of acetaminophen overdose, it has another use as an antioxidant. Treatment with antioxidants including NAC can correct GSH deficiency. Formal clinical trials are needed to determine if evaluation and treatment of GSH deficiency in MMA can alter the natural history of this disease.

Session: Genetics 79
SEARCHING FOR CLUES: FUNCTIONAL GENE ANNOTATION IN AUTISM SPECTRUM DISORDER
N. Krumm, S. Girirajan, E. Eichler Univ. Of Washington, Seattle, WA.

Purpose of Study: The Autism Spectrum Disorders (ASDs) are a highly heritable group of neurodevelopmental disorders; however, only approximately 20% of cases have a known genetic cause. In this study, we characterized the deleted or duplicated genes in genome-wide structural variation data in cases of autism. We developed a novel method of finding significant functional categories using the GeneOntology database in autism in order to guide further study and identification of target genes.

Methods Used: We compared annotated genes found deleted or duplicated in 308 cases of autism with those in 1643 controls. In order to compare our smaller sample set of cases to the controls, we sampled the CNVs from 304 random control individuals 1000 times with replacement. For each resampling, we recorded for each GO category how many unique genes were found to be deleted or duplicated in that resampling. The resulting distribution of each GO category estimates the tolerance that member genes of that category have for deletions or duplications in the control population. We compared the actual categorization of GO terms for the autism set to the distribution of the control resamples, and calculated a test-statistic for enrichment and a p-value for significance.

Summary of Results: In our analysis of both deletions and duplications, two enriched categories were related to the ubiquitin and proteasome system (UPS), mirroring previous work and analyses. The specific GO categories include “Proteasomal protein catabolic process” (GO:14098) and “ubiquitin-specific protease activity” (GO:4843), which together encompass seven different genes in six cases of autism. Additionally, 17 affected gene products in 14 cases of autism were annotated with categories of mRNA splicing, translation and binding. Finally, our analysis of duplicated genes also discovered four genes (ASA12, SGM1, SMPD2 and UGCO) in three cases in pathways related to sphingomyelin production (GO:6665), which to our knowledge has not yet been reported.

Conclusions: We found several candidate categories in autism which do not tolerate deletion or duplication in controls. We plan to find additional support for these enriched categories in replicate cohorts of autism, and via a targeted search for CNVs using array-CGH and deleterious or rare mutations using high-throughput sequencing of candidate genes and regions.

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EXPLORING THE NEURONAL PHENOTYPE OF AUTISM SPECTRUM DISORDERS USING INDUCED PLURIPOTENT STEM CELLS
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Purpose of Study: Autism spectrum disorders (ASDs) are highly heritable and genetically heterogeneous. Current clinical and laboratory tools are able to identify a specific genetic etiology in roughly 15% of individuals with ASD. The remaining cases have proven difficult to sub-classify. This has hampered the ability to conduct genetic studies of ASDs and to evaluate new therapeutics in a uniform population. We predict that the identification of neuronal phenotypes in individuals with ASDs will allow the definition of novel sub-classes of autism. We are utilizing induced pluripotent stem cell (iPSC) technology to generate cortical neurons from cultured skin fibroblasts of individuals with three genetic disorders associated with autistic symptomatology: the 22q11 and 22q13 deletion syndromes and Timothy syndrome (OMIM: 601005).

Methods Used: Skin fibroblasts are re-programmed into iPSCs according to published methods. The iPSCs are subsequently differentiated into neural progenitor cells and then cortical neurons using defined culture conditions and mechanical manipulation. Following differentiation we have started to assess neuronal subtypes, neuronal morphology, synapse formation and electrical activity using microscopy and patch-clamp techniques. Gene expression studies of cultured iPSC derived neurons are also underway.

Summary of Results: We have generated iPSC derived neurons from two individuals with 22q13 deletion syndrome, two individuals with Timothy...
syndrome and one individual with 22q11 deletion syndrome. The charac-
terized neurons are electrically active, form dendritic spines and functional synapses.

Conclusions: iPSC derived neurons are a promising model system for the study of cellular phenotypes in ASDs and likely other neuropsychiatric disorders. We are in the process of comparing neuronal phenotypes between 22q11 and 22q13 deletion syndromes, Timothy syndrome and control samples. In future work, we plan to evaluate the neuronal phenotypes of additional genetically defined cases of autism and ultimately to compare these phenotypes to those in neurons from subjects with idiopathic autism.

### Session: Genetics

#### DEFECTIVE SIGNALING PATHWAYS IN VCP ASSOCIATED INCLUSION BODY MYOPATHY (IBMPFD)

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**Purpose of Study:** Inclusion body myopathy associated with Paget’s disease of the bone and frontotemporal dementia (IBMPFD) is caused by mutations in the Valosin Containing Protein (VCP) gene resulting in progressive muscle weakness, malfunction in the bone remodeling, and premature frontotemporal dementia. The purpose of our study was to clarify molecular and cellular consequences of VCP mutations in patients’ and control subjects’ primary myoblasts and muscle tissues.

**Methods Used:** Western blotting, immunocytochemistry, microarray, qRT-PCR, pathway analyses.

**Summary of Results:** Patients’ myoblasts accumulated large vacuoles that were able to fuse with lysosomes. Lysosomal membrane proteins Lamp1 and Lamp2 were definitively N-glycosylated in patients’ myoblasts, and the maturation processes were affected. Additionally, mutant myoblasts demonstrated increased autophagy and apoptosis. Expression profiling revealed that 279 genes were differentially expressed in patients’ muscle (p < 0.001).

Down-regulation of Platelet-Derived Growth Factor Receptor Alpha (PDGFR-α, −7.5x) was specific to IBMPFD when compared to other muscle dystrophies. This finding was confirmed by qRT-PCR and Western blotting.

**Conclusions:** Our findings suggest that patients’ myoblasts and muscle biopsies can be used to clarify the molecular pathogenesis of IBMPFD. Additionally, PDGFR-α may play a role in the development of progressive muscle pathology in IBMPFD patients. Affected PDGFR-α signaling may also result in defective autophagy and accumulation of storage material in patients’ cells. This may be associated with increased apoptosis and defective myotube formation, which eventually result in muscle weakness in IBMPFD patients.

### Session: Health Care Research I

#### Concurrent Session

**Health Care Research I**

**8:30 AM**

Friday, January 29, 2010

#### EMERGENCY MEDICINE AND PSYCHIATRY AGREEMENT ON DISPOSITION OF EMERGENCY DEPARTMENT PATIENTS

A. Douglass1, J. Lour2, L. Baraff1 1David Geffen School of Medicine, Los Angeles, CA; 2UCLA Ronald Reagan Medical Center, Los Angeles, CA and 3UCLA Ronald Reagan Medical Center, Los Angeles, CA.

**Purpose of Study:** This purpose of this study is to determine the level of agreement between emergency physicians and consulting psychiatrists regarding the management of psychiatric patients in the emergency department (ED).

**Methods Used:** Each time a psychiatry consult was ordered for a patient in the UCLA ED, the emergency and consulting psychiatry residents were asked to complete similar short questionnaires regarding their diagnosis and disposition decisions after they consulted with their attendings. Completion of the questionnaires was optional and was not used to evaluate resident performance. The physicians and patients remained anonymous with unique research codes to identify the particular patient. After the emergency and psychiatry residents completed the questionnaires, a research assistant completed a data form, which included information about the patient’s age, sex, ethnicity, insurance status, and final disposition decision (i.e. whether the patient was admitted or discharged from UCLA or sent to another facility).

**Summary of Results:** 134 data sets were collected between June 15 to September 25, 2009. 87% (n = 117) of the emergency residents felt confident enough to make disposition decisions. Of the emergency residents who made disposition decisions, 72% (n = 84) agreed with the consulting psychiatry residents. Of those that disagreed, in 61% (n = 20) of the cases, the emergency resident wanted to discharge the patient. There was 71% (n = 75) agreement about the patient’s eligibility for a 5150 hold. Patients waited in the ED for an extra 225.6 minutes on average for psychiatric consultants.

**Conclusions:** Reducing the number of psychiatry consults would allow many of these patients to go home sooner with outpatient follow-up appointments and would help alleviate ED overcrowding problems. However, there is not sufficient agreement between emergency and psychiatry residents to warrant eliminating the need for psychiatry consults. This suggests the need to develop criteria for low risk psychiatric patients who could safely be evaluated by emergency physicians without psychiatric consultation. This could be used as an educational tool for emergency physicians.

### Session: Health Care Research I

#### ANALYSIS OF THE PRINCIPAL LANGUAGE SPOKEN PREVALENCE IN CALIFORNIA

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**Purpose of Study:** Communication barriers between providers and patients can result in inadequate healthcare. Miscommunication of symptoms may lead to misdiagnoses or inappropriate tests being ordered and a reduction in
adherence to medication or discharge information. Many studies indicate the need for diverse language services within the healthcare system. However, these studies are limited to a handful of non-English languages. The objective of this project is to identify language prevalence in California’s healthcare environment and to determine whether languages vary in different treatment settings as well as by county.

Methods Used: 2008 reports from hospital inpatient departments and 2009 first quarter reports from emergency and ambulatory surgery departments (EDs and ASCs) were examined for all patients discharged in California to determine principal language spoken. Languages reported as invalid, blank, unknown and other were then excluded.

Summary of Results: Cohorts of 560,946, 2,229,875, and 527,855 discharges were obtained from inpatient, ED, and ASC settings. Spanish and Chinese were identified as the top two non-English principal languages spoken across all three treatment settings statewide. Language prevalence then varied across the treatment settings and by county. For example, Armenian was identified as the 4th (1,875 discharges), 6th (2,416), and 7th (1,220) non-English language spoken statewide in the inpatient, ED, and ASC treatment settings respectively, but is the 2nd inpatient (1,761) and ED (2,552) principal language spoken in Los Angeles county.

Conclusions: This first-ever analysis of principal language spoken in California discharge data showed that different treatment settings and counties should emphasize different language services such as interpreter availability and multi-lingual reading materials. Additional data analysis should be performed to determine if there is any association between language prevalence and socioeconomic factors such as health insurance coverage in each of the treatment settings. Also, further analysis of languages reported as “other” is needed to determine if the language prevalence in California changes.

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THE PREVALENCE AND ASSOCIATION BETWEEN THE TYPE OF ALCOHOL DRINK CONSUMED AND EXPOSURE TO VIOLENCE: AN EMERGENCY DEPARTMENT STUDY
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Purpose of Study: There is a clear association between alcohol and violence and this association is even more pronounced among emergency department patients. Fewer studies have examined whether the type of alcohol consumed, irrespective of the number of drinks is associated with a higher exposure to violence.

Methods Used: (1) we compared the prevalence of exposure to violence across different types of alcohol used and (2) the association between the type of alcohol used and exposure to violence among a sample of 295 patients identified as having an alcohol problem (CAGE \geq 1). Outcome measures included the number of exposures to violence, assessed using the conflict tactics scale asking patients if in the last 12 months they had been: threatened or afraid for their safety; hit or slapped; kicked; pushed or shoved; stabbed; shot; sexually violated; physically threatened or none of the above. The main study predictor “type of alcohol drink” was measured by the type of drink usually consumed including: malt liquor beer, regular beer, wine cooler, wine, hard liquor, etc.

Summary of Results: Of the sample 64% were African American, 80% were male. Regular beer (55%), malt liquor beer (37%), and hard liquor (31%) were the most prevalent reported drinks regularly consumed. Exposure to violence was reported as 23.5% and 69.5% reported using at least one type of illicit drug. Using multiple linear regression analysis, malt liquor beer (p < .04), number of drinks in a one week period (p = .03) and the number of drugs used (p < .001) were independently associated with exposure to violence and together explained over 20% of the variations in exposure to violence in this sample.

Conclusions: Regular beer was the most prevalent alcohol used in this sample, however, malt liquor beer was identified as the independent predictor of exposure to violence. Further studies are needed to evaluate any discrepancy between the actual type of alcohol drink consumed by ED patients and what is reported.

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EFFECTIVENESS OF A 24/7 NURSE ADVICE LINE IN REDUCING NON-EMERGENCY VISITS TO THE EMERGENCY ROOM IN RURAL NEW MEXICO
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Purpose of Study: New Mexico is a poor and medically underserved state, with 30 of its 33 counties designated as Health Professional Shortage Areas. Individuals residing outside of the major urban centers (Albuquerque, Santa Fe, and Las Cruces) make greater use of the emergency room and urgent care centers and those needing specialty services must travel considerable distances to urban centers. One consequence is overuse of emergency departments by uninsured and non-urgent patients: resulting in fragmented healthcare and a great financial burden for patients and hospitals. The University of New Mexico Department of Family and Community Medicine worked with a consortium of safety net provider organizations to develop a statewide, 24-hour triage call center (NurseAdvice New Mexico) to offer every New Mexican an opportunity to access healthcare advice regardless of insurance status or geographic location. A study of the Line’s impact in Albuquerque demonstrated that the Advice Line diverted medically unnecessary emergency department visits to primary care providers. However, the impact of the Line in rural New Mexico has not been studied. The purpose of the study was to measure the NurseAdvice Line’s impact in reducing non-urgent visits to EDs in four rural NM counties.

Methods Used: Researchers were provided monthly lists of callers from the four counties between September, 2008, and December, 2008. The lists included the caller’s intent for seeking care upon calling NurseAdvice Line, the result of the triage conversation and the advice the caller received. The researchers telephoned callers whose initial intent was to go to the ED but were advised to seek primary care or administer self-care. These callers were asked the result of the encounter: whether they went to the ED or followed the advice given.

Summary of Results: Seventy-seven people were surveyed. Seventy percent (95% CI, 59–90%) followed the advice and did not go to the emergency department and 30% went to the emergency department despite the advice.

Conclusions: This study showed that NurseAdvice line was effective in diverting non-urgent patients to primary care or self-care in four rural counties of Southwest NM. This diversion rate could result in substantial financial savings for patients and hospitals.

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87
TREADMILL HEAT-STRESS TESTING IN A PRIMARY CARE SETTING CAN INCREASE PHYSIOLOGICAL STRAIN INDEX TO LEVELS ABOVE THOSE CREATED IN CLIMATIC CHAMBERS
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Purpose of Study: We aimed to evaluate ways to create heat stress in primary care settings, where candidates for work involving such stress might be evaluated without recourse to climatic chambers or field exercises.

Methods Used: We recruited 33 healthy volunteers for a 45-minute treadmill walk at 6 km/hr (5–10% grade) while wearing thermally restrictive apparel in a thermoneutral treadmill room (70F). Wrist and ankle weights simulated equipment carried during actual Hazmat responses. From changes in heart rate and body temperature (ingested thermistor, tympanic bolometer), we calculated the Physiological Strain Index (PSI) which Moran has validated in subjects wearing military protective clothing (PSI values of 5–6 reflect moderate strain, 7–8 and higher indicate severe and very severe strain, respectively.) We compared our PSI values with published results of other treadmill heat stress protocols performed in more specialized settings.

Summary of Results: PSI averaged 8.6 +/- 1.8SD in the 27 subjects who completed the 45-minute treadmill walk. The other 6 subjects who completed only 27 +/- 11 minutes (p < 0.01), limited by thermal discomfort or musculoskeletal pain, had PSI values of 5.6 +/- 0.7 (p = 0.01). PSI values derived from reports of treadmill walking in sauna or climatic chambers were
6.9 ± 1.1 in persons wearing impermeable ensembles like those used in Hazmat responses (4 reports, 28 subjects) and 7.4 ± 1.6 in those wearing firefighter turnout gear (4 reports, 48 subjects).

**Conclusions:** Treadmill walking for 45 minutes in our subjects yielded PSI values greater than those reported for firefighter turnout gear or Hazmat ensembles, which studies involved shorter treadmill times (33 and 43 minutes, respectively). The methods and apparel we used induced severe physiological strain, but only moderate strain in those who failed to complete the target of 45 minutes of treadmill walking. Implications of these findings obtained in a primary care setting, vis-a-vis actual performance during Hazmat responses or firefighting, remain to be determined.

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### Session: Health Care Research I
#### 88
**BRIEF EMERGENCY DEPARTMENT INTERVENTION ABOUT PERPETRATION OF INTIMATE PARTNER VIOLENCE: VICTIMS IMPROVED KNOWLEDGE ATTITUDES AND PRACTICE MORE THAN NON-VICTIMS**

**Purpose of Study:** To compare 2 brief randomized computer-based interventions about perpetration of IPV.

**Methods Used:** Prospective cross-sectional study of patients during randomized 4-hour shifts in an urban hospital-based, level 1 trauma center ED. A touch-screen computer program was developed in visual basic 2005 studio. A series of questions to evaluate IPV knowledge, attitude and practices (KAP) was given before and after the brief intervention. Subjects were randomized to one of two intervention groups. Both groups were shown a set of lecture slides addressing IPV prevention followed by either 1) A control group with nothing further (CONTROL) or 2) a 5-minute simulation video depicting IPV perpetration (SIM). Main outcome was net improvement in KAP scores with perpetrators and victims assessed separately. For demographics and prevalence, descriptive statistics and percentages were used. Wilcoxon Signed Ranks test was used for pre-post test paired data. Assuming a CONTROL group net improvement 10%, the study was powered at 80% with 100 subjects to find an absolute difference of 15% net improvement between groups.

**Summary of Results:** 239 patients completed the study, 118 in the CONTROL group, 121 in SIM. 115 (48%) were male and 124 (51%) female. Overall improvement in responses to KAP questions with correct answers to all questions in 46% before vs. 59% after computer intervention (Diff 13% 95% CI 4-22). Net improvement in KAP score in the CONTROL group was 8% and in the SIM group 22% (Diff = 15%, 95% CI = 6.24). Based on the PERP scale, 40 subjects (17%, 95% CI = 12,21) were perpetrators and 200 were non-perpetrators. Net improvement in KAP questions was 25% for perpetrators and 14% for non-perpetrators (diff 11% 95% CI = 3%,20%). Based on the OVAT scale, 52 subjects (22%, 95% CI = 17,27) were victims and 188 were non-victims. Net improvement in KAP questions was 37% for Victims vs 10% for non-victims (diff 27%; 95% CI 13, 41).

**Conclusions:** A brief IPV intervention in the ED resulted in a greater percent of victims’ showing improvement in KAP on IPV perpetration than non-victims. The brief IPV intervention did not result in improved perpetrator’s KAP on IPV perpetration when compared to non-perpetrators.

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### Session: Health Care Research I
#### 89
**COMPARING OUTCOMES OF PALLIATIVE CARE CONULTATIONS BY RACE AT SEATTLE ACADEMIC MEDICAL CENTERS**

**Purpose of Study:** Racial differences in end-of-life (EOL) decision-making and use of palliative services are well documented within the US health care system. Minorities tend to use these services less as compared to whites. This study examined the EOL care choices of patients who received an inpatient palliative care service consultation at Harborview Medical Center (HMC) or University of Washington Medical Center (UWMC) in 2008, in order to determine whether the most prevalent racial groups in the Seattle area differed in their decisions.

**Methods Used:** We conducted chart reviews of the 622 patients who had a documented palliative care service (PCS) consultation in 2008: 437 White, 61 African-American, 81 Asian/Pacific Islander, 25 Hispanic and 18 Native/Alaskan American patients. Through chart review, we recorded the status of 5 outcomes for each patient and examined these outcomes using chi square tests to determine whether differential rates existed between the groups of patients by race. Multivariate logistic regression analysis was also used to account for the effects of sex, age, insurance status, hospital, and marital status.

**Summary of Results:** Across the racial groups, there were no statistically significant differences in EOL outcomes. Overall, 20% of patients chose to make no change to their medical care plan, 21% completed an advance directive, 39% changed their code status, 26% opted for hospice, and 34% transitioned to comfort care.

**Conclusions:** These results indicate that in 2008 the palliative care services at HMC and UWMC offered EOL care that was equitable between races. This finding could be due to the PCS focus on patient-centered care that tailors care to achieve the patient’s goals and wishes.

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### Session: Health Care Research I
#### 90
**TOTAL RADIATION EXPOSURE DURING ACUTE STONE EVENT IN INSURED AND UNINSURED PATIENTS**

**Purpose of Study:** Radiation exposure from computed tomography (CT) is significant and linked to 2% of cancer cases in the United States. In addition to CT scans, stone patients are also exposed to ionizing radiation from plain films and fluoroscopy. Often, physician knowledge of radiation risks is poor and may contribute to excess exposure. Lack of health insurance may result in delays in treatment and subsequent increased radiation exposure. The purpose of this study was to determine radiation exposures in insured and uninsured patients presenting with a single stone episode.

**Methods Used:** A retrospective review of 150 consecutive patients who were treated for a single stone episode was performed. Diagnostic imaging, stone characteristics and demographics were recorded. Total radiation exposure was compared by insurance status (private, public and uninsured) using a regression with p < 0.05 considered significant.

**Summary of Results:** Insured and uninsured groups had statistically similar age, gender, and stone burden. Privately insured patients received less radiation per stone episode than those not privately insured (31.2 vs. 45.8 mSv; p = 0.015). 7 of 75 patients with private insurance received more than 50 mSv, the yearly recommended dose limit for occupational exposure by the International Commission on Radiological Protection, compared to 27 of 75 without private insurance (9% vs. 36%, p < 0.001).

**Conclusions:** Patients without private insurance are at greater risk for higher radiation exposure when presenting with urinary calculi. Efforts to reduce radiation exposure in all patients are required.
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HEALTH LITERACY AND DISEASE UNDERSTANDING AMONG AGING WOMEN WITH PELVIC FLOOR DISORDERS
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Purpose of Study: Health literacy is defined as the ability “to obtain, process, and understand basic health information and services needed to make appropriate health decisions”. Studies have shown that inadequate health literacy is associated with poor health outcomes and disease understanding. However, there is little research on this topic among patients with pelvic floor disorders. We sought to correlate disease understanding with health literacy, age, and diagnosis type among aging women with pelvic floor disorders.
Methods Used: Study subjects were recruited from urology and urogynecology clinics based on chief complaint suggestive of urinary incontinence (UI) or pelvic prolapse (PP). Subjects completed questionnaires to assess symptom severity and health literacy was measured using the Test of Functional Health Literacy in Adults (TOFHLA). Patient-physician interactions were audiotaped during office visit. Immediately afterward, patients were asked to describe and record diagnoses and treatments discussed by the physician, with follow-up 2–3 days later.
Summary of Results: A total of 36 women with pelvic floor disorders, aged 40–94 (mean age 62), were enrolled. The women had high educational status (26/36 had above high school education) and high health literacy (29/36 had a TOFHLA score of <90%). Patients with PP only had the lowest percentage recall and disease understanding (70%). Patients with both PP and UI had intermediate percentage recall and disease understanding (82%). Patients with UI only had the highest percentage recall and disease understanding (94%).
Conclusions: High health literacy as assessed by the TOFHLA may not correlate with patients’ ability to comprehend complex conditions such as pelvic floor disorders. Despite high health literacy and high educational status, patients with pelvic organ prolapse had poor recall of their diagnoses and poor understanding of their disease and treatment plan. Lack of understanding may lead to unrealistic treatment expectations and disappointment; use of appropriate and clear written educational materials may help improve patients’ disease understanding.

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EVALUATION OF DIETARY INTAKE AMONGST DISADVANTAGED AFRICAN YOUTH
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Purpose of Study: Brighter Smiles Africa, a global-health education partnership between our University and Makerere University includes the African Hearts Community (AfriHCO) in Kampala, Uganda. AfriHCO provides accommodation, food, schooling and a stable environment for 60 male street youth/AIDS orphans aged 6–19 yrs. Their director requested inclusion of dietary assessment and nutrition education in our 2009 program. This project evaluated current food intake.
Methods Used: A 24 hour validated dietary recall instrument was used. 1. The questionnaire allows investigation of dietary diversity as a proxy measure of nutritional adequacy. The tool was modified to incorporate local Ugandan foods. Boys interested in participation were interviewed individually after providing informed consent.
Summary of Results: 41 boys were involved (11 residents of AfriHCO’s Kampala House (KH) and 30 living in local homes). The reported intake reflected a usual day in terms of the type and quantity of food consumed by 78.0% of participants. Each individual’s dietary diversity score was calculated based on suggested food groupings1, with a maximum score of 14. The average dietary diversity score was 5.6, with KH residents having a slightly higher score than non-residents (6.2 vs. 5.4). Common foods consumed included rice, bread, matooke (green plantain), beans, added oils, fats and sweets. Food group analysis showed that 65.9% of the boys consumed either plant or animal-based food groups high in vitamin A. Only 48.8% of boys reported consumption of iron-rich food groups. Education on how to improve nutrition was provided while in Uganda and a summary document for the Director was prepared on return to Canada.
Conclusions: While energy intake amongst these boys may be adequate, a lack of dietary diversity could place them at risk of nutrient deficiencies. The use of a dietary diversity questionnaire provides a quick, easy and objective way of identifying potential nutritional concerns. Results can guide nutrition education and evaluate changes over time.

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QUALITY OF END-OF-LIFE CARE IN LOW-INCOME, UNINSURED MEN DYING OF PROSTATE CANCER
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Purpose of Study: We hypothesized that the quality of end-of-life care in disadvantaged men prospectively enrolled in a public assistance program. We evaluated end-of-life care in disadvantaged men dying of prostate cancer, who enroll in a comprehensive statewide assistance program, is high-quality.
Methods Used: We included all 60 low-income, uninsured men in a state-funded public assistance program who had died since its inception in 2001. To measure quality of end-of-life care, we collected information about timing of the institution of new chemotherapeutic regimens; time from administration of last chemotherapy dose to death; the number of inpatient admissions and intensive care unit stays made in the 3 months preceding death, and the number of emergency room visits made in the 12 months before dying. We also noted hospice use and the timing of hospice referrals.
Summary of Results: Eighteen men (30%) enrolled in hospice prior to death and the average hospice stay lasted 45 days (SD 32 range 2–143, median 41 days). Two patients (11%) were enrolled for fewer than 7 days and none were enrolled for more than 180 days. The average time from administration of the last dose of chemotherapy to death was 104 days. Chemotherapy was never initiated within 3 months of death, and in only 2 instances (6%) was the final chemotherapeutic regimen administered within 2 weeks of dying. Use of hospital resources (emergency room visits, inpatient admissions, and intensive care unit stays) was uniformly low (mean 1.0 ± 1.0, 0.65 ± 0.82, 0.03±0.18, respectively).
Conclusions: End-of-life care in disadvantaged men dying of prostate cancer, who enroll in a comprehensive statewide assistance program, is high-quality.

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USE OF THE ALCOHOL ABSTINENCE SELF EFFICACY SCALE IN WHITES VS. NON-WHITES
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Purpose of Study: To determine if there are existing cultural biases in the Alcohol Abstinence Self Efficacy (AASE) scale, when being applied to Whites vs. Non-Whites (as defined by Merriam-Webster, Concerning specifically Native Americans and Hispanics)
Methods Used: Participants had taken part in a study to determine the effects of Motivational Interviewing (M.I.) in person, by telephone, and tele-video conferencing. In this study there was no significant difference found between the groups. As part of the study the individuals underwent testing both before and after treatment with M.I., part of which was the AASE scale. The results from the White and Non-White groups were averaged per question and the before and after scores were compared using a standard t-test.
Summary of Results: There was no statistical difference found between the Whites and Non-whites when comparing the before and after M.I. AASE scores for any of the questions. P values ranged from 0.23–0.06 across all parts of the AASE.
Conclusions: According to this study there does not appear to be any evidence of cultural bias within the AASE scale that was detectable by our methods.
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95 PROPOSED DIABETES SCREENING IN ADULTS WITH DEVELOPMENTAL DISABILITIES
M. Hess
Purpose of Study: Adults with intellectual/developmental disabilities (I/DD) face the same major health problems as the general population in addition to health problems related to their disability and its treatment. Complex medical issues in combination with communication challenges, inadequate medical history and poor reimbursement for health care visits make this population challenging. As a result, patients with I/DD are less likely to receive screenings, preventative care or diagnosis and treatment of their acute or chronic health problems. Diabetes is a well characterized disease in the general population and a growing health concern for Americans, but is not well studied in adults with I/DD.

Methods Used: A literature review was conducted using MEDLINE/PubMed investigating four diabetes risk factors in adults with I/DD: diet, physical activity, obesity and use of atypical antipsychotics. Included articles were published between 1999 and 2009 and investigated adults 18 years of age and older.

Summary of Results: Twenty-nine studies reported on at least one of the four risk factors. Eleven studies had less than 100 participants and 9 studies used surveys completed by care staff, a method not yet validated. Collectively, studies showed risk factor levels comparable to or worse than the general population.

Conclusion: The prevalence of diabetes risk factors in combination with health disparities and low rates of preventative medicine suggest rates of undisagnosed diabetes in this population may be high. A diabetes screening study is proposed to investigate the levels of undisagnosed diabetes among adults with I/DD living in community residential settings in the State of Washington using fasting glucose and hemoglobin A1C. The proposal focuses on adults living in the community because they have more choice in how they spend their time and appear to have higher rates of obesity and sedentary lifestyle than those living in highly controlled environments or institutions. In addition, they may have less complete health records than those still living with their families.

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96 PREVALENCE OF DIABETES MELLITUS IN ADULTS WITH DEVELOPMENTAL DISABILITIES
M. Hess University of Washington School of Medicine, Seattle, WA.
Purpose of Study: Adults with intellectual/developmental disabilities (I/DD) face the same major health problems as the general population in addition to health problems related to their disability and its treatment. Complex medical issues in combination with communication challenges, inadequate medical history and poor reimbursement for health care visits make this population challenging. As a result, patients with I/DD are less likely to receive screenings, preventative care or diagnosis and treatment of their acute or chronic health problems. Diabetes is a well characterized disease in the general population and a growing health concern for Americans, but is not well studied in adults with I/DD.

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Summary of Results: Twenty-nine studies reported on at least one of the four risk factors. Eleven studies had less than 100 participants and 9 studies used surveys completed by care staff, a method not yet validated. Collectively, studies showed risk factor levels comparable to or worse than the general population.

Conclusion: The prevalence of diabetes risk factors in combination with health disparities and low rates of preventative medicine suggest rates of undisagnosed diabetes in this population may be high. A diabetes screening study is proposed to investigate the levels of undisagnosed diabetes among adults with I/DD living in community residential settings in the State of Washington using fasting glucose and hemoglobin A1C. The proposal focuses on adults living in the community because they have more choice in how they spend their time and appear to have higher rates of obesity and sedentary lifestyle than those living in highly controlled environments or institutions. In addition, they may have less complete health records than those still living with their families.

Session: Hematology and Oncology I

97 PHARMACOLOGICAL ANALYSIS OF CLOFARABINE IN COMBINATION WITH DECITABINE AND HDACi IN THE GFP-EXPRESSING ADENOCARCINOMA COLON CANCER YB5 CELL LINE
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Purpose of Study: It has recently been suggested that the ribonucleotide reductase inhibitor and highly toxic antineoplastic agent, clofarabine, may induce hypomethylating effects when used as a solo agent at low dose treatment. This study aims to evaluate the potential hypomethylating effects of low dose clofarabine on GFP-expressing colon cancer sw48 cell line [or YB5]; as well as to explore its synergistic effects with a known demethylating agent, decitabine, and three known HDACi (TSA, Apicidin and Depsipeptide).

Methods Used: YB5 cells were treated for 96 hours and utilized for FACS, real-time PCR and pyrosequencing analysis.

Summary of Results: Preliminary FACS indicated that clofarabine treated cells displayed a lack of GFP expression of a known epigenetically regulated gene when used a solo agent or in combination of decitabine or HDACi; although simultaneous combination with decitabine revealed a synergistic effect. Real-time PCR data indicated a lack of increased P16 or MLH1 expression in both solo clofarabine treated cells as well as in combination with other agents. However, re-expression of MLH1 was noted in simultaneous treatment of clofarabine with decitabine as well. Finally, pyrosequencing analysis revealed that clofarabine does not display a hypomethylating effect in this cell line when used as a solo agent or in combination.

Conclusion: These results seem to indicate that clofarabine is not a hypomethylating agent but its use in combination with decitabine, a well known hypomethylating agent, induces synergistic effect. Real-time PCR data indicated a lack of increased P16 or MLH1 expression in both solo clofarabine treated cells as well as in combination with other agents. However, re-expression of MLH1 was noted in simultaneous treatment of clofarabine with decitabine as well. Finally, pyrosequencing analysis revealed that clofarabine does not display a hypomethylating effect in this cell line when used as a solo agent or in combination.

Session: Hematology and Oncology I

98 THE IMPACT OF CLINICAL PARAMETERS ON THE FEASIBILITY OF ADOPTIVE T-CELL THERAPY IN CANCER PATIENTS
Purpose of Study: Adoptive T-cell therapy has shown promise in treating patients with advanced stage melanoma. Two potential hurdles exist, however, in applying T-cell therapy to patients with other tumor types: (1) such patients lack accessible tumor infiltrating lymphocytes (TIL) requiring the use of PBMC as a source of T cells and, (2) they have many treatment options available and often receive years of chemotherapy with diminished...
CRITICAL ROLE OF ARGINASE PATHWAY IN BREAST CANCER

R. Singh1,3, M. Braga1, JJ. Li2, SA. Li2, S. Pervin1,3

Purpose of Study: Breast tumor tissues are reported to have high polyamine levels, which are synthesized via arginase pathway. The precise mechanism by which the increase in polyamines occurs in breast tumor tissue is not known, although it suggested that estrogens modulate the growth of certain breast cancer cell lines by increasing the expression of ornithine decarboxylase (ODC), a critical component in the arginase metabolic pathway. The purpose of this study is to investigate the role of arginase pathway in estrogen-induced tumor from ACI rats, an experimental model that mimics the initial stages of human breast tumor development.

Methods Used: Mammary tumor was induced in ACI rats by subcutaneously implanting estrogen (2-3 mg) for 2-6 months. Control mammary gland and tumor tissues were analyzed by western blot, immunocytochemistry as well as for single and double immunofluorescence analysis. Primary cultures were established from tumor and control tissues using single cell suspension method. Breast cancer stem-like cells (BCSCs) were cultured in ultra-low attachment plates under mammosphere culture conditions and characterized by immunofluorescence, and quantitative real-time PCR (qPCR) analysis of various stem-cell surface markers including Sox2, Oct-4, Klf4, C-Myc, and nanog. Expression of various genes involved in arginase metabolic pathway was analyzed by western blot and qPCR.

Summary of Results: Arginase II was undetectable in normal mammary gland; whereas in breast tumor tissues treated with E2 (2-6 months) it was highly up regulated. On the other hand, the level of arginase I was undetectable in both control and E2-treated tumors. The expression of Arginase II and key metabolic enzymes were found to be highly up regulated in stem like cells from MCF-7 and Ras overexpressing human mammary epithelial cells. These preliminary data may suggest that arginine metabolic pathway could play an important role in breast tumor initiation via up regulation of arginase II.

Conclusions: These preliminary data suggest that clinical parameters associated with standard treatments may impact the ability to expand tumor specific T cells ex vivo and/or modulate T-cell expansion and persistence in vivo.

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100 GLOBLASTOMA PATIENT OUTCOMES AS A FUNCTION OF RADIATION DOSE TO NEURAL STEM CELL NICHES IN THE ADULT BRAIN

P. Evers, P. Lee, J. DeMarco, N. Agazaryan, J. Sayre, M. Selch, F. Pajonk

Purpose of Study: Glioblastoma is the most common and most malignant brain tumor in adults. The mechanisms leading to glioblastoma are not well understood but animal studies support the hypothesis that the inactivation of tumor suppressor genes in neural stem cells (NCS) is required and alone sufficient to induce the formation of malignant glial cancers. This suggest that the NCS niches in the brain may harbor cancer stem cells and in so doing, provide novel therapy targets. This is a retrospective study analyzing if the magnitude of radiation therapy to the anatomical niches of NCSs in the human brain - the subventricular zone (SVZ) and the subgranular layer (SGL) - plays any role in the progression-free survival (PFS) of patients suffering from a glioblastoma. We hypothesize that higher radiation doses to these NCS niches may improve patient survival by eradicating cancer stem cells and thereby impairing the capacity for malignant spread.

Methods Used: 55 adult patients with histopathologically diagnosed Grade 3 or Grade 4 glial cancer who were treated using conformal radiotherapy at UCLA between February of 2003 and May of 2009 were included in this retrospective study. Using commercial radiation planning software and patient radiological records, the SVZ and SGL were reconstructed for each of these patients and dosimetry data for these structures was extracted.

Summary of Results: Using Kaplan-Meier analysis we show that patients whose bilateral SVZ received greater than the median SVZ dose (~ 43Gy) had a statistically significant improvement in their progression-free survival if compared to patients whose SVZ was dosed less than the median dose (15.0 vs 7.2 months PFS; P = 0.028 log-rank test). Furthermore, a mean dose in excess of 43Gy to the bilateral SVZ yielded statistical significance in a multivariate Cox regression analysis (P = 0.030, Cox partial likelihood ratio). Importantly, similarly analyzing total prescription dose failed to illustrate a statistically significant impact.

Conclusions: Our study suggests that targeted radiotherapy of the stem cell niches in the adult brain could yield significant benefits in patient clinical outcomes over radiotherapy of the primary tumor mass alone which is the current standard of care.

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101 CAPTURE OF CIRCULATING PROSTATE TUMOR CELLS USING THREE-DIMENSIONAL SILICON NANOWIRE SUBSTRATES

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Purpose of Study: Circulating tumor cells (CTCs) are an emerging “biomarker” for detecting early-stage cancer metastasis and monitoring disease progression. However, isolation of CTCs has been technically challenging due to extremely low abundance (one to hundreds per mL) of CTCs among a high number of hematologic cells (10^9 per mL) in blood. We have developed a unique 3D nanostructured substrate-based CTC capture technology, in which high CTC capture efficiency is achieved by high cell affinity for nanoscale features on the substrates. In this study, we aimed to validate our CTC capture method clinically by using blood samples collected from prostate cancer patients and examining our results side-by-side with the leading CTC isolation technology, CellSearch.

Methods Used: Functionalized silicon nanowire (SiNW) substrates were fabricated using a wet chemical etching process, followed by treatment with anti-EpCAM. Blood samples were drawn from patients with advanced solid-stage prostate tumors (UCLA IRB #09-03-038-01). For each patient, samples were processed using both the SiNW platform and the CellSearch system. To capture CTCs using SiNWs, 1 mL of blood was directly loaded onto each SiNW cell capture surface and was incubated for 45 min (37°C, 5% CO2) to allow for CTC attachment. Next, immunocytochemistry was performed using DAPI, anti-CD45, and anti-cytokeratin for identification of nucleated cells, lymphocytes, and CTCs, respectively. Cells with dual staining for anti-cytokeratin and DAPI and standard size, shape, and nuclear size characteristics were scored as CTCs.
**Summary of Results:** For a relatively small patient cohort (n = 8), our SiNW CTC technology was faster (2hr vs. 4hr for CellSearch), cheaper ($20 compared to $2,800 for CellSearch), and more sensitive (we successfully captured CTCs from the blood samples that the CellSearch technology failed to get any CTC counts).

**Conclusions:** We have demonstrated the ability of novel SiNW substrates to capture CTCs in whole blood samples collected from prostate cancer patients. We anticipate further clinical validation by recruiting a larger and more diverse (e.g. stages, treatment status) patient cohort.

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**Session: Hematology and Oncology I**

**102 COMBINATION STRATEGIES USING KINASE INHIBITORS IN COLORECTAL CANCER IN VITRO**

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**Purpose of Study:** The RAS and PI3 kinase pathways play a critical role in cancer cell survival, motility, and angiogenesis. It has been recently shown in vitro and in vivo breast cancer cell lines that the growth inhibition caused by MEK (part of the RAS pathway) inhibitors is limited due to upregulation of the PI3k pathway. The aim of this research is to identify subsets of colorectal cell lines sensitive to a PI3k inhibitor alone and in combination with a MEK inhibitor. It is hypothesized that the combination of the inhibitors would provide synergistic inhibition.

**Methods Used:** We exposed colorectal cancer cell lines to 12 different concentrations of MEK inhibitors, PI3k inhibitors, and a combination of the two inhibitors. The ability of inhibitors to inhibit proliferation and induce cell death was measured and IC50 values were calculated.

**Summary of Results:** Sensitivities of the 27 cell lines exposed to the PI3k inhibitor varied from IC50 of .010 to .669 μM. Additionally, there was no clustering of sensitivities based on mutational statuses of the PI3k or KRAS genes. When applied in combination, PI3k and MEK inhibitors caused a synergistic growth inhibition effect in all cell lines exposed to the combination treatment.

**Conclusions:** These findings confirm the hypothesis of interaction between the PI3k and MEK pathways. Furthermore, it suggests study of additional colorectal cancer cell lines using combination treatment and exploring the mechanism of such synergy.

When applied in combination, PI3k and MEK inhibitors increased growth inhibition across all concentrations in the cell lines tested, including SW837 shown above. The growth inhibition observed in the combination treatment was a result of drug synergy as opposed to additivity in all cell lines exposed to the combination treatment (Combination Index >1).

**Purpose of Study:** Cytomegalovirus (CMV) disease of the central nervous system (CNS) occurs most commonly in patients with advanced AIDS but is rarely reported in stem cell transplant patients. We recently treated two patients without active graft-versus-host disease and on relatively low doses of immunosuppressive drugs who unexpectedly developed late onset fatal CMV encephalitis after umbilical cord blood transplantation. This prompted further investigation into the pathogenesis of the disease.

**Methods Used:** We performed a PubMed search of all reported cases of CMV encephalitis or meningitis after stem cell transplantation to date. Of these, only 10 cases in addition to the 2 we are reporting had confirmed diagnoses and are included in our analysis.

**Summary of Results:** We found that the patients in our analysis had multiple risk factors that predisposed them to an increased or prolonged state of immunodeficiency. These included receiving treatment for graft-versus-host disease at the time of presentation of CMV CNS disease (7 patients), use of a T-cell depleted graft and/or antithymocyte globulin (9 patients), low CD4 count at presentation of CNS disease (8 patients), and use of umbilical cord blood as source of hematopoietic stem cells (2 patients). We also found that in 11 of our 12 patients, the CMV central nervous system disease was preceded by recurrent CMV viremia treated with multiple courses of preemptive therapy using ganciclovir (11 patients), foscarnet (11 patients), or cidofovir (1 patient). A ganciclovir-resistant mutant strain of CMV was found in 8 patients, while three other patients had increasing levels of CMV viremia on ganciclovir, consistent with ganciclovir-resistance. Of the 12 patients we reviewed, 10 expired and 2 survived.

**Conclusions:** Review of our 2 patients plus previously reported cases of CMV central nervous system disease after stem cell transplantation suggests that this complication of CMV infection may be increasing as a consequence of antiviral resistance in a more susceptible patient population with protracted immunodeficiency. Given the high mortality of this disease, long-term antiviral prophylaxis may be indicated in high risk patients.

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**Session: Hematology and Oncology I**

**104 ANALYSIS OF TREATMENT MODALITIES FOR GASTRIC ADENOCARCINOMA**

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**Purpose of Study:** To conduct a retrospective study of patients diagnosed with gastric adenocarcinoma and compare mean and median survival rates and relative risks for death for patients undergoing one of 3 treatments: surgery only (SO) vs. surgery plus pre/post-operative chemotherapy (S+CH) vs. surgery plus chemoradiotherapy (S+CHR).

**Methods Used:** We accessed medical records from the University of Washington Medical System for patients receiving either SO, S+CH, or S+CHR, created Kaplan-Meier Survival Curves to estimate mean and median survival times for each treatment, and conducted Cox Regression Analyses (controlling for age at diagnosis and stage of disease) in order to determine any statistically significant differences between treatments.

**Summary of Results:** We accessed over 1,900 medical records and included 86 patients diagnosed with gastric adenocarcinoma and compared mean and median survival times for each treatment group. The Kaplan-Meier survival curves estimated did not indicate statistically significant differences between S+CH and S+CHR patients, but were significant for both S+CH (mean = 4.3 years; median = 5.4 years, p = 0.014) and S+CHR (6.7 years; 2.6 years, p = 0.004) patients when compared to SO patients (2.0 years; 1.3 years). Cox Regression analyses also did not indicate statistically significant differences between S+CH and S+CHR patients, but did indicate that SO patients were 3.203 times more likely to die than S+CHR patients (95% confidence interval: 1.130–9.076, p = 0.028) and 3.223 times more likely to die than S+CH patients (1.471–7.063, p = 0.003).

**Conclusions:** This preliminary analysis of gastric adenocarcinoma treatment modalities provides additional evidence for the use of either S+CH or S+CHR instead of SO. Further chart reviews with larger numbers of patients in each treatment group should be conducted in order to both validate these results and determine if significant mortality differences exist between S+CH patients and S+CHR patients. Furthermore, these studies should include analyzing toxicities experienced by patients in each of the treatment groups in order to determine if significant morbidity differences exist between the SO, S+CH, and S+CHR treatments.
**Session: Hematology and Oncology I**

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**IDENTIFICATION OF NOVEL RASSF1C INTERACTING PROTEINS**

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**Purpose of Study:** Recent research has identified the Ras association domain family 1 (RASSF1) as Ras effectors, and suggests that they play an important role in carcinogenesis. RASSF1 encodes two mRNA isoforms, RASSF1A and RASSF1C. These isoforms differ from each other in at least two important ways. The first is structural; RASSF1A lacks the amino-terminal diacylglycerol binding domain. The second is functional; RASSF1A is not expressed in the majority of human solid tumors, while RASSF1C is expressed. Due to the functional difference, RASSF1A has been studied extensively and is established as a tumor suppressor. In contrast, RASSF1C has been studied less extensively and its function remains to be elucidated. Previous work done in our laboratory on lung cancer cells suggests that RASSF1C is not a tumor suppressor gene, and may in fact be a tumor promoter gene. To further our understanding of the role of RASSF1C in tumor growth and progression, we carried out a yeast Two-Hybrid Screen to identify RASSF1C interacting genes.

**Methods Used:** RASSF1C was used as a bait to screen a human osteosarcoma cDNA library using high stringency conditions. The RASSF1C cDNA was fused to GAL4 DNA binding domain plasmid with tryptophan as a selection marker. The library was fused to GAL4 activation domain plasmid with leucine as a selection marker. The yeast reporter strain AH109 with three reporter genes - ADE2, HIS3, and lacZ - was utilized to carry out the cDNA library screen. Yeast colonies appearing on selection plates (-TRP, -LEU, -ADE2, and -HIS) were picked and transferred to plates (-LEU) to select for the interacting cDNA clones.

**Summary of Results:** Thirty cDNA clones exhibiting robust growth on selection media were chosen for further analysis. We have isolated the cDNA fragments from several clones and have submitted them for DNA sequencing analysis. The isolated clones are also being used to confirm their interactions with RASSF1C using the yeast reporter strain AH109.

**Conclusions:** We have identified several potential RASSF1C target genes. We anticipate that these newly identified RASSF1C interacting genes will help to elucidate the function of RASSF1C and the pathways involved.

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**PROTEASE-ACTIVATED RECEPTOR 1 IS UPREGULATED AND PROMOTES INVASION IN A MURINE MODEL OF METASTATIC OSTEOSARCOMA**

J.P. Sand1, K. Janeway2, J. Perry2, S. Orkin2 1University of Washington School of Medicine, Seattle, WA and 2Dana-Farber Cancer Institute, Boston, MA.

**Purpose of Study:** Survival rates for patients with metastatic osteosarcoma (OS) remain poor. The identification of pathways involved in OS metastasis has been limited by lack of tumor samples and disease models. Using a recently developed murine model of metastatic OS, which closely recapitulates the human disease, we found that protease-activated receptor 1 (PAR1) was differentially expressed in primary and metastatic tumors.

**Methods Used:** mRNA expression profiling of matched primary and metastatic tumor pairs was performed and individual results were validated with qRT-PCR. PAR1 was selected for further study. PAR1 expressing cell lines derived from matched primary and metastatic tumors was evaluated with qRT-PCR and western blotting. Changes in signaling and gene expression following PAR1 activation by thrombin and thrombin receptor activating peptide were evaluated. Functional consequences of PAR1 knockdown (KD) were assessed in cell lines expressing a tetracycline-inducible shRNA/Amir against PAR1. Allografts of cell lines engineered to co-express luciferase and PAR1 were evaluated. Functional consequences of PAR1 knockdown by transduction of lentivirus expressing PAR1 shRNA were utilized to assess the impact of PAR1 KD on metastasis formation in vivo.

**Summary of Results:** PAR1 mRNA was found to be significantly upregulated in metastatic versus matched primary tumors by gene expression analysis. PAR1 mRNA and protein levels were increased in 4 cell lines derived from metastatic tumors when compared to cell lines derived from matched primary tumors. Following PAR1 activation, OS cell lines expressing higher levels of PAR1 had a greater degree of Erk and Akt activation and a greater degree of upregulation of PAR1-responsive genes. PAR1 KD attenuated matrigel invasion by 70% but did not impact proliferation.

**Conclusions:** In this murine model of osteosarcoma, PAR1 is upregulated in metastatic OS and promotes invasion. Further study of the impact of PAR1 KD on metastasis formation in vivo and of PAR1 expression in human primary and metastatic OS is underway.

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**THE INFLUENCE OF MATRIX AVERAGING ON THE ACCURACY OF STEREOTACTIC COORDINATE TRANSFORMATIONS**

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**Purpose of Study:** We are developing a system for focal irradiation of the rat brain with protons, which is based on a commercially available clinical system. The purpose of this study was to evaluate the accuracy achievable with CT-based stereotactic localization and to study the effect of different matrix averaging methods on stereotactic localization accuracy.

**Methods Used:** A commercially available stereotactic QA phantom (Standard Imaging) was mounted to a Leksell halo equipped with a CT indicator box (Electra). The phantom was scanned on a LightSpeed VCT 64-slice GE Scanner with 27 cm field of view, matrix size 512 x 512, pixel size 0.625 mm, and slice thickness 0.625 mm. The phantom contains 20 distinct radiopaque markers with stereotactic coordinates known by dimensional inspection (Dim. Metrol. Lab., Inc., Riverside, CA) with an accuracy and precision of about +/- 0.1 mm. We used the CT-based localization procedure of Weaver et al. (Int J Radiat Oncol Biol Phys 18, 1990) which involves the calculation of two rotational matrices that can be multiplied into a single matrix. Every CT image in the study can be used to calculate these matrices but the statistical transformation error increases with increasing distance of the image from the target. For a composite transformation, one needs to average these individual matrices with a weighted averaging method. Two matrix averaging methods were employed: 1. Simple arithmetic averaging of matrix elements, and 2. Riemannian matrix averaging described by Moakher (SIAM J Matrix Anal Appl 24, 2002), which maintains orthogonality. The mean error of localization of the 20 Lucy phantom markers was used to evaluate the accuracy of each method.

**Summary of Results:** The mean transformation error from 5 single transformations was 0.44 mm (range, 0.31 – 0.77 mm). The mean transformation error of the simple matrix average was 0.268 mm and that of the Riemannian matrix average was 0.266 mm.

**Conclusions:** The accuracy of frame-based stereotactic CT localization using a single CT image is better than 1 mm. Further gain of accuracy can be achieved by averaging transformation matrices from multiple CT slices, with no apparent difference between simple arithmetic averaging and mathematically more complex Riemannian averaging.

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**UNCERTAINTY OF PROSTATE POSITION IN A COHORT OF PATIENTS UNDERGOING PROTON THERAPY WITH ENDORECTAL BALLOON**

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**Purpose of Study:** To evaluate the uncertainty of the prostate position relative to the CT-planned position during hypofractionated proton therapy.

**Methods Used:** Twenty-five patients enrolled in a clinical proton therapy study had 3 or 4 gold markers implanted into the prostate one week prior to the radiation planning CT study. To minimize prostate motion, a water-filled endorectal balloon was placed into the rectum, and the patients were instructed to comfortably fill the bladder by controlling their water intake prior to CT and treatment. During the first five treatment days, a set of orthogonal posterior-anterior and lateral x-ray films was taken immediately before and after treatment. The 3-D location of the centroid of the seeds was...
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HUMAN TYPE 2 DIABETES IS ASSOCIATED WITH ISLET AMYLOID DEPOSITION, DECREASED β-CELL AREA, AND INCREASED β-CELL APOPTOSIS

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Purpose of Study: Islet amyloid deposition and β-cell loss are pathological hallmarks of the pancreatic islet in type 2 diabetes mellitus (T2DM). Studies in animal models of T2DM have shown that islet amyloid deposition is associated with reduced β-cell mass, increased β-cell apoptosis, and decreased β-cell replication. We have shown that islet amyloid deposition occurs in human T2DM and is associated with a reduction in β-cell area. As part of this ongoing study, we sought to determine whether a similar relationship between islet amyloid deposition and β-cell apoptosis and/or replication exists in human T2DM.

Methods Used: Human autopsy samples of pancreas from subjects with and without T2DM (n = 18 and 20, respectively) were studied. Age and body mass index did not differ, but as expected, random blood glucose was significantly higher in subjects with T2DM (148.0 ± 6.9 vs. 100.0 ± 2.1 mg/dl, p < 0.001; data are mean ± SEM). Amyloid and β-cell area were quantified using thioflavin S-staining and insulin-immunostaining respectively. Apoptotic β-cells were identified as the percentage of insulin-positive cells with TUNEL-positive nuclei, while replicating β-cells were similarly identified as insulin-positive cells having Ki-67-positive nuclei. Summary of Results: Islet amyloid deposition was significantly higher (12.6 ± 3.1 vs. 0.59 ± 0.32%, p < 0.001) and β-cell area significantly lower (36.0 ± 3.7 vs. 45.6 ± 2.1%, p = 0.05) in T2DM than control subjects. In T2DM subjects, the rate of β-cell apoptosis was 2.8-fold higher than in control subjects (2.31 ± 0.38 vs. 0.84 ± 0.28%, n = 14–16, p = 0.006). In contrast, the rate of β-cell replication did not differ between subjects with and without T2DM (0.16 ± 0.06 vs. 0.14 ± 0.05%, n = 15–17, p = 0.71). Among subjects with T2DM, there was a strong inverse correlation between β-cell area and amyloid deposition (r = 0.84, p < 0.001); however, no correlation was observed between the increased rate of β-cell apoptosis and either amyloid deposition or β-cell area (r = 0.06, p = 0.85) or β-cell area (r = 0.15, p = 0.62).

Conclusions: Human T2DM is associated with islet amyloid deposition, decreased β-cell area, and increased β-cell apoptosis. While islet amyloid is strongly associated with decreased β-cell area, neither islet amyloid deposition nor β-cell area is correlated with β-cell apoptosis.

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IN VIVO AND EX VIVO MODELS OF ENHANCED ADIPOCYTE DIFFERENTIATION IN INTRAUTERINE GROWTH RESTRICTED NEONATAL RATS

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Purpose of Study: Enhanced adipocyte differentiation contributes to adipocyte hyperplasia and altered lipid metabolism. Intrauterine growth restricted (IUGR) newborns, when nursed normally, exhibit catch-up growth and hypertrophic adipocytes before onset of adult hypertriglyceridemia and obesity. Stearoyl-CoA desaturase enzyme 1 (SCD1) converts the saturated fatty acid stearate to the monounsaturated oleate (18:0 to 18:1) and is upregulated in obesity. Furthermore, SCD1 expression is induced during adipocyte differentiation. The desaturation index (ratio of oleate/stearate, DI) represents a measure of SCD1 activity and expression in adipocyte differentiation. The objectives are: 1) To compare adipose tissue DI in 1 day vs 3 week old IUGR rats and Controls. 2) To compare DI in primary adipocyte cell cultures from IUGR rats and Controls before and after differentiation induction.

Methods Used: 1) Subcutaneous adipose tissue was collected from 1 day and 3 week old IUGR and Control males. 2) Primary preadipocyte cell cultures were established from 3 week old IUGR and Control males. 3) Preadipocyte cell cultures were established from 3 week old IUGR and Control males. Differentiation was induced with methylisobutyrate/dexamethasone/insulin in a subset of preadipocytes. Fatty acids were extracted from all samples, analyzed by GC/MS, and DI calculated.

Summary of Results: IUGR adipose tissue had a higher DI ratio than Controls at 1 day (5.5 ± 0.1 vs 4.9 ± 0.2, p < 0.05) and at 3 weeks (5.3 ± 0.1 vs 3.2 ± 0.1, p < 0.05). Furthermore, the DI ratio was increased in IUGR preadipocytes vs Controls (1.13 ± 0.4 vs 0.91 ± 0.02, p < 0.05) with a similar trend in differentiated cells (0.97 ± 0.03 vs 0.86 ± 0.06, p = 0.08). The DI ratio was relatively lower in cell cultures than in adipose tissue.

Conclusions: The higher DI in IUGR adipose tissue vs Controls suggests a programmed increase in SCD1 activity and differentiation prior to onset of obesity. Primary adipocyte cell cultures largely preserve the programmed phenotype of cells, although the DI after differentiation is lower than in adipose tissue, indicating a metabolic difference between differentiated adipocytes ex vivo versus adipocytes in vivo. Nonetheless, primary adipocyte cell cultures may be useful for testing small molecule SCD1 inhibitors.

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EPIGENETIC REGULATION OF HIGH GLUCOSE-INDUCED PROINFLAMMATORY CYTOKINE PRODUCTION IN MONOCYTES BY CURCUMIN

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Purpose of Study: Diabetes is a pro-inflammatory state. We have previously shown increased monocyte pro-inflammatory cytokines in patients with Type 1 and Type 2 diabetes. High glucose induces pro-inflammatory cytokines via epigenetic changes. Curcumin, a polyphenol responsible for the yellow color of the spice turmeric, is known to exert potent anti-inflammatory activity in vitro. Recent studies indicate that it may regulate chromatin remodeling by inhibiting histone acetylation. In this study, we aimed to test the effect of curcumin on histone acetylation and pro-inflammatory cytokine secretion under high-glucose conditions in human monocytes.

Methods Used: Human monocytes (THP-1) cells were cultured in presence of mannitol (osmolar control, mannitol) or normoglycemic (NG, 5.5 mmol/L glucose) or hyperglycemic (HG, 25 mmol/L glucose) conditions in absence or presence of curcumin (1.5–12.5µg) for 72 h. Cytokine level, nuclear factor B (NF-κB) transactivation, histone deacetylases (HDACs) activity, histone acetylations (HATs) activity were measured by western blots, ELISA, Immunofluorescence (IF) staining. HG significantly induced histone acetylation, NF-κB activity and pro-inflammatory cytokine (IL-6, TNF-α and MCP-1) release from THP-1 cells.
Summary of Results: High glucose activates HAT (p300) which in turn acetylates p65 and suppresses HDAC2 resulting in NF-kB activation and increased transcription of IL-6 and TNF-α in monocytes. Curcumin acts at different levels and induces epigenetic changes by increasing HDAC2, decreasing HAT (p300) activity, thereby resulting in decreased NF-kB activation and inflammatory cytokine release (IL-6, TNF) (p < 0.01).

Conclusions: These results indicate that curcumin decreases HG-induced cytokine production in monocytes via epigenetic changes involving NF-kB. In conclusion, curcumin supplementation by reducing vascular inflammation may prevent diabetic complications.

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MATERNAL SEPARATION IN THE NEONATAL PERIOD DECREASES ADIPOSE GR AND 11βHSD MRNA IN THE ADULT RAT
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Purpose of Study: Early post-natal nutrition effects the development of adult onset obesity and metabolic disease. Infants hospitalized in the NICU encounter maternal separation and formula feeding. We have formerly shown that maternal separation and post-natal nutritional content alters adipose tissue gene expression in the juvenile rat; specifically the glucocorticoid receptor (GR) and the steroid activating reductase 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). Steroid signaling is an important component of maternal separation and postnatal diet on adipose tissue gene expression is unknown. We hypothesize neonatal maternal separation will decrease 11βHSD1 and GR mRNA levels in the adipose tissue of the rat at day 300 of life.

Methods Used: Mother fed (MF) pups were compared to those receiving one of three rat milk substitutes for 6 days via a gastroscope tube. The three isocaloric formulations contained either standard rat milk substitute (RMS), 150% Protein (RMS-PRO) or 150% Carbohydrate (RMS-CHO). 11βHSD1 and GR mRNA levels in subscapular adipose tissue from day 300 male and female adult rats were analyzed to determine the effect of maternal separation and neonatal diet on precursors of adiposity.

Summary of Results: Maternal separation significantly reduced GR transcript levels in the RMS group in subcutaneous adipose tissue in male adult rats (25.8% ± 7.0%) whereas supplemented milk substitute offset decreased levels in GR transcript levels only. 11βHSD1 levels were significantly decreased regardless of diet (RMS 23.9% ± 8.6%Pro 37.1% ± 17.6%CHO 41.3% ± 14.2%). No differences in female mRNA levels were detected.

Conclusions: Maternal separation decreases GR and 11βHSD1 mRNA levels in the adipose tissue of the adult male rat. While increased postnatal protein dampens the effect of maternal separation on GR mRNA, 11βHSD1 mRNA effects are independent of postnatal diet. Males and females are differentially affected. We speculate that mRNA changes observed will be accompanied by similar changes in protein levels and that long-term changes in adipose gene expression could be associated with altered glucocorticoid signaling thereby altering metabolism contributing to the development of obesity.

Session: Metabolism 113
DIETARY IRON RESTRICTION PROTECTS FROM DIABETES AND LOSS OF Beta CELL FUNCTION IN THE OB/OB MOUSE
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Purpose of Study: Increased iron stores are associated with type 2 diabetes. We have previously reported that humans with hereditary iron overload have a high prevalence of diabetes (22%). In the human disease and mouse models this is largely attributable to loss of insulin secretion and beta cell mass. We therefore tested whether dietary iron restriction would decrease diabetes risk in mouse models of type 2 diabetes.

Methods Used: We examined glucose tolerance and and insulin levels in Ob/Ob mice fed diets containing either 35 or 500 mg/kg iron, the latter being "normal" chow, and in wild type C57BL6 mice fed high fat diets containing those levels of iron.

Summary of Results: Intraperitoneal glucose tolerance testing (IPGTT) was performed on Ob/Ob mice after 30 d on the low or normal iron diets. Glucose tolerance on normal chow significantly worsened, while the group on the 35 mg/kg iron diet exhibited improved glucose tolerance (p < 0.001), equivalent to the wild type background strain, C57BL6. These effects were reversible, sustained for at least 3 mos. and not explained by changes in body weight. β-cell function as assessed by the homeostasis model assessment (HOMA-B) was significantly better in the Ob/Ob mice on low iron (p < 0.01 compared to normal chow, p < 0.0001 compared to pre-diet). As the diabetes status of the Ob/Ob mice on normal chow worsened between 60 and 90 d, insulin levels during the IPGTT declined, as did the ratio of insulin to the area under the glucose curve. In the Ob/Ob mice on low iron, in contrast, insulin levels increased, accompanied by markedly improved glucose tolerance, resulting in a significant increase in the ratio of insulin during the IPGTT to the area under the glucose curve. We also stressed wild type C57BL6 mice with a high fat diet that results in worsened glucose tolerance. In mice on the higher iron normal chow, β-cell function is significantly impaired compared to the low iron diet, with HOMA-B levels 55% lower than in mice on the lower iron chow (p < 0.01).

Conclusions: Decreased levels of dietary iron, but in a range that maintains normal hematopoiesis, significantly protect from declines in insulin secretory capacity that occur in the face of increased demands brought on by obesity or a high fat diet.

Session: Metabolism 114
INTERMITTENT HYPOXIA CAUSES HYPERTENSION AND INSULIN RESISTANCE IN MALE SPRAGUE DAWLEY RATS
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Purpose of Study: Sleep apnea is the most common sleep disorder in the United States affecting from 5–20% of the population. Sleep apnea is characterized by recurring bouts of hypoxia and can be simulated in vivo by exposing rats to intermittent hypoxia (IH). In humans, sleep apnea has been linked to hypertension, insulin resistance, endothelial cell dysfunction and atherosclerosis. All of these conditions are also associated with high levels of serum Plasminogen Activator Inhibitor 1 (PAI-1) and with adverse cardiovascular and metabolic outcomes. Therefore, we hypothesized that rats exposed to IH would develop hypertension, increased PAI-1 and impaired glucose metabolism.

Methods Used: Adult male Sprague Dawley rats underwent surgery to implant femoral artery catheters. All experiments were started at least one week after surgery. Rats were exposed during sleep to either IH (20 short exposures to 5% oxygen each hour) or air (21% oxygen) for 3 weeks. Fasting glucose and plasma PAI-1 were measured weekly. Intraperitoneal glucose tolerance tests were performed at baseline and repeated weekly.

Summary of Results: IH rats had elevated systolic blood pressure (Air = 100 mm Hg ±/−3, IH = 110 mm Hg ±/−2, p < 0.5, n = 10), elevated fasting blood glucose (Air = 140 mg/dL ±/−5, IH = 160 mg/dL ±/−6, n = 5) and a trend to higher plasma PAI-1 levels compared to air rats (Air = 0.5 ± 0.1, IH = 0.9 ±/− 0.3, p = 0.153, n = 5). They also had lower body weight than Air rats.

Conclusions: These data demonstrate that simulated sleep apnea in male Sprague Dawley rats causes hypertension, insulin resistance and elevated levels of PAI-1. Taken together, the data suggest sleep apnea even in the absence of obesity causes an insulin resistant phenotype.

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MATERNAL DHA SUPPLEMENTATION INCREASES ADIPOGENETIC EXPRESSION IN INTRAUTERINE GROWTH RESTRICTED RATS
H. Bagley, Y. Wang, C. Callaway, Y. Xu, R. McKnight, R. Lane, L. Joss-Moore University of Utah, Salt Lake City, UT.

Purpose of Study: Intrauterine growth restriction (IUGR) increases the risk of obesity and insulin resistance in adulthood, in humans and animal models.
Insulin resistance is inversely correlated with serum adiponectin levels. Adiponectin expression increases with PPARγ activation by docosahexaenoic acid (DHA). We have shown that IUGR results in PPARγ dysregulation in adipose tissue before the onset of obesity. However, the effect of IUGR and PPARγ activation on adiponectin production in the rat is unknown. We hypothesize that adding DHA to the maternal diet will increase subcutaneous adipose tissue (SAT) adiponectin and adiponectin receptor mRNA and serum adiponectin levels.

Methods Used: IUGR was induced by bilateral uterine artery ligation at E19 of gestation in Sprague Dawley rats. Maternal rats were fed a standard diet or a 1% DHA diet from E13 to term and during lactation. The effect of IUGR on mRNA levels of adiponectin and its receptors (AdipoR1 and AdipoR2) in SAT and visceral adipose tissue (VAT) of d21 rats was measured by real-time RT-PCR. Serum adiponectin levels were measured by ELISA. Summary of Results: Results are expressed as a % of control ± SEM. In standard diet rats, IUGR significantly increased mRNA levels of AdipoR1 (213 ± 72*) in VAT and AdipoR2 (169 ±175*) in SAT of male rats. There were no significant differences in mRNA levels of female rats or in adiponectin serum levels in either gender. In contrast, in offspring of maternal DHA supplemented rats, IUGR significantly increased mRNA levels of adiponectin (227 ± 196*) and AdipoR1 (179 ±136*) in male SAT. Serum levels of adiponectin (149 ± 136*) were also increased in rats. In contrast, VAT of female rats on DHA diets had significantly lower mRNA levels of adiponectin (32 ± 3%*) and AdipoR2 (45% ± 6%).* p < 0.05

Conclusions: We conclude that IUGR results in an altered expression of adiponectin receptors in an adipose depot and gender specific manner. However, maternal DHA increases adiponectin and AdipoR1 expression in male SAT while reversing adiponectin receptor dysregulation in VAT. Interestingly, DHA supplementation decreases adiponectin and AdipoR2 expression in VAT of female rats. We speculate that increased adiponectin production in the male rat due to DHA supplementation might protect against the development of insulin resistance in adulthood.

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A NOVEL GLUTATHIONE PRECURSOR PREVENTS HIGH FAT DIET-INDUCED STEATOSIS IN APOLIPROPROTEIN E (APOE)−/− MICE
I. Sinha-Hikim1, S. Ruoqing1, H. Kim4, A. Sinha Hikim2, S. French3, N.D. Vaziri1, A. Crum1, Norris K1/Charles Drew University & UCLA, Los Angeles, CA; 2HUMC & UCLA, Torrance, CA; 3HUMC & UCLA, Torrance, CA; 4UC-Irvine, Irvine, CA and 5Rheinbeck, NY.

Purpose of Study: Nonalcoholic fatty liver disease (NFLD) includes the whole spectrum of fatty liver, including steatosis, steatohepatitis, and cirrhosis. Oxidative stress is pivotal in the pathogenesis of NFLD. We examined the effects of a novel cystine based glutathione precursor fortified with selenium (FT061452 TM or F1) in preventing steatosis in ApoE−/− mice and emphasizes the

Methods Used: Adult (10 weeks old), male ApoE−/− mice fed normal diet with or without dietary supplementation of F1(0.5g/kg/day) for 16 weeks.

Summary of Results: Compared with ApoE−/− mice fed normal diet with or without F1, ApoE−/− mice fed high-fat diet exhibited significant weight gain, hepatomegaly, and increased serum cholesterol and triglycerides levels with no change in serum albumin levels. High resolution light microscopy (glutaraldehyde fixed, osmium tetroxide post-fixed, and epoxy embedded) revealed micro-and macro vesicular steatosis, and increased hepatocytic apoptosis. Image analysis revealed a significant increase in accumulated fat area (373 ± 48 μm2) compared with ApoE−/− mice fed with normal diet with (171 ± 9 μm2) or without F1 (143 ± 20 μm2). Electron microscopy of hepatocytes revealed a striking increase in lipid deposition of varying sizes along with a marked decrease in the amount of glycogen, smooth and rough endoplasmic reticulum. Addition of F1 to high-fat diet significantly reduced serum triglycerides levels (no change in cholesterol and albumin levels), liver weight, fat accumulation (373 ± 48 vs.128 ± 17 μm2), and apoptosis (by 87.4%). F1 also effectively prevented high-fat diet-induced alterations in hepatocyte ultrastructure.

Conclusions: These results demonstrate that dietary supplementation of F1 ameliorates high-fat induced-steatosis in ApoE−/− mice and emphasizes the suitability of this model for investigating the mechanisms of diet-induced steatosis.

Session: Metabolism
117
RECOVERY FROM OVERNIGHT HYPOGLYCEMIA IS NOT IMPAIRED IN HEALTHY ELDERLY SUBJECTS
P. Hicks, H. Theresa, MR. Burge University of New Mexico, Albuquerque, NM.

Purpose of Study: Elderly individuals are vulnerable to hypoglycemia. Overnight hypoglycemia is especially feared because of a perceived inability to respond rapidly to the warning signs of hypoglycemia that may occur. Nevertheless, the effect of sleep on recovery from hypoglycemia among healthy elderly adults has not been studied. Moreover, it is not known if endogenous recovery from hypoglycemia is impaired during the night as compared to hypoglycemia occurring during the daytime in healthy, elderly individuals.

Methods Used: Six healthy subjects (age 56 ± 4.9 yr, HbA1C = 5.3 ± 0.26%, BMI = 25 ± 2.1 kg/m2) were admitted to the UNM GCRC for two separate studies. During the nighttime study, subjects received a continuous intravenous infusion beginning at 0300 during stage 2 or greater sleep to induce hypoglycemia (plasma glucose < 50 mg/dl). During the daytime study, a similar insulin infusion was initiated at 0800 during wakefulness and was again continued until plasma glucose was < 50 mg/dl. Insulin was discontinued immediately upon achieving the glucose target. Plasma glucose was obtained at baseline and every 15 minutes during recovery. Insulin and counterregulatory hormones were obtained at baseline and every 30 minutes during recovery.

Summary of Results: The recovery of plasma glucose from nadir is shown in the table below. Free insulin, serum cortisol and total growth hormone concentrations did not differ between study conditions.

Conclusions: Contrary to expectations, recovery from insulin-induced hypoglycemia is not impaired during the nighttime as compared with the daytime in healthy elderly subjects.

<table>
<thead>
<tr>
<th>NADIR Glucose</th>
<th>T15 min</th>
<th>T30 min</th>
<th>T45 min</th>
<th>T60 min</th>
<th>T75 min</th>
<th>T90 min</th>
<th>T120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Study (mg/dl)</td>
<td>49±5</td>
<td>10±8</td>
<td>22±8</td>
<td>32±5</td>
<td>35±5</td>
<td>36±7</td>
<td>35±5</td>
</tr>
<tr>
<td>Nighttime Study (mg/dl)</td>
<td>42±6</td>
<td>24±5</td>
<td>31±7</td>
<td>35±10</td>
<td>38±9</td>
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</tr>
<tr>
<td>p-value</td>
<td>0.17</td>
<td>0.009</td>
<td>0.013</td>
<td>0.35</td>
<td>0.56</td>
<td>0.61</td>
<td>0.38</td>
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</tbody>
</table>

Session: Metabolism
118
YOUNG AGE OF ONSET, KETOACIDOSIS DO NOT DISTINGUISH BETWEEN GAD ANTIBODY POSITIVE ADULT TYPE 1 DIABETES AND LATENT AUTOIMMUNE DIABETES OF ADULTS
K. Djekic1,2, A. Mourzayan1, E. Ipp1 Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA and 1California State University at Long Beach, Long Beach, CA.

Purpose of Study: Latent autoimmune diabetes of adults (LADA) is an autoimmune disorder that may be different from Type 1 diabetes. LADA is defined as auto-antibody positive diabetes in patients with age of onset <25 yrs who initially do not use insulin. Ketoacidosis and age of onset of diabetes <25 yrs have been used to diagnose Type 1 diabetes and to exclude LADA. We tested the usefulness of these criteria for diagnosis of LADA by examining the phenotype of patients in a retrospective study of 126 GAD antibody positive patients.

Methods Used: Non-ketotic patients were studied as outpatients; those with ketoacidosis were fasting inpatients studied after ketoacidosis had cleared.

Summary of Results: Aside from age of onset/current age/duration of diabetes, no differences were found in clinical and biochemical measurements (mean ± SEM or median ± inter-quartile range) in the ketotic or non-ketotic groups, whether older or younger than 25yrs. BMI, C-peptide and lipid profiles were similar. In summary, we did not find any clinically significant phenotypic differences in GAD-antibody positive diabetic patients when a cutoff of 25 yrs for age of onset or a diagnosis of ketoacidosis were used to include/exclude the diagnosis of LADA.

Conclusions: We conclude that young age of onset and/or ketoacidosis are not helpful as exclusion criteria for the diagnosis of LADA. LADA and Type 1 diabetes in adults are more similar than different after about 5 years of disease.

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Session: Neonatal Pulmonary I

<table>
<thead>
<tr>
<th>N</th>
<th>Non-ketotic onset &lt; 25 yrs</th>
<th>Non-ketotic onset &gt; 25 yrs</th>
<th>Ketotic onset &lt; 25 yrs</th>
<th>Ketotic onset &gt; 25 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>17.7 (3.9)</td>
<td>40.0 (8.5)</td>
<td>15.2 (7.6)</td>
<td>40.1 (8.1)</td>
</tr>
<tr>
<td>36</td>
<td>25.8 (8.8)</td>
<td>48.5 (9.7)</td>
<td>27.0 (10.1)</td>
<td>44.8 (9.9)</td>
</tr>
</tbody>
</table>

(mean ± SEM or median ± interquartile range)

Session: Neonatal Pulmonary I

Concurrent Session

8:30 AM

Friday, January 29, 2010

Session: Neonatal Pulmonary I

120

SURFACTANT ADSORPTION IN VITRO: ROLE OF SURFACE PROTEINS

C.J. Chaplin, O. Danhaive, P. Ballard, P. Cogo, V.P. Camelli / Bambino Gesù Children’s Hospital, Rome, Italy; UC San Francisco, CA; University Padova, Padova, Italy and Children’s Hospital Ancona, Ancona, Italy.

Purpose of Study: The function of pulmonary surfactant in vivo is influenced by its lipid and protein composition as well as presence of inhibitory proteins. Ravasjo et al. (J Lipid Res 2008) developed a fluorescent high-throughput assay of surfactant adsorption. We hypothesized that surfactant function in the fluorescent assay is influenced by the content of surfactant protein(SP)-B.

Methods Used: We assessed dose-dependent behavior of commercial and natural surfactants in the Ravasjo assay, which measures by photofluorometry the amount of BODIPY-labeled surfactant adsorbing at the liquid-air interface in multiple wells filled with a light-absorbing quencher (Brilliant Black). Fluorescence was determined over time with phospholipid (PL) amounts of 0.1–3 μg/well; we assessed both maximal fluorescence at (3 μg PL, Max) and the PL concentration giving half-maximal fluorescence (1/2 Max). Purified human SP-B was added to some surfactant samples.

Summary of Results: Infasurf and rat surfactant behaved in a similar fashion with regard to Max fluorescence (18000 vs 23300 f.u.) and 1/2 Max (0.38 vs 0.46 μg PL) and Survanta gave lower Max (9000 f.u.) values. Addition of SP-B at 1.25% of PL to Infasurf did not change the adsorption parameters while addition of SP-B to Survanta markedly increased Max adsorption. When surfactant from term infants was fractionated, the PL fraction had low adsorption; reconstitution of PL with SP-B and SP-C fractions restored normal values. Surfactant isolated from ventilated premature infants demonstrated a range of Max (10000–35000 f.u.) and 1/2 Max (0.1–1.0 μg PL) values and 1/2 Max was inversely and significantly correlated with SP-B (r² = 0.55, n = 42). By contrast, there was no correlation between total protein content of surfactant and adsorption values. SP-B supplementation of premature infant surfactant produced a dose-dependent decrease in 1/2 Max values, indicating improved adsorption.

Conclusions: In this adsorption assay, low SP-B content of surfactant reduces the efficiency of surface film formation but does not affect the amount of surface PL at higher concentrations. SP-B content is likely an important determinant for function/dysfunction of surfactant in premature infants with lung disease.
Summary of Results: This model is a cipher for predicting both the pathophysiological breakdown of the lung and identifying molecular targets for the evolutionarily faithful recapitulation of the integrated lung phenotype.

Conclusions: In this new age of genomics, our reach must exceed our grasp. (Supported by NIH grants HL55268 (JT/VR), HL75405 (VR/JT), HD051857 (VR/JT), and the TRDRP (1R01-HD-0073, 15TF-0250 and 17RT-0170) (VR/JT)).

Session: Neonatal Pulmonary I 122

CALCULUM ACTIVATED CHLORIDE CHANNELS IN PULMONARY ARTERIAL VASOCONSTRICTION ARE INFLUENCED BY POSTNATAL MATURITY AND LONG-TERM HYPOXIC STRESS

S. Venulakonda1, D.G. Papanatkehis1, A. Forrest2, N. Leblanc2, J. Angermann4, L.D. Longo3, S. Wilson3 Loma Linda University Medical Center, Loma Linda, CA; 2University of Nevada, Reno, NV; 3University of Nevada, Reno, NV and 4Loma Linda University School of Medicine, Loma Linda, CA.

Purpose of Study: Pulmonary artery (PA) contractility is dependent on functional L-type Ca2+ channels (CaL); and that TMEM16A, a molecular candidate for ClCa, is expressed in sheep PAs.

Methods Used: These hypotheses were assessed by performing wire-myography, Ca2+ imaging, & RT-PCR analysis on isolated PAs from fetal, newborn and adult sheep. Maturation leads to an increased role for ClCa whilst LTH depresses the role of ClCa during 5-HT mediated PA contractility; that ClCa-mediated contractility is dependent on functional L-type Ca2+ channels (CaL); and that TMEM16A, a molecular candidate for ClCa, is expressed in sheep PAs.

Results: The ClCa blocker niflumic acid (NFA, 100 μM) inhibited PA constriction to 10 μM 5-HT in adult more frequently than fetus or newborn. LTH diminished this effect in adult. CaL inhibition with 10 μM nifedipine did not cause an additive response in normoxic fetus or adult suggesting ClCa and CaL are coordinated. However, in hypoxic fetus and newborn NFA and nifedipine worked in an additive manner, suggesting hypoxic stress causes the expression of other Ca2+ influx pathways that are activated by ClCa. RT-PCR analysis show that TMEM16A is expressed in sheep PAs.

Conclusions: These studies provide evidence indicating postnatal maturation increases CI Ca functionality in the pulmonary vasculature while hypoxic stress may alter this effect differentially in neonates and adult. The finding that TMEM16A is expressed in PA segments suggests this gene product may be responsible for the effects of nifedipine acid on these arteries.

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Session: Neonatal Pulmonary I 123

VITAMIN A+RETINOIC ACID PROMOTES ALVEOLAR FORMATION IN PRETERM LAMBS MANAGED BY MECHANICAL VENTILATION

B. Beck1, M. Dahl1, J. Alvor1, C. Blair1, Z. Wang1, L. Dong1, A. Wint1, M. McCoy1, R. McKnight1, D. Null1, B. Yoder1, R. DeGeronimo1, R. Lane1, N. Ambalavanan2, A. Ross1, K. Albertine1 1Uni of Utah, SLC, UT; 2Uni of Utah, SLC, UT; 3Loma Linda University, Loma Linda, CA; 4Penn State University, Hershey, PA.

Purpose of Study: Several human and animal studies suggest that vitamin A (VItA) therapy may reduce neonatal chronic lung disease (CLD), characterized by inhibition of alveolar development. However, VitA therapy on the preterm and ventilated neonate is problematic, in part because repeated intramuscular injections are required. This limits VitA therapy due to the infliction of pain and stress, as well as the minimal muscle mass of the preterm infant. An alternative VitA treatment approach may reduce these limitations: orogastric delivery of VitA+all-trans retinoic acid (VA+RA, admixed 9:1). Whether VARA treatment of chronically ventilated preterm neonates will improve alveolar formation is not known. We hypothesized that daily therapy with VARA will improve alveolar formation in the lungs of preterm (PT) lambs that are exposed to mechanical ventilation (VARA+MV).

Methods Used: Pregnant ewes were given dexamethasone before delivery of PT lambs (~131d gestation; term ~1150d). PT lambs were intubated, given surfactant, and managed by MV for 3d. VARA was given daily through an orogastric tube (equivalent of 5000 IU/kg/d VitAa). Control PT lambs were managed by MV, VitA+MV (5000 IU/kg/d vitamin A, im), or nasal CPAP (positive outcome control). Fetal lambs were used as gestational age reference. Lung tissue was analyzed by morphometry, as well as immunoblot for apoptosis (cleaved caspase 3) and proliferation (PCNA).

Summary of Results: VARA+MV, similar to VitA+MV or nasal CPAP resulted in thinner airspace walls (~75%, *p < 0.05; n = 4/group) compared to MV. Thinner airspace walls may result from attrition of cells in the airspace walls, such as interstitial cells. To begin to assess this possibility, we measured apoptosis and cell proliferation by immunoblot. Although not significantly different, a trend was evident for more apoptosis (+AH4-25%) in the VARA+MV, VitA+MV, and nasal CPAP groups compared to the MV group. Cell proliferation was similar among the groups.

Conclusions: Treating PT lambs with orogastric VARA is at least as effective in promoting alveolar formation as intramuscular VitAa, without the requirement for daily intramuscular injections. (HL62975, HL56401, HD41075, CHRC).

Session: Neonatal Pulmonary I 124

MATERNAL SUPPLEMENTATION WITH 1% DOCOSAHEXAENONIC ACID CAUSES DNA DAMAGE IN THE DEVELOPING RAT LUNG

E.A. O’Brien, L. Joss-Moore, C. Jiang, Y. Wang, C. Callaway, X. Yu, R. McKnight, R. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: Intratracheal growth restriction (IUGR) predisposes both humans and rats to bronchopulmonary dysplasia (BPD) which is characterized by mesenchymal thickening of distal airways. Using a rat model of IUGR, we have shown that IUGR rat lungs have thickened mesenchyme in association with decreased apoptosis; findings that were ameliorated by maternal supplementation with pharmacologic doses of docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid. Interestingly, DNA damage is known to stimulate apoptosis, and evidence suggests that DHA can cause DNA damage. The mechanism for how maternal DHA supplementation with pharmacologic doses of docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid. Interestingly, DNA damage is known to stimulate apoptosis, and evidence suggests that DHA can cause DNA damage. The mechanism for how maternal DHA supplementation blunts IUGR-induced changes in developing lungs remains unknown.

We hypothesized that maternal supplementation with pharmacologic doses of DHA will induce DNA damage.

Methods Used: To test this hypothesis, maternal rats were fed a diet containing 1% DHA (pharmacologic) or 0.1% DHA (physiologic) from E13 to term and were pair-fed with rats fed an isocaloric (regular) diet. Bilateral uterine artery ligation surgery was performed on rats at E19. Pups were killed and lungs were harvested at term (D0), D7 and D21. DNA damage was quantified using a commercially available kit measuring apoptotic/apyrinoid (APc) sites.

Summary of Results: The most significant finding in this study was that maternal supplementation with pharmacologic doses of DHA resulted in more DNA damage in control than IUGR rat lungs. Pups born to DHA supplemented control dams had more DNA damage compared with egh controls (AP sites/1000bp: D0 Cont 9.0 ± 0.25 vs DHA Cont 11.42 ± 0.63, p < 0.05). IUGR pups born to DHA supplemented dams also had more DNA damage compared with regular diet IUGR pups, but not compared with regular diet controls. In contrast, physiologic DHA supplementation did not cause DNA damage in control or IUGR rat lungs at D0.

Conclusions: When compared with controls, IUGR rat lungs had less DNA damage after maternal supplementation with pharmacologic doses of DHA. Importantly, DNA damage was not detected with physiologic doses of DHA. While pharmacologic doses of DHA ameliorated the IUGR-induced lung phenotype, we speculate that DHA is stimulating apoptosis via DNA damage.

Session: Neonatal Pulmonary I 125

INTRAUTERINE GROWTH RESTRICTION DECREASES PULMONARY TRPV4 EXPRESSION

E. Zinkhan, Y. Wang, A. Brown, C. Fung, L. Joss-Moore, R. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: Intratracheal growth restriction (IUGR) increases the risk for bronchopulmonary dysplasia (BPD) in neonatal humans and mice. BPD
is characterized by pulmonary edema with subsequent arrest of alveolar development. Activation of pulmonary endothelial cell transient receptor potential vanilloid 4 (TRPV4) channels leads to pulmonary edema in adult mice. Despite the potential importance of TRPV4 in the development of pulmonary edema, little is known about how TRPV4 and expression changes during normal postnatal lung development. Further, whether IUGR affects the normal ontological pattern of TRPV4 remains unknown. We hypothesized that IUGR increases TRPV4 mRNA and protein levels.

Methods Used: To test this hypothesis, murine IUGR was induced by implanting pumps to deliver 0.5% EtOH (control) or thromboxane in 0.5% EtOH at 2000mg/kg into the retroperitoneum of female mice at day 13 of pregnancy to create placental insufficiency. Pups allowed to deliver at term and lungs harvested at day 0 (DOL 0), day 21 (DOL 21), or day 90 (DOL 90). Real time RT PCR used to determine the quantity of TRPV4 mRNA at each time point. Western blotting was used to quantify TRPV4 protein.

Summary of Results: Results are presented as either DOL 0 relative to DOL 90 or IUGR relative to control, +/- standard error of the mean. Control TRPV4 mRNA and protein increased significantly from DOL 0 to DOL 90 in both males (40% +/- 100% mRNA and 285% +/- 59% protein) and females (420% +/- 100% mRNA and 417% +/- 52 protein). IUGR significantly decreased TRPV4 mRNA relative to control at DOL 0 in males (40% +/- 20%) and females (40% +/- 3%), and at DOL 21 in females (61% +/- 6%). At DOL 90 no statistically significant differences were seen in TRPV4 mRNA levels in IUGR mice. TRPV4 protein levels trended toward significant decrease in IUGR DOL 0 males (57% +/- 4%) with significant decrease in DOL 21 female IUGR mice (54% +/- 4%), and no change at DOL 90.

Conclusions: TRPV4 mRNA and protein levels increase during normal postnatal development. IUGR decreases TRPV4 mRNA and protein levels in an age and gender specific manner. These findings are intriguing because they demonstrate that the prenatal environment alters TRPV4 expression. We speculate that by decreasing TRPV4 expression, IUGR alters endothelial cell function throughout development.

Session: Neonatal Pulmonary 1

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MATURATION AND CHRONIC HYPOXIA INFLUENCE ALPHA ADRENERGIC FUNCTION IN THE PULMONARY VASCULATURE OF SHEEP

D. Papamatheakis1,2, Q. Blood2, T. Merritt2, S. Lauw2, S. Wilson2. 1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA.

Purpose of Study: Lung blood flow is regulated to maximize gas exchange. This is controlled by various factors including autonomic nervous stimulation. Before birth, the fetal lung has high vascular resistance and low blood flow as all oxygen supplied to the fetus is via the placenta. After birth, with the onset of respiration, pulmonary vascular resistance decreases significantly. Various factors including hypoxia (CH) can cause structural and functional pathology, with increased pulmonary pressure and vascular remodeling. Modern medications focus on alleviating pulmonary hypertension (PH) by blocking smooth muscle contractility, but they do not fully reverse disease progression. This inability to care PH in newborns and adults is partly because we do not understand the etiology of disease. Our aim is to understand this progression. Previous work from our group shows that CH does not affect norepinephrine induced pulmonary arterial contractility in fetus, but does influence cerebrovascular tone. We therefore tested the hypothesis that maturation and CH depress alpha adrenergic receptor (AR) dependent pulmonary arterial contractility.

Methods Used: Pulmonary arteries were isolated from near term sheep fetuses (~140 days) and adult ewes maintained under normoxia (300m) or CH conditions (3800m) for 100 days. Wire myography was performed to assess the role of alpha-ARs, with rings being stimulated with cumulative doses of phenylephrine (PE), a selective alpha-AR agonist, ranging from 10-9 to 5 x 10-4 M.

Summary of Results: PE caused arteries from adult normoxic animals to contract 69 ± 5% of that due to 124 mM potassium (%TKmax), with a Log EC50 of ~6.9 ± 0.22 M. Rings from adult CH animals had a similar magnitude, being 61 ± 4 %TKmax. However, the Log EC50 was shifted, being ~5.7 ± 0.18 M. PE caused greater tone in arterial rings from normoxic fetuses, being 100 ± 10 %TKmax. Yet, these arteries were less responsive than those of adult, with a Log EC50 of ~6.1 ± 0.25 M. Arteries from CH fetuses reacted similarly to normoxic controls with an EC50 of ~5.7 ± 0.20 M and tone being 90 ± 6 %TKmax.

Conclusions: Our preliminary studies show the role of alpha-AR to pulmonary arterial contractility is influenced by postnatal development as well as CH. This suggests that alpha-ARs may be therapeutically relevant in the treatment of pulmonary hypertension.

Session: Neonatal Pulmonary 1

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THE VASODILATORY EFFECTS OF SURFACANT ON LUNG AND SYSTEMIC ARTERIES

D. Hunt1, M. Chang1, QK. Blood1, TA. Merritt1, SM. Wilson2, AB. Blood1,2. 1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA.

Purpose of Study: Surfactant administration to premature infants can cause hypotension which increases the risk of adverse events such as compromised cerebral blood flow. This study tested the hypothesis that two commonly prescribed animal-derived surfactants have direct vasodilatory properties mediated by nitric oxide synthase and cyclooxygenase activity.

Methods Used: 4th generation pulmonary arteries or the superficial femoral artery were isolated from fetal sheep at 140 days gestation. The experimental procedure was the same for both arteries. Arteries were mounted on a wire myograph in Krebs solution at 37 C. Serotonin (pulmonary arteries) or phenylephrine (femoral arteries) induced vasoscontraction. Curosurf or Survanta was added in 6 cumulative doses while Krebs buffer was added as a control. The role of NOS or cyclooxygenase were assessed by adding N(O)-nitro-L-arginine methyl ester (L-NAME) or diclofenac. Vasodilatation was measured as percent relaxation of total constriction.

Summary of Results: In pulmonary arteries, Curosurf or Survanta resulted in a dose-dependent reduction in vessel tension to 73 ± 4% and 67 ± 7% of baseline values at the highest surfactant concentration. Both L-NAME and diclofenac blocked the vasodilatation of Curosurf, but did not affect Survanta. For femoral arteries, there was no significant change from baseline tension for either Curosurf or Survanta.

Conclusions: Both Curosurf and Survanta diluted pulmonary arteries, but not systemic femoral arteries. L-NAME and Diclofenac attenuated the vasodilating effects of Curosurf, but did not affect Survanta, suggesting that Curosurf’s mechanism involves both NOS and cyclooxygenase activation, but that neither pathway is involved with Survanta-mediated vasodilation. The vasoactive properties of surfactants appear more potent in pulmonary compared to systemic arteries. Future research will examine the properties of synthetic surfactants as well as the vasoactive properties of various surfactant components.

Session: Neonatal Pulmonary 1

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POSTNATAL ROSIGLITAZONE ADMINISTRATION TO NEONATAL RAT PUPS DOES NOT ALTER THE ADULT METABOLIC PHENOTYPE

NC. Truong1, A. Abbasi1, E. Shin1, R. Sakurai1, WN. Paul Lee2, JS. Torday1,2, VK. Rehan1. 1Harbor-UCLA, Torrance, CA and 2Harbor-UCLA, Torrance, CA.

Purpose of Study: We have previously shown that systemically administered Rosiglitazone (RGZ), a Peroxisome Proliferator-Activator Receptor-γ (PPAR-γ) agonist, up to 7 days of life significantly enhances lung maturation without affecting serum electrolytes, blood glucose, blood gases and serum lipid profile in the newborn period. Here we demonstrate that this intervention in early neonatal life does not lead to altered metabolic profile and phenotype in adult animals.

Methods Used: Sprague Dawley newborn rats were given either saline or RGZ (0.3mg, 1 mg, or 3 mg/kg body weight) in 100 μL volumes intraperitoneally from postnatal day 1 to 7. Pups were allowed to breast feed ad libitum and then were weaned to rat chow on day 21 of postnatal life. Glucose tolerance and insulin tolerance tests were performed at 14 weeks of age. To perform these studies, either glucose (0.2g/kg/100 gm body weight) or 1 g/kg body wt as 1:1 mixture of [2–2H] and [6–2H2]glucose, intraperitoneal) or insulin (1 unit/kg, subcutaneous) was administered after overnight fast. To assess the effects of early RGZ administration on glucose and fatty acid synthesis and incorporation into the tissues, a subset of animals received 0.09% NaCl in 99.9% D2O equal to ~4% of body weight intraperitoneally, and animals were given free access to drinking water containing 6% D2O. Animals were sacrificed after 7 days, when serum and tissues (skeletal muscle, liver, lung,
brown and white fat) were collected for the markers of adipogenic differen-
tiation by Western blot analysis. Glucose and fatty acid synthesis and incorpo-
ration into the tissue was analyzed via mass spectrometry.

**Summary of Results:** There was no effect of early postnatal RGZ admin-
istration on body weight, glucose or insulin tolerance, triglycerides, and fatty
acid synthesis in both males and females. Further characterization of the adult
metabolic phenotype of various treatment groups is in progress.

**Conclusions:** Treatment with PPARY agonist RGZ in early neonatal life
does not alter developmental metabolic programming and does not lead to an
altered metabolic phenotype in the adult. Further studies to characterize the
adult metabolic phenotype in greater detail are in progress.

**Neonatology - General I**

**Concurrent Session**

8:30 AM  
Friday, January 29, 2010

**Session: Neonatology - General I**

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**UTEROPLACENTAL INSUFFICIENCY DOWN REGULATES RENAL 11 
HYDROXYSTEROID DEHYDROGENASE TYPE 2 (11 
B-HSD2) EXPRESSION THROUGH EPIGENIC MECHANISMS**

MC. Baserga, R. Kaur, X. Yu, C. Callaway, R. McKnight, R. Lane  
University of Utah, Salt Lake City, UT.

**Purpose of Study:** IUGR increases the risk of serious adult morbidities
such as hypertension. 11B-HSD2 deficiency can lead to hypertension by not
metabolizing deoxycorticoids to an inactive form. Importantly, in an animal
model of IUGR, adult onset hypertension we reported a persistent
decrease in kidney 11B-HSD2 mRNA through juvenile stages. We now
investigate whether the decrease in 11B-HSD2 mRNA is due to changes in
epigentic determinants of chromatin structure, and/or due to alteration in
the binding activity of key transcription factors. We hypothesize that IUGR
affects kidney epigenetic determinants of chromatin structure resulting in
persistent down regulation of 11B-HSD2 expression.

**Methods Used:** We performed bilateral uterine artery ligation on e19
pregnant rats and harvested kidneys at P0 (term) and P21 (juvenile studies).
We assessed 1) the pattern of DNA methylation of the 11B-HSD2 promoter
using bisulfite modification, 2) the 11B-HSD2 DNA-histone associations
using chromatin immunoprecipitation (ChIP), based upon known alterations
in histone covariant modifications observed in the IUGR rat kidney; and 3) the
11B-HSD2 DNA binding activity of the transcription factors SP1, NF-kB and
growth early response (Egr1) using ChIP.

**Summary of Results:** The most important findings in this study were that
1) IUGR increased CpG methylation status, as well as modified the pattern of
methylation in 17 CpG sites analyzed in the 11B-HSD2 promoter when
compared to control kidneys at P0; 2) IUGR increased trimethylation of
H3K36 in exon 5 in both genders at P0 and P21, and 3) IUGR increased NF-
kB (p65) binding activity to 11B-HSD2 promoter in IUGR males, without
affecting SP1 and Egr1 binding properties.

**Conclusions:** We conclude that IUGR affects transcriptional regulation of
11B-HSD2 by affecting epigenetic marks along the 11B-HSD2 gene. More
specifically, we found that IUGR increased methylation in the promoter region
and decreased trimethylation in exon 5 of the 11B-HSD2 gene, which is
associated with decreased gene activation and elongation. Furthermore, IUGR
increased NF-kB binding to the 11B-HSD2 promoter, also possibly leading to
decreased transcriptional activity. These data support our speculation that
alterations in chromatin structure play a role in in utero reprogramming.

**Session: Neonatology - General I**

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**INTRAUTERINE GROWTH RESTRICTION RESULTS IN INCREASED INSULIN-STIMULATED PROLIFERATION BUT NOT HYPERTROPHY IN FETAL MYOCYTES**

L.D. Brown, PJ. Rozance, SM. Soto, WW. Hay Jr., JE. Friedman  
University of Colorado Denver, Denver, CO.

**Purpose of Study:** Reduced fetal skeletal muscle growth is a hallmark of
intrauterine growth restriction (IUGR) and may lead to increased risk for
adult insulin resistance; however the causative mechanisms are unknown.

Our purpose was to determine the effect of insulin on cellular proliferation
and protein synthesis in primary cultured myocytes from ovine IUGR and
control fetuses.

**Methods Used:** Studies were performed using an established ovine model
of placental insufficiency and IUGR. Fetal myoblasts were harvested from
control (n = 6) and IUGR (n = 3) fetuses at ~ 90% of gestation, cultured in
increasing insulin concentrations, and counted at 3 and 5 days to measure cell
proliferation. Fully differentiated myotubes were serum starved overnight
and incubated in insulin for up to 6 hours to measure protein synthesis rates using
L-[3,4,5-3H(N)] leucine incorporation.

**Summary of Results:** IUGR fetuses weighed 43% less, had 67% percent
lower blood oxygen contents, and 40% lower plasma glucose concentrations
than control fetuses (p < 0.01). Insulin increased proliferation in myoblasts
from both control and IUGR fetuses, however the proliferation rate was 2-
fold higher in IUGR myoblasts (p = 0.005). Insulin increased protein syn-
thesis rates in myotubes in a dose dependent manner (p = 0.009), but the
responses did not differ between control and IUGR.

**Conclusions:** Myoblasts from IUGR fetuses demonstrate strikingly
increased capacity for proliferation in response to insulin compared to cells
from control fetuses, however this is not associated with a further increase in
protein synthesis in mature myotubes. Thus, IUGR fetal myocytes have a
strong capacity for growth (myogenesis) when exposed to insulin, but limited
ability for catch up growth by hypertrophy.

**Session: Neonatology - General I**

131

**INTRANOCULAR GROWTH RESTRICTION (IUGR) DECREASES IGF-1 EXPRESSION IN THE MALE POSTNATAL RAT HEART**

E. Scherr, L.A. Joss-Moore, Q. Fu, RA. McKnight, EB. Clark, RH. Lane  
University of Utah School of Medicine, Salt Lake City, UT.

**Purpose of Study:** IUGR leads to increased risk of cardiovascular disease
in the adult. Low levels of insulin-like growth factor-1 (IGF-1) are associated
with significantly higher prevalence of ischemic heart disease. In humans and
rodents, IGF-1 appears to prevent the decline of myocardial function and
progression of heart failure. Our lab has previously shown that IUGR
decreases IGF-1 in other tissues. In this study, we hypothesized that IUGR
decreases IGF-1 mRNA expression in the rat heart. IGF-1 transcription is initiated
by 2 separate promoters, P1 and P2. Multiple variants are generated by
alternative splicing. IGF-1A lacks exon 5, while IGF-1B contains exon 5.
IGF-1 variant expression affects translational efficiency and production of
Ea/El protein products, which function as potential growth factors.

**Methods Used:** IUGR was induced by bilateral uterine artery ligation of the
pregnant rat on day 19 of gestation. Control animals underwent identical
anesthesia procedures. Tissue (female and male) was harvested for RNA isola-
tion at Day 0 (neonate), 21 (adolescent) and 120 (adult) in IUGR and control
animals (n = 5–8/group). Real-time RT-PCR was performed to measure expres-
sion of P1- and P2-initiated transcripts, IGF-1A and IGF-1B at each time-point.

**Summary of Results:** IUGR significantly decreases mRNA expression of
P1-initiated transcripts, IGF-1A and IGF-1B in male neonatal rats (29.44 
19.5%, 86.9 ± 7.4%, 63.32 ± 10.9% of control, respectively; p < 0.05) and
male adult rats (24.2 ± 11.3%, 72.7 ± 29.4%, 63.3 ± 23.8% of control, respectively;
p < 0.05). In contrast, female IUGR hearts are not different from control hearts
at day 0, 21 or 120. The P2-derived transcript, which is mainly expressed in
the liver, is unchanged in male and female hearts at all three time-points.

**Conclusions:** We conclude that IUGR decreases IGF-1 expression in the
male neonatal rat heart and this decrease persists into adulthood. This is
intriguing since IGF-1 has been shown to increase cardiac contractility by
increasing intracellular calcium content and enhancing calcium sensitivity of
myofilaments in cardiac myocytes. We speculate that decreased levels of
IGF-1 in the male adult IUGR rat heart may contribute to a suboptimal
response to cardiac ischemia.

**Session: Neonatology - General I**

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**INTRAUTERINE GROWTH RESTRICTION ALTERS GLUCOCORTICOID DOWNSTREAM SIGNALING IN RAT BONE IN AN AGE AND GENDER SPECIFIC MANNER**

AJ. Zabrocki, R. Lane, L. Moyer- Mileur, S. Miller, R. McKnight, C. Calloway, X. Yu  
University of Utah, Salt Lake City, UT.

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Purpose of Study: Intrauterine Growth Restricted (IUGR) newborns have smaller, weaker, and less mineralized bones, leading to more fractures throughout life and osteoporosis as adults. The molecular pathways underlying these physiologic bone abnormalities are unknown. Glucocorticoid hormones (GC) acting through GC Receptors (GR) are necessary for proper bone development, but harmful in excess. We have previously demonstrated that IUGR alters bone mineralization in the rat as well as increases serum corticosterone. In addition, we have found that IUGR causes changes in mRNA levels of other components of the GC pathway, namely; total GR, the active form GRα, and 11β-hydroxysteroid dehydrogenase 1. The sum influence of GC pathway on downstream genes in the IUGR setting is unknown. We hypothesize that IUGR will cause an overall increase in GC signaling, as measured by mRNA levels of relevant downstream genes: bone sialoprotein (BSP), osteocalcin (OC), runt-related transcription factor 2 (RUNX2), distal-less homeobox 5 (Dlx5), transcription factor Sp7 (SP7), frizzled-related protein (FRZB), serum/glucocorticoid-regulated kinase 1 (SGK1), lipocalin 2 (LCN2), and connective tissue growth factor (CTGF).

Methods Used: Bilateral intrauterine artery ligation was performed on rats on 19th day of gestation. Pups were sacrificed either at birth (d0) or on day 21 (d21). Femurs and tibias were collected and flash frozen. Whole bone mRNA was extracted and real time RT-PCR was performed for genes of interest.

Summary of Results: In d0 females, IUGR decreased mRNA levels of OC to 50% of control (p = 0.001), and increased mRNA levels of CTGF to 162% (p = 0.05). In d21 females, IUGR decreased mRNA levels of BSP to 79% (p = 0.02). In d21 males, IUGR increased FRZB mRNA levels 162% (p = 0.05). There were no other significant changes in mRNA levels of remaining genes.

Conclusions: We conclude that IUGR alters bone mRNA levels of OC, CTGF, BSP and FRZB in an age and gender specific manner. In published studies increased GC has been shown to directly decrease OC and FRZB mRNA levels and increase those of CTGF and BSP. Therefore, in the light of our results, we speculate that in d0 females IUGR overall increases GC signaling, whereas in d21 females and males, IUGR overall decreases GC signaling.

Session: Neonatology - General I
133
BREASTMILK FEEDING OF VERY LOW BIRTH WEIGHT INFANTS AS A FUNCTION OF HOSPITAL PERCENTAGE OF MINORITIES
HC. Lee1,2, JB. Gould3,2, RA. Dudley4 1University of California San Francisco, San Francisco, CA; 2California Perinatal Quality Care Collaborative, (CPQCC), CA; 3Stanford University, Stanford, CA and 4University of California San Francisco, San Francisco, CA.

Purpose of Study: Breastfeeding (BM) is the optimal nutrition in prematurity. African American and Hispanic infants are less likely to receive BM. Our purpose was to see to what extent population served by a hospital in terms of race influences BM feeding (BMF).

Methods Used: CPQCC prospectively collects data on 90% of California neonatal intensive care admits. Subjects had birthweight 500–1500 grams and were born at or transferred to CPQCC center within 2 days of birth 2006–2008. Primary outcome was any BMF at discharge home. Hospitals were divided into quartiles by hospital percentage of each race. BMF rates by race were compared.

Multivariable logistic regression was used to assess effect of hospital race percentage on likelihood of BMF adjusted for prenatal care, maternal age and birthweight.

Summary of Results: Hispanic BMF rates at hospitals with most Hispanics were lower (59%) vs. hospitals with lowest percentage of Hispanics (67%, p < 0.0001). African Americans had lower rates in hospitals with more African Americans (43%) vs. hospitals with less African Americans (59%, p = 0.003). Whites had higher BMF rates in hospitals with less minorities. Figure shows BMF rates by hospital proportion of minorities. Results were similar after risk adjustment.

Conclusions: Hospitals serving more minorities were less likely to have premature infants fed BM for all races. Targeting such hospitals for quality improvement may help to improve BMF rates overall and reduce disparities.

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134
DEVELOPMENTAL MASSAGE THERAPY IMPROVES MARKERS OF BONE GROWTH IN A NEONATAL STRESS MODEL
S. Haley, S. O’Grady, K. Gulliver, A. Thomson, R. Baldassarre, R. Lane, L. Moyer-Mileur University of Utah, Salt Lake City, UT.

Purpose of Study: Premature infants experience stressful events in the newborn intensive care unit (NICU). Neonatal stress impairs postnatal bone mineralization. Clinical studies have indicated that developmental massage therapy (DMT) in early life decreases stress hormones and improves bone mineralization. A rat model for DMT in neonatal stressed rats was used to test the hypothesis that DMT will improve bone mineral content (BMC), circulating markers of bone turnover, and growth plate morphology in later life. Furthermore, insulin-like growth factor (IGF1) is reputed to stimulate growth plate chondrocyte proliferation and hypertrophy. We predict an increase in bone specific mRNA expression of IGF1 related pathways.

Methods Used: Timed pregnant dams were delivered at term (E21). Litters were culled to 10 pups (5 M, 5 F) and divided into 2 groups: neonatal stress control (NS; maternal separation + injection + hypoxia/hyperoxia) and NS + DMT (10 min of stroking and limb movement). Treatments were given from D6 to D10 and tissue was harvested on D60, and D120 of life. Dual energy x-ray absorptiometry (DXA), bone morphology, serum levels of glucocorticoids and bone turnover markers, tartrate-resistant acid phosphatase (TRAP) and osteocalcin, as well as mRNA levels of IGF1, IGF1 receptor (IGF1R), and growth hormone receptor (GHR) were measured.

Summary of Results: DMT intervention increased BMC at D60 and D120 and tibial growth plate width at D60 compared to NS. DMT also resulted in higher osteocalcin, a marker for osteoblast, at D60 and D120, and lower serum TRAP, a marker for osteoclast, in males at D60 and females at D120 (p < 0.05). Furthermore, DMT results in three-fold, two-fold, and six-fold higher bone specific IGF1, IGF1R, and GHR, respectively at D60 (p < 0.001). There were no differences in serum glucocorticoids.

Conclusions: We conclude that DMT in early postnatal life, in this model, improves the long-term outcome for bone development. Neonatal stressed rats given DMT have improved BMC, bone turn over (TRAP and osteocalcin), and bone morphology (growth plate). IGF1 is an important mediator of GH’s effect on bone growth and elevated expression of IGF1 and related pathways may explain improved BMC. These changes do not appear to be linked to glucocorticoid levels.

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135
DEVELOPMENTAL MASSAGE THERAPY (DMT) TEMBERS ADIPOSE TISSUE ADIPONECTIN RECEPTOR-2 (adipR-2) mRNA LEVELS IN NEONATAL STRESS IN RAT PUPS
K. Gulliver, S. Haley, J. Thomson, B. Barrett, RH. Lane, L. Moyer-Mileur University of Utah, Salt Lake City, UT.

Purpose of Study: Elevated glucocorticoid (GC) levels in early life are linked to obesity in later life. Massage therapy lowers GC and may lessen obesity risk by modulating the adipose genes expression. We hypothesized that molecular events that arise from DMT would decrease GC and alter adipose tissue leptin and adiponectin mRNA levels in neonatal stressed rat pups.

Methods Used: Timed pregnant S-D rats were delivered at term, litters culled to 10 pups (5 M, 5 F) and randomized to : neonatal stress (NS; 60 min of maternal separation + injection + hypoxia/hyperoxia) and NS + DMT (10 min of stroking and limb movement). Treatments were given from D6 to D10 and tissue was harvested on D60, and D120 of life. Dual energy x-ray absorptiometry (DXA), bone morphology, serum levels of glucocorticoids and bone turnover markers, tartrate-resistant acid phosphatase (TRAP) and osteocalcin, as well as mRNA levels of IGF1, IGF1 receptor (IGF1R), and growth hormone receptor (GHR) were measured.

Summary of Results: DMT intervention increased BMC at D60 and D120 and tibial growth plate width at D60 compared to NS. DMT also resulted in higher osteocalcin, a marker for osteoblast, at D60 and D120, and lower serum TRAP, a marker for osteoclast, in males at D60 and females at D120 (p < 0.05). Furthermore, DMT results in three-fold, two-fold, and six-fold higher bone specific IGF1, IGF1R, and GHR, respectively at D60 (p < 0.001). There were no differences in serum glucocorticoids.

Conclusions: We conclude that DMT in early postnatal life, in this model, improves the long-term outcome for bone development. Neonatal stressed rats given DMT have improved BMC, bone turn over (TRAP and osteocalcin), and bone morphology (growth plate). IGF1 is an important mediator of GH’s effect on bone growth and elevated expression of IGF1 and related pathways may explain improved BMC. These changes do not appear to be linked to glucocorticoid levels.
Conclusions:

Summary of Results:

Methods Used:

J. Alvord, B. Beck, A. Wint, S. Elder, B. Clayton, D. Metcalfe, M. McCoy,

PRETERM LAMBS

APOPTOSIS OF REACTIVE ASTROCYTES IN CORTICAL

Session: Neonatology - General I

SUMMARY OF RESULTS:

Weight gain was similar during and post-

of maternal separation, n = 40). Treatments were given daily on D5-20 and

litters were cross-fostered D5-D20. DMT consisted of 5 min of tactile

stimulation followed by 5 min of range of motion to fore- and hind limbs.

Weight (g) during (D5

end of 3d, cortical white matter in the temporal lobe was isolated and analyzed

by quantitative real time RT -PCR and immunoblot for caspase 3, and double

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end of 3d, cortical white matter in the temporal lobe was isolated and analyzed
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139

Efficacy of Zinc Bis Glycol Porphyrin Inhibiting Heme Oxygenase Activity in the Heme-Loaded Newborn Mouse

CX. He, H. Zhao, F. Kalish, RJ. Wong, DK. Stevenson Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Heme oxygenase (HO) is the rate-limited enzyme in the degradation of heme to produce bilirubin. Because excess bilirubin production due to hemolysis can lead to neonatal hyperbilirubinemia, the use of HO-inhibiting drugs such as metalloporphyrins (Mps) may be an ideal preventive strategy. We have reported that tin mesoporphyrin (SnMP) is a potent HO inhibitor, but it is photoreactive and can induce HO-1 expression, thus limiting its clinical use. In this study, we investigated the efficacy of an alternative Mps, zinc bis glycol porphyrin (ZnBG), towards inhibiting in vivo HO activity following heme loading in newborn mice, a model analogous to that of a hemolytic infant.

Methods Used: 7d-old mice were given 30-μmol/kg of heme (H) or vehicle (V) by subcutaneous (SQ) injections on Day 1. On Day 2, mice were given 15-μmol/kg of ZnBG or V orally. On Day 3, V or a 2nd H load was injected SQ. On Day 4, liver, spleen and brain were harvested. HO activity and HO-1 protein were measured by gas chromatography and Western blot, respectively.

Summary of Results: After a 2nd heme load (H VH), liver HO activity was significantly induced. In the HZH group, the heme-induced liver HO activity was completely abolished to VV levels. Spleen HO activity was not significantly induced by the heme loads, but the HZH group showed significant spleen HO inhibition. In contrast, brain HO activity was not affected by heme loading or ZnBG treatment. Interestingly, spleen HO-1 protein levels were induced only in the HZH group. No statistically significant effects of heme loading or ZnBG treatment on HO-1 transcription were found in any tissue.

Conclusions: After a 2nd heme load, 15 μmol/kg ZnBG/kg suppressed heme-induced increases in liver and spleen HO activity, but may induce spleen HO-1 protein. We conclude that low doses of ZnBG are effective in inhibiting liver HO activity in the context of repeated heme loads. Thus, ZnBG may be another alternative compound for use in the treatment of neonatal jaundice caused by hemolytic disease.

%HO activity left (Mean ± SD, n = 5 for each tissue)

<table>
<thead>
<tr>
<th>Group</th>
<th>V-V-V</th>
<th>JH-V-H</th>
<th>H-ZnII</th>
</tr>
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<tbody>
<tr>
<td>Liver</td>
<td>100±0%</td>
<td>145±10%*</td>
<td>105±4%*</td>
</tr>
<tr>
<td>Spleen</td>
<td>100±0%</td>
<td>111±7%</td>
<td>72±15%</td>
</tr>
<tr>
<td>Brain</td>
<td>200±13%</td>
<td>111±14%</td>
<td>98±17%</td>
</tr>
</tbody>
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p ≤ 0.05, vs *V-V-V or †H-V-H groups

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140

Erythropoiesis Stimulating Agents Erythropoietin and Darbepoetin Increase Fetal Neurogenesis in Dose Dependent Fashion

U. Malik, S. McConaghy, R. Ohls University of New Mexico, Albuquerque, NM.

Purpose of Study: Studies have explored the effects of erythropoietin (Epo) in adult and neonatal animal models of neuroprotection. Limited evaluation has been performed in human neuronal cell cultures. We evaluated the effects of Epo and darbepoetin (Darbe), a long acting erythropoiesis stimulating agent (ESA), on fetal neuronal cultures, and hypothesized that both ESAs would increase total cell number, increase expression of antiapoptotic genes, and decrease expression of apoptotic genes.

Methods Used: Fetal brain samples were collected between 10 and 24 weeks of gestation (GA). Cell suspensions were created and plated at 5 × 10^5 cells/mL. Cells were grown in culture with 0, 0.1, 1 or 10 U/mL Epo, or in 0, 100, or 1000 ng/mL of Darbe for 10 days. Cells were identified histologically and cell counts performed. Total RNA was isolated and quantified spectrophotometrically. RNA was reverse transcribed and quantitative PCR performed using primers and probes to identify Bax and Bcl gene expression. GAPDH was used as an internal control in duplex reactions.

Summary of Results: Absolute cell counts increased significantly over baseline with both Epo and Darbe, in dose dependent fashion. Without growth factors added, cell counts increased approximately 4 fold over 10 days. There was no significant increase with the addition of 0.1 U/mL Epo. Both 1 and 10 U/mL Epo resulted in significant increases in cell number (7-fold and 10-fold increase in growth, respectively; p < 0.0001, 1 or versus 0). Darbe concentrations of 10 ng/mL resulted in similar growth as cells grown in 1 unit/mL Epo, and growth was significantly greater with increasing concentrations of Darbe (7, 10-, and 13-fold increases in cell number, respectively; p < 0.0001, 0 versus 10, 100 and 1000 ng/mL Darbe concentrations). When evaluated gestationally, cells isolated from low and mid GA (10–19 weeks) were more sensitive to both ESAs than cells isolated from greater GA (20–24 weeks; p < 0.001, low versus high GA). Baseline expression of apoptotic and antiapoptotic genes was similar at all GA tested. Gene expression of cells exposed to ESAs is ongoing.

Conclusions: ESAs significantly stimulated neurogenesis in human fetal brain. Cells isolated from lower GA were more sensitive to ESAs. We speculate that ESAs will have similar effects in vivo.

Neuroscience I

Concurrent Session

8:30 AM

Friday, January 29, 2010

Session: Neuroscience I

141

A Novel Preclinical Model of Germinoma Matrix Hemorrhage Using Neonatal Rats

K. Virbel, T. Lekic, A. Mananenko, W. Rolland, J. Zhang Loma Linda University, Loma Linda, CA.

Purpose of Study: Germinal matrix hemorrhage (GMH) is the most common neurological disorder of premature newborns. This brain injury occurs in 20% of premature infants (12, 240 annually in the U.S.A.) of less than 1500 g birth weight. These infants develop a number of neurological problems, including: post-hemorrhagic hydrocephalus, cerebral palsy (10%), and mental retardation. However there is not yet an ideal model to study outcomes after GMH, therefore this study was undergone to develop a novel animal model.

Methods Used: At P7 (age corresponding to prematurity) germinoma matrix hemorrhage was induced by injection of clostridial collagenase into the right periventricular region using stereotaxic techniques as having been previously routinely performed. Animal measurements were taken at days 1, 3, 7, 10, 14, 21, and 28 after GMH. Parameters evaluated were the body weight, crown-rump length, limb distance and head circumference (width and height). Neurological evaluation was performed over the first two weeks using the wire-suspension, negative geotaxis and righting reflex tests. At the end of experiment, the brain, spleen and heart were removed and weighed.

Summary of Results: At the completion of experiment, GMH had led to significant losses in brain weight, body weight, and increased head-size to body ratio. It was demonstrated that GMH also led to significant increases of the spleen and heart weights. This injury had also led to significant neurological deficits at both the short and long-term.

Conclusions: Germinal matrix hemorrhage is the most important neurological problem associated with prematurity. In order study this condition further, pre-clinical animal models need to be developed and characterized.
This present animal model led to reproducible cerebral bleeding, hydrocephalus, neurological deficits, brain atrophy, and splenic and cardiac hypertrophy. Further translational investigations can now be used to test treatment strategies using this model, in the hope of one day improving the clinical situation for the neonatal and pediatric population.

Session: Neuroscience I

142 CLINICAL UTILITY AND YIELD OF INPATIENT ROUTINE ELECTROENCEPHALOGRAPHY

LL. Harris, TE. Losey Loma Linda University, Loma Linda, CA.

Purpose of Study: We reviewed all adult, inpatient EEGs performed in our hospital to study the yield of the test, identify clinical factors associated with EEG abnormalities, and to examine the impact of EEG results on clinical outcomes.

Methods Used: We retrospectively reviewed the reports of all adult inpatient EEGs conducted at Loma Linda University Medical Center from 1/1/09 to 6/30/09. EEGs were obtained using the International 10–20 system of electrode placement with Nicolet digital equipment. The duration was 20–40 minutes, and photic stimulation and hyperventilation were performed as activating procedures except when contraindicated. EEG results were recorded, and patient charts were reviewed for pertinent clinical and laboratory data. Spearman rank correlation and multiple regression analysis were performed with p < 0.05.

Summary of Results: 207 routine EEGs performed on 195 patients 18 to 94 years of age were identified. 83% of the EEGs were abnormal. 77% showed focal and/or generalized slowing, 4% captured triphasic waves, burst suppression was seen in 1%. Epileptiform discharges were present in 15% and electrographic seizures were seen in 3%, including 1% with status epilepticus. 71% of the EEGs were documented in patient chart. EEGs done in the ICU were more likely to be abnormal (94% versus 73%, p < 0.0001) and more likely to capture seizures (6% versus 1%, p = 0.0388). EEGs including wakefulness and sleep were more likely to capture epileptiform discharges (20%) compared with wake-only (11%) and sleep-only (13%) studies (p = 0.0685). Patients with normal EEGs had a shorter hospital stay after the EEG (mean = 3.5 days) than those with abnormal EEGs (mean = 12.1 days, p = 0.0001). Patients with epileptiform activity were more likely to have an AED started or increased (34% versus 11%, p = 0.0004).

Conclusions: Our study demonstrates that routine EEGs show a high percentage of abnormalities (83%) with fewer showing epileptiform activity (17%) and seizures or status epilepticus (3%), with studies performed in the ICU having higher yields. Abnormal EEGs were associated with longer hospital stays. Patients with normal EEGs were discharged an average of 8.6 days sooner than those with abnormalities. Patients with abnormal EEGs were also more likely to have CT scans ordered, suggesting that evidence of cerebral dysfunction in these EEGs may lead clinicians to search for structural lesions.

Session: Neuroscience I

143 IMMUNOHISTOCHEMICAL VERIFICATION OF STEREOTACTIC PROTON RADIOSURGERY TARGETING ACCURACY IN THE RAT BRAIN

L. Plesiu, A. Semotiuk, I. Zubkov, Y. Nie, R. Schulte Loma Linda University, Loma Linda, CA.

Purpose of Study: We developed a system for targeting functional areas in the rat brain with narrow proton beams. Due to the extremely sharp lateral dose falloff of high-energy proton beams, a cross-fire technique with multiple shoot-through beams converging on the target will be used to selectively irradiate small regions in the rat brain. Verification of the spatial accuracy of dose-delivery is crucial and needs to be verified. This ongoing study intends to verify the accuracy and precision of the targeting method by developing immunohistochemical staining protocols based on IgG leakage through the radiation-induced break-down of the blood-brain barrier (BBB) and various DNA damage markers.

Methods Used: Male Sprague-Dawley (8 weeks, 150-190g) rats were subjected to hemisphere irradiation with a cross-fire technique using 250 MeV proton beams at doses of 0 Gy and 25 Gy. IgG extravasation was used to show BBB damage from 4 to 72 hours after irradiation. 4% paraformaldehyde-perfused rat brains were cryostat sectioned and slide mounted. Sections then underwent immunohistochemistry by the ABC method (Santa Cruz Biotechnology). Radiation-induced H2AX phosphorylation of DNA double strand breaks (DSBs) was detected using γH2AX, which was visualized by Donkey-anti-mouse IgG Alexa Fluor 488 (green), while nuclei were counterstained with propidium iodide (PI, red).

Summary of Results: After 25 Gy proton irradiation, radiation-induced BBB damage resulted in IgG extravasation. Focal anti IgG immunostaining in rat brain sections was positive compared with no staining in a control animal. γH2AX immunofluorescence method was first tested and found to perform well in an in vitro PC12 cell line (rat pheochromocytoma), but the protocol needs to be adapted for in vivo rat brain sections.

Conclusions: IgG staining is sensitive to local vascular radiation damage which has the advantage of being maintained during longer time intervals (weeks rather than hours) compared to short-term DNA damage markers. The DSBs marker γH2AX can be used for rapid confirmation of the targeted area. IgG staining plus γH2AX immunofluorescence are both useful for verification of the targeting accuracy of small animal radiosurgery procedures with sub-millimeter resolution.

Session: Neuroscience I

145 INDIVIDUALIZING CANCER TREATMENT USING IMAGING: GLIOBLASTOMA AND AVASTIN

SK. Berkowitz, G. Kim, J. Qiao, J. Huo, J. Young, X. Xue, W. Pope University of California, Los Angeles, Los Angeles, CA.

Purpose of Study: Glioblastoma multiforme (GBM) is the most deadly primary brain cancer with a median survival of one year, thus necessitating improved treatment. Bevacizumab (Avastin) prolongs survival time, but only for a subset of GBM patients. We aim to use Apparent Diffusion Coefficient (ADC) histogram analysis of pre-treatment MRI scans to identify those patients, both with recurrent and upfront (initially diagnosed) GBM, who will positively respond to Bevacizumab.

Methods Used: The MRI scans of 82 recurrent GBM patients (41 Bevacizumab-treated, 41 control) and 85 upfront GBM patients (42 Bevacizumab-treated, 43 control) were examined using whole tumor ADC histograms fitted with a bimodal curve. The Kaplan-Meier method was used to analyze overall survival. Informed consent was obtained for this IRB-approved, HIPAA-compliant study.

Summary of Results: For recurrent GBM patients, ADC histogram analysis can be used to stratify overall survival. Among control patients, those with a high mean ADC from the lower curve (ADC LM) had a median survival time 151 days longer than those with a low ADC LM (p=0.0443). Among Bevacizumab-treated patients, those with a high ADC LM survived 200 days longer than those with a low ADC LM (p=0.0093). Therefore, ADC analysis has significant prognostic value and potential predictive value. For upfront GBM patients, the ADC histogram analysis is still in progress.

Conclusions: Before initiating treatment for patients with recurrent GBM, ADC histogram analysis can be used to identify those patients (high ADC LM) whose survival is more likely to be prolonged with Bevacizumab treatment. This potentially allows glioblastoma patients to have earlier, more individualized treatment decisions.

Session: Neuroscience I

146 PHOSPHO-FLOW AS AN IMMUNE MONITORING ASSAY FOR GLIOBLASTOMA PATIENTS UNDERGOING IMMUNOTHERAPY

M. Safaee1, D. Lisiero2,3, H. Soto1, L.M. Liu1,4,5, RM. Prins2,3,4,5 UCLA, Los Angeles, CA, 2UCLA, Los Angeles, CA, 3UCLA, Los Angeles, CA, 4UCLA, Los Angeles, CA and 5UCLA, Los Angeles, CA.

Purpose of Study: Immunotherapy is as a promising treatment for glioblastoma, the most malignant form of primary brain tumor. Predicting the success of treatment has proven difficult due to the inability of immune monitoring assays to correlate with clinical outcomes. We hypothesized that FACS analysis of phosphorylated signal transduction and activator of transcription (STAT) proteins from peripheral blood mononuclear cells (PBMCs) may provide insight towards a patient’s ability to produce a clinically effective immune response.

Methods Used: Single-cell, phosphorylated-STAT-specific flow cytometry (Phosphoflow) was performed on PBMC’s from healthy donors and glioblastoma patients before and after dendritic cell vaccine therapy (FDA IND #11053).
PBMCS were stimulated with graded concentrations of interferon-gamma (IFN-\(\gamma\)) or interleukin-2 (IL-2). Signal transduction activity was determined by quantifying levels of phosphorylated STAT-1 (pSTAT-1) and phosphorylated STAT-5 (pSTAT-5) in CD3+CD4+ helper T cells, CD3+CD4- T lymphocytes, and CD3-CD4+ monocytes.

**Summary of Results:** Phosphoflow is capable of identifying discrete cellular variations in STAT phosphorylation. Increasing concentrations of IFN-\(\gamma\) and IL-2 produced a graded response in T cells and monocytes from healthy donor PBMCS. Variable responses were observed in comparing patients before and after dendritic cell vaccine treatment. While most appear to follow trends of increasing activity with stimulation, it is unclear whether or not these findings are statistically significant or correlate to clinical outcomes.

**Conclusions:** Phosphoflow provides a powerful assay for quantifying the ability of immune cells to respond to cytokine stimulation. Additional analysis will be performed on PBMCS from glioblastoma patients before and after treatment to identify possible correlations between responses to cytokine simulation and clinical prognosis and outcome. Identifying variations in cell signal transduction may aid in the identification of patient subpopulations most likely to mount effective clinical responses from immune-based therapies.

**Session:** Neuroscience 1 146

**RISK FACTORS FOR POSTTRAUMATIC CEREBRAL VSASOPASM**


**Purpose of Study:** Posttraumatic vasospasm (PTV) is an under-recognized cause of ischemic damage after traumatic brain injury (TBI) and independently predicts poor outcome. Guidelines for screening and management do not exist, partly due to limited understanding of its pathogenesis and risk factors. A detailed review of clinical, laboratory, and radiographic risk factors for PTV has not been previously reported.

**Methods Used:** A database review of 397 patients with TBI yielded 49 with severe TBI that met inclusion criteria. 11 of these developed clinically significant PTV, defined as decline in neurological function or brain tissue oxygenation associated with arterial vasospasm on CT angiogram. Demographic, clinical, laboratory, radiographic, and outcome data were compared in patients with and without PTV.

**Summary of Results:** The development of PTV did not correlate with age, gender, ethnicity, degree of severe TBI, or the following admission laboratory values: urine toxicology, hemoglobin, platelets, INR, serum Na+, K+, Ca2+, Mg2+, or glucose. Fever and leukocytosis on admission were strongly associated with PTV (\(p = 0.01, p < 0.01\)), and admission hypothermia was inversely related to PTV (\(p < 0.01\)). Rotterdam CT Score correlated with development of PTV (\(p = 0.02\)); patients with PTV were not only more likely to have cortical (\(p = 0.02\)) or subcortical hemorrhage (SAH), but also parenchymal contusions (\(p = 0.02\)). Skull fractures, midline shift, and epidural/subdural hematoma were not significant risk factors.

**Conclusions:** For the first time, we have identified strong correlations of fever and leukocytosis with the development of PTV, suggesting a role for inflammatory pathways in its pathogenesis. We have expanded radiographic risk factors beyond SAH, which is known to promote aneurysmal vasospasm, to include parenchymal contusions, which may be markers of diffuse mechanical injury to vessels. These results suggest that Rotterdam CT score may be more appropriate than GCS for determining PTV risk, and that anti-inflammatory therapies may be highly effective in the prevention and management of PTV. Since past studies correlate untreated PTV with poor outcome, our data suggest that aggressive treatment can prevent the permanent neurological consequences of PTV.

**Session:** Neuroscience 1 147

**EARLY METABOLIC CHANGES OF MILD TRAUMATIC BRAIN INJURY REVEALED BY 3D MAGNETIC RESONANCE SPECTROSCOPIC IMAGING AT 3T**


**Purpose of Study:** Conventional MRI does not accurately predict outcome in mild TBI, but proton MR spectroscopy has shown promise as a potential biomarker for injury severity and outcome. In this study, we utilized 3D MRSI at 3T to assess TBI in specific white matter tracts.

**Methods Used:** 18 patients with mild TBI (GCS 13-15) and 10 healthy volunteers were scanned on a GE 3T EXCITE scanner. All TBI patients witnessed lost consciousness and post-traumatic amnesia, and were scanned within two weeks of injury. NAA/Cho ratios from the patient group were compared with control subjects using a two-tailed t-test (statistical significance at \(p = 0.05\)). Regional comparisons were performed in posterior cingulum bundle (PCB), anterior cingulum bundle (ACB), superior longitudinal fasciculus (SLF), splenium of the corpus callosum (SCC), and superior corona radiata (SCR). Bilateral ROIs were placed in all the regions except SCC to evaluate for hemisphere asymmetry.

**Summary of Results:** NAA/Cho ratios for the right and left ROIs in PCB and ACB did not show statistically significant differences for both the control and patient groups and were averaged for the analysis. NAA/Cho ratios for the left and right ROIs in SLF and SCR did show significant differences and were not combined. NAA/Cho ratios were significantly lower in the TBI group than the control group for PCB and right SLF, with a strong trend towards lower NAA/Cho ratio in the left SLF. ACB also trended towards lower values in the TBI group.

**Conclusions:** This 3T MRSI study of early mild TBI demonstrates reduced NAA/Cho ratios in association tracts, specifically the cingulum bundle and the superior longitudinal fasciculus, but not in projection tracts such as the corona radiata and posterior commissural tracts such as the splenium of the corpus callosum. This regional metabolic variation among white matter tracts may reflect the cognitive impairment of mild TBI. Future work will correlate this tract-specific variability to neurocognitive and functional outcome measures to validate MRSI as a biomarker for mild TBI.

**NAA/Cho ratios for various regions**

<table>
<thead>
<tr>
<th></th>
<th>PCB</th>
<th>ACR</th>
<th>R SLF</th>
<th>L SLF</th>
<th>SCC</th>
<th>R SCR</th>
<th>L SCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild TBI</td>
<td>2.26±0.31</td>
<td>1.69±0.36</td>
<td>2.64±0.28</td>
<td>2.22±0.52</td>
<td>2.87±0.54</td>
<td>2.00±0.60</td>
<td>2.20±0.35</td>
</tr>
<tr>
<td>Control</td>
<td>2.78±0.61</td>
<td>1.97±0.53</td>
<td>3.34±1.35</td>
<td>2.63±0.90</td>
<td>2.54±0.54</td>
<td>1.96±0.52</td>
<td>2.39±0.49</td>
</tr>
</tbody>
</table>

**P value**

- 0.006
- 0.12
- 0.840
- 0.067
- 0.72
- 0.66
- 0.25

**Session:** Neuroscience 1 148

**NEUROPATHY INDUCED BONE LOSS FOLLOWING CHRONIC CONSTRICTION INJURY IN MICE**

AC. Rothenberg1,2, S. Bain3 University of Washington School of Medicine, Seattle, WA and 2University of Washington, Seattle, WA.

**Purpose of Study:** Nerve injuries associated with musculoskeletal trauma are known to effect bone homeostasis. However the precise mechanisms underlying neuronal effects on regulating bone metabolism remain unclear. In this context, animal studies have recently demonstrated that experimentally-induced nerve injuries can disrupt bone remodeling, leading to a deterioration and loss of trabecular bone. Up to now, nerve injury models have failed to assess the role that diminished osteoblastic activity may play in the pathogenesis of neuropathy-induced bone loss. Accordingly, we set out to characterize osteoblastic response and osteopathic changes due to a chronic constriction injury (CCI) of the sciatic nerve of wild type mice.

**Methods Used:** A CCI of the sciatic nerve was created in 5 animals by applying a polyethylene cuff to the sciatic nerve of the right hind limb. An identical dissection was performed on 5 control mice, omitting placement of the cuff (sham procedure). In vivo microCT scans of experimental limbs were performed on the day of surgery and at 14- and 28-day intervals afterwards to determine changes in bone architecture as well as calf muscle volumes. Histomorphometric analysis was performed using sections of experimental tibias taken following sacrifice.

**Summary of Results:** There was a significant (\(P < 0.05\)) decrease of trabecular bone volume, bone volume/tissue volume and trabecular number and an increase in trabecular spacing at the metaphysis of both CCI and sham groups at both 14 and 28 days post surgery. There were no significant changes in cortical bone or calf volume parameters. The periosteal bone formation rate of sham animals was decreased (\(P = 0.04\)). However, there were no other significant differences in endosteal or periosteal labeled surface, mineralizing surface, mineral apposition rate or bone formation rate.

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Conclusions: Measures of osteoblastic activity were inconclusive in elucidating their potential role in neuropathy-induced bone loss. Marked loss of trabecular bone following CCI further demonstrates that osteopathic changes are associated with nerve injuries. Even greater changes in sham animal trabecular bone measures expands the range of neuropathy models to include simple manipulation of a nerve. Future studies to corroborate this latter claim are necessary.

Session: Neuroscience I
149 TESTOSTERONE EFFECTS IN A MODEL OF PRETERM BIRTH
NC. Llarena1, SR. Mayoral2, G. Omar3, AA. Penn1 1Stanford University, Stanford, CA; 2Stanford University School of Medicine, Stanford, CA and 3Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Preterm birth puts infants at an elevated risk for lifelong cognitive and motor deficits. These handicaps are associated with reduced brain volumes and occur with greater frequency in males than in females. Consistent with this sex disparity, we have recently demonstrated sex-specific hippocampal volume loss in neonatal male mice exposed to chronic sublethal hypoxia. We are now testing the hypothesis that exogenous testosterone influences this brain volume loss.

Methods Used: C57BL/6 pups were implanted subcutaneously with 0.01mg testosterone or placebo pellets on postnatal day 2. Pups were exposed to hypoxic conditions (10% O2) from P3-P11. Control litters were kept in normoxic conditions (21% O2). Tail clippings were sex-typed by PCR. Fixed brains were cryoprotected, frozen and sectioned sagittally by sliding microtome at 90um. For unbiased stereological volume analysis, every 5th section from 1 hemisphere was collected, cresyl violet-stained and kept in normoxic conditions (21% O2). Tail clippings were sex-typed by

Summary of Results: Testosterone increases total body and brain weights relative to placebo-treated pups raised in chronic sublethal hypoxia. Treatment with exogenous testosterone does not alter hippocampal volumes under normoxic conditions. There are, however, sex-specific changes in brain volume with testosterone treatment. Testosterone treatment reduces hypoxia associated hippocampal volume loss in female pups. Further analysis is in progress to determine whether changes in hippocampal volume correlate with changes in cell proliferation or neuron size. Further experiments are in progress to investigate whether testosterone affects its affects through the androgen receptor or by conversion to estrogen via aromatase, and to elucidate the effects of dosing and treatment time.

Conclusions: Exogenous testosterone decreases hippocampal brain volume loss to the hippocampus in female pups. Testosterone treatment also reduces loss of body and brain weight induced by hypoxia in both sexes. These surprising results invite further investigation into the mechanisms of testosterone action.

Session: Neuroscience I
150 INFANT ARACHNOID CYSTS HAVE A DIFFERENT NATURAL HISTORY THAN ARACHNOID CYSTS IN LATER CHILDDOOD
D. Krivosheya, A. Singhal, DD. Cochrane, P. Steinbok University of British Columbia and British Columbia Children’s Hospital, Vancouver, BC, Canada.

Purpose of Study: Pediatric arachnoid cysts can be diagnosed as an incidental finding in head imaging studies. The literature provides little to guide decision making regarding need for follow-up. Given the limited natural history studies for this condition, the current study aims to examine growth patterns over time, and to identify any factors that are associated with cyst growth.

Methods Used: A retrospective chart review of pediatric patients with a diagnosis of intracranial arachnoid cyst was performed, selecting patients who did not initially undergo surgical intervention. Using cyst volume calculation on serial images, we determined whether asymptomatic arachnoid cysts in this population of patients change in size over time.

Summary of Results: 51 asymptomatic non-operated intracranial arachnoid cysts were identified. The majority of arachnoid cysts did not grow (n = 38, 75%) on serial imaging, while 20% (n = 10) increased in size and 6% (n = 3) decreased. In patients diagnosed under 1 year of age, 9/17 showed growth of the cyst, while only 1/34 patients diagnosed over 1 year of age showed growth of the cyst (p < 0.0001). The location and initial size of the cyst did not appear to correlate with cyst growth.

Conclusions: This represents the largest natural history study of pediatric arachnoid cysts, to date. Age at diagnosis correlated with growth of the arachnoid cyst, with infants having a high probability of growth. It may be that close serial imaging is justified in the younger child diagnosed with an asymptomatic arachnoid cyst, while less frequent imaging is indicated in the older child.

Session: Neuroscience I
151 USING FUNCTIONAL MAGNETIC RESONANCE IMAGING AND AN AUDITORY STROOP INTERFERENCE TASK TO ISOLATE LANGUAGE-ATTENTION NETWORKS IN THE BRAIN
J. Lockwood1, K. Almryde2, L. Fidler2, E. Plante2, T. Christensen2 1University of Arizona College of Medicine, Tucson, AZ and 2University of Arizona, Tucson, AZ.

Purpose of Study: The role of attention is a critical factor in understanding how the human brain processes language. Attention studies that involve functional magnetic resonance imaging (fMRI) have used mostly visual tasks to isolate the patterns of neural activation in the brain that result from varying attention demands. The purpose of this study was to use fMRI analysis along with an auditory Stroop interference task to help isolate the attention systems in the brain that are specifically engaged in processing spoken language.

Methods Used: Fourteen participants were scanned while listening through headphones to a series of common nouns spoken by both men and women. Words were female, male or neutral gendered. Trials where the voice gender matched the word gender (congruent) tested facilitation whereas trials where the voice and word gender were in conflict tested interference. Trials with words that had no gender connotation (neutral) served as controls. In the first task, subjects had to attend to the voice gender while attempting to ignore gender meaning. In the second task, they had to attend to the gender meaning irrespective of the voice.

Summary of Results: For all gender combinations, reaction times were significantly greater (p < 0.001) for attending to word gender. Both conflict and congruent conditions had longer reaction times (p = 0.02) and lower accuracy rates (p = 0.003) than controls. Cortical areas showing the strongest Stroop interference effect included middle cingulate cortex and cuneus (p < 0.05). Significant activity was also observed in subcortical areas (lentiform nuclei, thalamus, and medial temporal areas).

Conclusions: Using our auditory Stroop paradigm, we observed significant Stroop interference, but not facilitation. As expected, some brain regions (e.g., right cingulate cortex) agreed with previous visual conflict-processing studies. However, while our data support the hypothesis that cingulate cortex is involved in sensory conflict resolution, distinct sub-regions within cingulate and nearby cortical regions appear to be specialized for processing different sensory modalities.

Session: Neuroscience I
152 PERSISTENT ELEVATED HUMAN IMMUNODEFICIENCY VIRUS DNA LEVELS IN CD14+/CD16+ MONOCYTES IN PATIENTS WITH HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS
AW. Marshall, M. Agsalda, I. Kusao, D. Trolelstrup, V. Velasco, B. Shiramizu University of Hawaii, Honolulu, HI.

Purpose of Study: Neuronal damage can lead to HIV-associated neurocognitive disorders (HAND) with symptoms including: decline of cognitive, memory, and motor functions. Despite highly active antiretroviral therapy (HAART), HAND continues to cause morbidity. The neuronal pathology is thought to develop similar to the Trojan horse paradigm where HIV-infected activated monocytes (CD14+/16+) cross the blood brain barrier and release proinflammatory cytokines resulting in neuronal damage. The purpose of this study was to examine the role of CD14+/16+ cells as potential reservoirs of HIV DNA. We hypothesize that HIV DNA levels correspond to the patient’s degree of neurocognitive status.
Methods Used: Peripheral blood mononuclear cells (PBMC) were collected at 3 annual time points over 4 years from 12 HIV positive patients enrolled in the Hawaii Aging with HIV Cohort. At the time of entry, the patient’s neurocognitive status was diagnosed with HIV-associated dementia (HAD), minor cognitive motor disorder (MCMD), or normal cognition (NC). The PBMC samples were magnetically separated into CD14+/CD16+ and non-monocytic (CD14-) fractions. HIV DNA levels were measured using a multiplex real-time PCR assay.

Summary of Results: A significant increase (p < 0.05) in mean HIV DNA copies in CD14+/CD16+ cells from patients diagnosed with HAD versus patients with NC over the four consecutive years was observed.

Conclusions: The data suggest that HIV DNA copies in activated monocytes reflect the HAND status of patients and remain high in spite of HAART.

Pulmonary and Critical Care I Concurrent Session
8:30 AM Friday, January 29, 2010

Session: Pulmonary and Critical Care I
154 FREQUENCY COMB SPECTROSCOPY EXHALED BREATH BIOMARKERS
K. Crader, JJ. Repine, JE. Repine UCHSC, Denver, CO.

Purpose of Study: The purpose of our research is to determine if frequency comb spectroscopy could be adapted and used to measure molecules reflecting inflammation and oxidative stress in exhaled breath samples. Since the technique has not been rigorously used for this purpose previously, our initial goal is to define the optimal ways for collecting, standardizing, storing, transporting, and analyzing breath samples for study using frequency comb spectroscopy. The long-term objective is to eventually use the approach to assess inflammation and oxidative stress in individuals with a variety of diseases. The approach has appreciable potential for providing useful information because it is non-invasive and samples can be repeated frequently providing trend analysis. The technology also has the capacity to measure multiple molecules simultaneously with the advantage of providing a battery of factors. The latter might produce distinguishing patterns useful for diagnostic or therapeutic purposes. Finally, the technique measures molecules accurately and with great sensitivity (parts/billion).

Methods Used: The approach will be to measure multiple breath samples in individuals using mid-infrared frequency comb spectroscopy, which is a Nobel prize winning technology developed and utilized by John Hall and Jun Ye at the University of Colorado.

Summary of Results: Our first experiments will be to evaluate the breath of healthy men and women of all ages. We will determine the reproducibility of the measurements by repeating each measurement on a number of occasions. We will validate measurements made using frequency comb spectroscopy using conventional assays.

Conclusions: Frequency comb spectroscopy may provide a way of non-invasively evaluating individuals with a variety of diseases. The findings might provide new information regarding the causes of a particular disorder and new insights for treatment and prevention.

Session: Pulmonary and Critical Care I
155 HSP-70 LEVELS DECLINE IN DECEASED CRITICALLY ILL PATIENTS, RISE IN ALIVE CRITICALLY ILL PATIENTS FOLLOWING ADMISSION TO THE ICU
AG. Edwards, PE. Wischmeyer University of Colorado School of Medicine, Aurora, CO.

Purpose of Study: Heat Shock Protein 70 (HSP70) is a vital stress response protein key to cellular response/survival from illness and injury. Increased HSP70 levels have been shown in experimental models to reduce myocardial and lung injury, as well as improve clinical outcome in experimental sepsis. Very limited clinical data has revealed enhanced plasma HSP70 (pHSP70) expression may be associated with improved clinical outcome. We tested the hypothesis that elevated pHSP70 expression at ICU admission would correlate with reduction of 28 day ICU patient mortality. Second, we hypothesized ICU survival would correlate positively with increasing levels of pHSP70 relative to admissions levels.

Methods Used: 73 critically ill patients had blood collected at multiple timepoints for pHSP70 (ICU Day 0–7). Patients were from a non-selected subgroup obtained from a total of 200 patients enrolled in a prospective observational ICU trial. Plasma analyzed for HSP70 using Mesoscale technology (Mesoscale Discovery, Inc.). Data then correlated to 28 day ICU survival. Initial statistics via t-test.
Summary of Results: Patients alive 28 days post-ICU admit showed increasing pHSP70 levels over time relative to baseline admission pHSP70 (115.85% of baseline), whereas patients who expired showed a decrease in pHSP70 levels over time relative to baseline admissions levels (88.84% of baseline, p = 0.05). Additionally, patients who expired had higher mean admission pHSP70 (92.89 ng/ml) vs. patients alive at 28 days post-ICU admit. (44.68 ng/ml p = 0.05).

Conclusions: Our data reveal ICU patients who survived to day 28 post-ICU admission have lower baseline (admission) levels of pHSP70, and showed increasing pHSP70 over time. This suggests therapeutic enhancement of pHSP70 levels improve ICU survival. Further, elevated baseline pHSP70 levels may serve as predictor of ICU mortality.

Session: Pulmonary and Critical Care I
156
IMPLEMENTATION OF A POST-CARDIAC ARREST CARE BUNDLE INCLUDING EARLY GOAL-DIRECTED THERAPY AND THERAPEUTIC HYPOTHERMIA: A FEASIBILITY STUDY
K. Morawski, HB. Nguyen, D. Ramsingh, K. Lumen, C. Davis, J. Dorotta, D. Bland, K. Clem Loma Linda University, Loma Linda, CA.

Purpose of Study: Therapeutic hypothermia (TH) improves outcome in comatose patients with return of spontaneous circulation (ROSC) after cardiac arrest. Since the post-cardiac arrest syndrome (PCAS) has similar circulatory dysfunction as septic shock, guidelines also recommend early goal-directed therapy (EGDT) for post-cardiac arrest resuscitation. This study examines whether a standard care bundle including TH and EGDT will facilitate the management of PCAS and benefit patients suffering from out-of-hospital cardiac arrest.

Methods Used: A 2-year before-and-after study was performed at a tertiary academic medical center, including historical control (Year-1) and post-intervention (Year-2) comatose patients with ROSC after out-of-hospital cardiac arrest. Completion of the bundle components: 1) temperature 32–34°C within 4 hours; 2) TH maintained for 24 hours; 3) CVP;ScvO2 monitoring; 4) CVP > 12 mmHg, MAP > 65 mmHg, and ScvO2 > 70% within 6 hours; and 5) decreasing lactate within 24 hours was examined in Year-2. In-hospital mortality was compared between Year-1 and Year-2.

Summary of Results: Fifty-five patients with age 63+/-13 years, APACHE II 26+/-6 were enrolled. Completion of the bundle in 29 patients during Year-2 is shown in figure, with mortality 55.2% compared to 69.2% mortality in 26 patients during Year-1 (p=0.29).

Conclusions: A post-cardiac arrest care bundle can be implemented with similar clinical benefits observed in previous clinical trials examining TH.

Session: Pulmonary and Critical Care I
157
HIGH ALTITUDE HYPOXIA ALTERS RIGHT VENTRICULAR FUNCTION IN HEALTHY VOLUNTEERS
BJ. Jaiswal1,2, E. Kortekaas3, S. Vemulakonda1-2, K. Ruhl1, G. Foster1-2, J. Anholm1 Loma Linda University, Loma Linda, CA; 1VA Loma Linda, Loma Linda, CA and 3Unversity Medical Center Utrecht, Utrecht, Netherlands.

Purpose of Study: Ascent to high altitude (HA) reduces exercise capacity due to the fall in arterial oxygen tension and possibly impaired ventricular function. Left ventricular function is minimally altered at HA. The effects of prolonged hypoxia on right ventricular (RV) function are not well described. Tricuspid Annular Systolic Excceleration (TAPSE) is a sensitive echo-derived measure of RV systolic function. Doppler provides useful indices specific for RV diastolic function: tricuspid inflow (TI) velocity measures the rate of flow of blood from right atrium to right ventricle through the tricuspid valve and reflects RV relaxation. Tissue Doppler Imaging (TDI) of the velocity of the RV free wall motion is an additional measure of diastolic right heart function.

The purpose of this study was to determine the effects of altitude hypoxia on RV systolic and diastolic function in healthy volunteers.

Methods Used: 14 healthy participants of the Medex 2008 Expedition to the Dhaulagiri region of Nepal were included in the study. Transthoracic echocardiography was performed at sea level (SL) and after a 14 day trek to HA at 5050m. Systolic function was assessed by TAPSE. Diastolic function was assessed by tricuspid inflow (TI) E and A wave velocities and tissue Doppler imaging (TDI) of the velocity of the RV free wall motion was examined in Year-2. In-hospital mortality was compared between Year-1 and Year-2.

Summary of Results: Oxygen saturation and TAPSE were significantly decreased at HA compared with SL. TI peak velocities were significantly lower at HA than at SL.

Conclusions: A decrease in TAPSE and TI peak velocities suggests that both RV systolic and diastolic function is altered after prolonged hypoxic exposure at HA in healthy subjects.

Results

<table>
<thead>
<tr>
<th></th>
<th>Sea level (SL)</th>
<th>High Altitude (HA)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2 (%)</td>
<td>98.9±1.4</td>
<td>82.1±5.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>86±11</td>
<td>74±11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>25.4±3.2</td>
<td>22.1±2.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TI E/A</td>
<td>1.8±0.5</td>
<td>1.3±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TDI E/A*</td>
<td>1.6±0.6</td>
<td>1.5±0.7</td>
<td>NS</td>
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</tbody>
</table>

Session: Pulmonary and Critical Care I
158
SMOKING REDUCES SURFACTANT PROTEIN D AND PHOSPHOLIPID IN LAVAGE FROM SMOKING WITH AND WITHOUT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
JM. More1,2, D. Voelker1, ED. Chan1, RP Bowler1 National Jewish Health, Denver, CO and 2Stanford University, Stanford, CA.

Purpose of Study: Surfactant protein D (SP-D), a member of the collectin family of proteins, participates in innate immune processes of the lung. Although SP-D is predominantly in lung lining fluid, there are no reports of SP-D and phospholipids in the bronchoalveolar lavage fluid (BALF) of...
COPD patients. Thus, in this study, we hypothesized that COPD patients would have lower BALF SP-D levels compared to healthy smoking and non-smoking controls.

Methods Used: To test our hypothesis we measured BALF SP-D levels in 110 volunteers (46 smokers and 64 never smokers) using an enzyme-linked immunosorbent assay (ELISA). SP-D was corrected for lavage dilution using urea blood/BALF concentration. BALF phospholipid content was also measured. A diagnosis of COPD was made by post-bronchodilatory spirometry using forced expiratory volume at one second divided by forced vital capacity (FEV1/FVC).

Summary of Results: BALF SP-D (urea corrected) was found to be lowest in current smokers (12.8 μg/mL ± 11.0 μg/mL), higher in former smokers (25.2 μg/mL ± 13.7 μg/mL), and highest in never smokers (52.4 μg/mL ± 7.2 μg/mL; P < 0.008). BALF SP-D was lower in COPD subjects (19.1 μg/mL ± 12.9 μg/mL) compared to healthy non-smokers (51.8 μg/mL ± 7.2 μg/mL) but higher compared to healthy smokers (16.0 μg/mL ± 11.8 μg/mL; P < 0.012). Among smokers, there was a correlation between BALF SP-D and FEV1/FVC ratio (P < 0.016), but not percent-predicted FEV1. There were no correlations between BALF SP-D and age, sex, or pack years in smokers or non-smokers. Recovered BALF phospholipids were also lowest in current smokers (6.5 nmol ± 1.5 nmol), higher in former smokers (13.2 nmol ± 2.0 nmol), and highest in never smokers (14.9 nmol ± 1.1 nmol; P < 0.0001). Among all study groups, the ratio of SP-D to phospholipids in BALF remained relatively constant.

Conclusions: These data suggest that smoking and particularly current smoking are associated with lower recovered phospholipid and SP-D levels in lungs using fluid. Lower amounts of phospholipids, SP-D and other collectins may explain more rapid progression of disease and increased incidence of infections in COPD patients. Our findings also highlight the importance of standardized normalization of BALF SP-D measurements for future biomarker studies.

Session: Pulmonary and Critical Care I

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3- MERCAPTOPYRUVATE DITHIANE IN THE TREATMENT OF CYANIDE TOXICITY IN A RABBIT MODEL

J. Ju1,2, JG. Kim2, J. Lee2, S. Mahon2, D. Lemor2, S. Patterson3, M. Brenner1,2
1University of California, Irvine, Orange, CA; 2University of California, Irvine, Irvine, CA and 3University of Minnesota, Twin Cities, MN.

Purpose of Study: There are currently no agents capable of mass casualty cyanide (CN) treatment. Sodium 3-mercaptopyruate dithiane (3-MPDT) is a prodrug of 3-mercaptopyrivate (3-MP); a substrate for the enzyme, 3-mercaptopyrivate/cyanide sulfur transferase. 3-MPDT can convert cyanide to nontoxic thiocyanate. Because it has rapid onset of action and can be easily administered via intramuscular injection, we hypothesized that 3-MPDT has potential for development as a novel CN reversal agent.

Methods Used: New Zealand white rabbits were given 10 mg sodium cyanide, intravenously over 60 min. At the end of the cyanide infusion, the rabbits were injected with 3-MPDT via intravenous (n=6) at 0.05 mmol or intramuscular routes (n=12) at 0.05mmol or 0.21mmol, and compared to control animals who received CN without antidote. Quantitative continuous wave near infrared spectroscopy (CWNIRS) monitoring of tissue oxy- and deoxyhemoglobin concentrations were performed continuously and venous blood cyanide levels were measured at baseline and intermittently throughout CN infusion and reversal.

Summary of Results: The elevated concentrations of blood cyanide after cyanide infusion decreased progressively after both intravenous and intramuscular injections of 3-MPDT. The CWNIRS measured rate of recovery of deoxyhemoglobin concentration to baseline time constant for 0.05 mmol IV infusion of 3-MPDT in the muscles was 12.66 ± 4.83 min compared to 37.06 ± 16.59 min for 0.05 mmol IM injection, p<0.02. The time constants for 0.05 mmol IV infusion versus 0.21 mmol IM injection (which had a time constant of 12.42 ± 3.27 min), were similar, p=0.92.

Conclusions: 3-MPDT is a rapidly acting agent for cyanide poisoning that can be easily administered by intramuscular injection and appears to be effective in reversing the physiologic effects of cyanide toxicity. The cyanide reversal was more rapid with the IV compared to IM administrations at equivalent doses. However, high dose intramuscular injection of 3-MPDT appears equivalent to lower dose IV effects and suggest it may be a potential antidote for the treatment of mass casualty cyanide exposures.

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NITRIC OXIDE METABOLISM IN FETAL AND ADULT PLASMA

K. Vrancken1, GG. Power2, LD. Longo2, AB. Blood1,2 1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA.

Purpose of Study: Nitric oxide (NO) is an endogenous vasodilator. A portion of NO entering blood is oxidized to nitrite in the plasma. Recent study suggests plasma nitrite can be converted back into vasodilating amounts of NO by reaction with deoxyhemoglobin (deoxyHb). The fetus has higher circulating concentrations of deoxyHb than the adult. Furthermore, fetal deoxyHb reduces nitrite to NO approximately twice as fast as adult Hb, yet nitrite concentrations in the fetal blood are the same as in maternal blood under normal conditions. We hypothesized that, matching its more rapid disappearance by deoxyHb, nitrite would more rapidly form from NO in fetal than adult plasma.

Methods Used: We used plasma obtained from four sources: human adult and fetal cord blood and sheep adult and cord blood. In airtight chamber containing a NO probe, we determined the rate of NO disappearance from plasma after NO levels had been increased (7 μM) using an NO donor. Assuming a mono-exponential decay the half-life of NO in plasma and saline was determined.

Summary of Results: The half-life of NO in human cord plasma was 24.0 ± 1.2 sec (n = 6), significantly shorter than in adult plasma (32.4 ± 1.5 sec, n = 5; P<0.001). Conversely, the elimination half-life of NO was longer in sheep fetal plasma (59.5 ± 2.4 sec, n = 11) compared to the adult (48.0 ± 1.8, n = 10; P<0.001). The elimination of NO from saline was significantly slower than from all plasmas (276.0 ± 23.3).

Conclusions: Human cord blood plasma has a significantly faster NO metabolism than human adult plasma. Surprisingly, this difference is reversed in sheep plasma. We are currently trying to answer the questions this poses, speculating it may relate to ceruloplasmin, a plasma protein that may facilitate NO oxidation to nitrite.

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STUDYING THE FERROPORTIN EXPRESSION IN THE MOUSE EYE AND BRAIN

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Purpose of Study: Heparicin is a small peptide hormone that is the principal regulator of iron absorption and distribution among tissues. Heparcin binds to ferroportin (FPN), its receptor, on membranes of duodenal enterocytes, macrophages and hepatocytes. These cells normally export iron into plasma through ferroportin. Upon binding heparicin, ferroportin is endocytosed and degraded, and iron export to plasma is diminished. Continued consumption of iron then decreases plasma iron levels. Our understanding of iron regulation is limited to the periphery and little is known about iron regulation inside the blood-brain-barrier. To determine how the heparicin-FPN system functions in the CNS, I am analyzing the expression of ferroportin on the different cells within the retina and brain in knock-in mice whose endogenous FPN has been tagged with green fluorescent protein (GFP). FPN-GFP may be
directly observable in highly expressing tissues under fluorescence microscopy, or in lower-expressing cells by immunostaining for GFP.


Detecting protein expression in tissues requires fixing them in a solution of formaldehyde in order to immobilize proteins. Because this step can interfere with GFP detection by changing the protein’s conformation, I assessed a variety of fixation techniques to detect their effects on GFP fluorescence. I grew HEK 293 (Human Embryonic Kidney) cells that were expressing GFP-FPN on Poly-D-Lysine chamber slides and multi-well plates and induced them with ponasterone A. Fixatives at different concentrations (4% and 10% formalin, 4% paraformaldehyde) were used and fixations were stopped at different times (10 minutes up to 24 hours) and analyzed by epifluorescent microscopy and flow cytometry for GFP signals. These experiments suggest an optimal GFP signal at 10 minutes of fixation in 4% formalin, with a decline in GFP fluorescence intensity as fixation time is increased.

Summary of Results: These experiments suggest an optimal GFP signal at 10 minutes of fixation, with 4% formalin preserving the proteins the best. They also show a declining pattern in detection of GFP over time.

Conclusions: We are using the optimal fixation condition as well as the antibodies to understand ferroportin expression in the eyes intimately.

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CORRELATION BETWEEN VENOUS BLOOD GAS AND ARTERIAL BLOOD GAS MEASUREMENTS IN HEALTHY YOUNG ADULTS

R. Tone, J. Rook, M. Allard
Loma Linda University School of Medicine, Loma Linda, CA.

Purpose of Study: To determine whether VBG values can be used to predict ABG values in clinical settings.

Methods Used: 106 healthy volunteers between the ages of 18 and 30 years and mass between 50 and 100 Kg were consented to participate in this IRB approved study at Loma Linda University Medical Center. Each subject had one 22 gauge radial arterial line plus one 16 gauge peripheral IV placed and baseline samples were drawn and analyzed for arterial and venous pH, pCO2, base excess, HCO3-, on an ABL 800 radiometer. Following phlebotomy of 450 cL of blood, 3 additional time matched arterial and venous samples were obtained and analyzed during Isolyte hemodilution after the following intervals: 11% infusion, 78% infusion, and 100% infusion. Data from all 106 volunteers was analyzed using Pearson correlation and Bland-Altman limits of agreements (LOAs) for pH, pCO2, base excess, and HCO3-. Summary of Results: See table below.

Conclusions: Venous and arterial values for HCO3- and base excess correlate well according to Pearson correlation (R = 0.92 and 0.87 respectively). Additionally, by comparing the Bland-Altman limits of agreement (LOAs) with the standard reference ranges for arterial blood gas, we can make conclusions about whether or not the LOAs for each parameter represent clinically relevant ranges. The LOAs for HCO3- (~1.31 to 0.62) appear to be narrow enough for substitution as the reference range for arterial HCO3-. The LOAs for base excess (~2.3 to 0.3) also appear to be narrow enough for substitution as the reference range for arterial base excess represents a difference of ±6 mmol/L and the LOAs represent a difference of only 1.7 mmol/L. Thus, this data suggests that venous sampling can be substituted for arterial sampling when examining HCO3- and base excess in healthy young adults when these values are in the normal range.

The following table displays the reference ranges and results for pH, pCO2, base excess, and HCO3-.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Range</th>
<th>Mean VBG</th>
<th>Mean ABG</th>
<th>Mean Difference</th>
<th>95% LOA</th>
<th>±1.96 StdDev</th>
<th>R value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35 to 7.45</td>
<td>7.387</td>
<td>7.416</td>
<td>0.029</td>
<td>-0.003 to 0.061</td>
<td>0.032</td>
<td>0.74</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>35 to 45</td>
<td>44.04</td>
<td>38.02</td>
<td>-6.02</td>
<td>-12.3 to 0.2</td>
<td>6.2</td>
<td>0.74</td>
</tr>
<tr>
<td>HCO3- (mmol/L)</td>
<td>22 to 26</td>
<td>24.8</td>
<td>24.43</td>
<td>-0.35</td>
<td>-3.1 to 0.62</td>
<td>0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>base excess (mmol/L)</td>
<td>-3 to 3</td>
<td>-1.31</td>
<td>-0.12</td>
<td>-1.43</td>
<td>-3.2 to 0.3</td>
<td>1.7</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Surgery 1

Concurrent Session
8:30 AM
Friday, January 29, 2010

Session: Surgery I

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COMPARISON OF LOCKING AND GRASPING LOOP CONFIGURATIONS USING FIBERWIRE IN FOUR-STRAND CRUCIATE FLEXOR TENDON REPAIR

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Purpose of Study: The goal of flexor tendon repair is to achieve maximum strength at the time of repair to allow for early mobilization. In the few weeks following tendon repair, the strength of repair depends mainly on the tensile property of the suture material, the core suture geometry, and the grip of the sutures on the tendon. While previous studies focused on gap formation and ultimate failure as measures of strength of repair, our study investigates an additional measurement, the repair’s ability to resist stretch, which could potentially affect healing time. Keeping suture material and core geometry constant, the effects of different locking and grasping loops on mechanical failures in tendon suture repairs was investigated to determine which repair has the highest mechanical strength.

Methods Used: Forty-eight fresh porcine flexor digitorum tendons were dissected out and transected at the A-I pulley, analogous to a zone-II laceration. Tendon repairs were made using a cruciate repair with either a circle lock, cross lock, Lahey, or a simple four-strand grasping loop.

Summary of Results: The force at 2mm gap was highest for cross lock (23.99N + 9.29), followed by the Lahey (19.89N + 8.94), simple four-strand (19.81N + 6.78), and circle lock (16.27N + 6.82). The mode of failure was knot unraveling for all samples except for two circle locks which failed by suture pullout. When comparing the mean slope of load-displacement curves, the cross locks have a significantly higher tensile strength (4.34 N/mm) than the simple four-strands (0.74 N/mm).

Conclusions: When using fiberwire suture, a cross locking configuration should be considered over a grasping loop due to its increased tensile properties. However, future in-vivo or cyclical studies are required to determine which of the four repairs would offer the most clinical benefits.

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DURATION OF RED BLOOD CELL STORAGE AND POTASSIUM CONCENTRATIONS DURING ADULT LIVER TRANSPLANTATION

M. Memarzadeh, VW. Xia David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Increased potassium (K+) concentration poses serious perils to patients undergoing orthotopic liver transplantation (OLT). Although there are several interventions that can be used to lower serum K+, prevention remains most effective in the management of intraoperative hyperkalemia. Previous studies have shown that increased duration of red blood cell (RBC) storage is associated with higher mortality and risk of complications in patients receiving RBC transfusions. We tested the hypothesis that increased duration of RBC storage in transfused blood is associated with significantly higher K+concentrations during OLT.

Methods Used: After receiving IRB approval, we retrospectively studied 602 adult patients who underwent OLT at a major transplant referral center between January 2004 and April 2007. RBCs were categorized into two groups based on the mean storage duration (newer RBCs <14 days and older RBCs >14 days). The relationship between serum K+ and duration of RBC storage was analyzed at multiple time points of OLT using Student t test or chi-square analysis. The incidence of hyperkalemia (K+ >5.5 mmol/L) in these groups was also recorded.

Summary of Results: 258 patients received newer RBCs (mean RBC age of 9.3 days) and 397 patients received older RBCs (mean RBC age of 21.7 days). Baseline demographics including age, gender, MELD scores, K+, and creatinine were similar in both groups. Patients in both groups received similar amounts of RBCs, insulin and furosemide. However, patients in the older blood group had significantly higher serum K+at 1 hour pre-reperfusion...

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and at 15 minutes, 1 hour, 2 hours and 3 hours post-reperfusion (all p < 0.02). Patients in this group also had a significantly higher incidence of hyperkalemia at 1 hour post-reperfusion and at 15 minutes, 2 hours and 3 hours post-reperfusion (all p < 0.05).

**Conclusions:** Our results indicate that increased duration of RBC storage is associated with higher intraoperative potassium levels during OLT. These results may also be applicable to other operations requiring massive blood transfusions, such as trauma surgery or ruptured aortic aneurysm repair.

**Session:** Surgery I 165

**COMPARISON OF A REDUCED RADIATION FLUOROSCOPY PROTOCOL TO CONVENTIONAL FLUOROSCOPY DURING UNCOMPLICATED URETEROSCOPY**

D.J. Greene, C.F. Tenggardjaja, R.J. Bowman, G. Agarwal, K.Y. Ebrahimi, D.D. Baldwin Loma Linda University School of Medicine, Loma Linda, CA.

**Purpose of Study:** Although the long-term effects of radiation exposure are not completely predictable, the principle of keeping radiation exposure "As Low As Reasonably Achievable" (ALARA) should be employed in all cases.

The purpose of this study was to compare fluoroscopy times before and after the implementation of a protocol designed to reduce fluoroscopy usage during ureteroscopy.

**Methods Used:** A retrospective review was conducted of 299 consecutive stone patients at a single institution from January, 2007, to June, 2009. Patients undergoing simple ureteroscopy without ancillary procedures or balloon dilation were further evaluated to determine the effect of a reduced fluoroscopy protocol implemented in January of 2009. The protocol included several measures including use of a laser-guided C-arm, use of a designated fluoroscopy technician and substitution of visual and tactile for fluoroscopic cues during ureteroscopy. Fluoroscopy times were compared between groups using a paired t-test with p < 0.05 considered significant.

**Summary of Results:** Ureteroscopy cases prior to protocol implementation (n = 27) were compared to procedures following implementation (n = 21). Stone size and location were similar between groups. Protocol implementation significantly reduced the mean fluoroscopy exposure from 89.5 seconds (range 22-360) to 23.6 seconds (range 2-108) following protocol implementation (p = 0.001). There was no difference in mean operative time (71.1 vs 69.9 min; p = 0.91), or complications (2 patients vs. 2 patients; p = 0.80) between protocols groups. No complication in either group could be ascribed to the fluoroscopic technique. Similar stone free rates were seen in each group (89% vs. 85%; p = 0.92).

**Conclusions:** This reduced fluoroscopy protocol resulted in a 74% reduction in fluoroscopy time without altering patient outcome. These simple radiation-reducing techniques add no technical difficulty and improve safety for the patient, surgeon and operating room staff by lowering radiation exposure.

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**POLYMYTHETHACRYLATE PARTICLES INHIBIT HUMAN MESENCHYMAL STEM CELL DIFFERENTIATION INTO OSTEOBLASTS**

R. Chiu, R.L. Smith, S. Goodman Stanford University Medical School, Stanford, CA.

**Purpose of Study:** Orthopedic wear debris generated from total joint replacements causes osteolysis and implant loosening in part by stimulating osteoclast activity and impairing the function of osteoclast lineage cells. Previously, we have shown that particles of polymethylmethacrylate (PMMA) bone cement inhibit the osteogenic differentiation of murine primary marrow stromal cells and MC3T3-E1 osteoprogenitors with respect to proliferation, alkaline phosphatase production, and mineralization. We hypothesized that the inhibitory effects of PMMA particles are also observed with human mesenchymal stem cells (hMSCs) with respect to the aforementioned parameters.

**Methods Used:** Primary bone marrow-derived hMSCs were obtained from Lonza (Walkersville, MD). These cells were positively selected for mesenchymal markers CD105, 166, 29, and 44, and negatively selected for hematopoietic markers CD14, 34, and 45. hMSCs were induced to differentiate into osteoblasts in osteogenic medium containing dexamethasone (0.1 μM), ascorbic acid (50 μg/mL), and β-glycerophosphate (10 mM) and treated with PMMA particles at doses of 0.000, 0.075, 0.150, and 0.3060 v/v on this day first (day 0) of osteogenic differentiation. hMSC proliferation, alkaline phosphatase production (protein quantity, mRNA expression, and cell surface expression), and collagen type I mRNA expression were assessed during the first 8–10 days of osteogenic culture. Mineralization was assessed by quantifying calcium content in extracellular matrix on the fourth week of osteogenesis.

**Summary of Results:** hMSCs exposed to PMMA particles showed significant dose-dependent reductions in proliferation and type I collagen expression throughout the entire culture period. Alkaline phosphatase protein quantity, mRNA expression, and cell surface expression were also significantly reduced in a dose-dependent fashion. Matrix mineralization was significantly reduced as indicated by decreased matrix calcium content.

**Conclusions:** This study has shown that PMMA particles inhibit the osteogenic differentiation of hMSCs. This study along with our previous research shows that exposure of osteogenic lineage cells, including osteoblasts, osteoprogenitors, and mesenchymal stem cells, to wear debris particles compromises bone formation in the prosthetic bed.
Purpose of Study: Although the radiation exposures from CT and plain film imaging have been well characterized, the tissue and organ radiation levels received by the patient during fluoroscopy with modern equipment have not been well described. The purpose of this study was to determine absolute organ and tissue specific radiation exposures during ureteroscopy and to show how BMI and gender influenced these exposures.

Methods Used: Eight cadavers underwent a simulated left ureteroscopy. A fluoroscopy time of 145 seconds (mean of clinical ureteroscopies 2006–2008) was used to expose thermoluminescent dosimeters (TLD’s) using the OEC 9900 Elite General Electric C-arm utilizing automatic control settings. Total tissue exposures were compared by BMI and between genders. Radiation dosages were compared using the Wilcoxon Signed Ranks Test and the Mann-Whitney Test with p < 0.05 considered significant.

Summary of Results: Radiation dose was significantly lower in contralateral organs (kidney, ureter, and lung) (p < 0.05) except for the gonad had similar exposure (p > 0.05). For cadavers with a BMI <30 contralateral organs also experienced lower dosage than ipsilateral organs except for the gonads and lung (p<0.05). However, in cadavers with a BMI >30 relatively higher dosages were seen with contralateral organs resulting in no difference between different sides (all p<0.05). There was significantly higher mean bilateral gonadal dose in female cadavers (3.4 mSv left, 1.9 mSv Right) compared to males (0.37 mSv left, 0.28 mSv Right). The highest cancer risk increase was seen at the posterior skin equivalent to 104 additional cancers per 100,000 patients.

Conclusions: Nontargeted organs received less radiation exposure as expected except with BMI >30 where contralateral organs received a similar dose. Gonadal doses were similar bilaterally and were significantly higher in females. Fluoroscopy contributes a significant amount of radiation and steps should be taken to minimize patient exposure during ureteroscopy.

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THE IMPORTANCE OF LYMPH NODE REMOVAL DURING GASTRECTOMY AND T-STAGING OF ADENOCARCINOMAS AT UCLA
D. Ruiz 1,2, DT. Hiyama 1 David Geffen School of Medicine at UCLA, Westwood, CA and 2Charles Drew University of Medicine and Science, Los Angeles, CA.

Purpose of Study: The American Joint Committee on Cancer /International Union Against Cancer staging system suggest at least 15 regional lymph for adequate staging of gastric cancer. The staging of gastric cancer is important for the prognosis and treatment of gastric cancer. However, the controversial extent of D2 vs. D1 lymph node dissection as a curable treatment for gastric cancer remains debated. This study reviews the significance of extended lymph node removal in patients with primary adenocarcinoma undergoing therapeutic gastrectomy and the significance of additional lymph node removal.

Methods Used: The study is a retrospective case based review with IRB approval of UCLA patients that underwent full or partial gastrectomy as treatment for primary gastric adenocarcinoma from 2000–2009. The International Classification of Diseases (ICD-9) database was used in a broad to direct design to detect cases with gastric adenocarcinoma. These cases were further screened with Current Procedural Terminology (CPT) codes to detect cases in which the treatment was either total or partial gastrectomy. The T-stage (T1-T3) and the percent of positive lymph nodes were compared between two groups: group one where the recovered lymph nodes were less than 15 and group 2 where they were greater than ≥15 lymph nodes.

Summary of Results: During this 9.5 year span, data was collected from 265 patients of which 80 (M = 39 F41) fit the inclusion criteria. For each stage T1, T2, T3, two groups were compared, Grp1≤15 lymph nodes collected vs. Grp≥15 lymph nodes collected. In the T1 Grp1 only 1.13% of the nodes were positive for cancer and in Grp2, 1.42%, p = 0.8206. In T2 Grp1, 0% of the nodes were positive for cancer and in Grp2, 17.06%; p < 0.0001 and is considered to be extremely statistically significant. In T3 Grp1, 36.53% of the nodes were positive for cancer and Grp2, 30.96%, p = 0.4491. In addition, the higher the T-stage the higher percentage of positive lymph nodes harvested.

Conclusions: We conclude that reliable harvesting of an adequate number of lymph nodes greater than 15 for T2 cancers allows for proper detection of positive lymph nodes. In addition, the more aggressive D2 lymphadenectomy should be performed as part of gastrectomy for adenocarcinoma having curative intent.

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MODULATION OF IONIC STRENGTH TO TAILOR MECHANICAL PROPERTIES OF FIBRIN GELS FOR OSTEONECROPSIS
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Purpose of Study: Conventional methods for modulating mechanical properties of fibrin gels used for cell delivery involve altering the fibrinogen or thrombin content of the pre-gel solution. However, patients suffering from traumatic bone injury often experience hemostatic instability, creating a challenge when harvesting these clotting proteins in the large quantities necessary to fill a defect. As an alternative, we hypothesized that gel material properties could be optimized to obtain maximum bone-progenitor cell differentiation by solely adjusting the ionic concentration of the pre-gel solution.

Methods Used: Fibrin gels were fabricated by mixing equal volumes of human thrombin (2.5 U ml⁻¹, 50 mM CaCl₂) and fibrinogen (20 mg ml⁻¹, 0-3.6% w/v NaCl). Optical density and gel clotting time was measured using a UV-VIS spectrophotometer at 550 nm. The compressive moduli of the gels were determined using an Instron mechanical testing system. Equilibrium swelling ratios were determined by incubating the gels in PBS for twenty-four hours and comparing the swollen gel weight to the lyophilized weight. The in vitro osteogenic differentiation of human mesenchymal stem cells (hMSCs) encapsulated within gels was explored by quantifying ALP activity, DNA content, and cell secreted calcium after culture for 7 and 14 days under osteogenic conditions.

Summary of Results: Increasing the ionic concentration of the pre-gel solution resulted in an increase in gel clotting times, with gelation times ranging from 3.33 to 18.9 min. However a decrease in turbidity was only observed to a 1.8% NaCl concentration; the addition of further salt resulted in a slight rise of turbidity. Mechanical testing and equilibrium swelling ratio followed a similar trend as optical density, with compressive moduli and water uptake increasing to a 1.8% NaCl concentration before declining at higher salt concentrations. Correspondingly, DNA content significantly decreased up to 1.8% NaCl concentration while ALP activity increased.

Conclusions: The present data indicate that the ionic concentration of the pre-gel solution influences fibrin gel material characteristics which in turn play a role in hMSC osteogenic differentiation. Such results may provide a more feasible and cost-effective approach to filling defects with fibrin for bone repair.

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CHANGES IN FACIAL SHAPE WITH AGE: AN ANALYSIS WITH THREE-DIMENSIONAL IMAGING
CS. Carter, MC. Camp, WW. Wong, SC. Gupta Loma Linda University, Loma Linda, CA.

Purpose of Study: The appearance of the aged face has traditionally been attributed to soft tissue changes, with surgical treatments targeting plosis of skin, SMAS, and fat. However, true facial aging is recognized as a combination of soft tissue and skeletal changes, which continue to be integrated into a model for facial aging. This study examined the theory that mid-face regression occurs with advancing age.

Methods Used: Three-dimensional imaging technology was used in this study: Measurements correlating with mid- and lower face changes were compared for each three-dimensional facial image of 31 mother-daughter matched controls. Each mother image was superimposed on the corresponding daughter, using registration of the upper face to visualize mid-face differences between pairs. Also, measurements of women in four age groups were compared using a one-way ANOVA.

Summary of Results: The ratios of Po-A:Po-N were significantly greater in daughters in comparison to their mothers (p = 0.0073) with the majority of mother subjects showing a more acute Po-N-A angle (p = 0.042). An
investigation between age groups exhibited significant difference between the youngest (18-29) and oldest (60+) groups for Po-A:Po-N length ratio, Po-B:Po-N length ratio, Po-N-A angle, and Po-N-B angle. Differences between the 30-44 and 60+ age groups were also significant for the Po-A:Po-N and Po-B:Po-N length ratios.

Conclusions: The results from this study suggest a posterior movement of the mid- and lower face with age. This multi-factorial process makes facial rejuvenation more complex than initially perceived, and recognizing it will facilitate better rejuvenation strategies in the future.

Mean measurements

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Po-A (mm)</th>
<th>Po-B (mm)</th>
<th>Po-N-A (degrees)</th>
<th>Po-N-B (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daughters</td>
<td>95.8</td>
<td>101.8</td>
<td>109.1</td>
<td>1.064</td>
</tr>
<tr>
<td>Mothers</td>
<td>98.2</td>
<td>102.0</td>
<td>110.0</td>
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<tr>
<td>p-values</td>
<td>-</td>
<td>-</td>
<td>0.0075</td>
<td>0.0054</td>
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</table>

Session: Surgery I

172

COMPARISON OF PERCUTANEOUS RADIOFREQUENCY AND CRYOABLATION FOR THE TREATMENT OF SMALL RENAL TUMORS

P Mahdavi1, KY Ebrahimii2, RJ Bowman1, J Smith2, DD Baldwin1

Purpose of Study: Percutaneous ablative techniques are gaining acceptance for treatment of small renal masses with no previous study reporting a direct comparison of percutaneous cryotherapy (cryo) with percutaneous radiofrequency ablation (RFA) when performed by the same surgical team.

Methods Used: A retrospective review was performed of 41 patients (21 male, 20 female; mean age 67 yr) with solitary renal tumors < 4.0 cm treated with a percutaneous ablative technique. 63% of patients were without prior pathologic diagnosis and underwent biopsy prior to ablation. Follow-up imaging was performed at 3 months post ablation and then at 3-12 month intervals.

Summary of Results: 41 patients underwent 41 ablations (22 RFA and 19 cryotherapy). ASA score was similar between groups (2.1 RFA vs. 2.2 cryo; P = 0.27). Tumor size ranged from 1.1-3.8 cm (2.3cm RFA vs. 2.8 cm cryo; p = 0.01). Pathology revealed renal cell carcinoma in 16 cases. Eight complications in 7 patients were identified at 2 week follow up: 2 with abdominal pain and lactic acidosis (cryo), 2 peripheral nerve paresthesias (cryo), 2 skin burns (RFA), 1 pulmonary embolus (2 wks post cryo), and 1 intra-procedural cardiac arrhythmia (RFA). At mean follow up of 491 and 249 days in RFA and cryo patients respectively (p = 0.004) all patients recovered from these complications with lower extremity pain being the main complaint in 6 patients (3 RFA, 3 cryo). There were two recurrences (1 RFA, 1 cryo) at 2 year follow up.

Conclusions: There was no difference in treatment success rate between techniques. RFA was associated with more skin burns, cryoablative with more paresthesias. When both techniques are delivered by the same technique the outcomes seem more similar than previously reported series when different delivery strategies are employed. Further study with longer follow-up is necessary to compare long-term durability between approaches.

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HYBRID MANAGEMENT OF HYPOPLASTIC LEFT HEART SYNDROME AND ITS VARIANTS: THE NEVADA EXPERIENCE

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1Children’s Heart Center Nevada, Las Vegas, NV and 2University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: To review our experience in Nevada with the hybrid approach for hypoplastic left heart syndrome (HLHS) and its variants. Morbidity and mortality for stage I Norwood palliation of HLHS remains high. The hybrid management premise is to obviate the standard high-risk, open-heart stage 1 procedure in newborns and temporally shift it to a time when patients are older, bigger, and more stable.

Methods Used: We have managed 14 patients that fit our objective.

Summary of Results: Of the 14 patients, 11 had HLHS and 3 had aortic arch (AA) anomalies. Of the 3 with AA anomalies, 2 had hypoplastic AA with muscular ventricular septal defects, and one had an interrupted AA type B. Of the 14, 6 had birth weights ≤ 2.2 kg (1.1-2.2). Of the 14, 2 died (14%). Of the 14, 7 had balloon expandable ductus arteriosus (DA) stents: 3 required redilation; and 7 had self-expanding DA stents; 0 required redilation. Of the 11 with HLHS the atrial septum (AS) was opened by balloon septostomy alone in 2, atrial septal stent with redilation in 7, atrial septectomy following failed stent in 1, and a large primum ASD in 1. Of the 11 with HLHS, 4 had intact or highly restrictive ASs and all have increased pulmonary vascular resistance (PVR). Of the 11 HLHS, 7 underwent arch repair and pulmonary artery (PA) shunt: 4 with a Glenn and 3 with systemic to PA shunt due to increased PVR; 2 await arch repair and Glenn; and 2 died: 1 early with intact AS and left ventricle dependent coronary circulation and 1 late with bronchomalacia. Of the 3 with AA anomalies, 2 underwent biventricular repair with arch reconstruction, and 1 underwent a Damus-Kaye-Stansel procedure.

Session: Student Scientific Session I - Adolescent Med-Gen/Pediatrics/Neuroscience

8:30 AM

Friday, January 29, 2010

Session: Student Scientific Session I - Adolescent Med-Gen/Pediatrics/ Neurosciene

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PROPHYLACTIC TREATMENT OF AT-RISK PEDIATRIC ISCHEMIC STROKE PATIENTS WITH ASPIRIN AND LOW-DOSE HEPARIN

JC. Jackson-Morgan, S. Gizarian Charles Drew University of Medicine and Science, Los Angeles, CA.

Purpose of Study: To investigate the possible intervention of treating at-risk pediatric patients with either low-doses of aspirin and/or low molecular weight heparin as preventative measures for reoccurring ischemic episodes. Majority of current reviews and studies have shown data on white pediatric patients and there is little data reported regarding an array of ethnic and socioeconomic backgrounds.

Methods Used: Minority pediatric patients ranging from aged ≥6 months to ≤18 years with first onset of ischemic stroke confirmed by results of CT and MRI will receive either aspirin (4 mg/kg body wt per day; range, 2 to 5; n = 49) or low-dose LMWH (enoxaparin [1 to 1.5 mg/kg body wt per day]) or dalteparin [75 to 125 anti-Xa U/kg body wt per day]; 4-hour anti-Xa activity, 0.2 to 0.4 IU; n = 86 over a period of 9 months (range, 6 to 14 months). Data regarding whether the dosages are as beneficial in minority patients are unavailable. To investigate the short- and long-term effects of aspirin and LMWH antithrombotic therapy for minority ischemic pediatric stroke patients a new cohort (n = 135) will be observed for duration of 5 years to study the long-term effects of the antithrombotic therapy treatments and outcomes will be measured in 9-month intervals. At each 9-month interval patients will undergo CT and MRI scans to determine the continuation in the experiment and record any adverse reactions or side effects of the antithrombotic therapy.

Summary of Results: Expansion of knowledge for aspirin and LMWH dosage administration in minority pediatric ischemic stroke patients. Based
on the preliminary studies, minority patients may require a tailored treatment because race and gender were identified as important risk factors for ischemic and hemorrhagic stroke (Lo et al., 2009).

Conclusions: Larger population-based prospective studies (n ≥ 500) need to be conducted for further clarity of these disparities. Risk factors for childhood stroke are being clarified with mounting evidence for the role of hereditary prothrombotic states, vascular abnormalities such as arterial dissection, and infections such as varicella. Investigation into the ethnic and gender distribution of these risk factors may provide clues into the demographic disparities in stroke seen in both children and adults (Fullerton et al., 2003).

Session: Student Session 1 - Adolescent Med-Gen/Pediatrics/Neuroscience

A MOUSE MODEL OF POST-TRAUMATIC STRESS DISORDER FOR ASSESSMENT OF AVOIDANCE BEHAVIOR

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Purpose of Study: Avoidance of stimuli associated with a traumatic experience is one of the hallmark symptoms of PTSD. We aimed to determine if mice exposed to a traumatic event (predator odor) in the presence of a non-threatening object would demonstrate avoidance behavior toward the object in a different context. The ability to measure avoidance of a trauma-related stimulus will validate the predator exposure mouse model of PTSD.

Methods Used: 33 female C57BL/6 mice were assigned to one of three groups: no odor control (n = 12), predator odor-exposed (n = 12) or naïve (n = 9). Soiled, rat bedding was used as the source of the predator odor; clean bedding was used for the odor control condition. Mice were exposed, or not (naïve controls); three times (10 min each) to bedding in the presence of a non-threatening object (125 ml brown glass-stopper bottle). Subsequently, the animal’s response to the object was assessed in a standard open field/novel object test, in which the object was placed into the center of an open field.

Summary of Results: All three groups displayed an increased mean number of center entries in the presence of the object compared to the absence of the object. Two-way ANOVA found a significant effect of the object [F(1,30) = 37.75, p < 0.0001], while exposure condition showed no significance. However, a significant interaction between the object and exposure condition was found [F(2,30) = 3.74, p < 0.05]. Odor-control mice had the largest increase in number of center entries, followed by odor-exposed mice, with naïve mice having the smallest increase. The trend in odor-exposed mice to display avoidance towards the bottle was not statistically significant. Bonferroni post hoc analysis of all three groups did not reveal any significant (p < 0.05) differences in the number of center entries in the absence or the presence of the object.

Conclusions: The paradigm used for the pairing of an object with a trauma either will require modification in order to model avoidance behavior or may not be useful in the development of a mouse model of PTSD.

Session: Student Session 1 - Adolescent Med-Gen/Pediatrics/Neuroscience

HEMODYNAMIC ANALYSIS OF SMALL MIDDLE CEREBRAL AND BASILAR ARTERY ANEURYSMS

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Purpose of Study: The outcome of prophylactic treatment for small, unruptured brain aneurysms is controversial. The purpose of this study was to investigate hemodynamic properties that may distinguish such aneurysms that are at risk from those that are not, with a view to determining which aneurysms are at risk and therefore, candidates for treatment. This study utilized hemodynamic simulation tools to determine hemodynamic properties in ruptured and unruptured small aneurysms in the middle cerebral artery (MCA) of the anterior circulation and basilar artery (BA) of the posterior circulation.

Methods Used: This study examined three dimensional rotational angiography (3DRA) images of 10 different aneurysms (5 MCA/5 BA) via patient-specific computerized flow dynamic (CTD) application. Analyzed hemodynamic properties included flow pattern, impingement, and complexity. These factors were evaluated by two experts who were blinded to patient histories and outcomes. The results were also compared with previous studies utilizing a different simulation program.

Summary of Results: The ruptured MCA aneurysms tended to show flow complexity. However, ruptured BA aneurysm results did not indicate any clear trend with regards to the flow complexity. We also found that more than 80% of the aneurysms (both ruptured and unruptured) had a concentrated inflow jet and small impact zone, regardless of the aneurysm’s location.

Conclusions: The simulation results of this study revealed similar trends in the hemodynamic properties between ruptured and unruptured MCA aneurysms as those of previous studies utilizing different programs. However, the results for the BA cases were not as clear with describing hemodynamic properties. Given the small data sample, both aneurysm cases should be investigated further for better hemodynamic characterization.

Session: Student Session 1 - Adolescent Med-Gen/Pediatrics/Neuroscience

NEURAL EMBRYONIC STEM CELLS CULTURED IN A SIMULATED MICROGRAVITY ENVIRONMENT SHOW ENHANCED PROLIFERATION AND SURVIVAL

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Purpose of Study: In this study, we examined the effects of the three-dimensional (3D)-clonization, a simulated-model of microgravity, on cell survival, proliferation and commitment/differentiation of rat and human neural embryonic stem cells. Traditionally, neural embryonic stem cells (NSC) can be grown and propagated in normal gravity (1G). Although a 1G environment yields good numbers of progenies it occurs after long periods of time and effort in addition to inadequate numbers of committed cells for replacement therapies.

Methods Used: This study builds upon previous findings by Yuge, et al (in press) that demonstrated an increase in cell survival rate by maintaining an undifferentiated state of bone marrow stromal cells in microgravity. In 1G, the ability to direct a pluripotent NSC stem cell to commit and differentiate into a specific phenotype has been well documented by Espinosa-Jeffrey et al in 2002 and 2009 where specific phenotypes are instructed by the culture media. In the present work our immediate goal is to combine both methodologies and characterize the effects of microgravity on the yield of NSC as well as the commitment, the differentiation and proliferation rates of NSC as they become oligodendrocytes (OL). We will characterize the developmental progression of NSC, Oligodendrocyte Progenitors(OLP), and OL by double immunofluorescence using known OL developmental markers Nestin, PDGFβ, and Myelin Basic Protein, respectively.

Summary of Results: Our preliminary results have shown that cells are healthy and there seems to be an increase in cell numbers, and survival in both human and rat neural embryonic stem cells grown in microgravity with respect to their 1G counterparts.

Conclusions: The ultimate objective is to sustain a reproducible means of generating large numbers of oligodendrocyte progenitors. The idea is to start with a small sample size, such as a small biopsy of tissue from the Subventricular Zone, propagate them and commit the progenies in vitro. Once committed, then utilize the cell population as self-grafts that offers the advantage of not having the risk of graft rejection. Our future work will include grafting of NSC cultured in microgravity, into a rat spinal cord injured-model.

Session: Student Session 1 - Adolescent Med-Gen/Pediatrics/Neuroscience

SEIZURE OUTCOMES OF LESIONECTOMY WITH AND WITHOUT INTRAOPERATIVE ELECTROCORTICOGRAPHY IN CHILDREN WITH LESIONAL EPILEPSY

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Purpose of Study: Focal cortical lesions, such as low-grade tumors or vascular malformations, are often associated with intractable epilepsy in children. There is ongoing debate concerning whether the use of intraoperative electrocorticography (ECoG) improves seizure outcome after resection of these lesions.

Methods Used: We retrospectively analyzed seizure outcomes in 67 patients between the ages of 3 months and 16 years who underwent surgery for lesional epilepsy at British Columbia Children’s Hospital between 1984 and 2008. A minimum of one year postoperative follow-up was necessary to be included in the study. Thirty-four patients underwent ECoG, and in 20 of these 34 patients, ECoG was used to direct further cortical resection in addition to lesionectomy. Thirty-three patients had a lesionectomy without ECoG.

Summary of Results: Seventy-nine percent (79%) of patients who had intraoperative ECoG were seizure free, compared to 61% of patients who underwent lesionectomy without ECoG (mean follow-up 69 months; odds ratio [OR], 2.5; 95% confidence interval [CI], 0.84–7.42; p = 0.11). In the subgroup of patients in whom ECoG was used to direct resection of epileptogenic cortex surrounding the lesion, 85% were seizure free postoperatively (OR, 3.21; CI, 0.62–12.56; p = 0.14). There was no increase in neurological morbidity in patients who had further ECoG guided cortical resection. There were no postoperative infections in the series. Of several preoperative variables examined (including lesion type and location, seizure type and frequency, the existence of preoperative focal neurological deficits, duration of epilepsy, age at surgery, and preoperative electroencephalogram results), none were found to be independently associated with seizure outcome.

Conclusions: Overall, the use of ECoG to guide additional cortical resection may lead to better seizure outcomes in children with lesional epilepsy, regardless of age, epilepsy semiology, or lesion type.

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**REPRODUCIBILITY AND PREVALENCE OF AUDITORY GATING DEFICITS IN MANIC ILLNESSES**

T. Parker, L. Martin, R. Freedman, A. Olincy University of Colorado Denver School of Medicine, Aurora, CO.

Purpose of Study: Deficits in the ability to inhibit evoked EOG responses to repetitive auditory stimuli are noted in a variety of mental illnesses. This gating deficit is most markedly noticeable in schizophrenia, however those with a history of mania are also commonly affected. This study is being undertaken to provide further data concerning the effects of bipolar disorder, and the reliability of auditory gating as an objective measure.

Methods Used: Men and women between the ages of 15 and 60, both smokers and nonsmokers, were recruited from the Denver metro area. Diagnosis of either Bipolar Disorder, Type I, with or without psychosis, or Schizoaffective Disorder, Bipolar Type, was confirmed through the Structured Clinical Interview for DSM-IV Diagnoses (SCID) and a detailed life history. Three standardized surveys assessed current symptoms: Beck Depression Inventory, Young Mania Rating Scale, and the Brief Psychiatric Rating Scale. Two separate EEG recordings of the P50 auditory evoked potential were collected per subject, in sessions spaced one week apart.

Summary of Results: It is anticipated that nearly all subjects with gating deficits will demonstrate deficits of similar degree upon their second EEG recording, and those subjects with initially normal gating ability will demonstrate normal gating upon retesting. Other studies have indicated that increased adrenergic activity causes P50 gating deficits as well. We therefore also predict that auditory gating deficits will tend to be more frequent and pronounced for those with a greater degree of psychosis history. Specifically, bipolar subjects with psychosis are expected to show a higher prevalence of deficits - and to a greater degree - than those without psychosis, and schizoaffective subjects are expected to generally demonstrate the highest prevalence and most significant deficits.

Conclusions: High reproducibility of P50 auditory gating ability in bipolar disorder and schizoaffective disorder would support the use of this measure as an objective data point in interventional studies of these diseases. Degree of deficit correlating to degree of mania/psychosis would support the involvement of nonadrenergic inhibition of interneurons as a contributing etiological pathway in P50 gating deficiencies.

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**DECREASED α7 NICOTINIC RECEPTOR EXPRESSION MAY CONTRIBUTE TO SCHIZOPHRENIA-ASSOCIATED IMMUNE DYSREGULATION**

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Purpose of Study: Schizophrenia has been associated with higher levels of inflammatory cytokines such as tumor necrosis factor α (TNFα) and increased risk for autoimmune disorders. The mechanism for the immune dysregulation is not known, but may be due in part to schizophrenia-associated alterations in α7 nicotinic receptor expression. Activation of α7 receptor appears to be required for normal function of the vagal cholinergic anti-inflammatory pathway. If α7 receptor expression in immune cells of schizophrenics is reduced, as it is in schizophrenic brain, this could alter immune system regulation leading to autoimmune pathologies. Hypothesis: Alterations in immune function seen in schizophrenia are caused by decreased α7 nicotinic receptor expression.

Methods Used: Male and female C3H α7 wild type (WT), heterozygous (HET) and knockout (KO) mice (8–12 weeks of age, n = 5/group) were injected intraperitoneally with 6mg/kg endotoxin (LPS, E. coli L4130 0111:B4; Sigma) or saline (control) and euthanized by decapitation 1.5h after injection. Blood was collected and processed to isolate serum, which was used for TNFα analysis by ELISA (R&D System) according to manufacturer’s protocol.

Summary of Results: Preliminary data indicate that baseline levels of TNFα as well as TNFα levels following saline injections were minimal across genotypes and gender. However, a non-significant trend towards higher TNFα levels was observed in heterozygous females injected with LPS.

Conclusions: The preliminary data suggest that reductions in α7 receptor levels may alter immune function leading to higher levels of inflammatory cytokine release and increased risk for autoimmune disorders. Additional data will be required to fully address this issue. If α7 downregulation is shown to contribute for the pro-inflammatory tendency seen in schizophrenics, targeting this deficiency could reduce these patients’ risks for autoimmune disorders.

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**STABILITY OF P50 SENSORY GATING IN PRESCHOOLERS**

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Purpose of Study: Event-related potentials can be used to study the developing human brain and lead to earlier identification of neurological disorders. One such potential, the P50, is used to measure the strength of auditory sensory gating, which represents an individual’s ability to filter out irrelevant sensory stimuli. Weak sensory gating has been linked to several neuropsychiatric disorders in which there is a defect in ignoring irrelevant stimuli, including schizophrenia and bipolar disorder. Previous studies have shown that P50 sensory gating can be measured during REM sleep in infants to avoid state dependence. Also, P50 sensory gating has been shown to be stable in infants between trials. In our current study, we evaluate whether P50 sensory gating remains stable as subjects grow from infants into preschoolers.

Methods Used: 15 preschool children from a database of previously tested infants were recorded during an overnight stay at a children’s hospital. After the onset of sleep, Ag/AgCl electrodes were attached to the child and paired clicks were presented through two speakers positioned on either side of the bed. Throughout sleep, ongoing electroencephalogram (EEG) was recorded from the vertex of the scalp (site Cz). To aid in sleep staging, bipolar electrooculogram (EOG) and electromyogram (EMG) were also recorded. After recording, active sleep stage was identified using EOG, EMG and EEG patterns. From the REM sleep periods, a 15-minute period was retained and used for analysis to obtain the average test-conditioning ratio (T/C) for the P50 component.

Summary of Results: Interclass correlation between the current preschool trials and the previous infant trials was used to assess stability of P50 sensory gating.

Conclusions: We expect there to be a significant stability between the infancy and preschool T/C ratios in P50 sensory gating. The human brain
Purpose of Study: The feasibility of using diffusion tensor imaging (DTI) as a predictive outcomes measure in a population of children with CP undergoing treatment induced an increase in Plasminogen mRNA after 12 hours. Whole limb vibration resulted in increased MEP amplitudes at post vibration. However, the mean MEP was elevated at each post vibration interval. To test reliability, participants had average MEP s recorded at the EDC hot spot. TMS and EMG electrodes were removed, then replaced, and average MEP’s recorded at 10 minutes post-vibration and repeated every 5 minutes for 35 minutes. Ten MEP s were measured starting at 10 minutes post-vibration and averaged over 35 minutes and 9 underwent twice daily CIMT for 2 weeks. Clinical assessments and diffusion tensor imaging were obtained before therapy, at the conclusion of therapy, and three months post therapy. The relationship between baseline FA as determined by DTI and change over time of various clinical outcomes measures was determined using t-tests. Summary of Results: Four subjects provided adequate imaging data for analysis. FA of the posterior limb of the internal capsule on the affected side was reduced compared to the unaffected hemisphere in all subjects. In addition, all subjects undergoing treatment showed significant improvement in grip strength and the nine hole peg test after therapy; an effect that endured to the 3 month post-treatment assessment point. The subject with the highest FA value in the internal capsule on the affected side had the greatest improvement of grip strength shown immediately and at 3 months post treatment. After omitting the oldest subject as an outlier, there was a trend toward positive correlation between FA of the internal capsule prior to therapy and baseline behavioral measures although not reaching statistical significance: grip (r = 0.71), pinch (r = 0.07), pegboard (p = 0.093) and box test (p = 0.193). There was no significant correlation between FA and improvement after therapy.

Conclusions: DTI is feasible in children with hemiplegic CP, and correlates with behavioral measures. A larger sample size is required to determine whether FA is predictive of treatment response.

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WHITE MATTER ORGANIZATION AND RESPONSE TO CONSTRAINT INDUCED THERAPY IN CHILDREN WITH CEREBRAL PALSY
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Purpose of Study: Constraint induced movement therapy (CIMT) has been used in patients with cerebral palsy (CP) to improve use of the affected upper extremity. Selecting appropriate patients for CIMT can be difficult, and is currently done through clinical assessment alone. A more accurate targeting of therapy to patients would be of great clinical value. The goal of this study was to determine the feasibility of using diffusion tensor imaging (DTI) as a predictive outcomes measure in a population of children with CP undergoing CIMT. Our hypothesis was that fractional anisotropy (FA) of the internal capsule is predictive of outcome in response to therapy. Methods Used: Six children with spastic hemiplegic CP between ages of 5 and 9 underwent twice daily CIMT for 2 weeks. Clinical assessments and diffusion tensor imaging were obtained before therapy, at the conclusion of therapy, and three months post therapy. The relationship between baseline FA as determined by DTI and change over time of various clinical outcomes measures was determined using t-tests. Summary of Results: Four subjects provided adequate imaging data for analysis. FA of the posterior limb of the internal capsule on the affected side was reduced compared to the unaffected hemisphere in all subjects. In addition, all subjects undergoing treatment showed significant improvement in grip strength and the nine hole peg test after therapy; an effect that endured to the 3 month post-treatment assessment point. The subject with the highest FA value in the internal capsule on the affected side had the greatest improvement of grip strength shown immediately and at 3 months post treatment. After omitting the oldest subject as an outlier, there was a trend toward positive correlation between FA of the internal capsule prior to therapy and baseline behavioral measures although not reaching statistical significance: grip (p = 0.71), pinch (p = 0.07), pegboard (p = 0.093) and box test (p = 0.193). There was no significant correlation between FA and improvement after therapy.

Conclusions: DTI is feasible in children with hemiplegic CP, and correlates with behavioral measures. A larger sample size is required to determine whether FA is predictive of treatment response.

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WHOLE LIMB VIBRATION EFFECT ON MAGNETIC EVOKED POTENTIALS
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Purpose of Study: Single tendon vibration has been shown to increase cortico-spinal excitability measured as increases in the Evoked Potential (MEP) to antagonist muscles. This study evaluates whether whole limb vibration affects cortico-spinal excitability. Should excitation occur, whole limb vibration may augment upper limb skill training in patients with upper motor neuron paresis.

Methods Used: Two healthy subjects had measurements of resting MEP’s of the right extensor digitorum communus (EDC) prior to vibration, followed by whole arm vibration at 30Hz for two 45s periods with 15s rest intervals. Resting MEP’s were measured starting at 10 minutes post-vibration and repeated every 5 minutes for 35 minutes. Ten MEP’s were averaged at each interval. To test reliability, participants had average MEP’s recorded at the EDC hot spot. TMS and EMG electrodes were removed, then replaced, and average MEP’s recorded at 10 minute intervals.

Summary of Results: MEP data were collected from two healthy subjects. Results showed no statistical significance in magnitude of MEP’s pre and post vibration. However, the mean MEP was elevated at each post vibration interval. The reproducibility data showed no statistical difference between the mean MEP’s after removing and replacing TMS and EMG electrodes, indicating good reliability of the mean MEP amplitude.

Conclusions: Whole limb vibration resulted in increased MEP amplitudes at each measurement for the entire 30 minutes of the experiment, suggesting increased excitability of the cortico-spinal system. Due to MEP variability and lack of statistical significance, the study size should be increased. Findings should be confirmed in subjects with upper motor neuron paresis. If confirmed, vibration induced cortico-spinal excitability may facilitate skill training trials in individuals with upper motor neuron paresis and lead to improved motor control.

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THE EFFECT OF CEREBRAL AMYLOID ANGIOPATHY ON TRANSITION METALS HOMEOSTASIS IN ALZHEIMER’S DISEASE
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Purpose of Study: Transition metals dyshomoeostasis has been suggested to play a central role in Alzheimer’s disease (AD). Excessive iron, secondary to metabolic disturbance or exogenous deposition, could generate significant levels of free radicals and oxidative damage. This claim is supported by...
subjective data but little objective data, such as atomic absorption data, upholds this theory. A significant portion of AD patients also have vascular injury due to amyloid peptide deposition but this is not present in all cases. This vascular injury, called cerebral amyloid angiopathy (CAA), causes brain microbleeds and could be the source of excessive iron and other transition metals. We believe that once separated into two groups (AD versus AD+CAA), there will be an increase in metals concentration due to vascular injury specific to cases with CAA.

Methods Used: Using atomic absorption spectrophotometry, an objective method of analysis, allowed for an accurate analysis of metal atom concentration. We analyzed 22 samples of human temporal lobe (8 AD only, 8 CAA+AD, and 6 controls) in both grey and white matter.

Summary of Results: In the white matter total iron analysis there is a trend of increased iron in CAA+AD compared to control (p = 0.0516) while in grey matter there was no significant difference. In the non-heme iron test we see the same trend in the white matter and a significant increase in the grey matter between CAA+AD and control (p = 0.0309). For the copper analysis we saw significant decrease in both CAA+AD and AD only in both white matter (p = 0.0341 and p = 0.0317) and grey matter (p = 0.0147 and 0.0098). Finally, in the zinc analysis we see no statistical difference between any of the groups for white matter but see a significant increase in the grey matter for both CAA+AD (p = 0.0035) and AD only (p = 0.0186).

Conclusions: The iron analysis data supports our hypothesis of CAA being associated with increased concentrations of free iron. Our hypothesis is not supported by the zinc and copper results because the same changes were seen in both test groups. We will be continuing this study by analyzing samples taken from the occipital and frontal lobes and confirming this data with a modified Perl's stain.

Western Student Medical Research Forum

Student Scientific Session II - Community Health
8:30 AM
Friday, January 29, 2010

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LOW BACK PAIN PREVENTION AND EDUCATION IN THE HISPANIC MIGRANT WORKERS OF WENATCHEE, WASHINGTON

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Purpose of Study: Columbia Valley Community Health (CVCH), the main clinic that serves the migrant workers of Wenatchee, WA, has many patients present with low back pain (LBP). Heavy lifting and dynamic movements in agricultural work increases the likelihood of sustaining a back-related injury. Standard management of LBP involves NSAIDs, painkillers and patients exercising and stretching on a daily basis. However, CVCH has an outdated and illegible stretching and exercise handout that is seldom given to patients. Furthermore, migrant workers are given no education on how to decrease the chances of experiencing LBP before presenting to the clinic. Therefore, the purpose of this project was to design an educational pamphlet on how to prevent LBP and distribute it at migrant camps and CVCH.

Methods Used: Observations of migrant workers presenting with LBP at CVCH and migrant camps, as well as discussions with providers and patients, revealed a need for education on LBP prevention. A literature review was performed to determine the most effective way of decreasing musculoskeletal injuries, in particular back pain, for manual laborers. It was found that a consistent exercise regimen focusing on core muscles was effective in decreasing recurrence rate of LBP. Aided by an outreach coordinator, a pamphlet was created that gave instructions on how to increase flexibility and strength of core muscles. The pamphlet was designed with the target population in mind; text was in Spanish and used simple wording.

Summary of Results: Sixty pamphlets were distributed at the local migrant camp and a brief explanation of the purpose of the routine was given to each recipient. Almost every person that received a pamphlet had experienced LBP in the past and many were willing to attempt the routine in order to decrease the chances of another episode. The pamphlet was also distributed to CVCH employees both in paper copies and electronically so that it could be given to migrant workers that come to the clinic. Conclusions: The pamphlet had clear and concise instructions on how to perform the exercise routine, easily understandable drawings, and was written in Spanish. It was well received and made easily available for future use, so it is highly likely that it will be used in the future to help educate migrant workers on prevention of LBP.

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BRIGHTER SMILES AFRICA: EDUCATIONAL EVALUATION OF AN INTERNATIONAL ORAL HEALTH PARTNERSHIP

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Purpose of Study: The medical schools of the Universities of British Columbia (UBC) and Makerere (MU) deliver a school-based oral health program for children in 5 communities in Uganda. The partnership, delivery of the program, and evaluation of impact of the program provide educational opportunities for participating students as well as benefits for the schools and children served.

Methods Used: Core educational components are: Working to establish and sustain health-promoting schools with ongoing health promotion and practices; having established sites for community-based learning; developing and delivering child-health education; learning to conduct validated oral health evaluation methodology (Decayed, Missing, Filled teeth Score - DMFS) on all the children in the program; the provision of preventive care (topical fluoride application); the acquisition of evaluation and research skills and experience; participation in an international partnership with other students/faculty.

Summary of Results: All MU dental students have participated in this program over the last 4 years with UBC students from medical, dental, and other faculties joining them in Ugandan communities each summer. All participants are actively involved with the children and teachers in the health-promoting schools and provide written evaluations. All the core educational components are highly valued, and especially: the practical experience of examining large numbers of children, using the DMFS score, and practicing preventive dentistry. Also the range of oral health pathology seen, opportunities to teach and participate in research, and interactions with international partners. The major practical lesson was the need for children to care better for their posterior teeth. One improvement suggested was to include conduct of minor surgical procedures during community program delivery.

Conclusions: The Brighter Smiles Africa program is providing valued educational opportunities summed up by the verbatim student comment “Working with the children and seeing their knowledge and attitudes to oral health change over the years has been amazing.”

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BRIGHTER SMILES: CONTRIBUTIONS OF AN ABDORGINAL COMMUNITY TO AN INTERNATIONAL GLOBAL HEALTH PARTNERSHIP

D. Rockcamatii, W. Cannon, M. Sanghera, Y. Wang, N. Radziminski, W. Jang, A. Macnab1UBC/BC’s Children’s Hospital, Vancouver, BC, Canada.

Purpose of Study: Hartley Bay (HB) is the first aboriginal community to partner with our Residency Program to deliver the child health education project ‘Brighter Smiles.’ This partnership proved that a “Health-promoting School” could successfully employ a school-based oral health program to reduce the incidence of childhood caries. HB then expanded this model to address other health issues of community concern, and is now integral to the successful translation of Brighter Smiles into an international global health partnership.

Methods Used: A health-promoting school (HPS) ‘recognizes that social, economic and environmental factors influence a child’s health, and facilitates healthy development, knowledge, sound practices and positive vision and behavior’ (Gray G et al. 2008. http://www.euro.int/ENHPS). Our residents stay in HB to contribute to educational content and health care delivery, and gain unique insights in return. Elder/resident dialogue led to low immunization rates, poor nutritional practices, obesity and risk factors for
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IMPROVING CHILDREN’S HEALTH THROUGH YOGA IN SEWARD, ALASKA

M. Ashraf University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Seward, Alaska is a small town of 3,025 people located in Alaska’s Kenai Peninsula. Childhood illnesses such as asthma, obesity and mental health problems are prevalent in Seward, and can be partially attributed to both social conditions (sedentary lifestyle) and geography (isolation, vegetation and poor weather). Yoga has been shown to have a therapeutic effect on children suffering from the above mentioned diseases. The purpose of this project was to address childhood health issues (asthma, obesity and mental health) through yoga at Seward’s Teen Youth Center (TYC).

Methods Used: Observing cases in the clinic, polling medical staff and clinicians, and talking to TYC staff were all methods used to identify childhood health issues as the focus of a community project. Discussions with an R/UOP clinical preceptor revealed yoga as a possible tool for tackling a multitude of childhood diseases, including asthma, obesity and mental health problems. A literature review was performed to validate the correlation between yoga and increased weight loss, mental health and respiratory function. Efforts were combined with TYC staff and a local yoga instructor in order to develop and implement a children’s yoga program at the TYC.

Summary of Results: Combined efforts between TYC staff and a local yoga instructor led to the development and implementation of a yoga program at the TYC. Fifteen children and two TYC staff members participated in a one hour yoga session led by a local volunteer yoga instructor. The session began with 15 min of stretching, followed by 30 minutes of yoga involving various poses and ending with 15 minutes of breathing exercises and relaxation poses. An oral poll subsequent to the event revealed a high level of interest and enthusiasm among participating children as well as TYC staff and yoga instructor.

Conclusions: The commitment and experience of HB provides our trainees with unique opportunities for insight, and practical lessons on how an educational partnership such as this evolves and is sustained - invaluable contributions to our international partnership.

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ANALYSIS OF EMERGENCY DEPARTMENT MORTALITIES WITH A FOCUS ON PREVENTION

EA. Neufeld, K. Harold, B. Koo, S. Cherry, B. Chakravarthy Loma Linda University, Colton, CA.

Purpose of Study: This study sought to assess data points of patients who died in the ED. Looking at demographic and physiologic data of decedents in the ED will shed light on prognostic patterns of deaths in the Inland Empire.

Methods Used: 1135 patient files of decedents at Loma Linda’s ED from 2000 to 2009 were used. 304 of these deaths were traumatic and had extra parameters. Patients were excluded if they were dead on scene prior to EMS arrival or if they survived surgery prior to their death. Patient files were evaluated through HPF and Powerchart. Death certificates were reviewed for exact cause of death. All data was recorded numerically and entered into a data sheet to allow for statistical analysis. EMS data was included when pertinent. Laboratory results from death certificates were used to whether a patient had a notable BAC or had used illegal narcotics. Trauma patients were assessed via trauma run sheets in addition to their patient files. The mean, median, mode, and SD were calculated for each data point. Binomial regression will be performed later to find significant correlations.

Summary of Results: 26.81% (304) of deaths were traumatic. Of these 304 traumatic deaths 33 were pediatric. The mean ISS was 37.83 with a SD of 21.2. The mean GCS upon entry to the ED was 4.34 with a SD of 3.38. Alcohol use was noted in 4.14% (47) of the deaths, 35 of these traumatic. The mean BAC of these patients was 12 with a SD of.09. Illegal narcotics were associated with 33 of the deaths. 7.3% (83) of the deaths were firearm related. 78 of these 83 patients had a notable BAC at the time of death. Of the 83 firearm related deaths 10 were suicides, 68 were homicides, and 5 were deemed accidental by police reports. The mean EMS transit time was 22.89 minutes with a SD of 9.16. EMS data will be correlated with ED data at a later time. Further analysis of vital signs and laboratory values are pending and will be completed in the near future. Geographic analysis likewise will be analyzed further.

Conclusions: Few data points showed strong independent relationships to mortality in the ED. The current scores used to determine the likelihood of survival of patients in the ED are inadequate as they are either specific to trauma or too cumbersome to be of any use. Also, it is clear that efforts need to be made to reduce methamphetamine related deaths in San Bernardino County.

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UNIVERSAL NEWBORN HEARING SCREENING IN VALLEY COUNTY, IDAHO

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Purpose of Study: Hearing Loss is the most frequent birth defect and interferes with the most basic human need to communicate. The incidence of permanent childhood hearing loss is 6 per 1,000. Without Universal Newborn Hearing Screening (UNHS) the average age of diagnosis is almost 2 years. Early intervention (before 6 months of age) results in significantly improved cognitive and linguistic development. The purpose of this study was to identify barriers that rural/underserved families experience during the screening process.

Methods Used: Interviews were conducted with administrators, nurses, screeners, childbirth educators, social workers, physicians and families to identify concerns. These included data collecting, tracking and management, screener training, communication and loss to follow-up. A Literature Review identified standard of care, guidelines, and recommendations for UNHS programs. The Joint Committee on Infant Hearing, the Academy of Pediatrics, and US Preventative Services Task Force have supported the following three benchmarks:
1. Screening coverage rates >95%
2. Initial referral rates <16%
3. Follow-up rescreen rates >70%

Training materials and parent brochures (Spanish and English) were obtained from Idaho Sound Beginnings.

Updated data-tracking software was obtained from the manufacturer.

Summary of Results: Nine primary care physicians attended a presentation about the role of the Medical Home in facilitating timely follow-up and importance of early intervention.

Training was provided to 8 screeners, highlighting strategies to achieve benchmarks.

A new coordinator was trained on data management and resources available.

Hospital social workers were counseled to identify barriers and assist with follow-up.

A curriculum to increase awareness of UNHS was presented to 20 parents during Childbirth Education classes.

Conclusions: The goal of this project was to improve UNHS delivery for all infants, but especially for those with congenital hearing loss. Barriers to early hearing loss detection in a rural community were attributed to lack of parental awareness, language barriers, financial concerns, distance to appointments, weather and transportation. All of the stakeholders in the UNHS program
were given training, education, strategies and resources to address these challenges and facilitate early identification of hearing loss.

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192
CAMPAIGN TO PROMOTE CHILD BICYCLE HELMET USE IN GARDEN VALLEY, IDAHO
MD. Swanson University of Washington School of Medicine, Seattle, WA.
Purpose of Study: Head trauma due to bicycling accidents is a serious cause of morbidity and mortality across the United States, particularly in underserved rural communities where bicycle helmet use is less prevalent than in urban areas. Garden Valley Family Medicine is a rural clinic which sees a large number of bicycle-related injuries every summer, particularly among children who were not wearing helmets at the time of their accident. The purpose of this project was to decrease childhood injury in Garden Valley by making bicycle helmets available to area youth and educating parents about the importance of their proper use.

Methods Used: Consumer Product Safety Commission-certified helmets were purchased from the Helmets R Us non-profit helmet manufacturer at a cost of $3.65 per helmet and distributed for free through the Garden Valley clinic. This clinic-based campaign to promote bicycle helmet use was initiated with a helmet giveaway at the Garden Valley Fourth of July celebration. Each helmet was given away with 2 informational brochures (acquired from the Bicycle Helmet Safety Institute) targeted to parents of children 6–12 years of age, one on the importance of bicycle helmet use and the other describing the appropriate way to size and fit a helmet to their child's head. A discussion of bicycle helmet use was also added to the annual exam and well-child exam protocol at the clinic.

Summary of Results: The project received high visibility in the community, as much of the Garden Valley population was present for the Fourth of July celebration. As of the Fourth of July celebration, 24 helmets have been acquired by children through this program. Several children have been observed wearing their new helmets while bicycling in the community. The immediate success of the program has led the clinic to order further helmet shipments in order to meet increasing community demand.

Conclusions: In order to successfully increase bicycle helmet use among children in underserved communities, a campaign must have the following characteristics: 1) offer free helmets; 2) high visibility in the clinical setting and the community; 3) target parents to raise awareness of the effectiveness of helmets in preventing injury; and 4) include information on how to size and fit helmets appropriately.

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INCREASING PHYSICAL ACTIVITY FOR PRESCHOOL-AGED CHILDREN ON THE FLATHEAD RESERVATION
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Purpose of Study: Obesity and related diseases, such as Type II Diabetes, are a serious problem facing the Confederated Salish and Kootenai tribes of Montana’s Flathead Reservation and are increasingly a problem for children. Incorporating physical activity early in childhood is a crucial component in preventing childhood and adult obesity. The purpose of this project was to incorporate preschool aged children into current community efforts to increase physical activity.

Methods Used: A program was designed after discussion with community health staff, physicians, and community elders, in addition to consultation of current literature on obesity prevention and culturally relevant programs. It builds on an annual program called “Walking the Rez,” where participants walk or run and keep track of distances in a community wide effort to increase physical activity. The intervention created would incorporate Head Start school programs into this effort by having 15 minutes of very active play time count as 1 mile of walking in the “Walking the Rez” program. To do this, community health staff can use resources created, such as activity ideas and logs, to implement the program with educators and parents. This includes teaching children different ways to be physically active, such as traditional dancing, and incorporates elders and community members as healthy role models.

Summary of Results: Materials created include a program description, information for parents and educators on appropriate activity levels and ideas, and activity logs which were distributed to the community health staff to be reviewed and modified to meet community needs. The intention is to have community health staff work with educators on the program for the coming school year.

Conclusions: While the intervention was not able to be followed to completion due to the time and nature of the program, key features include incorporation of preschool aged children into a well established program in the community and creation of a multigenerational approach to increasing physical activity. Also, having community health staff implement the program meets recommendations on the importance of community driven and culturally relevant programs in Native American communities.

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IMPLEMENTATION OF A FRIENDLY VISITOR PROGRAM: PROVIDING RESpite CARE FOR A RURAL MONTANA COMMUNITY
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Purpose of Study: Lewistown is a rural community located in central Montana. Nearly 25% of its population is over the age of 65 and this percentage is growing every year. Many of these senior citizens live independently with the assistance of a caregiver. Those providing care for ill, disabled, or elderly persons often struggle with their own health issues and stress has been shown to increase caregiver mortality rate by 63%. The purpose of this project was to identify how to ease the burden on family caregivers and improve their health and well-being.

Methods Used: Based on the input of physicians, medical staff, home health, county extension, and the Council on Aging, it was determined that the community was in need of respite services for caregivers. A volunteer program was developed to provide caregivers a temporary break from their daily responsibilities. Next, a literature review was conducted to validate the need for the program and to identify best practices. Community organizations were engaged to recruit volunteers and a training manual with a position description and confidentiality agreement was developed. Finally, a poster was created to publicize the program and solicit caregivers in need.

Summary of Results: The Friendly Visitor program provides in-home respite care to caregivers in the community. It allows caregivers to leave the home for hour-long periods of time to go for a walk, meet friends for lunch, or attend a support meeting. The service is free of charge and available on an as-needed basis. A poster advertising the program was distributed to doctors’ offices, the hospital, pharmacies, grocery stores, nursing homes, churches, the senior citizens’ center, library and post office. In the future the program will be managed by Home Health Services, a not-for-profit organization.

Conclusions: The Lewistown community was in dire need of a caregiver respite program. Previous programs were expensive and required the care receivers to be transported out of their home. The Friendly Visitor program addressed these issues while assisting caregivers in their role. Caregivers who participate in respite services are generally very satisfied and experience enhanced mental and physical health. Those receiving care benefit from the social interaction and have improved mental health, which may delay their out-of-home placement for care.

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BRIDGING THE GAP BETWEEN THE CORRECTIONAL DEPARTMENT AND COMMUNITY HEALTH CARE IN CANYON AND ADA COUNTIES, IDAHO
K. Boggess University of Washington School of Medicine, Seattle, WA.
Purpose of Study: People in the prison system have higher rates of chronic conditions, infectious disease, exposure to violence, substance abuse, and mental health problems than the general population. This has substantial health and social consequences for communities where prisoners are released. As the largest urban area in Idaho, Ada and Canyon County community health centers see the largest number of released inmates in the state. Providers at the community health centers see disjointed care for previous inmates and long gap periods between release and seeking care. The purpose of this project was to link recently or soon-to-be released inmates to community health centers in Ada and Canyon Counties through information made available upon release or through probation and parole officers.

Methods Used: Polling local community health center providers, social workers, and administrators, as well as observing clinical challenges,
revealed the lack of continuity between released prisoners and community health centers. A literature review showed a positive correlation between a connection to healthcare for released inmates and the impact on community health and recidivism. Educational brochures were designed for the inmate population with information on accessing community health centers. Brochures were distributed to local Community Work Centers, the Department of Re-Entry, and probation and parole officers for Ada and Canyon Counties. A presentation was given to the manager of parole and probation officers in the Department of Re-entry on the community health resources in the area.

**Summary of Results:** Both the community health leadership and Department of Corrections leadership identified the connections made as valuable to their organizations and the community. Information about community health centers was made available to inmates at release or through probation and parole officers.

**Conclusions:** The most important impact of this project was developing a connection between the Department of Corrections and community health centers in Ada and Canyon County. In addition, both inmates and probation and parole officers now have information on how to access the health and mental health services provided by local community health centers.

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**DIABETES MELLITUS TYPE TWO PREVENTION IN THE JUVENILE POPULATION OF DILLINGHAM, ALASKA**

J. Pennell-Walklin, *University of Washington School of Medicine, Seattle, WA.*

**Purpose of Study:** 76% of the approximately 3000 residents in Dillingham, Alaska are Native Alaskans. From 1990 to 2004 diabetes mellitus rates in Dillingham census area increased 240%. 2004 obesity rates for Alaska Natives stood at 34.5%, compared to a national rate of all races of 22.7%. 14% of Alaska Native high school students are overweight and 44% do not exercise regularly. This community in particular is at high risk for development of diabetes. The purpose of this project was to improve community awareness and increase discussion about diabetes mellitus type 2 risk factors present in the juvenile population.

**Methods Used:** A literature review was conducted about diabetes mellitus type 2 and health education practices. Community education through written and oral teaching was identified as a reasonable target for this project. Permission was obtained from the chamber of commerce to operate a prevention booth during the yearly 4th of July community salmon bake. An education brochure displaying prevention techniques, health risks of diabetes type 2, and statistics for the local population was produced and distributed.

Health topics were presented with cultural issues and the educational level of the population in mind. Material resources were obtained courtesy of the regional public health office. Two volunteers participated in educational activities.

**Summary of Results:** Approximately 500 people attended this event and 56 brochures were distributed. Prevention topics were presented throughout the three-hour event. The education booth was met with positive responses from local residents.

**Conclusions:** This project provided an accessible venue for public education. Many residents in this community were educated on risk factors that juveniles are susceptible to regarding diabetes mellitus type 2. However, diabetes is just one of many health problems that this population battles. While health education is a crucial step toward the prevention of diabetes, many other factors need to be addressed as well. Combinations of poor nutritional practices, limited recreational activities, social and cultural ideals, and sedentary lifestyle remain to confound efforts to prevent diabetes in this population. Continued involvement and diligence of local government officials in conjunction with community elders/leaders is needed on many levels to improve the situation.

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**MEDICATION ADHERENCE EDUCATION FOR SOMALI IMMIGRANT WOMEN IN SEATTLE, WASHINGTON**

K. Kelly, ¹University of Washington School of Medicine, Seattle, WA and ²WSMRF, Seattle, WA.

**Purpose of Study:** Harborview (HMC) Family Medicine is an urban underserved clinic in Seattle that sees a large population of Somali immigrant women with chronic diseases who face numerous barriers to medication adherence. The majority of these patients require interpreted encounters due to limited or no English proficiency. Many received little or no education in Somalia, and do not read in any language. These communication barriers make it difficult for patients to understand medication instructions, resulting in unintentional non-adherence. Intentional non-adherence can result from cultural and religious beliefs that inform medication-taking behaviors. The purpose of this project was to improve medication adherence in this population through culturally appropriate health education.

**Methods Used:** Discussions with clinicians and clinical observations of medication adherence challenges were used to identify this population as the project focus. A literature review identified factors affecting adherence and helped determine an effective, culturally appropriate means of health education. HMC Community House Calls advised on educational materials and community outreach. Taking Medication Safely, a Somali-language DVD, was purchased. HMC clinicians participated in two medication adherence dialogues with members of Daryel, the Somali Women’s Wellness Project. Members were invited to bring medications.

**Summary of Results:** 10–15 members participated in each session; one brought her medications. The DVD was well-received. The discussions included the importance of trust and honest communication, primary versus specialty care, medication adherence and safety, OTC medications, concerns that Western medications are ineffective, the stigma of TB and STDs, and altered dosing during Ramadan fasting. An open, lively dialogue ensued about sociocultural and other barriers this population must overcome to access healthcare in the United States.

**Conclusions:** Health education in the form of in-person discussions is particularly effective for this population because Somali society is largely an oral one, and its members receive the majority of their healthcare information from family and friends. These dialogues help to bridge language and cultural divides while building the trust and open communication so vital to an effective healthcare partnership.

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**NEONATAL JAUNDICE EDUCATION OF LATINOS IN YAKIMA VALLEY**

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**Purpose of Study:** Screening for physiological and pathological jaundice is a standard part of the physical exam of a newborn. Over half of newborns experience some jaundice with around 10% requiring intervention to prevent kernicterus. The prevalence of neonatal jaundice amongst babies born to Latino mothers at Yakima Valley Memorial Hospital in Yakima, Washington was the motivation for education of the Latino community of Yakima Valley about the causes, risks, and treatments of neonatal jaundice.

**Methods Used:** An informal survey of Latino mothers and fathers whose newborns experienced jaundice was conducted to assess the level of knowledge about neonatal jaundice and identify concerns. Local clinicians and lactation specialists were consulted about management and treatment of neonatal jaundice. Resources available for educational efforts in the Latino community were identified. A literature review was employed to verify the usefulness of community radio in general and radio dramas in particular as methods for outreach.

**Summary of Results:** A total of seven Latino mothers with newborns who required closer observation and/or treatment for neonatal jaundice were interviewed. Issues of concern included a lack of familiarity with neonatal jaundice, guilt for causing it, and beliefs that breastfeeding should cease due to its association with jaundice. Mothers stated that the fathers were generally less worried than they were. An hour long Spanish radio program, “Salud en Sus Manos,” was used for educational outreach. The following topics were discussed: signs and symptoms of neonatal jaundice, when and why to treat, and the need for appropriate breastfeeding practices to minimize breastfeeding jaundice. Maternal guilt was addressed by stressing the prevalence of neonatal jaundice and the availability of safe and effective treatments. Additionally, a ten-minute radio drama dealing with these same issues was written and submitted to the station manager for future production.

**Conclusions:** Community radio is a culturally appropriate and effective means for neonatal jaundice health education of Latinos in Yakima Valley. Radio dramas in particular are effective in increasing knowledge about
neonatal jaundice and there is a need for the future production of the script written to accomplish this goal.

Western Student Medical Research Forum
Student Scientific Session III - Developmental Biology/Neonatology/Morphogenesis
8:30 AM Friday, January 29, 2010 Western Student Medical Research Forum

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis
199 LOW MUSCLE MASS AND LOW BMI IN OREGON WOMEN ARE ASSOCIATED WITH INCREASED ANTIOXIDANT EXPRESSION IN THE TERM PLACENTA

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Purpose of Study: Placental oxidative stress is defined as an imbalance between antioxidants and reactive oxygen species and is found in all pregnancies, but when heightened it can be detrimental to placental function. It contributes to the pathogenesis of preeclampsia and intrauterine growth restriction [Myatt 2004, Histochemistry & Cell Biology (122), 369–382]. We aimed to determine whether maternal muscle mass (as measured by arm muscle area (AMA)) and/or body mass index (BMI) in early pregnancy influenced antioxidant gene expression and markers of oxidative stress in the placenta.

Methods Used: Fifty women - recruited during their third trimester of pregnancy as part of the Oregon Women’s Study - were categorized into groups based upon muscle mass [low, LMM: 20.1 ± 3.4, mid, MHH: 37.4 ± 2.2, high, HMM: 71.3 ± 16.2 cm²] and BMI [low: 19.3 ± 1.4, mid: 27.3 ± 1.9, and high: 38.4 ± 2.5 kg/m²]. Placental tissue was obtained at delivery for molecular analyses. Placental antioxidant gene expression, specifically glutathione peroxidase (GPX) 1 and 4, was quantified by QPCR. Markers of oxidative stress (8-isoprostane, 8-hydroxy-2′-deoxyguanosine (8-OHdG)) were also measured.

Summary of Results: SOD 1, SOD 2, GPX 1 and GPX 4 mRNA levels were inversely related to maternal AMA, while CAT expression showed an opposite trend. Placental 8-OHdG staining showed a trend of increasing oxidative DNA damage as maternal AMA and BMI increased. Maternal plasma levels of 8-isoprostane significantly increased with AMA and BMI (R = 0.36, P < 0.05).

Conclusions: We found that maternal AMA in early pregnancy is a better predictor of both oxidative stress and antioxidant gene expression than BMI. This is consistent with previous evidence that high levels of physical training/muscle mass result in increased antioxidant gene expression. The relationship between muscle mass and oxidative stress in pregnancy had not previously been investigated. The HMM and high BMI women had placental antioxidants expression patterns that closely mirrored those of pre-eclamptic women, raising concerns that their fetuses may be at higher risk for poor outcomes.

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200 EXPLORING THE ROLE OF H3K18ac HISTONE MODIFICATIONS IN CELLULAR DIFFERENTIATION

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Purpose of Study: Cancer cells harbor epigenetic alterations that may contribute to uncontrolled cell division and loss of differentiation, leading to progressively aggressive phenotypes. The loss of selected histone modifications, especially that of histone H3 lysine 18 acetylation (H3K18ac), may constitute these molecular events. Reduction in cellular levels of H3K18ac predicts poor prognosis in multiple cancers and is also caused by DNA tumor virus oncoproteins during cellular transformation. These findings suggest a role for H3K18ac in carcinogenesis that may underlie changes in cell differentiation. Human embryonic stem cells (hESC) have the ability to regulate differentiation processes to sustain an undifferentiated state and provide a suitable model to explore the potential role of H3K18ac in cellular differentiation. This study was employed in an effort to determine the role of H3K18ac in cellular differentiation to ultimately understand the similarities and differences in epigenetic requirements for maintaining a de-differentiated state in cancer and hESC.

Methods Used: Global levels of H3K18ac in hESC were assessed using Western Blotting. Next, chromatin immunoprecipitation (ChIP) combined with high-throughput sequencing for genome-wide analysis was employed to determine the molecular distribution of H3K18ac in hESC and somatic cells. Using highly specific anti-H3K18ac antibodies, ChIP was performed 4 times from 100 million purified H1 hESCs. Pooled Input and ChIPed DNA were ligated to specific primer adapters, size-selected, amplified and were sequenced at the UCLA Microarray Core facility.

Summary of Results: Preliminary sequencing data points toward global hypomethylation of H3K18ac in hESC compared to fibroblasts. Attempts to map these hypomethylated sites to specific promoter regions are in progress.

Conclusions: Preliminary data analyzing global H3K18ac in hESC and normal somatic cells (fibroblasts) suggest a role for H3K18ac in cellular differentiation. Further work to understand function and mechanism are planned.

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis
201 A HOX REGULATORY MODULE WITHIN THE LIMB SPECIFIC SHH REGULATORY REGION EXHIBITS DUAL ENHANCER AND INHIBITOR ACTIVITY

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Purpose of Study: The expression of Sonic hedgehog (Shh), a potent patterning factor, in chick limb buds is regulated by a limb-specific Shh regulatory region (LSSRR), non-coding region 1Mb upstream of the Shh promoter. We have identified four conserved non-coding regions (CNR) within the LSSRR which we designate as A, B1, B2, and B3. We further found a cluster of 3 presumptive Hox-binding sites (AATA) at the 3′ end of CNR B3. Hox transcription factors, particularly Hoxd13, have been reported to bind to the LSSRR and regulate Shh expression. Thus, we hypothesize that the HOX-binding sites in B3 might act as a regulatory sensor of Hox expression and be critical for Shh regulation during limb development.

Methods Used: To determine the importance of the Hox-binding sites, we inserted a portion of the LSSRR with the B3 region into a plasmid containing a minimal promoter and GFP reporter. This construct with robust enhancer activity was then subjected to progressive digestion from the 3′ end to sequentially eliminate the Hox-binding sites. In addition, we performed site directed mutagenesis of the terminal two Hox binding sites. These constructs were then transfected into the presumptive wing of stage 14 chick embryos using electroporation. After 48 hours the chick embryos were harvested and the activity of the enhancer within the wing bud was recorded by fluorescent microscopy.

Summary of Results: Full enhancer activity was retained up to -112 bases (L3-112) from the 3′ end. Removal of an additional 5 bases (L3-117) and the terminal Hox-binding site resulted in marked reduction in enhancer activity. Although removal of the terminal and penultimate Hox-binding site added no further statistical reduction in enhancer activity, site directed mutagenesis of the second to last site alone also exhibited marked reduction in enhancer activity. Interestingly, removal of all three Hox-binding sites nearly recovers enhancer activity.

Conclusions: These data suggest that the cluster of Hox-binding sites in the 3′ end of the LSSRR (region B3) provide dual regulation, with the two terminal Hox-binding sites enhancing Shh expression, while the third or most 5′ of these terminal sites, inhibits Shh expression.

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202 LIMB REGENERATION IN NORMAL AND OLIGOZOEGODACTYLY CHICKS

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Purpose of Study: The application of fibroblast growth factor 2 (Fgf2) to amputated chick wing buds at Hamburger and Hamilton stage 23 (HH23) up-regulates Sonic hedgehog (Shh) and induces limb regeneration; however,
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SEXUALLY DIMORPHIC DIRECTIONAL ASYMMETRY IN HAND TRAITS AND CORRELATION WITH DIABETES MELLITUS

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Purpose of Study: Asymmetry in body measurements is thought to be an indicator of variations in level of early sex hormones exposure. Females have been shown to have more rightward asymmetry of digit length and hand width than males and vice versa, linking low levels of early androgen exposure to rightward asymmetry, and high levels to leftward asymmetry. Type II diabetes mellitus (DMII) has also been shown to have some correlation to early androgen exposure: DMII females have different ulna:stature ratios from control females, but they do not differ from male ratios. The purpose of this study is to investigate sexual dimorphism in directional asymmetry (DA) of hand traits, and whether DMII correlates to abnormal early androgen exposure, which may predispose individuals to the disease later on. We analyze DA in wrist width, hand width, and hand length and assess whether DA in these traits show the sexual dimorphic pattern as stated above, and whether it correlates with DMII in different ethnic groups.

Methods Used: We examined data collected at 5 clinics in Southern California. Bilateral wrist width, hand length and hand width were measured in triplicate with digital calipers and averaged. Diagnosed illness and ethnicity were self-reported. Data analysis was performed using GraphPad Prism 5 and GB-Stat.

Summary of Results: Wrist data shows 4/8 female groups with rightward laterality compared to 1/8 male groups. Hand width data shows 6/8 rightward female groups compared to 4/8 male groups. Hand length data shows 1/8 leftward female groups compared to 4/8 male groups. The rest of the groups in the 3 traits are not significantly asymmetrical.

Among the 9 female comparison pairs DMII vs. control the DMII mean was more rightward in 7 cases. Among the 9 male comparison pairs the DMII mean was more leftward in 5 cases. The difference was not significant using t-test for each pair.

Conclusions: These 3 hand traits show the same sexual dimorphic pattern as previous results. females tend to be more rightward and males more leftward. DMII does not appear to have a definite correlation to DA in these 3 traits.

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DEVELOPMENTAL MASSAGE THERAPY (DMT) DURING NEONATAL STRESS TEMPER SUBCUTANEOUS ADIPOSE EXPRESSION OF GENES INVOLVED IN GLUCOCORTICOID RECEPTOR (GR) SIGNALING

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Purpose of Study: Elevated glucocorticoid (GC) levels are linked to greater adiposity. Massage therapy lowers GC and may decrease adiposity by modulating adipose tissue gene expression. We hypothesized that molecular events that result from DMT will lower circulating GC, lessen adipose tissue deposition, and alter subcutaneous (SQ) and retroperitoneal (RP) adipose tissue expression of genes involved in GC signaling in neonatal stressed rat pups.

Methods Used: Timed pregnant S-D rats were delivered at term, litters culled to 10 pups (5 M, 5 F) and randomized to: neonatal stress (NS; 60 min of maternal separation + injection + hyperoxia/hyperpnea; n = 40); NS + developmental massage therapy (DMT = NS + 10 min of DMT; n = 40), or Control (C; 60 min of maternal separation, n = 40). Treatments were given daily on D5-D9; litters were cross-fostered D5-D21. DMT consisted of 5 min of tactile stimulation followed by 5 min of range of motion to fore- and hind limbs. Weight (g) during (D5-D9) and post-intervention (D14, and D21), body composition (D21) by dual energy x-ray absorptiometry (DXA), serum levels (D21) by ELISA for GC, and SQ and RP adipose tissue mRNA levels (D21) for glucocorticoid receptor (GR) and 11-beta hydroxysteroid dehydrogenase -1,-2 (11HSD-1,-2) were measured. Results are presented as percent (%C) of C values.

Summary of Results: Weight gain was similar during and post-intervention among treatment groups by gender. Relative body fat (%) was lower in NS females (65.2 ± 9.0%) and DMT males (88.5 ± 9.8%) at D21 (p < 0.01). SQ tissue GR mRNA was lower in NS males (68.4 ± 13.6%) compared to DMT (111.5 ± 25.8%) or C (p < 0.01). SQ adipose tissue 11β-HSD-2 mRNA levels were decreased in NS males (30.8 ± 9.0%), DMT males (51.0 ± 10.0 %), and NS females (43.6 ± 16.8%), (p < 0.001). Serum GC levels did not differ across treatments or gender.

Conclusions: GC is inactivated by 11β-HSD-2 and we speculate that the lower SQ 11β-HSD-2 mRNA levels may reflect greater GC exposure of SQ adipose tissue in response to neural stress. We conclude that stress during early postnatal life affects adipose tissue mRNA expression. More importantly, DMT appears to temper mRNA levels of SQ adipose tissue genes involved in GR signaling in female neonatal stressed rat pups.

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POSSIBLE ROLE OF 2ND TO 4TH DIGIT RATIOS (2D:4D) AS A MARKER FOR ADULT OBESITY

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Purpose of Study: Obesity is a growing epidemic and has been linked to metabolic diseases. Previous studies have also linked obesity to early abnormal hormonal exposure. Low levels of testosterone have been linked with increased abdominal obesity in men and women. Studies have shown that 2nd and 4th digit ratio may be an indicator of early androgen exposure, like testosterone. Lower ratios indicate higher androgen exposure and women tend to have higher 2D:4D ratios compared to men. The purpose of this study is to examine the relationship between early androgen exposure and obesity. Our hypothesis was that as BMI increases, 2D:4D ratios would rise in males and females.

Methods Used: A total of 246 females (n = 193) and 154 males (n = 50) were measured for 2D:4D ratio. Controls were defined as subjects with BMI of 18-25 and no co-morbidities, overweight subjects as 25-30, and obese as 30+. Lengths of 2nd and 4th digits were measured with a digital caliper, from the proximal crease of the digits to the distal tip on the ventral side of the hand. Measurements were made in triplicates for each hand then averaged. Body weight, height, and diagnosed medical illnesses were self reported on a questionnaire.

Summary of Results: We performed Kruskal-Wallis test and found that obese males had a significantly larger left 2D:4D ratio then normal and overweight males (FW = 6.698, p = 0.0304); however, while we did notice...
an increase in average left 2D:4D ratio at higher BMIs in women, this relationship was not statistically significant (FW = 1.049, p=0.4994). Additional analysis, when subjects were divided by ethnicity, showed a strong positive correlation between 2D:4D ratio and BMI was found in white males (FW = 17.17, p = 0.0002), and black females (FW = 9.391, p = 0.0091). We found no statistically significant positive correlation among Hispanic males or females, white females, or black males.

Conclusions: Men with higher 2D:4D ratio demonstrated an increased incidence of obesity. This supports previous research studies that linked low back pain exposure might play less of a role in later development of obesity for them. Further research is needed to determine if 2D:4D ratios can be used to predict increased risk of obesity in men.

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis 206

DIRECTIONAL ASYMMETRY IN THREE TRAITS IN LOW BACK PAIN PATIENTS

J. Meyers Western University of Health Sciences, Pomona, CA.

Purpose of Study: Some anatomical traits, e.g., digits, are sexually dimorphic with men tending to have increased leftward asymmetry and females increased rightward asymmetry. This is important because it suggests that variation in asymmetry may result from alterations in prenatal androgen exposure. Past data from our laboratory have shown that chronic low back pain (LBP) patients tend to have increased rightward asymmetry in the ulna in comparison to controls. Whether LBP patients have abnormal asymmetry in other traits and whether other traits are sexually dimorphic is not clear. Thus, we hypothesize that other hand traits are sexually dimorphic in terms of asymmetry and that LBP males will have less leftward asymmetry, i.e., more rightward asymmetry, while LBP females will have noticeably higher rightward asymmetry when compared to same sex controls. To test this hypothesis, we compared males and females, and we compared LBP subjects to controls using three different trait measurements: wrist size, hand length, and hand width.

Methods Used: Measurements were made in triplicates using a digital caliper.

Summary of Results: Our results indicate that there is rightward asymmetry in the wrist in females (p = .0012), but not in males (p = .12). Furthermore, females with LBP but not males, have significantly greater rightward asymmetry than same sex controls (p = .0084). Hand length and hand width showed no significant sex differences, and LBP patients did not differ from controls in these traits.

Conclusions: In conclusion, there is evidence from wrist asymmetry measurements that suggests that LBP in females may be associated with abnormally low exposure to androgens during early development. Further studies of asymmetry in other traits are necessary to test this interpretation.

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis 207

THE PANCREATIC RENIN-ANGIOTENSIN SYSTEM AND ITS CONTRIBUTION TO DIABETES IN THE OFFSPRING OF PROTEIN DEPRIVED MOTHERS

C. Wong, R. Goyal, L.D. Longo Loma Linda University, Loma Linda, CA.

Purpose of Study: The classical systemic renin-angiotensin system (RAS) and its end product angiotensin II acts on its receptors, angiotensin II subtype 1 (AT1) and angiotensin II subtype 2 (AT2), to increase vascular tone and blood pressure. Despite a major emphasis in medicine of the systemic RAS, there exist tissue-specific RASs. Specifically, the pancreatic RAS has been shown to be altered in disease states, such as type 2 diabetes mellitus, pancreatitis, and chronic pancreatitis. Previous studies also report a significantly increased incidence of diabetes mellitus in female offspring of mothers fed a 50% low protein diet (MLPD). In the present study, we tested the hypothesis that with MLPD during gestation, expression of the pancreatic RAS is altered, which may lead to increased blood sugar in the offspring.

Methods Used: To test this hypothesis, we performed quantitative PCR and in-cell western immunoblots with pancreatic tissue from control, 50% and 33% MLPD offspring at 3 weeks and 33 weeks of age.

Summary of Results: Pancreatic transcripts of angiotensinogen, renin, angiotensin converting enzyme (ACE) 1, ACE 2, AT1, and AT2 were all increased at 33 weeks in female offspring whose mothers were fed a 50% MLPD. Nonetheless, protein levels did not correlate with the mRNA increases. In the same group, protein levels of angiotensinogen decreased while levels of the other proteins in the RAS stayed at control levels.

Conclusions: Our study demonstrates that with MLPD there are significant alterations in the pancreatic RAS. We speculate that the increase across the board of the RAS transcripts could be due to epigenetic factors such as hypomethylation of gene promoter regions and/or histone modifications. The drop in angiotensinogen protein levels could be mediated through microRNAs, which decrease protein translation. Since only angiotensinogen protein levels changed, angiotensinogen may be the key player in regulating diabetes mellitus 2 before its onset. Further research will look at angiotensinogen and the effects of stresses upregulating its translation, leading to increased RAS components and causing the diabetes mellitus 2 that is found in offspring of antenatal protein deprived dams.

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis 208

LONG TERM HYPOXIA MODULATION OF UCP-1 IN PERIRENAL ADIPOSE TISSUE IN THE LATE GESTATION OVINE FETUS

MK. Urquhart1, K. Furuta1, D. Myers2, SM. Yellow1, CA. Ducsay1 2Loma Linda University, Loma Linda, CA and 3University of Oklahoma, Oklahoma City, OK.

Purpose of Study: Uncoupling protein-1 (UCP-1) catalyzes adaptive thermogenesis in brown adipose tissue. In the ovine fetus, perirenal adipose tissue (PAT) also expresses UCP-1 even though it is considered white adipose tissue. We have previously shown that long term hypoxia (LTH) results in enhanced mRNA expression of UCP-1. The aims of the present study were to) test the hypothesis that ovine fetal PAT is comprised of distinct cell populations, exhibiting either brown (UCP-1) or white (not expressing UCP-1) adipose tissue phenotypes and 2) to test the hypothesis that LTH enhances protein expression of UCP-1 in PAT compared to tissue from normoxic control fetuses.

Methods Used: Ewes were maintained at high altitude (3,820 m) from 40 to 137 days gestation (dG). Animals were transported from high altitude to the lab at which time a maternal tracheal catheter was placed. Reduced PO2 was maintained by nitrogen inflation at a level comparable to that observed at high altitude. Age matched normoxic fetuses were used as controls. At 138-141 dG fetal PAT was collected (n = 5 for each group). The tissue was paraffin blocked, sectioned, and immunohistochemically stained with antibodies to UCP-1. Photomicrographs were taken with fluorescent and light microscopy, and analyzed for density of UCP-1 staining using ImagePro analysis system.

Summary of Results: Distribution of UCP-1 was diffuse throughout the PAT. There was a combination of unilocular and multilocular cells, indicating that late gestation fetal adipose expresses characteristics of both brown and white adipose without distinct populations. There was no significant difference in PAT UCP-1 distribution density between LTH and normoxic fetuses.

Conclusions: 1) Fetal PAT is comprised of a “mixed phenotype” that has the characteristics of both white and brown adipose tissue that does not include distinct cellular expression of UCP-1. 2) Based on immunohistochemical methods, there was no difference in protein expression of UCP-1 between control and LTH PAT. Together with our previous data, these data suggest that although LTH upregulates UCP-1 transcription, translation occurs at a level similar to normoxic controls. This adaptive mechanism may be important in regulating energy balance after birth. (NIH grant HD31226).

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis 209

AGE-DEPENDENT EXPRESSION OF HEME OXYGENASE-1 IN MICE FOLLOWING ORAL ADMINISTRATION OF ZINC BIS GLYCOL PORPHYRIN

CX. He, H. Zhao, F. Kalish, RJ. Wong, DK. Stevenson Stanford University School of Medicine, Stanford, CA.

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Purpose of Study: Metalloporphyrins (Mps) competitively inhibit heme oxygenase (HO), the rate-limiting enzyme in bilirubin production, and thus are potential compounds for treating neonatal jaundice. We have previously reported that tin mesoporphyrin (SnMP) potently inhibits HO, but is photoactive and induces HO-1 gene expression, properties that limit its clinical use. The objective of this study was to determine the efficacy of another alternative Mp, zinc bis glycol porphyrin (ZnBG), towards inhibiting HO activity in target and non-target tissues of mice of various ages, and the subsequent effects on in vivo HO-1 gene transcription and in vitro HO-1 protein levels.

Methods Used: 1-, 3-, and 5-wk-old HO-1-luc mice, with a transgene containing the full-length HO-1 promoter driving expression of the reporter gene luciferase, were given 15-μmol ZnBG/kg body weight or vehicle by oral gavage. 24 hrs after administration, HO activity in the liver, spleen, and brain was determined by gas chromatography. % inhibition (mean±SD) of HO activity from age-matched control values were calculated (Table). In vivo HO-1 gene transcription and in vitro HO-1 protein levels were assessed by bioluminescence imaging and Western blots, respectively, and calculated as fold change from control values.

Summary of Results: Liver HO activity was significantly inhibited in mice at 1- and 3-wks of age. Spleen and brain HO activities were not significantly inhibited in mice of any age. No statistically significant effects on HO-1 transcription were found in any tissue or at any age. HO-1 and HO-2 protein levels were induced in liver and spleen at 1-wk of age only.

Conclusions: ZnBG at a low dose significantly inhibits HO activity in the liver with the greatest inhibition occurring in 1-wk-old mice. In addition, ZnBG does not appear to induce any changes in HO-1 gene transcription levels, but does induce HO-1 and HO-2 protein levels. Thus, we conclude that ZnBG may be another attractive alternative compound to SnMP or CrMP for use in the treatment of neonatal jaundice.

% Inhibition of HO Activity (mean ± SD), *p < 0.05, n ≥ 5 for all times

<table>
<thead>
<tr>
<th>Age (Wk)</th>
<th>1</th>
<th>3</th>
<th>5</th>
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<tbody>
<tr>
<td>Liver</td>
<td>32±19%*</td>
<td>28±16%*</td>
<td>3±22%</td>
</tr>
<tr>
<td>Spleen</td>
<td>24±21%</td>
<td>-18±17%</td>
<td>-18±17%</td>
</tr>
<tr>
<td>Brain</td>
<td>-6±19%</td>
<td>-19±28%</td>
<td>-2±43%</td>
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</table>

Session: Student Session III - Developmental Biology/Neonatology/Morphogenesis 210

ELEMENTAL ANALYSIS OF NANOPARTICLES IN THE ENVIRONMENT WITH THE USE OF SCANNING ELECTRON MICROSCOPY AND ENERGY-DISPERSIVE X-RAY SPECTROSCOPY

B. Alva1, M. Malecki2 1University of La Verne, La Verne, CA and 2Western University of Health Sciences, Pomona, CA.

Purpose of Study: Environmental pollution in California is primarily resulting from motor vehicle traffic emissions. This pollution is directly correlated with lung diseases. Incidences of such diseases increase with the increased exposure to these emissions. While nanoparticles and ozone are in the focus of the attention of EPA (www.airnow.gov), this environmental pollution analysis is primarily concerned with the size of the particles. However, our hypothesis is that elemental composition of these particles is of critical importance for all aspects of the human health (e.g., heart diseases, pregnancy complications, etc), when heavy metals contained in some of these particles are released in the human body. Herewith, we report the results of our work on the elemental composition and atomic structure of nanoparticles polluting the environment.

Methods Used: Energy Dispersive X-ray Spectroscopy (EDS), Scanning Electron Microscopy (SEM), and x-ray and electron beam crystallography were used for analysis. Pollutants were collected on stubs with adhesive carbon tape, or grids placed for 24 hours in three locations: i. on CA 57 freeway experiencing constant heavy traffic, ii. 200 feet from the freeway on the public school grounds, iii. one mile from the freeway practically with a very limited traffic. The samples were analyzed on a JEOL JSM-6460LV SEM, HB505 VG (STEM) and an Oxford Instrument INCA X-sight EDS.

Summary of Results: We were able to demonstrate significant concentrations of the nanoparticles consisting of heavy metals present on or in the immediate vicinities of the heavy motor vehicle traffic. The concentrations of nanoparticles increased with the increasing proximity to the heavy traffic. The elemental compositions of the nanoparticles’ profiles were changing with the distance to the heavy traffic.

Conclusions: We conclude that analysis of elemental composition of the motor vehicle emissions should become the major focus of studies of the effects of environmental pollution on human health. We plan to continue this work by exposing the cells in cultures to the nanoparticles collected from the areas of various degree of pollution and characterized by their atomic structure and elemental composition.

Adolescent Medicine and General Pediatrics Concurrent Session 1:30 PM Friday, January 29, 2010

Session: Adolescent Medicine and General Pediatrics 211

BODY SURFACE AREA DOES NOT INFLUENCE TIMING OF ONSET FOR CARDIOMYOPATHY IN BOYS WITH DUCHENNE OR BECKER MUSCULAR DYSTROPHY

S. Sikder, C. Canniff, B. Barber, JG. Andrews, F. Meaney Research Network M. University of Arizona College of Medicine, Tucson, AZ.

Purpose of Study: Using a population based cohort of boys with Duchenne or Becker Muscular Dystrophy (DBMD), we examined the variable of Body Surface Area (BSA) as a risk factor for earlier or later onset of cardiomyopathy (CM).

Methods Used: We calculated BSA and the onset of CM in 157 boys with DBMD. Based on previously published studies of boys with DBMD, we used BSA instead of Body Mass Index as a measure for obesity. BSA was calculated by the Haycock method. CM was defined by echocardiographic parameters of systolic function –28% and/or ejection fraction <55%. We divided the population into 4 groups: (1) early onset, including boys with normal echo prior to age 12; (2) normal onset, including boys between 12-16 when they developed CM; (3) late onset, including boys with normal echo before age 16 and abnormal echo beginning at age 16 or older; and (4) no onset, which includes cases with documented normal echos before and after age 16. A General Linear Model using age-adjusted BSA was used to test group mean differences in BSA among the 4 groups described above.

Summary of Results: There were 17 (11%) boys in the early onset group, 80 (51%) in the normal onset group, 30 (19%) in the late onset group, and 30 (19%) in the no onset group. There were no significant differences in the mean BSA between any of these groups.

Conclusions: In general, obesity is a risk factor for poor cardiac health. This analysis did not attempt to categorize subjects as obese or non-obese. However, we did examine possible differences in mean BSA among those with earlier or later onset of CM in the DBMD population. Although greater BSA may be associated with increased cardiac workload, we could find no association that this increased work is leading to an early onset of CM. In this investigation we did not analyze possible effects of corticosteroids, which may increase BSA and which have been shown to be cardioprotective in some studies. Additional features that may also affect onset of CM include ambulation status and genotype. The effects of BSA on CM are likely to be complex, and the mechanisms that underlie cardiac dysfunction in boys with DBMD are deserving of further scrutiny.

Session: Adolescent Medicine and General Pediatrics 212

REVERSIBILITY OF HYPERTHYROTROPINEMIA IN OBSESE CHILDREN ASSOCIATED TO WEIGHT LOSS AND CHANGES IN TRIGLYCERIDES

J. Collazo3, WN. Evans1,2, H. Restrepo1, K. Bourque1, A. Marquez1, E. Bonabain1 Children's Heart Center Nevada, Las Vegas, NV and 2University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: To assess the changes in thyroid hormones and serum lipids in obese children participating in a 12-week weight management program.

Methods Used: Data from 183 children with BMI ≥95th percentile, enrolled in a 12-week weight management program, without any endocrine/
metabolic disorders. Fasting free thyroxine (T4), TSH, T3 uptake, cholesterol, triglycerides (TG), HDL, and LDL were obtained at weeks 1 and 12. According with the joint statement from the American Association of Clinical Endocrinologists, American Thyroid Association, and the Endocrine Society, we classified our patients in 2 groups, Group A (TSH ≥ 2.5 mIU/ml) and Group B (TSH ≥ 2.5 but ≤ 5.5 mIU/ml), furthermore, we analyzed those children who decreased the BMI Z-score ≥ 3.5 % by week 12 to assess the relationship of changes in thyroid hormones with changes in serum lipids.

Summary of Results: Groups A and B had similar distribution in mean age (11.4 ± 2.4 years; range 7 to 17 years), race (Hispanic 60%, Caucasian 23% and Others 17%), and gender 50% boys. Cholesterol, TG, HDL, and LDL were similar in both groups at week 1. Table summarizes significant findings in changes in triglycerides in obese children.

**Conclusion:** Lipid profile in obese children with hyperthyrotropinemia. Reversibility of hyperthyrotropinemia is related to level of TSH.

**Summary of Results:** To examine the effects of a 12 week, psychology and peer concerns.

**Conclusions:** There is no necessity to treat obese children with these levels of hyperthyrotropinemia. Reversibility of hyperthyrotropinemia is related to changes in triglycerides in obese children.

<table>
<thead>
<tr>
<th>Group A (n = 35)</th>
<th>Group B (n = 48)</th>
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<tbody>
<tr>
<td><strong>BMI Z-score</strong></td>
<td>2.27 ± 0.29</td>
</tr>
<tr>
<td>Cholesterol mg/dl</td>
<td>172 ± 32</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>104 ± 28</td>
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</table>

**Conclusions:** Lipid profile in obese children with hyperthyrotropinemia. Reversibility of hyperthyrotropinemia is related to level of TSH.

**Summary of Results:** To examine the effects of a 12 week, psychology and peer concerns.

**Conclusions:** There is no necessity to treat obese children with these levels of hyperthyrotropinemia. Reversibility of hyperthyrotropinemia is related to changes in triglycerides in obese children.

**Session:** Adolescent Medicine and General Pediatrics

**PHYSICAL, SOCIAL, AND BEHAVIOR CHANGES IN OVERWEIGHT CHILDREN TREATED IN A PSYCHOLOGY SUPPORTED WEIGHT MANAGEMENT PROGRAM**

B. Creel1, W. Evans1,2, GA. Mayman1,2, L. Coviello1, A. Gustafson1, H. Restrepo1,2 1Children’s Heart Center Nevada, Las Vegas, NV and 2University of Nevada, School of Medicine, Las Vegas, NV.

**Purpose of Study:** To examine the effects of a 12 week, psychology supported childhood weight management program on changes in physical, social, and behavior domains. Childhood obesity is associated with limited physical activity, socialization issues and behavior problems.

**Methods Used:** Data from 305 patients with BMIs ≥90th percentile treated between 08-2006 and 05-2009. Patients were pre- and post-tested for physical, behavior, and social domains by completing the Child Health Questionnaire (CHQ). For purpose analysis, we classified the population into 2 groups: those who reduced their BMI Z-score at week 12 by at least 5% (group A) and those who did not reach this goal (group B).

**Summary of Results:** Mean age was 12.5 ± 1.9 years (range 9–17 years) and mean BMI Z-score was 2.24 ± 0.32, with 51% of girls and race distribution of 60% Hispanic, 23% African-American, and 11% other races. Groups A and B were similar in mean age, race distribution and BMI Z-score at week 1. By week 12, the scores for participants in group A improved significantly in all the domains, exceeding the national norms, in contrast to children in group B who only improved significantly in physical functioning and behavior domains. Comparison between groups showed that by week 12, children in group A had higher scores in physical functioning and social/physical domains than children in group B. Table summarizes results pre and post intervention and provides the norms for each domain.

**Conclusions:** We found an interdependence of improvement in BMI Z-score and improvement CHQ scores. A 5% improvement in BMI-Z score was associated with improvement of all 4 domains with each score exceeding national norms. Patients who did not achieve a 5% improvement in BMI Z-score showed significant improvement in only 2 domains; it is possible that there are social factors affecting these outcomes, such as academic, family, and peer concerns.

**Session:** Adolescent Medicine and General Pediatrics

**RELIGIORITY AND HIGH RISK SEXUAL BEHAVIORS IN AFRICAN AMERICAN MALES: A THEORETICAL MODEL**

Y. Evans University of Washington/Seattle Children’s Hospital, Seattle, WA.

**Purpose of Study:** In the 2007 Youth Risk Behavior Surveillance, African American teen males are more likely than Hispanic and Caucasian youth to have had sexual debut before age 13 years and to have had more than 4 lifetime partners, which put these teens at increased risk for contracting HIV and other sexually transmitted infections. Religiosity has been shown to have protective effects in adolescents on risky behaviors in general, and has been shown to delay sexual debut in samples using Caucasian teens and national samples. Many studies use religion related variables when evaluating adolescent sexual behavior, but few of those use theory and explanatory models to hypothesize how religion may be protective. Reference group theory is based on the idea that an individual’s behaviors are decisively shaped by the groups in which they participate. This paper aims to use the reference group theory to hypothesize possible protective effects of
Session: Adolescent Medicine and General Pediatrics

216 PREDICTING WHICH CHILDREN NEED SEDATION FOR CT SCAN
N. Bonfanti1, J. Hartz1, G. Park2,1 1University of New Mexico School of Medicine, Albuquerque, NM and 2University of New Mexico School of Medicine, Albuquerque, NM.

Purpose of Study: One challenge faced by Pediatric Emergency Departments arises when young children require computed tomography (CT) scanning. Some children have difficulties remaining motionless during the scan, which can reduce the scan’s clinical value. In order to reduce motion artifact, children are provided pharmaceutical sedation. Unfortunately, pharmaceutical sedation is associated with serious adverse reactions. To reduce need for sedation, an improved understanding of the characteristics of children who require sedation is necessary.

Methods Used: This study was a cross-sectional analysis of patients aged 0 to 36 months who underwent CT scan of the head at the University of New Mexico Hospital. Success was defined as completion of CT scan without pharmaceutical sedation.

Summary of Results: Children under the age of 12 months were less likely to require sedation to undergo a CT scan as compared to older children. The mean age in the CT success group was 9.7 months, but was 15.3 months in the CT failure group (Odds-ratio = 0.93, p-value = 0.001). Other characteristics, such as gender, ethnicity, and vital signs were not associated with a successful CT scan.

Conclusions: Very young children (0 to 12 months) have a higher success rate with CT scans. Children aged 12 to 24 months more often require pharmaceutical sedation to complete CT scans.

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217 CREATION OF HEALTH RECORDS FOR ORPHEANED CHILDREN AND YOUTH IN KAMPALA, UGANDA
W. Jang1, Y. Wang1, D. Roccamatiss1, M. Sanghera1, M. Kagoda2, K. Kipruto2, N. Kizito2, A. Kasangaki2, W. Cannon1, A. Macnab1 1UBC/BC’s Children’s Hospital, Vancouver, BC, Canada and 2Makerere University, Kampala, Uganda.

Purpose of Study: Personal health records (PHR) improve treatment and aid continuity of health care. African orphans commonly lack such documentation which compromises emergency management and long-term health planning. A PHR was generated for boys in a Kampala orphanage as part of a global-health partnership project run jointly by our University (UBC) and Makerere University (MU). The interactive teaching module delivered promotes caries prevention, a significant problem amongst enrolled children. The module was based on one used successfully in Canadian aboriginal communities and modified by MU faculty/students to ensure content appropriate for delivery in Uganda. The conveyed message and practices are simple, based on validated practices and employ visual, oral and hands on education plus audience participation. Information on caries formation/prevention for school children

AN INTERACTIVE TEACHING MODULE FOR CARRIES PREVENTION FOR SCHOOL CHILDREN
Y. Wang1, N. Agiremabazi2, W. Jang1, M. Kagoda2, N. Kalyesubula2, K. Kipruto2, D. Kisakye2, N. Kizito2, D. Roccamatissi2, M. Sanghera1, O. Tabaro2, A. Kasangaki2, W. Cannon1, A. Macnab1 1UBC/BC’s Children’s Hospital, Vancouver, BC, Canada and 2Makerere University, Kampala, Uganda.

Purpose of Study: Caries is the commonest infectious disease and chronic health condition affecting children worldwide. Research indicates effective oral health promotion (OHP) can drive behavioral change. We developed an OHP education module that can be delivered in various cultural and social contexts to promote better oral hygiene.

Methods Used: School children at 5 community sites in Uganda are part of a ongoing global health education program run jointly by our University (UBC) and Makerere University (MU). The interactive teaching module delivered promotes caries prevention, a significant problem amongst enrolled children. The module was based on one used successfully in Canadian aboriginal communities and modified by MU faculty/students to ensure content appropriate for delivery in Uganda. The conveyed message and practices are simple, based on validated practices and employ visual, oral and hands on education plus audience participation. Information on caries formation/prevention is provided via a comic strip involving individuals representing a ‘tooth’, a ‘sugar bug’, ‘plaque’ and a ‘toothbrush’. Children are involved through questions and answers and interactive participation, and the use of visual aids and paper-based materials for coloring and quizzes.

Summary of Results: All children were readily engaged and enthusiastic to learn and contribute. The interactive opportunities demonstrated and reinforced knowledge and sound practices (dietary choice, brushing technique, flossing). Answers at the end of the session indicated acquisition of core concepts. Toothbrushes were provided for each student. Teachers undertook to ensure continuation of brushing at school, and repeat key learning concepts.

Conclusions: Feedback by participating children, teachers and the students delivering the module were positive. Initial follow up indicates all communities continue to provide opportunities for children to brush at school. However, future evaluation of knowledge retention and continued healthy practices are required to confirm behavioral change has taken place. The Canadian/Ugandan University partnership promoting this program will provide this opportunity.
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INFLAMMATORY FIBROID POLYP IN A NEONATE PRESENTING AS GASTRIC OUTLET OBSTRUCTION
J. Warolin 1,2, MM. Jami 1 UCSF Fresno Medical Education Program, Fresno, CA and 2 Children’s Hospital Central California, Madera, CA.

Purpose of Study: Inflammatory fibroid polyps (IFP) are rare, benign lesions that can occur throughout the digestive tract, but are found most commonly in the antrum or pre-pyloric region of the stomach. Infrrequently seen in children, IFP’s are found most commonly in late adulthood. Case reports have been presented of children with IFP’s throughout the digestive tract, but to the best of our knowledge, no cases have been reported of an IFP causing gastric outlet obstruction in the neonatal period.

Methods Used: We report a case of gastric IFPs in a 9-day-old who presented with persistent vomiting and weight loss.

Summary of Results: A 9-day-old, term, 2,600 gram male presented with non-bilious vomiting occurring with every feed since birth. He was exclusively breastfed and emesis appeared to be undigested breast milk. Mother reported no fever or fussiness, but stated persistence of meconium stool. At presentation, the patient’s weight was 700 grams below birth weight. A CT with contrast showed heterogeneous density of a thickened gastric body with numerous small cysts. Endoscopy showed erythema of the esophagus with multiple polyoid lesions and a large, fungating mass with thickened mucosal folds causing distal gastric outlet obstruction. Biopsies revealed spindle cell lesions consistent with IFP (testing positive for vimentin, CD34, and negative for CD31, CD68, CD79a, CD99, CD117). The patient was found to have a partial gastrectomy Billroth procedure type I. Per pathology, tumor cells were seen in children, IFP’s are found most commonly in late adulthood. Case reports have been presented of children with IFP’s throughout the digestive tract, but to the best of our knowledge, no cases have been reported of an IFP causing gastric outlet obstruction in the neonatal period.

Conclusions: This is the first reported case of an IFP causing gastric outlet obstruction in a neonate. It is thought that IFP’s are not a neoplasm and have no malignant potential; instead, they represent a reactive process. Proposed irritants causing this reactive process are chronic, including H. pylori infections and autoimmune diseases triggering an immunological reaction. In our patient, there was no evidence in the history to suggest any chronic infections, autoimmune diseases, or other source of a chronic irritant causing the progressive formation of an IFP in utero. The emesis in our patient suggests presence of the IFP causing obstruction at birth, which raises new questions as to the etiology and natural history of IFP.

Session: Adolescent Medicine and General Pediatrics 220
THE PREVALENCE OF ELBOW FLEXION CONTRACTURE IN CHILDREN WITH BRACHIAL PLEXUS BIRTH PALSY
LC. Sheffler 1, 2, A. Bagley 2, MA. James 1, 3 1 University of California, Davis, Sacramento, CA; 2 Shriners Hospital for Children, Northern California, Sacramento, CA and 3 University of California, Davis, Sacramento, CA.

Purpose of Study: Elbow flexion contracture is a well-known complication of brachial plexus birth palsy (BPBP) that adversely affects function and appearance. The prevalence of elbow flexion contracture in this population is not known, nor is it understood whether BPBP severity is associated with elbow flexion contracture severity.

Methods Used: A retrospective chart review of 319 patients with brachial plexus birth palsy who were seen between 1991 and 2009 was performed to identify patients who developed elbow flexion contracture. BPBP severity was classified according to Narakas (type I: C5/6 palsy; type II: C5/6/7 palsy and type III: global palsy).

Summary of Results: Elbow flexion contracture was present in 166 of 319 (52%) children with BPBP. Divided into age subgroups of 0–4 years (n = 123), 5–11 years (n = 126) and 12–20 years (n = 70), 25%, 60% and 84% of children had documented elbow flexion contractures, respectively. The median age of onset of elbow flexion contracture was 4.8 years. Elbow flexion contracture was present in 49% of patients with Narakas type I BPBP, 53% with type II and 60% with type III.

Conclusions: The prevalence of elbow flexion contracture in children with BPBP may be greater than clinicians perceive and increases with patient age and severity of BPBP. Because elbow flexion contracture has a negative impact on upper extremity function and appearance, future research should address the etiology and treatment strategies of elbow flexion contractures in children with BPBP.

Cardiovascular II Concurrent Session 1:30 PM Friday, January 29, 2010
Session: Cardiovascular II 221
AORTIC STIFFNESS IS A CAUSE OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS
IB. Alomari 1, K. Awad 1, C. Qualls 1, C. O’Rourke 1, J. Sharrar 1, W. Sibbitt 2, C. Roldan 3 1 University of New Mexico, Albuquerque, NM and 2 University of New Mexico, Albuquerque, NM.

Purpose of Study: Aortic stiffness (AoS) occurs in systemic lupus erythematosus (SLE), but its impact on left ventricular (LV) function has not been established. Thus, we sought to determine that AoS in SLE patients is an independent cause of LV diastolic dysfunction (DD).

Methods Used: Forty nine SLE patients (mean age 38 ± 12 years) and 21 healthy volunteers matched for age, gender, and body mass index underwent transesophageal echocardiography (TEE) to assess stiffness of the descending thoracic aorta using the Pressure-Strain Elastic Module as = [k(sBP – dBP)/(sD-dD)/dD]/100 (where k = 133.3 is a conversion factor from mmHg to Pascal units, sBP = systolic blood pressure, dBP = diastolic blood pressure, sD = systolic diameter, and dD = diastolic diameter). Preceding TEE, a transthoracic echocardiogram (TTE) was performed to assess LVDD. Mitral inflow and mitral annulus tissue peak Doppler velocities were measured during rapid LV filling (E & E’) and atrial systole (A&A’) respectively. Also LV isovolumetric relaxation time (IVRT) was measured using septal tissue Doppler imaging. LVDD was defined according to ASE guidelines.

Summary of Results: AoS was higher in patients as compared to controls (8.2 vs. 6.13 units, respectively, p = 0.01). Overall and type I LVDD were more prevalent in patients than in control (56% and 54% vs. 18% and 18%, respectively, both p < 0.004). Type II/III LVDD was not different among groups (12% vs. 0%, p = 0.17). AoS was higher in SLE patients with than without LVDD (9.5 versus 6.46 units, p = 0.004). Also, AoS was higher in SLE patients with than without type I DD (9.7 versus 6.36 units, p = 0.002), but was not different in those with type II/III LVDD (p = 0.3). By univariate analysis, AoS, age, hypertension, SLE duration, and SLE damage score were predictors of LVDD (all p ≤ 0.05). However, by multivariate logistic regression analyses, AoS was the only independent predictor of overall and type I LVDD (odds ratio 2.7, 95% CI 1.2–6.2, p = 0.02 and odds ratio 3.2, 95% CI 1.3–7.4, p = 0.01, respectively).

Conclusions: In young SLE patients 1) AoS is common; 2) LVDD is highly prevalent; and 3) AoS is the strongest independent predictor of LVDD. Thus, AoS is a cause of LVDD in SLE patients.

Session: Cardiovascular II 222
LAMBL’S EXCRESENCES IN SYSTEMIC LUPUS ERYTHEMATOSUS: PREVALENCE, PATHOGENESIS, AND CARDEOEMBOLIC RISK

Purpose of Study: Lambl’s excrescences (LEX) are frequently noted in patients undergoing transesophageal echocardiography (TEE) for suspected cardioembolism. However, their pathogenesis and cardioembolic risk are still undefined. Patients with systemic lupus erythematosus (SLE) have associated systemic inflammation, hypercoagulability and high incidence and recurrence of stroke or transient ischemic attacks (TIA). Thus, we sought to prospectively determine the prevalence, distribution, pathogenesis, and embolic risk of LEX in SLE patients with and without acute stroke/TIA and healthy controls.

Methods Used: Sixteen SLE patients with acute stroke/TIA (mean age 40 ± 12 years, range 18–58 years), 34 SLE patients without stroke/TIA (mean age 37 ± 12 years, range 19–60 years), and 22 age and gender matched healthy controls (mean age 34 ± 12 years, range 19–59 years; for all ages, p = 0.32) underwent clinical, laboratory, and TEE evaluations. LEX were defined as thin (≤ 2 mm) and elongated (< 3 mm) structures with independent, undulating...
hypermobility, noted near the leaflet’s line of closure, on atrial side of mitral valves and on ventricular side of aortic valves. TEE studies were interpreted by an experienced blinded observer.

**Summary of Results:** The prevalence of left heart valves, mitral, and aortic LEs were similar in patients with stroke/TIA (50%, 38%, 25%, respectively), without stroke/TIA (74%, 56%, 26%, respectively) and healthy controls (59%, 45%, 33%, respectively). Of clinical relevance, mean values for inflammatory markers (c3a, c5a, P-selectin, and endothelial-platelet- and monocyte derived microparticles) and for coagulation and fibrinolysis (thrombin generation, thrombin-antithrombin complexes, tissue plasminogen activator, and plasminogen activator inhibitor) was similar among all groups (p = 0.06). In SLE patients with and without stroke/TIA, disease duration, activity, severity, parameters of inflammation, anti-cardiolipin antibodies, anti-inflammatory and immunosuppressive therapy was similar (p ≥ 0.08).

**Conclusions:** Lamb’s excrescences: 1) are likely normal variants due to mechanically induced endothelial denudation and subsequent fibrin deposition and reendothelialization; 2) do not have a hypercoagulable or inflammatory pathogenesis; and 3) do not appear to be a source of cardioembolism in patients with SLE.

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**Session: Cardiovascular II**

**224 CEREBRAL BLOOD FLOW BY CAROTID DUPLEX IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ACUTE NEUROLOGIC SYNDROMES**

TT. Issac, C. Qualls, J. Sharrar, C. O’Rourke, R. Greene, W. Sibbit, C. Roldan  
*University of New Mexico, Albuquerque, NM.*

**Purpose of Study:** Cerebral blood flow (CBF) in these patients. Demonstrated by radionuclide studies (SPECT and PET) of the brain. In these patients, relative, focal decrease in cerebral perfusion has been demonstrated by radionuclide studies (SPECT and PET) of the brain. However, there are limited studies assessing absolute cerebral blood flow (CBF) in these patients.

**Thus, we sought to determine hemispheric and whole cerebral blood flow using carotid Duplex in patients with SLE with or without major NPSLE as compared to controls (1046, 1071, and 1038 ml/min, respectively, p = 0.71). Also, whole CBF was similar in SLE patients with or without acute stroke/TIA as compared to controls (p = 0.29). Significantly higher heart rate and double product (HR x SBP) may explain the preservation of CBF in SLE patients with acute neurologic syndromes (both p < 0.003).**

**Conclusions:** (1) Assessment of CBF in patients with SLE is easily performed with carotid Duplex and it offers assessment of both functional and anatomical data. (2) Of clinical relevance, CBF is preserved in SLE patients with acute neurologic syndromes. (3) To our knowledge, this is the first controlled study done in SLE patients using carotid Doppler to assess absolute CBF.

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**Session: Cardiovascular II**

**225 NOVEL PLASMA BIOMARKER CANDIDATES IN PATIENTS WITH CONGESTIVE HEART FAILURE**

C. MacLellan, J. LeBlanc, T. Horwich, G. Fonarow, R. MacLellan  
*UCLA, Los Angeles, CA.*

**Purpose of Study:** Despite improvements in the diagnosis and treatment of congestive heart failure (CHF), these patients remain at high risk of cardiac mortality and ongoing morbidity. We proposed to find novel CHF biomarker candidates that may allow clinicians to more accurately identify high-risk patients, individualize therapy, and provide new insights into the pathophysiology of CHF.

**Methods Used:** We analyzed plasma samples collected from 60 CHF and 44 normal subjects. These samples along with demographic data were collected over a 28 month period from 1/1996 to 5/1998. Depleted plasma samples were diluted in binding buffer and bound to reversed phase hydrophobic C18 magnetic beads. The bound proteins were eluted using increasing concentrations of acetonitrile. The intact masses of the eluted plasma proteins were determined by high-resolution MALDI-TOF mass spectrometry.

**Summary of Results:** The mean age of the CHF subjects was 54, 80% were male and 41.5% had an ischemic etiology with a mean left ventricular ejection fraction (LVEF) of 26%. 794 distinct proteins were detected within the plasma samples by MALDI TOF-MS. Of these proteins, the occurrences of 35 proteins were significantly different between the CHF patients and normal patients, using a T-test (P<0.05) with Bonferroni Correction. Secondary analyses demonstrated that the levels of 19 of these proteins correlated with etiology, 15 with LVEF, 2 with NYHA, and 2 with outcome. Multivariate analysis that adjusted for age, sex, statin use and etiology (for LVEF, NYHA and outcome only) showed that 9 proteins remained significant correlated, 4 with etiology and 5 with LVEF. Two of these proteins were tentatively identified based on accurate mass measurements as apolipoproteins ApoA-C-II, and two isoforms of APO C-III. We are currently identifying the unknown proteins.

**Conclusions:** We have identified a number of marker candidates that are differentially detected in the plasma of CHF subjects compared to controls that correlate with a panel of CHF variables. Integrating a multi-marker approach into the care of CHF patients may allow clinicians to more accurately identify high-risk patients and may facilitate the optimization of medical therapy.
Session: Cardiovascular II

226  HEART FAILURE PATIENTS HAVE SEVERE BRAIN HIPPOCAMPAL VOLUME LOSS

C. Abouzeid, P. Macey, R. Kumar, M. Woo, R. Harper, USC, Los Angeles, CA; UCLA, Los Angeles, CA; VA Central California Health Care System, Fresno, CA

Purpose of Study: Heart failure (HF) patients have a high incidence of short-term memory loss, which adversely impacts their quality of life and self-care management of their disease. The hippocampus is a brain region which modulates short-term memory, however, its structural status in HF has not been evaluated.

Methods Used: We compared 9 HF and 15 healthy controls using high-resolution T1-weighted MRI scans. Hippocampal volumes were manually traced and then calculated from these tracings, and corrected for total intracranial volume variations. Statistical analyses consisted of t-tests and Chi-square.

Summary of Results: HF patients had lower hippocampal volumes in comparison to controls.

Conclusions: Changes in the hippocampus are likely to play a major role in short-term memory loss in HF.

Characteristics (± standard error) for subjects, with p-values for group comparisons (ANOVA). BMI: body mass index; LVEF: left ventricular ejection fraction.

<table>
<thead>
<tr>
<th></th>
<th>Control (N=15)</th>
<th>Heart Failure (N=9)</th>
<th>p</th>
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<tr>
<td>Age (years)</td>
<td>55±2</td>
<td>55±2</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI</td>
<td>25±1</td>
<td>29±1</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEF</td>
<td>1.35±0.04</td>
<td>1.37±0.06</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Left Hippocampal Volume (mm³)</td>
<td>2646±155</td>
<td>2327±164</td>
<td>0.04</td>
</tr>
<tr>
<td>Right Hippocampal Volume (mm³)</td>
<td>2658±171</td>
<td>2310±160</td>
<td>0.04</td>
</tr>
<tr>
<td>Total Intracranial Volume</td>
<td>1.35±0.04</td>
<td>1.37±0.06</td>
<td>&gt;0.01</td>
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</tbody>
</table>

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227  LOWER BMI AND DIABETES ARE ASSOCIATED WITH INCREASED HOSPITALIZATION AND ALL CAUSE MORTALITY IN ELDERLY HEART FAILURE PATIENTS

M. Ghali, S. McFarland, P. Dedeianni, J. Evans, R. Mallion, P. Goebel, A. Cohen, J. Huang, VA Central California Health Care System, Fresno, CA; VA Central California Health Care System, Fresno, CA; University of California, San Francisco - Fresno MEP, Fresno, CA; VA Central California Health Care System, Fresno, CA; University of New Mexico, Albuquerque, NM

Purpose of Study: Heart failure (HF) is the leading cause of hospitalization and healthcare cost in the elderly. Thinner HF patients are known to have poorer prognosis and benefit of tight glycemic control in elderly diabetes(DM) is controversial. We sought to determine the impact of BMI and DM on admission and mortality rates in elderly HF patients.

Methods Used: VA Central California Heart Failure Registry (HFR) is a database of clinical and demographic data on HF patients. Data from the immediate past two years were analyzed using Chi square test or multi-variable logistic regression model.

Summary of Results: There were 2510 HF patients in this HFR. Mean age was 74 years. Males accounted for 98% and 51% were diabetic. Majority of HF patients were on beta blockers (88%) and ACE-I/ARB (83%). Two-year all cause admission and mortality rates were 42% and 22%, respectively. Death rate was significantly higher (P<0.0001) among those with BMI of <20 (34%). In addition to low BMI, independent predictors for mortality included concomitant diagnosis of A-fib, DM, COPD, PVD, and higher LDL (≥100) and A1c (≥7). Hospital admission rate was also significantly higher (P<0.0001) among thinner (BMI<20 65% versus BMI≥20 40%) and diabetic patients (DM 48% versus non-DM 35%). The differences remained significant after adjusting for age, certain medications and co-morbid conditions including A-fib, DM, COPD, HTN, CAD, MI, and PVD.

Conclusions: In this population of predominantly male and elderly HF patients, compliance to the standard therapeutic guidelines was high. Lower BMI and presence of DM were associated with significantly higher mortality and hospitalization rates after adjusting for other contributing co-morbid conditions. Some of these thinner patients may represent advanced HF cases with cachexia. Further delineating the cause(s) of increased admission and death in diabetic and underweight HF patients may help develop targeted interventions to reduce hospitalization and mortality.

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228  MARKED GENDER VARIATION IN THE PREVALENCE OF A THIRD HEART SOUND IN HOSPITALIZED HEART FAILURE PATIENTS

K. McDonnell, K. Desser, R. Gerkin, Banner Good Samaritan Medical Center, Phoenix, AZ; Banner Good Samaritan Medical Center, Phoenix, AZ.

Purpose of Study: Prior investigation has indicated that jugular venous distention (JVD) and an audible third heart sound (S-3) are associated with a worse prognosis in patient with heart failure. It is unknown whether or not these physical findings are found with equal frequency in hospitalized women and men with heart failure. We assessed the hypothesis that there might be gender variation in the prevalence of JVD and S-3 in subjects with heart failure.

Methods Used: The initial 150 women and 150 men admitted to a non-VA hospital with heart failure were studied. These subjects were evaluated as follows: JVD +, S-3 +, hospital length of stay, in-hospital mortality and echocardiographic findings.

Summary of Results: JVD was noted in 47% of women and 53% of men (p=NS) whereas an S-3 was present in 3% of women and 22% of men (p<0.001). JVD did not predict hospital length of stay, but S-3 did (S-3 +, 10 days, S-3 -, 6 days, p=0.043). In-hospital mortality was rare (3%). When echocardiographic findings were evaluated, there were significant differences (p<0.001) between women and men, respectively, as follows: left ventricular ejection fraction 43% vs. 31%, systolic dysfunction 19% vs. 31% and diastolic dysfunction 38% vs. 9%.

Conclusions: There is significant gender variability in heart failure characteristics of hospitalized patients with a marked difference in the frequency of S-3. This difference may be related to a higher prevalence of preserved systolic function and greater than four-fold presence of diastolic dysfunction in women with heart failure.

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229  RAPIDLY PROGRESSIVE PERIPARTUM CARDIOMYOPATHY PRESENTING PRENATALLY

I. Alomari, A. Awad University of New Mexico, Albuquerque, NM.
Case Report: Peripartum cardiomyopathy (PPCM) is a rare disorder that affects pregnant women between 36 weeks of gestation and 5 months postpartum. It is associated with relatively high morbidity and mortality, making prompt diagnosis and management very critical. We present a rare case of rapidly progressive PPCM that started prenatally. A healthy 33 years old female (G4,P3), with no significant history, presented at 38 weeks of gestation with three days of worsening dyspnea at rest, PND and orthopnea. She denied having any recent illness, chest pain, or similar complaints in the past. She had marked hypoxia, bilateral diffuse rales and bilateral pedal edema on exam. Her CXR revealed bilateral diffuse airspace disease, consistent with pulmonary edema. EKG showed sinus rhythm and LBBB. Troponin-I was 0.026, and BNP was 3300. Chest CT ruled out pulmonary embolism. An Echocardiogram showed severe global hypokinesis with an Ejection fraction (EF) of 25%, severe pulmonary hypertension (PHTN), severe mitral and tricuspid regurgitation. Within few hours, her respiratory status deteriorated, requiring intubation. She underwent an uncomplicated cesarean section. After delivery, she was started on ACE inhibitors (ACEI) and Beta Blockers (BB) with rapid improvement. A repeat TTE, demonstrated near resolution of the valvular regurgitation, and severe LV dysfunction (EF 20–25 %). She was discharged on an ACEI, a BB, and a diuretic. On clinical follow up, she was very well compensated. A repeat Echocardiogram, showed improvement of the LV function (EF 35%), with persistence of the PHTN. PPCM occurs in 1:15,000 deliveries in the U.S. Symptoms usually start after delivery. Risk factors include: multiparity, advanced maternal age, multifetal pregnancy, preeclampsia, gestational hypertension, and African American race. The underlying pathology involves myocarditis, abnormal immune response, and stress-activated cytokines. Therapy should be initiated using standard heart failure protocols. ACEI should be avoided prenatally, but are the mainstay of therapy after delivery. Immunosuppressive can be considered if endomyocardial biopsy indicates myocarditis, or if there is no improvement after 2 weeks of standard therapy. Normalization of left ventricular size, indicates favorable prognosis, although sequelae with repeat pregnancy are unknown.

**Summary of Results:** To report the findings in children with idiopathic dilation of the ascending aorta (ID of the AA). We searched our electronic database for patients with AA dilation. We found 30 patients that met criteria. Of the 30, 20 (67%) were males. Although 4 patients were identified prenatally, for this report all measurements were made postnatally with an age range of 2 days to 17.5 years. Of the 30, 26 had normal intracardiac anatomy and 4 had minor abnormalities, 3 with foramen ovale and 1 with a small ventricular septal defect. The AA Z-scores ranged from 2.1–4.1 (median: 2.8, average: 3.0 ± 0.6).

**Conclusions:** Ascending aorta dilation can occur in the absence of detectable aortic valve disease. We postulate that aortic wall abnormalities leading to AA dilation may be similar to those patients with aortic valve disease. Further study is needed to help determine whether such patients may benefit from medical treatment similar to the type employed in AA dilation with aortic valve disease.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Peds to Adults</th>
<th>Control</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>33</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Subsequent 5-Year Actuarial Survival</td>
<td>79%</td>
<td>82%</td>
<td>0.63</td>
</tr>
<tr>
<td>Subsequent 1-Year Freedom from Any-Treated Rejection</td>
<td>97%</td>
<td>100%</td>
<td>0.18</td>
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</table>

**Session: Cardiovascular II**

231

SAFE TRANSITION OF PEDIATRIC HEART TRANSPLANT PATIENTS TO THE ADULT HEART TRANSPLANT PROGRAM

Z. Goldstein, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Pediatric renal transplant patients that transition to adult transplant programs have been reported to have increased episodes of rejection. This may be due to a lapse of continuity of care or due to the psychological stress of the transition. The purpose of the current study was to determine if this phenomenon exists in heart transplant recipients in a large single center.

**Methods Used:** Between 1987 and 2005, 1499 patients, adult (n = 1266) and pediatric (n = 233), were transplanted at our institution. Of those, 33 pediatric heart transplant patients transitioned to our adult heart transplant program when they reached their 21st birthday. We compared outcomes of these 33 patients to an adult heart transplant population (n = 66) matched in a 2:1 fashion for gender and time from transplant, where outcomes included rejection, survival, lost to follow-up (see table).

**Summary of Results:** There was only one rejection episode in the pediatric transplant group that occurred within 1 year after transitioning to the adult program. All patients who transitioned to the adult program were alive at 2.5 years post-transition. These patients exhibited comparable subsequent 5-year actuarial survival compared to the adult heart transplant recipients (79% vs. 82%, p = 0.63).

**Conclusions:** Pediatric heart transplant patients who transition to the adult heart transplant program do not appear to have increased number of rejection episodes following the transition and have comparable survival to the adult cohort. This offers further support to the policy of safely transitioning pediatric heart transplant recipients to the adult program once they have reached their 21st birthday.

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232

IDIOPATHIC DILATION OF THE ASCENDING AORTA IN CHILDREN

KC. Rollins1,2, WN. Evans1,2, H. Restrepo1,2 1Children's Heart Center Nevada, Las Vegas, NV and 2University of Nevada, School of Medicine, Las Vegas, NV.

**Purpose of Study:** To report the findings in children with idiopathic dilation (ID) of the ascending aorta (AA) without detectable aortic valve disease. To the best of our knowledge this is the largest series of such patients. Ascending aorta dilation is associated with aortic valve disease. Idiopathic dilation of the AA in children, however, is less well described. We describe a series of such patients, and we speculate about the prognosis and possible treatment of children with ID of the AA.

**Methods Used:** We searched our electronic database for patients with AA dilation seen between March 2003 and August 2009. All patients had 1 or more echocardiograms performed by a pediatric cardiologist. Only patients with normal trileaflet aortic valves and no aortic root abnormalities were included.

**Summary of Results:** We found 30 patients that met criteria. Of the 30, 20 (67%) were males. Although 4 patients were identified prenatally, for this report all measurements were made postnatally with an age range of 2 days to 17.5 years. Of the 30, 26 had normal intracardiac anatomy and 4 had minor abnormalities, 3 with foramen ovale and 1 with a small ventricular septal defect. The AA Z-scores ranged from 2.1–4.1 (median: 2.8, average: 3.0 ± 0.6).

**Conclusions:** Ascending aorta dilation can occur in the absence of detectable aortic valve disease. We postulate that aortic wall abnormalities leading to AA dilation may be similar to those patients with aortic valve disease. Further study is needed to help determine whether such patients may benefit from medical treatment similar to the type employed in AA dilation with aortic valve disease.

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PHONOCARDIOGRAPHY AS A TOOL FOR ENHANCING MURMUR CHARACTERIZATION AMONG PEDIATRIC RESIDENTS

NA. Hindoyan, D. Schidlow, R. Chang
1:30 PM
Concurrent Session
Gastroenterology and Hepatology
Preliminary results suggest that phonocardiography, when increasing accuracy amongst pediatric housestaff in murmur characterization and identification of underlying diagnosis.

Methods Used: Pediatric residents completed a multiple-choice questionnaire characterizing 10 pre-recorded heart sounds. Timing, place in cardiac cycle, shape, quality and extra/split heart sounds were evaluated. Participants were also asked to identify underlying diagnoses. Subjects completed the questionnaire first while listening to the murmurs alone and subsequently while listening and concurrently viewing the corresponding phonocardiograms. Analysis was conducted using the paired-t test.

Summary of Results: Responses were acquired from seven residents. With phonocardiography, subjects showed improvement in ability to recognize murmur timing within the cardiac cycle (avg missed 5.71 vs 5.57; p-value 0.45), position in cycle (2.57 vs 2.14; 0.20), shape (5.71 vs 5.57; 0.45), quality (3.15 vs 2.57; 0.12) and presence of extra heart sounds/splitting (1.71 vs 1.29; 0.10). Data collected additionally suggested increased accuracy in murmur diagnosis (5.14 vs 5.00; 0.40) with phonocardiography use.

Conclusions: Preliminary results suggest that phonocardiography, when used in conjunction with cardiac auscultation, may increase accuracy in murmur characterization and diagnosis amongst pediatric residents. Furthermore, phonocardiography may be a useful aid in cardiac diagnosis and resident education. More participants are needed to adequately power the study.


Gastroenterology and Hepatology
Concurrent Session
1:30 PM
Friday, January 29, 2010

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235
ROLE OF OCCLUDIN IN INTESTINAL EPITHELIAL TIGHT JUNCTION BARRIER

MA. Youssef, K. Khatib, R. Al-Sadi, T. Ma UNM, Albuquerque, NM.

Purpose of Study: Background: Defective intestinal epithelial tight junction (TJ) barrier has been implicated as an important pathogenic factor of Crohn’s disease (CD) and other inflammatory conditions of the gut. Patient with CD have decreased levels of transmembrane TJ protein occludin in the intestinal tissue. We hypothesize that loss of occludin protein in the intestinal epithelial cells causes an increase in intestinal epithelial TJ permeability.

Purpose of Study: Investigate the role of occludin protein in Caco-2 intestinal epithelial tight junction barrier function by small interference RNA (siRNA) targeted silencing of occludin.

Methods Used: Filter-grown Caco-2 intestinal epithelial monolayers were used as an in-vitro intestinal epithelial model system to assess epithelial TJ barrier function. Occludin siRNA transfection was performed to knock-down occludin in Caco-2 cells. TJ protein expression was measured using Western blot analysis and immunostaining.

Summary of Results: siRNA occludin transfection resulted in a near complete knock-down of occludin expression and alteration in junctional localization of occludin in filter-grown Caco-2 monolayers. siRNA induced knock-down of occludin caused a dramatic increase in permeability to paracellular markers inulin (25-fold increase) and mannitol. In response to occludin knock-down, expression of another transmembrane TJ protein claudin-2 was significantly increased.

Conclusions: Our data show that expression of occludin was essential in maintaining the Caco-2 intestinal epithelial tight junction barrier function. In response to occludin knock-down, there is an adaptive increase in claudin-2 expression. These finding suggest that occludin depletion present in intestinal tissue of CD patients could explain in part the observed increase in intestinal permeability in these patients. Our findings suggest that occludin may be an important therapeutic target in preserving the tight junction barrier in patients with CD.

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234
REGULATION OF LIVER SINUSOIDAL ENDOTHELIAL CELL (SEC) PHENOTYPE AND THERAPEUTIC IMPLICATION

G. Xie1, GC. Kanel2, LD. DeLeve1

Purpose of Study: To identify mechanisms that regulate liver sinusoidal endothelial cell (SEC) phenotype and to evaluate their therapeutic potential.

Method Used: SEC were cultured for 2 days with inhibitors or agonists of the cGMP/PKG pathway or with 40 ng/ml VEGF (fully fenestrated). Thioacetamide-induced cirrhosis was assessed blindly by GCK (semi-quantitative score 0–6).

Summary of Results: SEC grown with VEGF plus either ODQ (sGC inhibitor) or Rp-8-pCPT-7-cGMP (PKG inhibitor) defenestrated completely. SEC grown with VEGF plus ODQ and 8-pCPT-cGMP (cGMP analog) remained fully fenestrated. These findings demonstrate that the cGMP pathway is necessary to maintain fenestrated SEC. SEC grown with DETA NONOate (6mM) produced similar levels of NO and cGMP to SEC cultured with VEGF, but failed to maintain fenestration. Thus NO alone is insufficient to maintain SEC phenotype. SEC grown with VEGF plus 3mM L-NAME defenestrated while SEC grown with VEGF, L-NAME and DETA NONOate maintained normal fenestration. Thus maintenance of SEC phenotype requires both VEGF and NO. In vivo studies with BAY 60-2770: 1-week treatment completely reversed capillarization (normal porosity 6.80 ± 0.31%; 6.24 ± 0.37% in treated vs 3.14 ± 0.22% in solvent controls (p < 0.01)), but cirrhosis persisted. 2-week treatment caused reversal to occasional bridging fibrosis vs persistent cirrhosis in solvent controls.

Conclusions: VEGF plus VEGF-stimulated NO acting through the sGC/cGMP/PKG pathway are necessary and sufficient to maintain SEC differentiation. Stimulation of sGC initially reversed capillarization and subsequently accelerated resolution of cirrhosis.
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ROLE OF PARATHYROID HORMONE-RELATED PROTEIN (PTHrP) IN INTESTINAL EPITHELIAL CELL APOPTOSIS IN THE PATHOGENESIS OF NECROTIZING ENTEROCOLITIS

H. Sierra, B. Ibe, J. Torday, V. Rehan
LA Biomedical Research Institute, Torrance, CA.

Purpose of Study: Necrotizing Enterocolitis (NEC) is a multifactorial disease and intestinal epithelial cell apoptosis is a prominent feature in its pathogenesis. The molecular pathways underlying apoptosis are not well known. PTHrP is expressed by the intestinal epithelium and is known to play a key role in cell proliferation and differentiation in many tissues. We hypothesize that down-regulation of PTHrP signaling plays a key role in intestinal epithelial cell apoptosis associated with NEC and modulation of PTHrP signaling can be exploited to prevent or treat NEC.

Methods Used: 80% confluent IEC-6 cells were exposed to hypoxia (% O2) or hypoxia + lipopolysaccharide (LPS) up to 72 hrs. Then cell proliferation was determined by thymidine incorporation, and cell differentiation was determined by Western blotting for Bcl-2, Bax, surfactant protein (SP) C, and PTHrP expression.

Summary of Results: Hypoxia decreased thymidine incorporation time dependently: 87%, 66% and 60% by 6, 24, and 72 hrs, respectively compared to normoxia. A similar effect was obtained with addition of LPS (10 ng/ml–1000 ng/ml): 34%, 40%, 48% for 10, 100 1000, respectively. Hypoxia decreased Bcl-2 expression by 64%, 91%, and 95% by 24, 48 and 72 hrs respectively, while Bax expression increased with time in hypoxia lasting 80% augmentation by 48 hr hypoxia. SPC and PTHrP expression also decreased with time in hypoxia.

Conclusions: Our results show that in vitro exposure to hypoxia results in IEC apoptosis by a mechanism, involving up-regulation of the pro-apoptotic protein Bax, down-regulation of the anti-apoptotic protein Bcl-2, and this is accompanied by the down-regulation of SPC and PTHrP. Bacterial toxin, LPS, augments the hypoxia-induced increase in IEC apoptosis. Experiments are in progress to see if PTHrP treatment prior to and concomitant with hypoxia exposure blocks the hypoxia-induced IEC apoptosis. Based on the evolutionarily conserved expression of PTHrP in gut and organ systems, we speculate that up-regulation of PTHrP signaling can effectively block hypoxia-induced IEC apoptosis. Grant support: NIH (HL75405, HD051857, HD058948) and TRDRP (15IT-0250 and 17RT-0170).

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A SYSTEMATIC REVIEW COMPARING IMMUNOPROPHYLAXIS REGIMENS AFTER LIVER TRANSPLANTATION WITH HEPATITIS B CORE ANTIBODY POSITIVE DONORS

B. Waterman, A. Chi, S. Saab UCLA, Los Angeles, CA.

Purpose of Study: Orthotopic liver transplant recipients without Hepatitis B (HBV) infection who receive liver grafts from HBV Core Antibody (HbcAb) positive, HBV surface antigen (HbsAg) negative donors have an increased risk of developing de novo HBV infection. We compared the two most common prophylactic regimens - lamivudine (LAM)+Hepatitis B Immunoglobulin (HBIG) monotherapy and LAM+Hepatitis B Immunoglobulin (HBIG) combination therapy - to determine the relative efficacies of these two protocols in preventing de novo HBV infection.

Methods Used: A comprehensive search of the Cochrane Database of Systematic Reviews, MEDLINE (1966–2009) was conducted. Eligible studies included OLIT recipients who received HbcAb(+) liver grafts and were treated prophylactically with either LAM monotherapy or HBIG+LAM combination therapy. Patients were excluded if the donor or recipient was HbsAg(+) or HBV DNA(+) at time of liver transplantation.

Summary of Results: 13 studies were identified as meeting eligibility criteria. Data for all relevant patients within these studies was abstracted and incidence of de novo HBV infection, mortality, and mortality due to de novo HBV infection were assessed. Incidence of de novo HBV infection in patients receiving LAM-only prophylaxis was 2.7% (n = 73) compared with 3.6% (n = 110) in patients receiving HBIG+LAM combination therapy. Risk of developing de novo HBV infection based on pre-transplant recipient HBs serology in each treatment group could not be calculated due to incomplete data and the limited number of de novo HBV infection cases in the series reviewed.

Conclusions: Published studies have not shown HBIG+LAM therapy to be more effective than LAM-only treatment. Nucleoside analogue monotherapy should therefore be considered when treating HBV(-) patients who have received liver allografts from HbcAb(+) donors.

Number of HBV Recurrences Grouped by Recipient Pre-Transplant Serologies and Post-Transplant Prophylaxis Regimens

<table>
<thead>
<tr>
<th>Recipient Serology</th>
<th>Pre-Transplant Serology</th>
<th>Post-Transplant Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbcAb</td>
<td>LAM Alone</td>
<td>Total Number</td>
</tr>
<tr>
<td>HbcAb(+)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>HbcAb(-)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>HbcAb(+)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>HbcAb(-)</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

Session: Gastroenterology and Hepatology 238

TREATMENT OUTCOME OF PROTON PUMP INHIBITOR VERSUS HISTAMINE-2 RECEPTOR ANTAGONIST THERAPY FOR GASTROESOPHAGEAL REFUX DISEASE IN PEDIATRIC PATIENTS

M. Cox, DA. Gremse University of Nevada School of Medicine, Las Vegas, NV.

Purpose of Study: Proton pump inhibitors (PPIs) are reported to be more effective than H2-receptor antagonists (H2RAs) for the treatment of gastroesophageal reflux disease (GERD) in children and adults. However, there are fewer studies comparing PPI to H2RA therapy for GERD in pediatric patients than in adults. The aim of this study was to assess the treatment outcome of 4-weeks of lansoprazole versus ranitidine therapy for the treatment of GERD in infants and children.

Methods Used: Children 1 month to 4 years of age with clinically-diagnosed GERD were identified by review of medical records from the UNSOM Pediatric Gastroenterology Clinic during 2007–2009. Treatment outcome was assessed by the GERD Assessment Symptom Questionnaire (GASQ), based on a 7-day recall of symptom frequency and severity (J Pediatr Gastroenterol Nutr 2005;41:178–185). GERD symptoms were assessed after one-month of ranitidine therapy. Ranitidine was stopped and lansoprazole was prescribed. GERD symptoms were re-assessed after 4 weeks of treatment with lansoprazole. Dichotomous variables were compared by chi-squared analysis with Yates correction. Continuous variables were compared using paired t-test.

Summary of Results: 14 children (9 males, age 11.8 ± 1.8 mos., mean ± SD) with GERD diagnosed by GASQ scoring were studied. GASQ scores 4 weeks after ranitidine therapy were compared to GASQ scores after 4 weeks of lansoprazole therapy. GERD symptoms decreased in 11 of 14 patients (79%, p = 0.001) after treatment with lansoprazole compared to ranitidine. In addition, four patients achieved a normal GASQ score (<20) after 4 weeks of lansoprazole therapy. Overall, the cumulative GASQ scores significantly decreased on lansoprazole therapy (107 ± 118, x ± SD) compared to ranitidine therapy (236 ± 182, x ± SD, p = 0.006).

Conclusions: The results showed that GERD symptoms in patients 1 month to 4 years of age significantly decreased after one month of lansoprazole therapy compared to the symptoms observed after 4 weeks of treatment with ranitidine. We conclude that acid suppression therapy with lansoprazole yields a greater reduction in GERD symptoms than ranitidine therapy in infants and young children.

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INFLIXIMAB AS A RESCUE THERAPY FOR PREVENTION OF URGENT COLECTOMY IN ULCERATIVE COLITIS PATIENTS

T.S. Rihani, M. Othman, P. Roy University of New Mexico School of Medicine, Albuquerque, NM.
Purpose of Study: The aim of this study is to systematically review the efficacy of infliximab as a rescue therapy for adult UC patients in need of urgent colectomy and to determine the effects of infliximab on long-term colonic remission rates for those who were able to avoid urgent colectomy.

Methods Used: We searched the following sources: MEDLINE, EMBASE, CINAHL, PUBLMED, COCHRANE, AGA, AIG from 1990–2009, April. Key terms included, but not limited to, infliximab, inflammatory bowel disease, ulcerative colitis, and anti-tumor necrosis factor. Two reviewers independently screened studies for inclusion. Studies included needed to address ulcerative colitis patients, refractory to conventional therapy, needed an urgent colectomy, and were given infliximab as a rescue therapy.

Summary of Results: Ten studies, with a total of 214 patients, evaluated infliximab as a rescue therapy in UC patients with moderate to severe disease, in need of urgent colectomy. All patients were also refractory to conventional therapy including: corticosteroids, hydrocortisone, cyclosporine, 5-aminosalicylates and/or 6-mercaptopurine, either intravenous or oral. Infliximab, 5mg/kg, was given to all patients as a single or multiple infusions. Six studies looked at the efficacy of infliximab, 44 of 61 patients (72.13%) achieved clinical response within days of receiving an infusion, with 67 of 98 patients (68.37%) achieving complete clinical remission. Of the patients in need of urgent colectomy, 47 underwent surgery after an infusion of infliximab (21.96%), while 166/214 (77.57%) avoided urgent colectomy up to an average of 12.57 days. Of the 166 patients who avoided urgent colectomy on admission, 153 of these patients were further evaluated: 22 of the 151 patients (14.57%) underwent colectomy at a later date, 122/151 patients (80.79%) avoided colectomy at an average of 16.42 months. Of all patients, only 32.24% needed colectomy, whether urgent or not, 122/151 patients (80.79%) avoided colectomy at an average of 16.42 months. Of all patients, only 32.24% needed colectomy, whether urgent or not, 122/151 patients (80.79%) avoided colectomy at an average of 16.42 months.

Conclusions: For patients who do not respond to conventional therapy, surgical intervention with colectomy is the only curative option. Since colectomies have dangerous complications and adverse events of infliximab are independent screened studies for inclusion. Studies included needed to address ulcerative colitis patients, refractory to conventional therapy, needed an urgent colectomy, and were given infliximab as a rescue therapy.

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240
A CASE OF BEHCET’S DISEASE WITH INTESTINAL INVOLVEMENT DUE TO CROHN’S DISEASE

F. Rasool Loma Linda University Medical Center, Loma Linda, CA.

Purpose of Study: Behcet’s disease is a multi-systemic vasculitis characterized by systemic organ involvement. Gastrointestinal (GI) and systemic features of Behcet’s disease and inflammatory bowel disease overlap to a considerable extent, they are generally viewed as two distinct diseases. We present a case of Behcet’s disease along with Crohn’s disease.

Methods Used: 21 year old Caucasian lady presented with painful, recurrent oral and genital ulcers, tender nodules on lower extremities and polyarthralgia. Few months later she experienced anorexia, abdominal pain, diarrhea and heart burn. Patient also developed uveitis involving both eyes, papulo-pustular lesions and acneform nodules on skin. Physical exam showed tender nodules on the anterolateral aspect of both legs, measuring up to 5 cm. Patient also had axillary and perineal lymphadenopathy up to 1.5 cm. The vaginal introitus and labia minora showed multiple pustules and ulcers with surrounding erythema. Laboratory findings showed normal blood cell counts with normal differentials and chemistry. Sedimentation rate of 34 mm/hr, C-ANCA and P-ANCA negative. Biopsy of skin nodules showed septal inflammatory infiltrate composed of lymphocytes, histiocytes and scattered neutrophils within the subcutaneous tissues. Features of lobular panniculitis were seen. Finding was consistent with erythema nodosum.

Biopsy of genital lesion showed very dense mixed inflammatory cell infiltrate of numerous neutrophils, lymphocytes and plasma cells. Diagnosis of Behcet’s disease was made. Patient underwent Esophagogastroduodenoscopy (EGD) and Colonoscopy. EGD showed focal ulceration with active inflammation. Colonoscopy showed diffuse colitis, anal fissure, diffuse cobblestoning, ulceration and granulomatous appearance in the terminal ileum. Increased nodularity in cecum and severe nodularity, ulceration and scarring in ascending colon. Biopsy of the colon showed active inflammation with ulceration and submucosal non caseating granulomas, the hallmark of Crohn’s colitis.

Summary of Results: A 21-year-old lady presenting with oral and genital ulcers, uveitis, and erythema nodosum diagnosed as having Behcet’s disease. Colonoscopy revealed finding consistent with Crohn’s colitis.

Conclusions: While being of different pathogenic origin, Behcet’s and Crohn’s disease may coexist within same patient and cause diagnostic and therapeutic problems.

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241
DOES PRE-BIOPSY CONTRAST ENEMA DELAY THE DIAGNOSIS OF LONG SEGMENT HIRSCHSPRUNG’S DISEASE?

J. Chen1, E. Skarsgard1, D. Jamieson2 BC Children’s Hospital, Vancouver, BC, Canada and 3 BC Children’s Hospital, Vancouver, BC, Canada.

Purpose of Study: The diagnosis of long segment Hirschsprung’s disease (LSHD) is frequently delayed. Our purpose was to: 1) evaluate utility of contrast enema (CE) by comparing LSHD patients managed with/without pre-biopsy CE, 2) summarize CE findings in LSHD patients, and 3) evaluate the impact of initial CE reports on outcome.

Methods Used: All LSHD cases (transition zone {TZ} at or proximal to splenic flexure) treated between 1984 and 2009 were stratified by whether a pre-biopsy CE was done (Group 1), or not (Group 2). Group comparisons included elapsed days from admission to diagnostic rectal biopsy, first operation, and initial length of hospital stay (LOS). CEs were reviewed by a single pediatric radiologist, and original reports were categorized as “helpful”, “non-specific”, or “misleading.”

Summary of Results: 29 patients (16-Group 1; 13-Group 2) were identified. Group 1 patients experienced a significant delay in time to biopsy (p = 0.047), first operation (p = 0.005), and showed a trend towards prolonged LOS. CE review revealed TZ in 7/16 (44%); and of these, 6 (86%) under-estimated actual aganglionic segment length. 6/16 (38%) original CE reports were “misleading” and those patients showed a trend towards a delay in rectal biopsy and experienced significantly longer lengths of stay. There was a significantly higher proportion of patients with small bowel aganglionosis in the group with misleading reports.

Conclusions: Pre-biopsy CE offers little to the diagnosis of LSHD and likely contributes to diagnosis/treatment delays. Even if a TZ is recognized in biopsy proven HD, the predicted aganglionic segment length should not guide operative planning.

TABLE 1

<table>
<thead>
<tr>
<th>All (n=10)</th>
<th>RTZ-PTZ</th>
<th>RTZ/PTZ</th>
<th>RTZ absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal to SF (n=9)</td>
<td>1</td>
<td>3 (33%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Proximal to HP (n=6)</td>
<td>0</td>
<td>2 (33%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Total colon or greater (n=5)</td>
<td>0</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
</tbody>
</table>

RTZ-radiologic transition zone; PTZ-pathologic transition zone

TABLE 2

<table>
<thead>
<tr>
<th>3.0-0/7 to 3.5-0/7</th>
<th>3.5-0/7 to 3.5-0/7</th>
<th>3.5-0/7 to 3.6-0/7</th>
<th>&gt; 3.6-0/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU Admissions, N</td>
<td>660</td>
<td>751</td>
<td>887</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>46%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Infection</td>
<td>7.6%</td>
<td>9.7%</td>
<td>9.1%</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>14%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>11%</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>20%</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Stay in Days (Median)</td>
<td>11.7</td>
<td>9.9</td>
<td>8.3</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Stay in Days (Median)</td>
<td>8.9</td>
<td>7.4</td>
<td>5.4</td>
</tr>
<tr>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CE-contrast enema; TZ-transition zone; LOS-length of stay p<0.05.

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242
MAPPING OF CHROMATIN DYNAMICS IN THE CUP1/RUF5 LOCUS DURING CUP1 GENE ACTIVATION

L.M. Wilson1,2, O. Yazgan1, J.E. Krebs2,1 University of Washington, Seattle, WA and 1University of Alaska Anchorage, Anchorage, AK.
Purpose of Study: Copper is an essential trace element used in many cell processes. However, physiological copper concentrations must be tightly controlled, as excess amounts are toxic. In humans, misregulation of copper homeostasis is seen in diseases such as Wilson’s and Menkes. In the model organism Saccharomyces cerevisiae, the CUP1 gene codes for abundant metallothionein in response to exposure to excess copper. CUP1 is upregulated within minutes of increasing copper levels and is rapidly downregulated to a new steady-state level after 20–30 minutes. These changes in gene expression are accompanied by rapid changes in the modifications of histones associated with the locus. The CUP1 locus generates an overlapping transcript on the opposite strand called RUF5. Despite being a non-(protein) coding RNA generated from a cryptic promoter, RUF5 is thought to participate in CUP1 regulation by transcriptional interference.

Methods Used: In order to explore the chromatin dynamics in this region, we performed chromatin immunoprecipitation (ChIP) assays to map the histone tail modifications and detect presence of chromatin associated proteins in the locus, along with real-time reverse transcriptase PCR (qRT-PCR) assays to quantify changes in gene expression after addition of copper.

Summary of Results: As expected, we found increased Ser5-phosphorylated RNA Polymerase II association with the promoter region of CUP1 during the time of activation, which is an indicator of active transcription at beginning of genes. Interestingly, we also found active transcription beyond the end of the CUP1 gene, a region that corresponds to the beginning of the RUF5 gene, suggesting that RUF5 is actively transcribed. In addition, we found lower levels of H2A at the promoter region of CUP1, which suggests the presence of a nucleosome-free region (NFR) as frequently found at canonical promoters. The RUF5 promoter does not have lower levels of H2A, consistent with other cryptic promoters that also lack NFRs.

Conclusions: This study presents further confirmation that RUF5 is actively transcribed and provides an approach for future studies that will look into CUP1/RUF5 dynamics in mutants with defects in CUP1 regulation.

Health Care Research II
Concurrent Session
1:30 PM
Friday, January 29, 2010

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243
CHARACTERISTICS OF WOMEN UNDERGOING TUBAL LIGATION IN LAS VEGAS, NEVADA

C. Graham1, L. Rosenfield2, C. Mangalindan1, E. Ezeanolue1, M. Kirgan2, S. Elsadat1
1University of Nevada School of Medicine, Las Vegas, NV; 2University of Nevada School of Medicine, Las Vegas, NV

Purpose of Study: Despite its convenience, safety, and efficacy, not all women who desire tubal ligation (TL) actually have the surgery. Our study aimed to determine the characteristics of women who completed the procedure.

Methods Used: We performed a chart review of all women who attended prenatal care between January 2007 and December 2008 in our university affiliated clinic. Women who expressed desire for TL by signing consent were identified. Hospital records were used to identify women who completed the procedure. Demographic data were obtained and descriptive analysis performed using SAS 9.2.

Summary of Results: 4,151 women attended prenatal care during this study period; 83 signed consent for TL. 46% (38/83) completed the procedure and 54% (45/83) did not. Mean age was 31.7 years and 32.2 years for those who completed and did not complete procedure respectively. 61% (23/38) were Hispanic, 16% (6/38) Black, 23 (9/38) White among those who completed. The completion procedure compared to 56% (25/45), 24% (11/45), and 18% (8/45) respectively in those who did not. 24% (9/38) had insurance and 66% (25/38) single compared to 44% (20/45) and 56% (25/45) respectively for those who completed and did not complete procedure.

Conclusions: Although not every woman who signed consent for BTL completed the procedure, no significant socio-demographic differences were identified. Understanding reasons for non-completion of procedure is important to overcome barriers to obtaining desired procedure.
recommendations. The findings of the review and corresponding recommendations are published every 10 years. Washington conducts enhanced surveillance for maternal deaths. Identified cases are assessed by the Maternal Mortality Subcommittee but no recommendations or actions are proposed. The vital statistics office in Wyoming, Montana, and Idaho record MMR; no committee is present to review the data or propose any recommendation. χ² test showed that differences in MMR were not statistically significant.

**Conclusions:** There was no statistically significant difference in MMR among the WWAMI states. Although Alaska appeared to have a lower rate than the other states, this trend may be secondary to population differences, surveillance methods or other unexamined variables.

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Total # Live Births</th>
<th>Total # Maternal Deaths</th>
<th>Average MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington</td>
<td>660,137</td>
<td>69</td>
<td>10.45</td>
</tr>
<tr>
<td>Wyoming</td>
<td>55,128</td>
<td>7</td>
<td>12.70</td>
</tr>
<tr>
<td>Alaska</td>
<td>82,835</td>
<td>3</td>
<td>3.62</td>
</tr>
<tr>
<td>Montana</td>
<td>92,345</td>
<td>10</td>
<td>10.83</td>
</tr>
<tr>
<td>Idaho</td>
<td>178,559</td>
<td>21</td>
<td>11.76</td>
</tr>
</tbody>
</table>

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**Session: Health Care Research II 247**

**SHOULD WE ROUTINELY SCREEN ALL NEWBORNS FOR METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS?**

A. Weiner¹, E. Ezeanolue¹,³, M. Buttner²,³, P. Cruz²,³, C. Cross¹, J. Henry², I. Jack¹

¹University of Nevada School of Medicine, Las Vegas, NV; ²University of Las Vegas, Nevada, Las Vegas, NV; ³University of Las Vegas, Nevada, Las Vegas, NV.

**Purpose of Study:** Reported cases of neonatal infection with methicillin resistant Staphylococcus aureus (MRSA) have been on the increase nationally and locally in Nevada. A previous study showed higher rates of MRSA colonization in healthy pediatric populations in Nevada compared to national rates. This study sought to determine the incidence of MRSA colonization in newborns and to evaluate potential correlate associations between maternal and neonatal colonization.

**Methods Used:** Vaginal and nasal swabs for MRSA were obtained from 307 pregnant women who received prenatal care at a university affiliated clinic from November 2008 through April 2009. Nasal and umbilical stump swabs were collected from vaginally-delivered neonates 24–48 hours after birth. Data were collected on demographics and pertinent medical history through a survey completed by participants. Swab specimens were plated on media selective for S. aureus and MRSA. Antibiotic susceptibility testing was performed on all isolates. Descriptive and inferential statistics were calculated using SPSS version 17.0, SAS version 9.2, and NCSS/PASS 2004.

**Summary of Results:** During the study period, 156 infants were born vaginally. Of these, 7.7% (118/156) were African American, 75.6% (12/156) Hispanic, 11.5% (118/156) Caucasian, 0.6% (1/156) Native American, and 2.6% (4/156) other races. Race was not reported for 1.9% (3/156). Of the isolates, 1.0% and 0.3% of maternal nasal and vaginal specimens and 0% and 0.6% of neonatal nasal and umbilical specimens were positive for MRSA, respectively. No relationship was identified between maternal and neonatal colonization.

**Conclusions:** Routine screening of all newborns would likely not be cost-effective given current low MRSA colonization rates in newborns and absence of correlation between maternal and newborn colonization.

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**Session: Health Care Research II 249**

**IMPACT OF AN ASTHMA CLINICAL PATHWAY ON JOINT COMMISSION INPATIENT ASTHMA PERFORMANCE MEASURES**

B. Fassl, F. Nkoy, T. Simon, R. Srivastava, C. Maloney University of Utah, Salt Lake City, UT.

**Purpose of Study:** Asthma is the most common chronic childhood illness and one of the most common reasons for pediatric hospitalization. To improve and monitor the quality of inpatient asthma care, the Joint Commission (JC), in collaboration with the National Association of Children’s Hospitals and Related Institutions, introduced 3 clinical inpatient asthma performance measures (JC IAPM) in 2007.

Objectives of this study are to 1) examine provider compliance with JC IAPM and 2) describe clinical (1 year readmission rate, ICU admissions, and deaths) and resource utilization (length of stay and costs) outcomes before and after implementation of an asthma clinical pathway (ACP) in a tertiary care children’s hospital.

**Methods Used:** This prospective study included children aged 2–18 years, admitted to the study hospital between 1/1/2006 and 1/1/2009 for acute asthma. Asthma was defined using the primary ICD-9-CM diagnosis code 493.xx. Administrative data determined compliance with JC IAPM #1 (use of beta agonist bronchodilators) and #2 (use of systemic corticosteroids), and chart review determined compliance with #3 (hospital discharge with completed asthma home management plan of care). Clinical outcomes and resource utilization outcomes were determined from the administrative database. We used time series analysis to compare trends in compliance before and after ACP implementation. The ACP was implemented incrementally: Interventions targeting JC IAPM #1 and #2 started 1/1/2007, those targeting JC IAPM #3 started 1/16/2008.

**Summary of Results:** Over two years, 811 children were admitted for acute asthma. Mean compliance with JC IAPM #1–3 before and after ACP implementation was 85% vs.100%, 95% vs. 100% and 2% vs.90%, respectively. Trends in compliance with JC IAPM#1 [p < 0.01], JC IAPM#2 [p < 0.01] and JC IAPM/#3 [p < 0.02] all significantly increased after ACP implementation.

No change in trends was seen for readmission rates, ICU admissions, median length of stay, or costs following implementation of the ACP. No deaths occurred in the study period.

**Conclusions:** Implementation of an asthma clinical pathway significantly improved compliance with all JC clinical inpatient asthma performance measures. Improved compliance with JC inpatient asthma performance measures did not have an impact on clinical or administrative outcomes.

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**Session: Health Care Research II 249**

**HOW DOES STRUCTURED DATA ENTRY AFFECT MEASURED QUALITY OF CARE?**

S. Almeida¹, C. Roth³, D.B. Reuben², N.S. Wenger², D.A. Ganzz², UCLA David Geffen School of Medicine, Los Angeles, CA; ¹UCLA, Los Angeles, CA and ²RAND Corporation, Santa Monica, CA.

**Purpose of Study:** Structured data entry and electronic medical records are increasingly prevalent in the healthcare industry. However, an understanding of how structured data affects quality measurement and patient care is unknown. This study examines how structured visit notes (SVNs) are utilized and how they affect measured quality of care across 3 clinics in the Assessing Care of Vulnerable Elders: Practice Redesign for Improved Medical Care of Elders (ACOVEprime) study. We had 3 primary objectives: 1) Compare the measured quality of care between patients with and without an SVN 2) Analyze the utilization of SVN components at each site, and 3) Evaluate the SVN’s potential for serving as a substitute for full-chart reviews in analyzing quality of care.

**Methods Used:** We reviewed a total of 226 primary care records. We checked for the presence of the SVN and abstracted patient data from it. We calculated descriptive statistics regarding how often various sections of the SVN were utilized and developed algorithms for measuring quality of care for falls solely from the SVN. These were then compared to previously calculated quality scores based on abstraction of the whole chart.

**Summary of Results:** Of 226 patient charts, 41% contained the structured visit note. Among those charts containing the SVN, Site A, Site B, and Site C had quality scores of 87%, 89%, and 74%, respectively. Without an SVN, the quality scores were 30% and 45% for Site A and Site B, respectively; similar results for Site C cannot be computed since it was a fully-electronic site. The “History” and “Exam” sections of the SVN had much higher rates of utilization (80.9% and 70.9% respectively) than the “Assessment” and “Plan” components (16.8% and 20.8% respectively). An average of 55% of the charts had identical quality scores using SVN-based and full-chart based quality measurement algorithms, while the SVN was shown to underestimate chart-based quality in 34% of patients and overestimate in 10%.

**Conclusions:** Structured visit notes may serve as a tool for more complete and detailed documentation, a prompt for physicians as to appropriate protocols for patients with falls and mobility disorders, or both, accounting for the higher quality scores observed in those charts containing SVNs.
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250  SLEEPINESS IN TRAINING HOUSE STAFF DESPITE REGULATED WORK HOURS
GP. Singh, RS. Sirohi, T. Singh, J. Saffier San Joaquin General Hospital, French Camp, CA.

Purpose of Study: This study aims to document the residual sleepiness in training house staff physicians. Residency review committee (Accreditation Council for Graduate Medical Education) has regulated weekly work hours for this group of trainees.

Methods Used: The sleepiness was evaluated by administering a survey instrument to training medical house staff (n = 17) and controls students (N = 5) and attending physicians (n = 1). The work environment, schedules and similar type of work were matched in both groups.

Summary of Results: A total of 23 training physicians participated in the survey. Major age group was 20 to 40 years (n = 22). Most (87%) slept for 4 to 8 hours but also (73%) reported non-refreshing sleep. Only 3/23 respondents were on call the night before. The medical house staff in general slept less than the controls. They also captured less lecture information (86% vs. 48%). Almost one third of the house staff (31% vs. 69%) reported caffeine intake along with 2 reminders (2007, 2008) obtained a 49.6% (62/125) initial response. 25% of responses were on call the night before. The medical house staff in general slept less than the controls. They also captured less lecture information (86% vs. 48%). Almost one third of the house staff (31% vs. 69%) reported caffeine intake along with 2 reminders (2007, 2008) obtained a 49.6% (62/125) initial response.

Conclusions: Training physician documented less nightly sleep and moderate daytime sleepiness despite weekly work hour regulations. It seems to affect their ability to learn new information. Caffeine intake seems to improve their performance. More studies are needed to further investigate the true impact of work hour regulation on training house staff measures of performance.

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251  TRENDS IN TOBACCO-DEPENDENCE CURRICULA IN U.S. MEDICAL SCHOOLS BASED ON 1998 AND 2008 SURVEYS
D. Stillman, R. Lee, D. Chu, S. Yu Loma Linda Medical School, Loma Linda, CA.


Methods Used: We faxed a survey to all US medical schools (15 items, 1997–1998) & an online survey (20 items, 2007–2008). Both surveys asked comparable topical items. The 2008 survey added 11 items on the schools’ curricular methods, identification of key faculty & stop-smoking training sites. Mean national curricular trends over 10 years will be assessed. In addition, curricular changes for individual schools (2008) will be compared to their baseline (1998).

Summary of Results: We had a 70% initial response to the faxed survey & 2 phone reminders (1998) with a 96.8% final response rate. The emailed survey along with 2 reminders (2008) obtained a 49.6% (62/125) initial response rate. In 2008, 88.3% of schools reported their curriculum includes tobacco dependence. Although 79% (49/62) schools reported having faculty experts in tobacco dependence, only 21% of schools identified a key tobacco curriculum coordinator. By 2008, most schools adopted 3 new FDA approved medications into the curriculum (> 85%). Required course hours for tobacco-dependence treatment skills doubled over 10 years for both categories of >1-3 hours & >3–5 hours. More schools reported they require clinical tobacco training (30.8% to 78.7%). Required clinical training increased in “teaching settings without patients” (12.5% to 36.4%) & “clinical settings with actual patients” (13.3% to 29.1%). Required performance evaluations also increased (5% to 29.1%).

Conclusions: Tobacco education in US medical schools appears to have increased in hours of educational time in the last decade, yet only 1/3 of schools require clinical training & skill evaluation. Medical educational culture is slow to attain the aggressive benchmark established by public health advancements in order to combat the most deadly global epidemic.

Session: Health Care Research II

252  USE OF THE VETERANS AFFAIRS COMPUTER DATABASE TO DETECT UNDIAGNOSED PRIMARY HYPERALDOSTERONISM
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Purpose of Study: Based on reports in the literature, the estimated prevalence of primary hyperaldosteronism is approximately 10-20% in patients with poorly controlled hypertension. A pharmacy database was used to identify patients with resistant hypertension for the potential presence of primary hyperaldosteronism.

Methods Used: Retrospective review of computerized data was used for this analysis. Patients were included if they had: 1) uncontrolled hypertension and use of 3 antihypertensive medications or 4 or more antihypertensive medications regardless of blood pressure, 2) low or normal potassium levels, and 3) received continuous health care from 10/1/08 to 2/28/09. Exclusion criteria were: 1) Past or current use of an aldosterone antagonist, 2) medication possession ratio <80% for any antihypertensive, and 3) elevated potassium level. Patient lists were sent to providers suggesting they evaluate their patients for hyperaldosteronism using the angiotensin renin ratio (ARR) >30. For patients in whom these data were available, we determined the precision and utility of computer screening.

Summary of Results: 5,516 patients were on three or more antihypertensive medications. 746 patients remained after applying inclusion and exclusion criteria using computer analysis. Manual chart review was conducted two months following computer analysis for each patient to verify and update the inclusion and exclusion criteria. 333 patients remained for analysis; their providers were sent letters suggesting they obtain ARR. In the 184 individuals in which ARR was obtained, 39 (21.2%) had an elevated value. There was a statistical but not clinically significant difference in potassium when comparing patients with elevated ARR vs. those with normal ARR (4.0 vs. 4.2, respectively; p = 0.023). There were no statistically significant differences in class of antihypertensive medication use, age, blood pressure, or serum creatinine.

Conclusions: The VA computer database is a useful tool to screen for patients with undiagnosed primary aldosteronism.

Session: Health Care Research II

253  REPORTING OF CONTINUOUS OUTCOME MEASURES IN RANDOMIZED CLINICAL TRIALS: IS THE WHOLE STORY BEING TOLD?
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Purpose of Study: The CONSORT statement defines elements to be included in reports of randomized controlled trials (RCTs) but says very little about the depiction of outcome data. Some reports of RCTs contain only a minimal summary of the available data; a 2 arm, 1000 patient trial might report only two means and two standard deviations. Such austere reduction may lead to misinterpretation of the meaning of a trial. We designed our study to investigate the extent of such data reduction.

Methods Used: We scored 10 randomly selected RCTs with one or more continuous primary outcomes from 2007–2009 issues of 20 leading medical journals. Using methods we developed for the quantification of density of data in tables and graphs we measured the degree of data reduction in two ways. First, we noted the format (text, table, figure) that conveyed the most detailed information about the outcome and the way that information was conveyed (e.g., mean alone; mean with SD, SEM or CI; histogram; scatterplot). Second, we counted the number of data points & descriptive statistics presented for the outcome (the numerator) and the number of data points that could have been presented (the denominator) and calculated the percentage of available data presented using denominators of varying stringency.

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Summary of Results: In general, only a small fraction of available data is presented (mean for best outcome, 22%, median, 6%, range, 0.2%-100%). There was considerable heterogeneity by journal: mean range (2%-72%), median range (1%, 100%). For over half the journals the median percentage of data presented for the best outcome was under 10% and for 19 of 20 journals it was below 25%. The percentage of data presented for the best outcome was higher when presented in a figure (n = 74, mean 47%, median 22%), than a table (n = 117, mean 11%, median 5%), or as text (n = 9, mean 6%, median 5%).

Conclusions: Reports of randomized trials present a small fraction of the available data. While the extent to which this leads to misinterpretation of trial results is unknown, scientific discourse would be enhanced by the presentation of the all of the data either in the paper or in online supplements.

Immunology and Rheumatology I
Concurrent Session
1:30 PM
Friday, January 29, 2010

Session: Immunology and Rheumatology I

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CHARACTERIZATION OF C-REACTIVE PROTEIN-INDUCED SUPPRESSIVE MACROPHAGES
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Purpose of Study: Systemic lupus erythematosus (SLE) is a devastating autoimmune disorder with estimated prevalence of 322,000 in the USA. Multiple genetic and environmental factors have been established as risk factors in disease development and severity, one of which is a genetic polymorphism in the promoter for the acute phase protein, C-reactive protein (CRP).

In previous studies, CRP was found to suppress disease activity in mouse models of SLE and immune thrombocytopenia (ITP). However, the mechanism of this suppression is incompletely understood. It is hypothesized that CRP may provide disease suppression by inducing the formation of regulatory macrophages which can dampen the immune response and limit inflammation, leading to inhibition of immune-mediated disease. To examine the phenotype of these suppressive macrophages, the cytokine profile of CRP-treated splenocytes was analyzed.

Methods Used: Spleen cells from C57BL/6 (wild type) mice were treated with CRP, CRP+Lipopolysaccharide (LPS), Immune Complexes (IC), LPS alone, and a non-treatment control group. RNA was isolated from the adherent cells (primarily macrophages). The cDNA from mRNA for each treatment group were analyzed for relative expression levels using Taqman primers and probes in RT-PCR for IL-10, IL-12, CCL2, IL-1β, Arg1, Nos2, Tnfα14, RetnA and TGF-β. These markers were chosen to characterize the spectrum of macrophage populations based on the work of Mosser et al. The 2^-ΔΔCT method was used to analyze the relative gene expression data.

Summary of Results: CRP treatment resulted in: 1) Down-regulation of CCL2, IL-12β, and IL-1β, cytokines typically expressed by classically-activated macrophages. 2) Minimal up-regulation of Tnfα14 and down-regulation of IL-10, both typically expressed by regulatory macrophages. 3) Up-regulation of RetnA which is associated with wound-healing macrophages.

Conclusions: Our studies suggest that CRP treatment of adherent splenocytes generated a unique class of macrophage that shares expression profiles with both regulatory and wound-healing macrophages and differs from classically-activated (pro-inflammatory) macrophages. The down-regulation of IL-12β and IL-1β is indicative of a suppressive phenotype. These findings may explain CRP’s ability to suppress disease in the SLE and ITP models.

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HYPOXIA INDUCIBLE FACTOR 1 α (HIF-1α) REGULATES NEUTROPHIL EXTRACELLULAR TRAP (NET) FORMATION IN MODEL POLYMORPHONUCLEAR LEUKOCYTES (PMN)
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Purpose of Study: PMNs form complex layers of chromatins and anti-bacterial proteins termed NETs which facilitate extracellular microbial killing. Newborn infant PMNs exhibit impaired NET formation and increased morbidity and mortality associated with infection. Due to its role as an effector molecule in acute inflammation, we considered HIF-1α as a candidate regulatory molecule governing NET formation. We hypothesized that decreased expression of HIF-1α protein in PMNs inhibits NET formation and that deficiency of NET formation in neonatal PMNs results from decreased HIF-1α activity.

Methods Used: We differentiated HL60 promyelocytic leukocytes with DMSO to generate a surrogate for mature PMNs and transduced them with lentiviral plasmids coding for green fluorescent protein (GFP) and a short hairpin loop of mRNA designed to “knock down” the expression of HIF-1α (HIF-1α KD). We quantified HIF-1α mRNA expression via qPCR in all cell types. We stimulated all cell types with LPS (100 ng/ml) for 1-4 hours and used western blotting, live cell imaging and immunocytochemistry to assess for HIF-1α protein expression, intracellular topography and activity.

Summary of Results: We documented a 69% decrease in HIF-1α mRNA expression as well as decreased HIF-1α protein expression following lentiviral knockdown in HIF-1α KD cells as compared to GFP control cells. HIF-1α KD cells demonstrated complete inhibition of NET formation as compared to GFP controls. Finally, despite higher baseline expression of HIF-1α protein as compared to adult PMNs, we demonstrated decreased nuclear translocation of HIF-1α protein at 4 hours in PMNs isolated from preterm and term infants as compared to those isolated from healthy adults.

Conclusions: Decreased HIF-1α protein expression impairs NET formation in differentiated HL60 leukocytes used as a surrogate for mature PMNs, and neonatal PMNs exhibit impaired HIF-1α nuclear translocation as compared to healthy adult PMNs. We speculate that decreased expression and activity of HIF-1α exists in neonatal PMNs leading to failed of NET formation in response to microbial infections.

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INNATE IMMUNE RESPONSE OF NEUTROPHILS TO PROPIONIBACTERIUM ACNES
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Purpose of Study: To explore the innate immune activity of neutrophils against Propionibacterium acnes in order to evaluate whether the response plays a predominantly inflammatory or protective role in the development of acne vulgaris.

Methods Used: Neutrophils were isolated using the Ficoll-Paque (GE Healthcare) and dextran sulfate sodium salt (Sigma-Aldrich) gradients from human blood of normal healthy volunteers according to protocol approved by Institutional Review Board at UCLA. P. acnes strain 6919 was obtained from American Type Culture Collection (Manassas, VA) and used live or prepared by probe sonication as described previously (Kim et al., 2002). Cytokine enzyme-linked immunosorbent assay (ELISA) was performed on neutrophils to evaluate levels of IL-8 (BD PharMingen, San Diego, CA); additionally, ELISA was performed on samples sent out to Aushon Biosystems (Billerica, MA) for testing of remaining cytokines. Confocal microscopy was used to obtain immunofluorescent photographs of neutrophils within acne lesions and from those isolated from human blood. Killing assays were performed using live P. acnes, isolated neutrophils, toll-like receptor 2 blocking antibody and 4-aminophenyl sulfone (Sigma-Aldrich).

Summary of Results: Neutrophils were found inside active acne lesions and from those isolated from human blood. Killing assays were performed using live P. acnes, isolated neutrophils, toll-like receptor 2 blocking antibody and 4-aminophenyl sulfone (Sigma-Aldrich).

Conclusions: These data indicate that the response of neutrophils to P. acnes is both protective through bactericidal activity and also pro-inflammatory through production of multiple inflammatory cytokines and chemokines. It also appears that dapsone decreases the inflammatory effects of neutrophils.
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DIFFERENTIAL PHOSPHORYLATION OF RAPTOR IN POLYMORPHONUCLEAR LEUKOCYTES ISOLATED FROM PREMATURELY BORN INFANTS AS COMPARED TO THOSE ISOLATED FROM HEALTHY ADULTS

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Purpose of Study: The mammalian Target of Rapamycin (mTOR) protein is a critical regulator of translational events. It is inhibited by rapamycin and neutralization of mTOR activity inhibits overall protein translation by approximately 15%. Raptor is a regulatory protein associated with mTOR Complex 1. When phosphorylated at its serine792 residue, Raptor inhibits mTORC1 downstream phosphorylation of 4EBP1 and halts translation of key regulatory genes such as retinoic acid receptor α and interleukin-6 receptor α.

We have previously shown that PMNs isolated from prematurely born infants exhibit differential expression of these regulatory proteins and differential patterns of 4EBP1 phosphorylation following stimulation with platelet activating factor (PAF) as compared to PMNs isolated from healthy term infants and adults. We hypothesized that preterm PMNs exhibit differential phosphorylation of Raptor protein following stimulation as compared to term neonatal and healthy adult PMNs.

Methods Used: We stimulated human PMNs isolated from infants, term infants and preterm infants with PAF [10-5M] for 5-60 minutes. We examined phosphorylation and protein expression of Raptor and 4EBP1 using immunocytochemistry and In-Cell Western analysis.

Summary of Results: Analysis of Raptor and phosphorylated Raptor protein expression using non-specific and phospho-specific (serine792) Raptor antibodies demonstrates a decrease in phosphorylation of Raptor protein consistent with mTOR activation in adult PMNs over 30 minutes with a return to baseline phosphorylation levels by 60 minutes. Preterm PMNs, however, express phospho-Raptor at baseline with no change in phosphorylation following PAF stimulation over 60 minutes.

Conclusions: Treatment with PAF fails to induce Raptor dephosphorylation at the serine792 site in preterm PMNs as compared to healthy adult PMNs. We speculate that differential Raptor phosphorylation may account for differential expression of regulatory proteins governing the PMN response to tissue injury and infection and thereby contribute to syndromes of dysregulated inflammation such as necrotizing enterocolitis and neonatal chronic lung disease.

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AN INTACT HUMAN ENDOTHELIAL CELL MONOLAYER INHIBITS NEUTROPHIL EXTRACELLULAR TRAP FORMATION BY POLYMORPHONUCLEAR LEUKOCYTES

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Purpose of Study: Polymorphonuclear leukocytes (PMN) form complex lattices of chromatin and antibacterial proteins termed neutrophil extracellular traps (NET) which facilitate extracellular microbial killing. However, unregulated formation of NETs with release of PMN granular degradative proteins may exacerbate inflammatory tissue damage. PMN agonists such as lipopolysaccharide (LPS) stimulate NET formation by PMN in vitro when assayed on poly-L-lysine coated surfaces. We hypothesized that an intact endothelial cell monolayer would inhibit NET formation and that intravascular and extracellular matrix proteins would support NET formation in vitro by LPS-stimulated PMNs.

Methods Used: We co-incubated control or LPS-stimulated PMNs [100 ng/ml] with human umbilical vein endothelial cells (HUVEC) grown to 1 day post-confluence in fibronogen coated tissue culture wells with and without disruption of the HUVEC monolayer. We also incubated PMNs on glass coverslips coated with fibronogen, pooled human plasma or fibronectin. We assayed for NET formation at 1 hour via confocal microscopy.

Summary of Results: An intact monolayer of HUVEC cells inhibits NET formation by both control and LPS-stimulated PMNs, but disruption of the monolayer precipitates PMN chemotaxis to areas of wounding with subsequent NET formation. While human plasma reduces NET formation in vitro, LPS-stimulated PMNs form NETs robustly on surfaces coated with fibronogen. Fibronectin coated surfaces, however, stimulate NET formation in both unstimulated control and LPS-stimulated PMNs.

Conclusions: An intact endothelial cell monolayer inhibits NET formation by stimulated PMNs although NETs readily form at areas of mechanical wounding. Surfaces coated with human plasma or fibronogen support but do not stimulate NET formation by human PMNs. However, surfaces coated with fibronectin, an extracellular matrix protein, not only support NET formation in vitro by LPS-stimulated PMNs but also stimulate control PMNs to form NETs. We speculate that the intravascular milieu suppresses NET formation by circulating PMNs in vivo while exposure to extravascular matrix proteins stimulates NET formation as a response to tissue damage and potential infection.

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EFFECTS OF AM580 AND ROSIGLITAZONE ON B CELL CD1d EXPRESSION AND NK CELL FREQUENCY

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Purpose of Study: X-linked lymphoproliferative disease (XLP) is characterized by fatal lymphoproliferative disorders associated with the inability to control Epstein Barr Virus (EBV) infection. Individuals with XLP fail to develop natural killer T (NKT) cells, a subset of T lymphocytes that recognize lipid antigens presented on the MHC-like molecule CD1d. We observed that EBV-transformed B cells (lymphoblastoid cell lines, LCL) downregulate CD1d expression, suggesting NKT cells may regulate the expansion of EBV-infected cells. Synthetic molecules such as retinoic acid receptor-α agonist AM580 and peroxisome proliferator activator receptor-γ agonist rosiglitazone (RSG) have previously been shown to increase CD1d expression on monocyteic cells. The purpose of this project was to determine the effect of AM580 and RSG on LCL CD1d expression and NKT cell-mediated control of EBV infection.

Methods Used: LCL were generated by infecting tonsillar B cells with EBV 95.8 in vitro. LCL CD1d expression following 24, 48 and 72 hr treatment with AM580 was analyzed using flow cytometry. LCL pretreated for 24 hrs with AM580 and RSG were co-cultured with human NKT cell lines. NKT cell interferon-γ (IFN-γ) production and cytotoxicity were then analyzed using ELISA and chromium release assays. Peripheral blood was collected from RSG-treated patients or age-matched controls and B cell CD1d expression and NKT cell frequencies were determined by flow cytometry.

Summary of Results: Maximal CD1d expression on LCL was induced after 72 hrs of AM580 pretreatment. Co-culturing of NKT cells with AM580-treated LCL resulted in NKT cell IFN-γ production and susceptibility to NKT cell-mediated cytotoxicity compared to untreated LCL. Patients treated with RSG had a higher average NKT cell frequency compared to age-matched controls but no measurable change in B cell CD1d expression.

Conclusions: Treatment with AM580 restores CD1d expression on LCL, resulting in NKT cell IFN-γ production and cytotoxicity. Patients treated with RSG have a higher proportion of NKT cells, suggesting RSG treatment during acute EBV infection of healthy individuals may decrease EBV associated disease severity.

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RAS ABNORMALITIES IN LUPUS T CELLS

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Purpose of Study: The purpose of this study was to detect abnormalities in Ras signal transduction in lupus T lymphocytes. We used farnesylatedhyocyanate (FTS), a direct Ras inhibitor that inactivates it by displacing it from the inner cell membrane, to measure the effect on cytokine levels and CD40 ligand expression in lupus T lymphocytes versus controls subjected to stimulation protocols.

Methods Used: Blood from a healthy donor and a lupus patient were obtained. The lymphocytes were separated using the Facil-Hypaque
Methods Used: Subsequently, T lymphocytes were separated by negative selection using an enrichment protocol. Half of the samples from each group were treated with anti-IgG and anti-IgM (TS) for 2 hours. The samples were then divided equally to receive a TCR independent stimulus (TPA plus ionomycin), a high and low grade TCR stimulation with anti CD3 plus anti CD28 antibodies, or left unstimulated in the control group. The cells were harvested after 2 hours and fixed on slides. After centrifugation, the supernatants were saved for cytokine analysis. Both T helper(TH)-1 (IL-2, TNFα, INFγ) and TH-2 (IL-4, IL-10, IL-13) dependent cytokines were measured using a Luminex assay. The fixed cells on the slides were labeled with fluorescent anti-CD40L as well as anti H- and N-Ras antibodies and analyzed using a laser scanning cytometer (LSC).

Summary of Results: In the TCR independent stimulation protocol, treatment with FTS lowered the cytokine levels in lupus T cells as opposed to an increase in the levels of cytokines that was seen in controls. The same effect was seen in the low grade TCR stimulation protocol. The results from the LSC analysis for the CD40L expression are still in progress.

Conclusions: We observed a difference in cytokine secretion in lupus T cells versus controls, in response to Ras inactivation by FTS, followed by stimulation with TCR independent and dependent stimuli. In our previous study, Ras inactivation by FTS was able to markedly decrease the level of CD40L in lupus T cells and did not affect healthy T cells. The present study furthermore suggests that a Ras abnormality is present in lupus T lymphocytes, which may account for the differences observed. We are currently analyzing the data for the CD40L expression as well as repeating the experiment using more samples from different lupus and control subjects, which we plan to present at the time of the meeting.

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ABERRANT B LYMPHOCYTE HOMEOSTASIS IN AUTOIMMUNE HUMAN SPLEEN AND PERIPHERAL BLOOD AND ITS POTENTIAL IMPLICATIONS IN AUTOIMMUNE DISEASES

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Purpose of Study: Abnormalities in the distribution of B cell subsets are a feature of a number of autoimmune diseases, suggesting that B cell homeostasis is deregulated. The developmental events that contribute to disparate B cell homeostasis are unclear. Memory B cells (CD27+) are reported to predominante in the peripheral blood (PB) of some patients with lupus (SLE). The aim of this study is to compare the emergence of memory B cells in autoimmune and normal spleen and to correlate changes in splenic memory B cell subsets with those in PB. Our approach is to translate data on splenic B cell development obtained using the mouse model to examine developmental events in the human spleen.

Methods Used: Normal and autimmune spleen and PB were stained for four color flow cytometry. Human naive follicular mature B cells (FM), marginal zone B cells (MZ), and subsets of transitional B cells (T1 and T2) were identified based on co-staining with CD21, CD24 and IgM (markers used to identify murine splenic B cell subsets) and was validated using human markers (CD38, CD23). Emergence of memory B cells was assessed based on the progressive acquisition of CD27.

Summary of Results: Based on expression of CD27, we identified 3 distinct B cell subsets, naive (CD27+), emerging memory cells (CD27 LO) and memory B cells (CD27 HI). In the autimmune spleen we saw an increased frequency of memory B cells (40%) as compared to normal spleen (18%). Importantly, we saw that the frequency of emerging memory B cells (CD27 LO) was 3 fold higher in the diseased spleen. These emerging memory B cells included both MZ and follicular memory B cells, based on surface immunophenotype. Consistent with the increase in production of memory B cells in the autoimmune spleen, memory B cells in the periphery were 2 fold higher than observed in normal PB.

Conclusions: The disturbances in B cell homeostasis that results in increased memory B cells in the periphery of autoimmune patients correspond to increased production of memory B cells in the spleen. This study suggests that the ability to target memory B cells in the spleen is likely to be a requirement for therapeutic success in the reduction of memory B cells in the periphery.

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A CASE OF VOGT-KOYANAGI-HARADA (VKH) SYNDROME

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Purpose of Study: Vogt-Koyanagi-Harada syndrome is a rare systemic disease. It is due to autoimmune reaction against various melanocyte-containing organs. Bilateral uveitis associated with cutaneous, neurologic, and auditory abnormalities are manifestations of this inflammatory granulomatous disorder. It can be associated with other autoimmune disorders such as autoimmune polyglandular syndrome, hypothyroidism, hashimoto thyroiditis, diabetes mellitus and IgA nephropathy. We present an isolated case of VKH syndrome without other autoimmune disorders.

Methods Used: 52 year old Hispanic man presented with sudden onset of severe bifrontal headache followed by blurry vision, eye pain and photophobia in both eyes. Patient also complained of arthralgia, vertigo, dizziness, neck stiffness, severe nausea and tinnitus in bilateral ears. Physical exam showed white patches of vitiligo on the skin. On ocular exam visual acuities were 20/80 in right eye and hand motion in left eye. Slit lamp exam showed + 1 cell in anterior chambers in both eyes. Intraocular pressures were 14mmHg in right eye and 13mmHg in left eye. Dilated fundoscopic exam showed macular edema in right eye and severe retinal detachment in left eye. Laboratory tests showed normal cell counts with differential and chemistry. Patient was seen by Ophthalmology secondary to rapid deterioration in vision involving both eyes. Clinical features for other autoimmune disorders were negative. Lumbar puncture was performed secondary to complaints of neck stiffness. Cerebrospinal fluid (CSF) showed some pleocytosis. CSF was negative for any viral, fungal and bacterial infection. Skin biopsy of depigmented area showed lack of melanin, other histologic finding include mononuclear infiltrates consisting mostly of T lymphocytes. Diagnosis of VKH syndrome was made. Patient was pulsed with high dose IV steroids followed by prednisone by mouth. Patient noticed dramatic improvement in neurologic and ocular symptoms.

Summary of Results: 52 year old man with severe headaches, menin-gismus and bilateral uveitis diagnosed with rare condition called VKH syndrome.

Conclusions: VKH syndrome manifest as multorgan disorder. Early diagnosis and treatment helps prevent permanent vision loss. Skin changes may be permanent, even with the treatment, but hearing is usually restored in most patients.

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DOES SONOGRAPHIC NEEDLE GUIDANCE AFFECT THE CLINICAL OUTCOME OF INTRAARTICULAR INJECTIONS?

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Purpose of Study: The present randomized controlled study addressed whether sonographic needle guidance affected clinical outcomes of intra-articular joint injections.

Methods Used: 148 painful joints were randomized (NCT 00651625) to intraarticular triamcinolone acetonide injection by conventional palpation-guided anatomic injection or sonographic image-guided injection enhanced with a one-handed control syringe (the reciprocating procedure device). A one needle, two syringe technique was used where the first syringe was used to introduce the needle, aspirate any effusion, and anesthetize and dilate the intraarticular space. After intraarticular placement and synovial space dilitation were confirmed, a syringe exchange was performed, and corticosteroid was injected with the second syringe through the indwelling intraarticular needle. Baseline pain, procedural pain, pain at outcome (2 weeks and 6 months), and changes in pain scores were measured with the 0-10 cm Visual Analogue Pain Scale (VAS).

Summary of Results: Relative to conventional palpation-guided methods, sonographic guidance resulted in 43.0% reduction in procedural pain (p < 0.001), a 58.5% and 22.6% further reduction in absolute pain scores at the 2 week and 6 months outcome respectively (p < 0.01), a 75% reduction in significant pain (VAS pain score ≥ 5 cm) (p < 0.001), (p < 0.01), 62.0% reduction in the non-responder rate (reduction in VAS score < 50% from baseline) (p < 0.01), and an increase in duration of therapeutic effect by 22.1%
Case History:

The patient first presented UCLA at age 14 years. He already had been diagnosed with RPF a few years earlier and already required ureteral stents. He had also developed pulmonary fibrosis with PFT’s showing very severe restriction that required supplemental oxygen. Initial work-up did not find autoimmune disease. He was initially treated with high dose corticosteroids plus daily steroids with minimal improvement. Approximately a year later he was started treatment with tamoxifen (20 mg-BID). He did respond well to this therapy and the ureteral stents were able to be removed. His pulmonary disease also improved, and he was able to function without supplemental oxygen. However, after about 6 months of tamoxifen therapy, he developed severe leg pain and was diagnosed with deep vein thrombosis (DVT). The tamoxifen was stopped, and he was started on anticoagulant therapy. At about the same time, he was noted to have a low IgG (down to 244 mg/dL). His IgA and IgM were also low, but B and T cell subsets were normal and he was diagnosed with common variable immunodeficiency (CVID). He was then started on intravenous gammaglobulin, which he tolerated well and has had no significant infections.

He has developed more DVT’s and a cutaneous vasculitis (treated with oral steroids and hydroxychloroquine) but no more signs of RPF or pulmonary fibrosis. Conclusion: This patient has developed CVID after recovering from RPF. There are no previous report of CVID associated with RPF.

Infectious Diseases

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1:30 PM
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IDENTIFICATION OF TWO NOVEL SECRETED PROTEINS INVOLVED IN TRICHOMONAS VAGINALIS PATHOGENESIS
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Purpose of Study: Trichomonas vaginalis is the cause of the most common non-viral sexually transmitted infection worldwide. Because T. vaginalis is an obligate extracellular pathogen, adherence to epithelial cells is critical for parasite survival, infection, and cytopathogenicity. Despite the importance of surface proteins in parasite adherence, there has been no systematic investigation of them for this parasite. This project compares the membrane proteome of six strains; three that are highly adherent to vaginal epithelial cells and three that are not.

Methods Used: The surface proteins of the parasite were biotinylated followed by protein purification on a streptavidin resin and relative quantification of corresponding tryptic peptides by mass spectrometry. Specific proteins identified were analyzed by BLAST analyses. The subcellular localization of the proteins expressed in the parasite was determined by IFA and secretion and gain of function assays were performed.

Summary of Results: Of the 438 proteins identified, two were significantly differentially expressed between adherent and non-adherent strains. Genome analysis of these two hypothetical proteins revealed a family of about a hundred proteins but only these two were differentially expressed, suggesting a possible role in pathogenesis. Although no clear homology with previously described proteins was detected, BLAST search hits include biofilm-adhesion like proteins and a Candida adhesion protein. By IFA, both proteins exhibited Golgi and punctate vesicle-like staining inside the cell, indicating they could be secreted. Western blot analysis of parasite culture supernatant confirmed secretion of both proteins and validated their presence in the proteome analysis.

Conclusions: Transfection of these two proteins into a non-adherent strain increased attachment to vaginal epithelial cells three fold. These data indicate that the two proteins identified in this study play a role in adhesion and thus may participate in pathogenesis. Further research into this family of proteins may provide new insights into the host-pathogen interactions of T. vaginalis infections.

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THE ROLE OF BOPA AND BOPB IN BRUCELLA SPP PATHOGENESIS
V. Alturi1,2, AB. den Hartigh1, Y. Sun2, M. de Jong2, R. Tsolis1 UC Davis, CA and University of California, Davis, Davis, CA

Purpose of Study: The type IV secretion system (T4SS), encoded by the virB genes, is essential for Brucella spp survival in macrophages and persistence within the reticuloendothelial system (RES) of the host. Secreted effector proteins of the T4SS have only recently been identified. The goal of our studies is to determine how these effectors contribute to intracellular survival and persistence of Brucella in the host. Here we report the initial characterization of two of these proteins, BopA and BopB. Both BopA and BopB are similar at the protein level to the Pseudomonas syringae type III secretion system effector HopAN1, which reduces the plant hypersensitive response to P. syringae infection.

Methods Used: We construct a Brucella melitensis bopA mutant to determine if Brucella survival or persistence in the host is partially dependent on BopA. We also use a calmodulin dependent adenylate cyclase-Bop fusion protein assay to learn the requirements for Bop translocation into host cells.
Summary of Results: We showed that the mutant is attenuated for growth in J774 cells, a murine macrophage cell line. We also showed evidence that BopA, and possibly secreted by wild-type Brucella, is a virulence factor. BopA production enhanced the survival of B. melitensis in a macrophage line, possibly by interacting with host proteins after being translocated into host cells. The exact function of BopA is still unknown and future studies will focus on determining that function.

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THE EVOLUTION OF HEPATITIS C VIRUS INNER IMMUNE EVASION

PS. Pang1, PJ. Planet2, EA. Pham1, JS. Glenn1,3 1Stanford University, Stanford, CA; 2Columbia University, New York, NY and 3VA Medical Center, Palo Alto, CA.

Purpose of Study: Patients chronically infected with hepatitis C virus (HCV) require significantly different durations of therapy and achieve substantially different sustained virologic response rates to interferon-based therapies depending on the HCV genotype with which they are infected. One possible explanation for these variable response rates is that, over the centuries that HCV has exclusively infected the human host, it has accumulated adaptive mutations that confer increasing resistance to the human immune system. Given that interferon therapy functions by triggering an immune response, we hypothesize that clinical response rates are a reflection of viral evolutionary adaptations.

Methods Used: We have performed the first phylogenomic analysis to include all available full-length HCV genomic sequences (n = 345). Clinical outcome data was then mapped onto this new tree. Ancestral protein sequence reconstruction was subsequently used to identify loci within the HCV genome that correlate with clinical outcome. Site-directed mutagenesis of these loci in a model virus is being used to characterize the role of these loci.

Summary of Results: We have established for the first time the relative evolutionary ages of the major HCV genotypes. The resultant tree also reveals a correlation between genotype-specific responses to therapy and respective genotype age. 55 loci within the HCV genome that correlate with clinical outcome have been identified. These loci include the previously identified PKR inhibitory regions of E2 and NS5A, leading us to believe that our evolutionary strategy is able to identify critical interactions between HCV and the innate immune response. To date, we have generated a series of mutations at these loci, in an attempt to enhance the ability of a model HCV genotype to resist interferon treatment. Preliminary data indicates that replication is preserved in these mutants, despite the fact that they alter residues absolutely conserved in all HCV genotype 2 viruses.

Conclusions: Our evolutionary analysis suggests that immune selection was a significant driving force in the divergence of the major HCV genotypes. This provides a systematic framework by which to explore the molecular nature of non-responsiveness to clinical treatment for HCV.

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TYPE VI SECRETION IN BURKHOLDERIA THAILANDENSIS: REGULATION OF A VIRULENCE LOCUS AND DISCOVERY OF A SECRETED PROTEIN

B. Ohlson, J. Mougous 1

Purpose of Study: Bacterial secretion systems have long been implicated as a virulence mechanism against other organisms. Six conserved secretion systems have at present been detected, most recently, the type VI secretion system (T6SS). However, due to its relatively recent characterization, little is known about the T6SS secretome. The discovery of three novel pairs of T6SS effector proteins, a bioinformatics screen can be used to identify potential substrates of this system. By identifying common properties to these effectors, a bioinformatics screen can be used to identify potential substrates in Burkholderia thailandensis (BT). BT has near sequence homology to Burkholderia pseudomallei (BP), but is significantly less virulent. As the causative organism of melioidosis and a potential bio-terror threat, BP can be studied by working with BT as a safer surrogate. Consequently, recent work by Schwarz et al. has demonstrated that a deletion of a single T6SS locus in BT results in a complete loss of virulence.

Methods Used: To screen the BT genome in silico, a set of protein characteristics were adapted from the known Pseudomonas aeruginosa effector protein. A list of protein pairs resulted from the search of BT. To screen the pairs, molecular cloning techniques were employed to create expression vectors. Following transformation of the vectors into BT, secretion was monitored via Western blot analysis.

Summary of Results: We demonstrate that the previously identified virulence locus in BT is regulated by a two-component regulatory system, virAG. From our genomic screen, two pairs of proteins, a secreted pair and a toxin-antitoxin system were also identified. The secreted protein was verified in various BT T6SS knockout mutants. The toxin-antitoxin system actively kills both BT and E. coli SM10 cells when expressed ectopically. An expansion of the in silico analysis to other T6SS-containing organisms has also resulted in the identification of other potential effector proteins.

Conclusions: We demonstrated a simple, elegant model of screening bacterial genomes for the presence of T6SS effector proteins. Consequently, we discovered an effector protein in BT, a toxin-antitoxin system, and have established the role of virAG in regulation of a single locus.

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REVERSE ENGINEERING OF NATURAL INFECTION REVEALS A MEANS TO PHENOCPY VIRAL IMMUNE RESPONSES USING NON-MICROBIAL VACCINES

JS. Kurche, R. Kedl

Purpose of Study: Potent, safe, non-microbial vaccines could be used to prevent opportunistic infections in immunocompromised patients or promote prophylactic or therapeutic tumor immunity. In this study, we attempted to reverse engineer CD4+ and CD8+ T cell responses to vaccinia virus in order to realize this promise.

Methods Used: We compared infection with recombinant vaccinia virus expressing the CD4+ T cell epitope 2W1S to immunization of antigen with Toll-like receptor (TLR) agonists and a CD40 agonist in 4-8 week-old C57BL/6 mice. Under some conditions, mice were given blocking antibodies to tumor-necrosis superfamily member (TNFSF) ligands CD70, OX40L, 41BBL, and CD40L. We used antigen-specific MHC tetramers and intra-cellular cytokine staining to quantify CD4+ and CD8+ T cell responses.

Summary of Results: We found that CD40-CD40L interactions are important for primary T cell responses to vaccinia. Disparities in the kinetics of antigen presentation or those elicited by vaccinia. However, vaccinia because: 1) CD4+ T cells induced by TLR/CD40 were functionally superior to vaccinia-elicited CD4+ T cells, and 2) CD8+ T cells elicited by TLR/CD40 had lower expression of the senescence marker KLRG1 than those elicited by vaccinia. Disparities in the kinetics of antigen presentation or adjacent stimuli may play an important role in these differences. This research is a major step toward developing safe, potent, non-microbial vaccines.

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PANDEMIC (H1N1) 2009 INFLUENZA A IN THE CENTRAL VALLEY: A REVIEW OF PEDIATRIC CASES TREATED AT A TERTIARY CHILDREN’S HOSPITAL

K. Umapathy, N. Banh, G. Pullen, D. Pugatch Children’s Hospital Central Valley, Fresno, CA.

Purpose of Study: In April 2009, the CDC reported the first two human cases of Pandemic Influenza A (H1N1) in the United States. By June 11, 2009 the WHO raised the world pandemic alert to phase 6. This study...
describes the seasonal incidence, clinical features and outcomes of children with 2009 H1N1 Influenza treated at a tertiary children’s hospital in Madera, CA during the early phase of the H1N1 pandemic. **Methods Used:** We conducted a retrospective chart review of 71 patients treated at Children’s Hospital Central California. All children with confirmed or probable Pandemic H1N1 infection between May 1, 2009 and September 3, 2009 were included. Patients were identified by the hospital infection control department through routine surveillance. All patients had respiratory specimens tested for Pandemic H1N1 by the Fresno County Health Department via reverse transcriptase polymerase chain reaction. Data was gathered from the Pandemic H1N1 state reporting forms as well as medical record review. **Summary of Results:** Of the 71 cases reviewed, 60% are confirmed pandemic H1N1, 40% are probable. The study population was 73% Hispanic, 61% male; mean age of 6.5 years old. The incidence of infection is shown in table 1. Of the 71 cases, 34% were seen in the emergency department and discharged home, 51% required inpatient admission, and 15% required PICU care. Predominant symptoms at presentation were fever (92%), cough (79%), rhinorrhea (41%), nausea/vomiting (39%), dyspnea (32%), sore throat (23%), and diarrhea (13%). The most common predisposing conditions were chronic pulmonary disease (32%), prematurity (17%), neuromuscular disease (16%), use of immunosuppressive medication (16%) and metabolic disorder (13%). Tamiflu was prescribed for 66% of patients. The most prevalent complication was pneumonia (28%), followed by sepsis (7%), and ARDS (7%). Seven patients were mechanically ventilated (10%), and 2 died (3%). **Conclusions:** Little is known about the burden of disease caused by H1N1 especially in children. Active influenza surveillance will provide valuable clinical data about this novel virus and help us best target prevention and treatment measures.

**TABLE 1**

<table>
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<th>MONTH (2009)</th>
<th>MAY</th>
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<th>JULY</th>
<th>AUG</th>
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<td>24</td>
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</table>

*Data collection still in progress.

**Session: Infectious Diseases**

**CHEMICALLY SYNTHESIZED PEPTIDES AND PEPTOIDS AFFECT HERPES SIMPLEX VIRUS - TYPE 1 ENTRY IN CELL CULTURE**

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**Purpose of Study:** Herpesvirus causes significant health problem in the United States. The herpesvirus has the ability to infect a variety of tissues and lay dormant for many years and can cause many different ailments including encephalitis and corneal blindness. Herpes simplex virus type-1 (HSV-1) entry involves the initial attachment of the virus to cell surface heparan sulfate (HS) and subsequent membrane fusion. According to the current model of HSV-1 entry, viral envelope glycoprotein B (gB) mediates the initial contact with host cell surface HS. After attachment gB along with gD, gH/gL allow the virus to bind with cellular receptors (nectin-1, HVEM or 3-OST-F3) for membrane fusion. Because HSV is involved in both viral entry and spread it represent an attractive target for therapeutic development. Various peptides and peptoids (peptide like molecules with side chains attached to nitrogen instead of carbon) characterized for their ability to bind HS were tested against HSV-1 entry in cell culture model.

**Methods Used:** Various peptides and peptoids (peptide like molecules with side chains attached to nitrogen instead of carbon) characterized for their ability to bind HSV were tested against HSV-1 entry in cell culture model. HeLa cells were pre-incubated with peptides/peptoids at various concentrations followed by infection with reporter HSV-1 virions. The binding of these virions were tested using a spectrophotometer.

**Summary of Results:** Infected cells pre-incubated with peptides or peptoids shows decreased absorbance as compared to controls. This data provides a preliminary dosage response curve that provides evidence that peptides and peptoids have the ability to block HSV-1 entry via HS interference, thus reinforcing the significance of HS in viral infection.

**Conclusions:** The results reinforce the significance of HS in viral infection, and enlighten the possibility of developing drug therapeutics from peptides and peptoids against Herpes. Continued research will be needed to provide further insight into the specific amino acid residues and mechanisms that block HSV-1 heparan sulfate mediated entry and spread.

**Session: Infectious Diseases**

**CALCIUM OXALATE CRYSTALS DECODE THE PULMONARY RHIZOPUZZLE IN A PULMONARY ABSCESS**

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**Case Report:** The patient is a 69 year old male admitted for pneumonia, who developed a necrotizing pulmonary abscess. Tracheobronchial cultures initially grew out large sepsae hyphae suggestive of aspergillus. A left anterior thoracoplasty with pectoral and intercostal muscle flap was performed. Calcium oxalate crystals were present in the abscess fluid suggestive for an infection by Aspergillus niger. However, rib resection grew out aseptae hyphae suggestive of a zygomycete rhizopus microsporus, which was also confirmed by culture. Discussion: Muromycosis, a devastating fungal infection that often cause necrotizing abscesses of the sinuses and brain in rhinoenecrotic manifestations, can sometimes cause pulmonary infections in immunocompromised individuals. Rarely do these zygomycetes produce calcium oxalate crystals, which are essentially pathognomonic for necrotizing aspergillosis, particularly aspergillus niger. There have only been 3 documented cases of pulmonary mucormycosis with evidence of calcium oxalate crystals, two of which were in patients with concomitant oxalosis. This documented case of pulmonary mucormycosis, emphasizes that calcium oxalate crystals can be found in patients with fungal infections other than aspergillus.
a score of 3 representing the flattest philtrum and most thin vermilion border of the upper lip and a score of 1 representing the most prominent philtral column and upper lip morphology. Recently we have developed a lip/philtrum guide for the mixed race population of South Africa (SA), the population with the highest prevalence of FASD in the world. The purpose of this study was to compare the ease of use and specificity of the new SA lip/philtrum guide with the original Astley/Clarren guide produced from North American subjects.

Methods Used: To produce the guide, we analyzed 400 photographs of SA children of mixed racial background obtained during evaluation for a potential FASD. Once the guide was produced, we compared the Astley/Clarren guide with the new SA guide during the clinical evaluation of 1057 school children in the Western Cape Province for a potential FASD.

Summary of Results: For the overall sample the two guides produced a highly significant Pearson correlation coefficient of .793 for the philtrum and .781 for the vermilion. The mean score was 3.36 (±.023) for the Astley/Clarren guide and 3.43 (±.027) for the SA guide (t = -4.042, p < .0001, df = 1056), a significant difference in means, with the SA guide producing a higher mean. In rating both features, the result produced by the SA specific guide was significantly higher, therefore producing indicators of slightly greater hypoplasia.

Conclusions: The SA guide utilizes two innovations: 1.) racially specific SA facial morphology, and 2.) in addition to the frontal view, a novel view taken at a 45° angle for gauging the prominence of the philtral columns. The SA guide is a more sensitive tool for assessing children in the Western Cape population, specifically among the mixed race children who comprise 88% of school children.

Session: Morphogenesis and Malformations

ANALYSIS OF GENETIC VARIATION WITHIN FOXE1 AND RISK FOR OROFACIAL CLEFTS

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Purpose of Study: A previous genome wide linkage scan discovered a novel locus for cleft lip with or without cleft palate at 9q22-q33. To identify a gene of interest within this region, Moreno et al. used a frequentative and complementary fine mapping strategy. They initially identified several candidate genes (PTCH, FOXE1, FGID3, TGFB1, ZNF189, and GABABR2) and screened them for alterations, revealing 24 new variants. Additional localized hybridization studies on mouse tissue samples taken during the formation of the palate showed FOXE1 expression in the epithelia of the fusing palatal processes. Significant SNP and haplotype association signals (p = 1.45E-08) clustered near FOXE1, indicating that it is a major gene for cleft lip and/or palate.

Methods Used: DNA samples have been obtained from a population-based sample of 1,386 newborns from three counties in California from 1999–2004. Of these samples 523 are DNA samples from babies born with cleft lip and/or palate, and cleft palate alone (cases) and 863 controls (normal babies born without any defect). The method for SNP genotyping is based on the Sequenom MassARRAY platform. We genotyped these infants for 22 SNPs localized hybridization studies on mouse tissue samples taken during the formation of the palate showed FOXE1 expression in the epithelia of the fusing palatal processes. Significant SNP and haplotype association signals (p = 1.45E-08) clustered near FOXE1, indicating that it is a major gene for cleft lip and/or palate.

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Summary of Results: For the overall sample the two guides produced a highly significant Pearson correlation coefficient of .793 for the philtrum and .781 for the vermilion. The mean score was 3.36 (±.023) for the Astley/Clarren guide and 3.43 (±.027) for the SA guide (t = -4.042, p < .0001, df = 1056), a significant difference in means, with the SA guide producing a higher mean. In rating both features, the result produced by the SA specific guide was significantly higher, therefore producing indicators of slightly greater hypoplasia.

Conclusions: The SA guide utilizes two innovations: 1.) racially specific SA facial morphology, and 2.) in addition to the frontal view, a novel view taken at a 45° angle for gauging the prominence of the philtral columns. The SA guide is a more sensitive tool for assessing children in the Western Cape population, specifically among the mixed race children who comprise 88% of school children.

Session: Morphogenesis and Malformations

SPREDI AND NF1 EXON 22 ANALYSIS OF INDIVIDUALS WITH PIGMENTARY DYSPLASIA

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Purpose of Study: Syndromes of the Ras-MAPK pathway have phenotypic overlap. Cafe-au-lait macules are frequently seen in these disorders and are a cardinal feature of neurofibromatosis type 1 (NF1). Most NF1 individuals develop age-related tumorigenic manifestations, although a subset of individuals with a 3-bp in frame deletion in exon 22 (c.2970-2972delATT of NF1 [GenBank Reference NM_001042492.1]) have a milder phenotype with primarily pigmentary manifestations. Mutations in SPRED1 cause Legius syndrome presenting with multiple cafe-au-lait macules, although some individuals fulfill diagnostic criteria for NF1. We report the molecular findings of 3 individuals (a simplex case, and two familial cases) with pigmentary findings of NF1, who were thought to have Legius syndrome.

Methods Used: Bidirectional sequencing for the coding regions and intron/exon boundaries of SPRED1 and exon 22 of NF1 were performed. Single nucleotide extension and pyrosequencing were used for confirmation of the mosaic genotype.

Summary of Results: SPRED1 sequencing did not identify a specific mutation. Sequencing of exon 22 of NF1 showed a single base pair insertion c.2866-2867insA for the 4-year-old child, while his father showed 20% germline mosaicism. A 3-bp in frame deletion in exon 22 of NF1 (c.2970-2972delATT) was identified in the 11-year-old boy.

Conclusions: Mutations in NF1 and SPRED1 can result in autosomal dominant cafe-au-lait macules leading to clinical diagnostic complications which impact management. Genotype-phenotype correlations are not well established in NF1, but the milder phenotype of the child with the 3-bp deletion in exon 22 is consistent with other reports. However, in the familial case, the mild phenotype of the father is probably secondary to low-level germline mosaicism, while the mild phenotype of the child is likely age-related. Although the familial mutation is in exon 22, it is unlikely that this would result in a milder phenotype based on the predicted truncated protein product from the frameshift mutation. NF1 is frequently determined clinically, but pigmentary findings in younger individuals makes the NF1 diagnostic criteria unreliable in the absence of mutation analysis.

Session: Morphogenesis and Malformations

CORONARY ARTERY FISTULAS IN INFANTS LESS THAN 6 MONTHS OLD

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Purpose of Study: To review our experience with coronary artery fistulas (CAFs) in infants < 6 months detected by echocardiography. A CAF is a rare anomaly. Most reports in infancy are case reports of symptomatic patients requiring either surgical or cardiac catheterization intervention.

Methods Used: We reviewed our electronic database for the 5 years from 02-2004 to 02-2009. We identified 10 patients with a CAF < 6 months old out of 19,491 patients evaluated < 6 months old at the time of their first evaluation.

Summary of Results: Of the 10 patients, 7 (70%) were female. Of the 10, only 2 had additional congenital heart disease: 1 coarctation of the aorta, 1 small muscular VSD. Of the 10, 9 (90%) were small. Only 1 patient had a large CAF that required surgery. Of the 9 small CAFs, 6 were from the left coronary artery (LCA), and 3 were from the right (RCA). Of the 7 from the LCA, 4 entered the left atrium, and 3 entered the main pulmonary artery. Of the 2 from the RCA, 1 entered the right ventricle, and 1 entry site was not recorded. The large CAF was detected at birth and was from the LCA to the right atrium. The 9 small CAFs were detected incidentally during echocardiography for cardiac murmur evaluation and none was felt to be the cause of the murmur. The average age of detection of the small CAFs was 42 days (range 0–142 days). Electrocardiograms were normal in all 9 patients with small CAFs. Of the 9 small CAFs, 5 spontaneously closed by an average age of 4 months (range 3–7 months), 1 patient remains asymptomatic > 2 years, 1 is pending follow-up, and 2 were lost to follow-up.

Conclusions: Coronary artery fistulas are rare. This is the largest series of infants < 6 months of age with CAFs. In our series, the anomaly was more common in girls. Most CAFs were from the LCA. Infants with small CAFs were asymptomatic. The majority of small CAFs spontaneously closed.
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OCULOCEREBROCUTANEOUS (DELLEMAN) SYNDROME: A NEW CASE WITH PRENATAL FINDINGS AND DIFFERENTIAL DIAGNOSIS

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Case Report: Oculocerebrocutaneous syndrome (OCCS) is a sporadic disorder, first described by Dellemann and Oorthuys in 1981, characterized by cystic micro-abscess, anal atresia, dural aplasia, mid- and hindbrain malformations, atypically located skin tags, and mental retardation. The majority of patients are male. In order to increase awareness of this rare condition, we report a new female case of OCCS and discuss the differential diagnosis of related syndromes.

She was born at full term and noted to have microcephaly, a widely patent anterior fontanel, open posterior fontanel, skin tags on the right forehead and in the left naris, areas of aplasia cutis posterior and superior to the left ear, and a mass protruding from the right palpebral fissure. There was no history of neurodevelopmental disability or early death in the family. DNA ultrasonic at 23 weeks of gestation revealed a possible Dandy-Walker malformation and arachnoid cyst. Amniocentesis, FISH for common aneuploidies, and maternal serum screens were normal. Fetal brain MRI at 23 and 31 weeks showed ventriculomegaly, a posterior fossa cyst, an incomplete cerebellar vermis, small pons, periventricular transmantle dysplasia or gray matter heterotopia, and mineralization in the left cerebral hemisphere above the fourth ventricle. Gestation and birth proceeded without complications. Comparative genomic hybridization was normal. Repeat MRI and orbit CT showed a proptotic, cystic, anophthalmic right eye; the additional finding of an abnormal corpus callosum was noted. The cystic eye was enucleated and replaced with a silicone prosthesis in the first few days of life. The infant was discharged home shortly thereafter. OCCS has clinical features that overlap with several other conditions, including OA V spectrum, cleft palate, and mental retardation, and may be present on prenatal head imaging.

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MICRODUPlication 21q22.3 IN A CHILD WITH DEVELOPMENTAL DELAY, MARFAN SYNDROME AND 47,XXY KARYOTYPE

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Purpose of Study: Genomic microarrays are increasingly used in the diagnosis of developmental delay. Our case is the first to associate developmental delay, pervasive developmental disorder and hypotonia with 17q12 deletions, suggesting that the microdeletion is also associated with a wider ‘chromosomal’ phenotype.

Methods Used: We present a 3 year old male referred for developmental delay. The patient had delayed language and gross motor development. Height, weight and head circumference were greater than the 97th percentile, suggestive of an overgrowth syndrome. The karyotype was 47,XXY.

Summary of Results: Ophthalmologic assessment revealed dislocated lenses, and he had mild dilatation of the aortic root consistent with Marfan syndrome. DNA sequencing of the COL18A1 gene identified a nonsense mutation confirming this diagnosis. Because neither Marfan syndrome nor his 47,XXY karyotype appeared to fully explain the patient’s developmental delay, comparative genomic hybridization oligonucleotide array was performed thorough Signature Genomics. This revealed a microduplication at 21q22.3. The duplication is 259.2 Kb in size and contains at least 4 genes: POFUT2, ADAR81, LOC642852 and COL18A1. The microduplication is not within the Down Syndrome Critical Region. The same microduplication was identified in the mother by FISH; she has had minimal formal education but performs all household activities without assistance.

Conclusions: There is no information in the literature regarding microduplications of 21q22.3. Signature Genomics reports 12 patients with similar sized microduplications, 9 of which are inherited and 5 probands presented with developmental delay. Further analysis of these 12 patients is planned. We hypothesize that microduplication 21q22.3 contributes to developmental delay by overexpression of genes in this region. In this particular case, multiple factors likely contribute to produce his unusual phenotype.
unaffected monozygotic twins discordant for BWS. Patients with BWS have increased tumor risk compared to the general population. Emerging evidence suggests tumor risk is dependent upon clinical and molecular findings. The collective clinical literature has not reported tumors in the clinically unaffected twin.

Conclusions: The question of molecular testing and tumor surveillance in increased tumor risk compared to the general population. Emerging evidence has suggested that molecular findings in both blood and fibroblasts which may provide further insight into the current management controversy.

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STUDIES OF THE FREQUENCY OF ASSISTED REPRODUCTIVE TECHNOLOGY (ART) BIRTHS AND TWINNING IN PRADER-WILLI SYNDROME
J. Gold, C. Ruth, V. Kimonis
University of California, Irvine, Orange, CA.

Purpose of Study: To determine the association between ART and Prader-Willi Syndrome (PWS) by evaluating the frequencies of ART-births in three distinct molecular groups, compared with ART-births in the USA. To evaluate the natural frequency of twinning with and without ART in the PWS group.

Methods Used: Data was collected from surveys administered by: 1) The Prader-Willi Syndrome Association of the USA (PWSAUSA) 2) The University of California, Irvine, Orange, CA.

Summary of Results: Total number of PWS patients was 1,888. Total frequency of ART was 2.3% (44/1,888), 95% confidence interval (CI) 1.62%–2.98%. There was no statistical significant difference in the frequency of ART-conceived PWS patients, chi squared = 1.024 df = 0.599. However the difference in frequencies of the genetic subtypes in the ART-conceived patients and naturally conceived patients was statistically significant (p = 0.019). By comparison ART conceived patients were more likely to have UPD and imprinting center defects. This study also demonstrated that there was no increased frequency of natural twinning without ART in the PWS population above the U.S. population.

Conclusions: Studies have concluded that the effects of ART procedures may be restricted to imprinting disorders in which the maternal allele is hypomethylated or in which an imprinting defect accounts for a significant proportion of affected cases. This study shows a significant increase in UPD in PWS from ART-births suggesting an association with ART and UPD. At this time, the mechanisms causing this association have not been fully established. Growth factor genes are implicated in the growth disturbance of the fetus and the placenta. Certainly advanced maternal age is a cause of increased risk for trisomy. One of the mechanisms for maternal disomy is trisomic rescue. Women of increased age have a higher occurrence of maternal uniparental disomy and also have a higher likelihood of pursuing ART.

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FETAL ULTRASOUND AND PRENATAL MOLECULAR DIAGNOSIS ELUCIDATE THE PROGNOSIS OF PFEIFFER SYNDROME
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University of San Francisco, San Francisco, CA.

Case Report: Pfeiffer syndrome (PS), one of several related craniosynostoses, occurs in 1/100,000 births. The diagnosis is primarily based on the clinical findings of bilateral coronal craniosynostosis, midface hypoplasia, with broad thumbs and great toes. Due to phenotypic variability, the syndrome has been divided into three subtypes. Of the three, Type II is most severe, with associated cloverleaf skull, ptosis and CNS involvement. Previously diagnosed in the newborn, with improved prenatal imaging and molecular genetic diagnosis, PS can be diagnosed in utero. We present a case of PS that was identified on prenatal ultrasound at 34 3/7 weeks gestation by findings of polyhydramnios, a cloverleaf skull configuration, distortion of the intracranial anatomy with ventriculomegaly and frontal horn involvement, hypertelorism, marked orbital proptosis, mid face hypoplasia, short limbs with broad digits, an abnormality of the spine with disordered appearance suggesting segmentation abnormalities along with an abnormal spinal canal with possible diastematomyelia and fluid at the distal spinal canal without evidence of an open neural tube defect.

Not only can PS now be diagnosed prenatally, the phenotypic variability can also be correlated with specific FGFR1 and FGFR2 genetic mutations. In our case the specific mutation was associated with an especially severe phenotype. The ultrasonographic findings in conjunction with the molecular diagnosis allowed us to better inform the patient about the diagnosis and prognosis.

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A NEW FAMILY WITH CAMPTODACTYLY, ARTHROPATHY, COXA VARA, PERICARDITIS (CACP) SYNDROME AND A PREDOMINANTLY RHEUMATOLOGICAL PRESENTATION
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UCSF, San Francisco, CA.

Case Report: We present three Yemenese siblings with a clinical diagnosis of Camptodactyly, Arthropathy, Coxa vara, Pericarditis (CACP) syndrome. The siblings presented with camptodactyly of the fingers observed within days of birth, which partially resolved with physical therapy. The siblings then developed progressive polyarthritis, with gradually increasing joint swelling involving the elbows, wrists, knees and ankles. In two of the siblings, hips and shoulders were also involved. The polyarthritides was not associated with night sweats, fever, stiffness or the elevation of inflammatory markers. The siblings were initially treated as for idiopathic juvenile polyarthritides, but they had no response to NSAIDs and DMARDs. A synovial biopsy in one child revealed hypertropy of the synovium, with synovial fluid consistent with inflammation, infection or crystal accumulation. Imaging revealed coxa magna. No sibling has pericarditis, pleuritis or effusions. The parents are unaffected and have three additional healthy children. In the wider family, an aunt and a first cousin also have CACP. The parents are consanguineous, and both the grandparents and the great-grandmothers of the siblings are cousins. Sequencing of the PRG4 gene is pending.

CACP syndrome is an autosomal recessive condition caused by truncating mutations in the PRG4 gene, leading to absence of lubricin in the synovial fluid and causing progressive accumulation of non-inflammatory synovial fluid in the joint spaces. PRG4-/- mouse models also reveal similar features of non-inflammatory polyarthritis, with articular cartilage destruction and marked synovial cell overgrowth. It is not clear why CACP patients develop pleural and/or pericardial hypertrophy and effusions, but these are also characterized by gradual accumulation of fluid. These siblings presented with a non-remitting polyarthritides with minimal camptodactyly, showing that the phenotype of this condition can be largely confined to joint disease. Recognition of CACP as one of the differential diagnoses of childhood arthritis is very important for appropriate management, because of the poor response of these patients to standard treatments.

Neonatology – General II Concurrent Session 1:30 PM Friday, January 29, 2010

Session: Neonatology - General II 285
SERIAL B-TYPE NATRIURETIC PEPTIDE LEVELS AND CHANGE IN PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS
S. Chen, R. Clyman, T. Tacy
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Purpose of Study: Patent ductus arteriosus (PDA) is a common condition among preterm infants. Echocardiogram is the gold standard for evaluating
Methods Used: This was a retrospective study of infants born between 24–32 weeks gestation and admitted into our intensive care nursery. A cardiologist blinded to clinical data reviewed all echocardiograms and graded PDAs as closed, or if open, as small, moderate or large left-to-right shunts. Serial studies were recorded as increase, decrease or no change in PDA shunts, and changes in BNP levels over the same time interval were recorded as increase, decrease or no change. BNP levels from infants who were less than 5 days old, septic, hypotensive or with necrotizing enterocolitis, pulmonary hypertension, or elevated creatinine were excluded as these factors elevate BNP levels. We used Wilcoxon rank sum, chi-squared test, and logistic regression to examine the association between change in PDA and change in BNP. Sensitivities and specificities were calculated.

Summary of Results: 88 infants with 146 BNP-echo pairs (defined as a BNP level drawn on the same day as an echocardiogram) were included. 36 infants had serial BNP-echo pairs. We found that BNP levels were significantly associated with increases in PDA shunts, and vice versa, independent of gestation, birthweight, gender, and age (p < 0.01). A BNP increase of >15% (the limit of the assay’s accuracy) was 59% sensitive and 75% specific for detecting an increase in PDA shunt. A BNP decrease of >15% was 82% sensitive and 54% specific for detecting a decrease in PDA shunt.

Conclusions: We found that higher BNP levels were associated with larger PDA shunts and that changes in BNP levels were associated with changes in PDA shunts. Unfortunately, the clinical utility of using serial BNP levels to monitor changes in PDA shunts was limited by poor sensitivity and specificity. Serial BNP levels cannot replace echocardiograms for monitoring PDAs.

Session: Neonatology - General II

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BRAIN NATRIURETIC PEPTIDE AND ECHOCARDIOGRAPHIC INDICES OF LEFT VENTRICULAR PERFORMANCE IN VERY LOW BIRTH WEIGHT INFANTS

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Purpose of Study: Cardiac dysfunction occurs in Very Low Birth Infants (VLBWI). However prospective serial assessments of biochemical and echocardiographic indices of Left Ventricular (LV) function in VLBWI have been limited. In this study we describe serial two dimensional echocardiographic (2DE) indices, B-type Natriuretic peptide (BNP) and neonatal outcome in VLBWI.

Methods Used: We evaluated serial 2DE indices and BNP in VLBWI (BW < 1500g) on day 1, 2, 3, 7 and after birth. Using 2DE and color flow Doppler, we calculated left atrial/aortic ratio (LA/Ao), LV dimensions, LV volumes (Simpson method), ejection fraction (EF), cardiac output (CO), end systolic wall stress (LV-ess) and mean velocity circumferential fiber shortening (mVcf) normalized for heart rate and ess (mVcf/hr-ess). mVcf/hr-ess is a “load independent” measure of LV function. Samples for BNP were obtained at the approximate time of 2DE. Data for SNAPPE-II and serial Troponin will be analyzed in batch mode at conclusion of the studies. Data were analyzed using linear regression analysis and ANOVA for multiple group comparisons.

Summary of Results: To date, 17 VLBWI have been enrolled. (GA 25 1/7 wks (23 5/7–29 5/7 wks) [median (M) and interquartile range (IQR)]; BW 745g (622–886g), BNP = 301pg/ml (201–743), 746 (423–1265), 368(260–2168) and 177 (130–317) on day 1, 2, 3 and 7 respectively. Using published norms for VLBWI, BNP was increased in 5, 10, 6 and 1 infant/s on day 1,2,3 and 7 respectively. Two infants died before 28 days of life due to cardiorespiratory dysfunction. Seven infants were treated for significant PDA during the study. Mean mVcf/hr-ess was inversely related to LV-ess (r = -0.71, p < 0.001) and directly related to LV EF (r = -0.34, p < 0.001) and C.O (r = 0.41, p < 0.005). There was no correlation between the BNP level and 2DE indices of LV function.

Conclusions: The mVcf/hr-ess describes LV performance in VLBWI. Relatively high mVcf/hr at zero load (1.76 circs/sec) suggests increased contractile state sensitive to afterload. However increased BNP was unrelated to 2DE LV ejection indices. Increased BNP levels may reflect a functional “mismatch” of the capacity of the preterm LV with dynamic postnatal changes of preload and afterload.
placed under the somatic oxyensor in the flank but not on the forehead. The somatic oxyensor site was visually checked at 12 and 24 hours to determine if there was skin reaction to the probe using the International Contact Dermatitis Research Group Guidelines.

**Summary of Results:** So far, we have enrolled five preterm infants (mean birth weight 801 grams, mean gestational age 26 weeks) in the study. There was no skin reaction on any infant at 12 and at 24 hours after continuous monitoring with the INVOS cerebral somatic oximeter with a protective piece of tegaderm placed on the flank under the somatic oxyensor.

**Conclusions:** These preliminary data suggests that continuous monitoring with INVOS oximeter is safe in extremely preterm infants when tegaderm is utilized as a protective barrier under the somatic oxyensor to prevent skin reaction during the first postnatal day. The potential effect of tegaderm on NIRS signal quality is being investigated in a separate ongoing study.

**Session:** Neonatology - General II

**INDUCTION OF PANETH CELL ANTIMICROBIAL PRODUCTS IN EXPERIMENTAL NECROTIZING ENTEROCOLITIS**

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1UC Davis School of Medicine, Sacramento, CA; 2UC Davis School of Medicine, Davis, CA and 3University of Arizona, Tucson, AZ.

**Purpose of Study:** Necrotizing enterocolitis (NEC) is a common and devastating complication of prematurity with high morbidity and mortality. Abnormal host-microbe interactions at the intestinal mucosa may underlie disease pathogenesis. Antimicrobial peptides play a central role in mucosal immunity, but expression of many of these peptides is low in both premature infants and in newborn rat pups. We hypothesized that low expression of antimicrobial molecules contributes to susceptibility to NEC in the rat pup model of NEC. We further hypothesized that expression of intestinal antimicrobial peptides in rat pups with NEC would be augmented in an attempt to respond to insult.

**Methods Used:** Neonatal Sprague-Dawley rats were collected by Cesarean section 1 day before scheduled birth, hand fed with rat milk substitute formula, and exposed to asphyxia and cold stress twice daily (NEC, n = 8). Two control groups were also studied. Dam-fed stressed pups (DF-S, n = 8) remained with their dams following vaginal birth, but were exposed to the same asphyxia and cold stress as the NEC group. Dam-fed non-stressed pups (DF-NS, n = 6) remained with their dams following vaginal birth and were not exposed to asphyxia or cold stress. All pups were sacrificed at day 4. Intestinal tissues were collected for histology, immunohistochemistry and quantitative real-time PCR.

**Summary of Results:** mRNA expression by qRT-PCR was increased in the rat pups with NEC compared to the two control groups for the antimicrobial enzymes benzoyl homoserine and secretory phospholipase A2, the alpha defensin cryptdin 5, and the C-type lectins HIPPIPA1 and HIPPIPA3 (p < 0.05 for each molecule, one way ANOVA), but not for the alpha defensin cryptdin 6 or for the housekeeping gene GAPDH.

**Conclusions:** We have previously shown that expression of intestinal antimicrobial peptides is low in the young rat pup and increases exponentially with development. Here we demonstrate that expression of several intestinal antimicrobial molecules is induced in NEC. These results are similar to observations in premature infants with NEC and may represent an attempt to respond to insult. Intestinal antimicrobial molecules may play an important role in the defense against NEC.

**Session:** Neonatology - General II

**LACTOBACILLUS FEEDING INCREASES CD8AA+ INTESTINAL INTRINSC CELLS IN THE INTESTINE OF SUCKLING MICE**

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**Purpose of Study:** Introduction: Intestinal intraepithelial lymphocytes (IEL) are a unique subset of mostly CD8+ T cells. CD8+ T cells expressing CD8 as an alpha alpha (CD8a) homodimer secrete predominantly anti-inflammatory cytokines which play a role in the maintenance of tolerance, compared to T cells expressing CD8 as an alpha beta heterodimer (CD8ab). which secrete mostly pro-inflammatory cytokines important in host defense. The paucity of CD8aa+ IEL in the intestine of neonatal mice immediately after birth may result in exaggerated inflammatory responses to microbial infection in the intestine perhaps contributing to the development of diseases.

Our objective was to determine whether early feeding of suckling mice with lactobacillus GG (LGG) resulted in an earlier increase in CD8aa+ regulatory T cells in neonatal mice. Objective: To determine whether early feeding of suckling mice with lactobacillus GG results in an earlier increase in CD8aa+ regulatory T cells in neonatal mice.

**Methods Used:** Lactobacillus GG (LGG) was administered to suckling neonatal mice by OG intubation once on day 3 of life. The mice were allowed to suckle normally before and after LGG administration until the termination of the study. IEL were isolated at weekly intervals from cohorts of experimental and control mice. The expression of CD8 isoform usage was determined by FACS of cells stained with Buthromycin-conjugated mAb.

**Summary of Results:** We found that LGG feeding to suckling neonatal mice resulted in an earlier increase in CD8aa+ T cells in the small intestinal epithelium.

**Conclusions:** Probiotic supplementation may improve the balance of pro- and anti-inflammatory cytokines in the intestine by selective increases in CD8aa+ IEL. The increase in CD8aa+ IEL may contribute to the reduction of inflammatory immune responses such as those observed in NEC.

**Session:** Neonatology - General II

**NITRITE SUPPLEMENTATION FOR THE PREVENTION OF NECROTIZING ENTEROCOLITIS IN NEWBORN RAT PUPS**

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**Purpose of Study:** Necrotizing enterocolitis (NEC) is characterized by infection and necrosis of the bowel wall, occurs in approximately 12% of preterm infants, and has high rates of morbidity and mortality. While the exact etiology of NEC is unclear, intestinal ischemia is widely accepted as an initiating factor. Nitric oxide (NO) is protective in the normal GI tract by increasing blood flow, thickening the mucous lining, and killing bacteria. NO is produced from ingested nitrate in the stomach by a non-enzymatic reaction. The role of ingested nitrate (NO2−) in the etiology of NEC has not been studied. This study tests the hypothesis that supplemental oral nitrate would protect against the development of necrotizing enterocolitis.

**Methods Used:** Sprague-Dawley rat pups were delivered twelve hours before term by Cesarian-sections. The pups were separated from their mothers and housed in a temperature- and humidity-controlled incubator. Pups were gavage-fed 0.2 ml (approximately 300 cal/kg/day) with Similar Special Care8 admixed with a dose of NO2− (0 μM, 30 μM, or 300 μM) five times daily and subjected to hypoxia (5% O2, 95% N2) for seven minutes twice daily. Ten percent of the pups delivered were placed with a foster dam, allowed to breast feed ad libitum and not subjected to hypoxia. Ileal and jejunal sections were scored by a blinded pathologist for signs of NEC. Animals with histological scores ≥2 were considered to have NEC.

**Summary of Results:** At this time of writing we have studied eighty pups (nine litters), yet only one experiment has been done with NO2− supplementation. In the twenty seven dam-fed control pups, the gut histology remained normal. Of the thirty-seven pups that received no NO2−, 97% developed NEC. Of the six pups that received 30 μM NO2−, 67% developed NEC. Of the five pups that received 300 μM NO2−, 20% developed NEC.

**Conclusions:** Based on these preliminary results nitrate appears to be protective against the development of NEC in rat pups. Further studies are under way to confirm this effect.

**Session:** Neonatology - General II

**THE EFFECTS OF DIFFERENT THAWING METHODS ON THE NUTRITIONAL PROPERTIES IN HUMAN MILK**

J. Treidl, G. Cheng, G. Gill University of Utah, Salt Lake City, UT.

**Purpose of Study:** Human milk is considered the ideal feeding for both preterm and term infants. For feeding the hospitalized preterm infant, the mother’s milk is expressed and frozen before use. Then the frozen milk is thawed and fed to the infant. The effects of different thawing methods on thawing mice with lactobacillus GG results in an earlier increase in CD8aa+ regulatory T cells in neonatal mice.

Objective: To determine whether early feeding of suckling mice with lactobacillus GG results in an earlier increase in CD8aa+ regulatory T cells in neonatal mice.

**Methods Used:** Lactobacillus GG (LGG) was administered to suckling neonatal mice by OG intubation once on day 3 of life. The mice were allowed to suckle normally before and after LGG administration until the termination of the study. IEL were isolated at weekly intervals from cohorts of experimental and control mice. The expression of CD8 isoform usage was determined by FACS of cells stained with Buthromycin-conjugated mAb.

**Summary of Results:** We found that LGG feeding to suckling neonatal mice resulted in an earlier increase in CD8aa+ T cells in the small intestinal epithelium.

**Conclusions:** Probiotic supplementation may improve the balance of pro- and anti-inflammatory cytokines in the intestine by selective increases in CD8aa+ IEL. The increase in CD8aa+ IEL may contribute to the reduction of inflammatory immune responses such as those observed in NEC.
Our findings of increased morbidity and length of stay are consistent with earlier reports on late preterm infants. Efforts to decrease late preterm infant morbidity are needed.

## Methods Used

**A retrospective cohort study of NICU admissions ≥34 weeks gestation for the period starting from January 1993 to December 2007 was done using our computerized database. Infants with congenital malformations or those admitted secondary to positive maternal HIV status were excluded. All infants of diabetic mothers were admitted to our NICU and monitored for 3 consecutive feedings with blood glucose measurements. Maternal factors and infant specific clinical data were abstracted and analyzed for differences between late preterm infants <37 weeks and term defined as ≥37 weeks using Two-sample Wilcoxon rank-sum (Mann-Whitney) to compare Late Preterm Infant morbidity at our institution in the past 14 years.**

## Summary of Results

The mean fat content was 6.0 ± 1.9 (RF), 5.9 ± 2.3 (RT), 4.9 ± 1.8 (HW), and 4.1 ± 1.8 % (MW), P < 0.001. The mean epidermal growth factor level was 1.25 ± 0.23 (RF), 1.21 ± 0.28 (RT), 1.26 ± 0.28 (HW), and 1.28 ± 0.36 pg/mL (MW). The mean antioxidant level was 1.35 ± 0.23 (RF), 1.21 ± 0.28 (RT), 1.26 ± 0.28 (HW), and 1.28 ± 0.36 pg/mL (MW). The mean antioxidant level was 8.3 ± 0.6 (RF), 8.2 ± 1.2 (RT), 7.9 ± 1.5 (HW), and 7.1 ± 1.1 nm/L (MW), P < 0.001.

## Conclusions

From our study, thawing at 4 degrees C had the least effects with microwaving having the most effects on human milk free fatty acids, fat content, and antioxidant levels. Regarding fat content, thawing in hot water yielded a reduced fat content similar to thawing by microwaving, approximately 1.1 % lower than the fat content of the room temperature and refrigerator thawing methods.

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**Session: Neonatology - General II**

**293 MORBIDITIES OF LATE PRETERM INFANTS BORN FROM 1993-2007 IN A TERTIARY CARE CENTER**

KK. Rezaie, KC. Bui, L. Barton, R. Ramanathan

**Purpose of Study:** To describe the population characteristic and trends of Late Preterm Infant morbidities at our institution in the past 14 years.

**Methods Used:** A retrospective cohort study of NICU admissions ≥34 weeks gestation for the period starting from January 1993 to December 2007 was done using our computerized database. Infants with congenital malformations or those admitted secondary to positive maternal HIV status were excluded. All infants of diabetic mothers were admitted to our NICU and monitored for 3 consecutive feedings with blood glucose measurements. Maternal factors and infant specific clinical data were abstracted and analyzed for differences between late preterm infants <37 weeks and term defined as ≥37 weeks using Two-sample Wilcoxon rank-sum (Mann-Whitney) to compare Late Preterm Infant morbidity at our institution in the past 14 years.

**Summary of Results:** Cesarean section accounted for 43% of late preterm deliveries and 36% of term deliveries. Twenty percent of 34 weeks gestation infants required mechanical ventilation for respiratory distress compared to 12% at 35 weeks and 8% at 36 weeks and beyond. The rate of neonatal sepsis and hypotension requiring vasopressor support was not different among groups. Meconium aspiration syndrome was present in 5.8% of term infants admitted to the NICU. The NICU length of stay increased with decreasing gestational age.

**Conclusions:** Our findings of increased morbidity and length of stay are consistent with earlier reports on late preterm infants. Efforts to decrease late preterm births should be given priority.

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**Session: Neonatology - General II**

**294 LIVER IGF-1 mRNA EXPRESSION IS DECREASED BY MECHANICAL VENTILATION OF PRETERM LAMBS**

CA. Blair, C. Amundsen, D. Metcalfe, MJ. McCoy, B. Beck, A. Whitworth, A. Smith, J. Alford, L. Dong, MJ. Dahl, L. Joss-Moore, L. Moyer-Mileur, DM. Null, BA. Yoder, RH. Lane, RA. McKnight, KH. Alberine

**Purpose of Study:** Neonatal chronic lung disease (CLD) is associated with poor postnatal growth. Growth is modulated by insulin-like growth factor-1 (IGF-1). Because serum concentration of IGF-1 is low in preterm infants with CLD and the liver is a source of IGF-1 in the serum, we measured IGF-1 and IGF-1 binding protein 3 (IGF-1 BP3) mRNA expression in the liver of chronically ventilated preterm lambs. We also measured signal transducers and activators of transcription 5b (STAT5b) because IGF-1 expression is mediated by STAT5b. We hypothesized that prolonged mechanical ventilation (MV) will lead to decreased IGF-1, IGF-1 BP3, and STAT5b gene expression in the liver of preterm (PT) lambs.

**Methods Used:** PT lambs (~131d gestation; term ~150d), treated with antenatal steroids and postnatal surfactant, were managed by MV or a variation of nasal CPAP (nasal high-frequency ventilation; positive outcome control) for 3 or 21d. Liver tissue was analyzed by quantitative real time RT-PCR (normalized for GAPDH) and immunoblot (STAT5b only; normalized by MemCode kit).

**Summary of Results:** Liver tissue from PT lambs managed by MV for 21d had significantly less IGF-1 mRNA expression (~90%; p < 0.05; n=4) compared to PT lambs managed with nasal CPAP for 21d. STAT-5b protein abundance, which mediates IGF-1 gene transcription, also was less (~50%; p < 0.05) in the 21d MV group. Although not significantly different, IGF-1 BP3 mRNA expression was ~50% lower in the 21d MV group. STAT5b mRNA expression was unaffected by ventilation mode at 21d. These differences in mRNA and protein abundance in the liver were partially mirrored at 3d of ventilation, although the differences were not statistically significant.

**Conclusions:** Ventilation mode affects liver expression of IGF-1 and its upstream mediator, STAT5b. Specifically, MV for 21d decreases liver IGF-1 mRNA expression and STAT5b protein abundance compared to nasal CPAP as the positive gold-standard because alveolar formation is nearly normal when preterm lambs are managed by nasal CPAP. We speculate that low IGF-1 and STAT5b in the liver of PT lambs managed by MV contributes to poor growth postnatally that is characteristic of neonatal CLD (HL62875, HL56401, HD41075, CHRC).

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**Session: Neonatology - General II**

**295 EXPERT MODELING IMPROVES THE RETENTION OF BEHAVIORAL SKILLS IN SIMULATION-BASED NEONATAL RESUSCITATION TRAINING**

D. Leonard1, H. Hackman1, G. Desandre2, K. Boyle3, J. Leflore4, A. Jodee1

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**Purpose of Study:** Despite the positive impact of the Neonatal Resuscitation Program (NRP) on neonatal outcome, many of the skills acquired in the traditional NRP training do not translate well to actual delivery room practice. Root causes analyses of infant death and disability have identified a lack of expertise in requisite behavioral skills contributing to poor outcome. The ideal training paradigm will decrease the amount of real-life experience required to attain expert behavioral skills. Exploring expertise may allow refinement of our educational strategies in resuscitation training and improve behavioral skill performance. Previously we reported an improved behavioral skill acquisition when novices underwent expert modeling compared to learner modeling. We retested these subjects 6 months after initial training to investigate how expert modeling impacts retention of behavioral skills.

**Methods Used:** 31 subjects underwent simulation-based neonatal resuscitation training; they were randomized to a control group (learner modeling) or experimental group (expert modeling). Six months later they returned for testing. Demographic information, including rotation through the NICU, how many deliveries and neonatal resuscitations they attended, and a subjective measure of confidence were collected. Participants individually led a
simulated resuscitation of an apparently stillborn baby with a confederate team of a neonatal nurse and a respiratory therapist. These simulations were videotaped; a blinded reviewer then scored the videos with a validated behavioral assessment tool (BAT). Mean scores were calculated and compared for each group using a two tailed t-test.

**Summary of Results:** There was no significant difference between the groups in age, gender, simulation experience, NICU experience, delivery room experience, resuscitation experience, or confidence. The experimental group (expert modeling) scored significantly higher in behavioral skills than the control group (p < 0.001).

**Conclusions:** The addition of expert modeling to simulation-based neonatal resuscitation training improves the retention of CRM-based behavioral skills.

**Session:** Neonatology - General II

**EXPERT MODELING IMPROVES THE RETENTION OF TECHNICAL SKILLS IN NEONATAL RESUSCITATION TRAINING**

D. Leonard¹, H. Hackman¹, K. Leaning¹, J. LeFlore², J. Anderson¹ ¹OHISU, Portland, OR and ²University of Texas at Arlington, Arlington, TX.

**Purpose of Study:** Evidence suggests current training in neonatal resuscitation is not transferring to the real environment. Video analysis of resuscitations shows that NRP guidelines are not followed more than 50% of the time. There is also evidence of decreased technical skill retention during a 2 year interval recommended for re-certification. Current literature on medical expertise suggests that modeling may facilitate the acquisition of expert technical skill sets. During observation, learners selectively take in information about performing; from these observations a mental image is created that provides a cognitive reference for the learner. Previously we reported an improvement in technical skill acquisition when novices underwent expert modeling compared to learner modeling. We retested these subjects 6 months after initial training to investigate how expert modeling impacts retention of technical skills.

**Methods Used:** 31 subjects underwent simulation-based neonatal resuscitation training; they were randomized to a control group (learner modeling) or experimental group (expert modeling). Six months later they returned for testing. Demographic information, including rotation through the NICU, how many deliveries and neonatal resuscitations they attended, and a subjective measure of confidence were collected. Participants individually led a simulated resuscitation of an apparently stillborn baby with a confederate team of a neonatal nurse and a respiratory therapist. These simulations were videotaped; a blinded reviewer then scored the videos with a validated delivery room technical skills assessment tool. Mean scores were calculated and compared for each group using a two tailed t-test.

**Summary of Results:** There were no differences in NICU experience, delivery experience, neonatal resuscitation experience, or confidence between the two groups. The group exposed to expert modeling scored significantly higher in the technical skills: control group 10.9 ± 4.9, expert modeling group 16.8 ± 6.1; p < 0.007.

**Conclusions:** The addition of expert modeling to simulation-based neonatal resuscitation training improves retention of technical skills over a 6 month period. This may be secondary to the creation of an expert cognitive reference during initial training after viewing an expert model.

**Session:** Neonatology - General II

**SKILL DEGRADATION VERSUS INEFFECTIVE TEACHING: DEVIATIONS FROM THE NEONATAL RESUSCITATION PROGRAM**

K. Townes McMann, D. Leonard, J. Anderson ¹OHISU, Portland, OR.

**Purpose of Study:** According to NRP, if a newborn is not breathing or has a heart rate less than 100 after the initial steps of suctioning, stimulation, positioning, and drying, providers should begin positive pressure ventilation (PPV). During PPV, providers should “take corrective action when heart rate is not rising and chest is not moving.” Video analyses of resuscitations performed by skilled providers show frequent deviations from NRP guidelines, including failure to assess ventilation and take corrective action. This may be attributable to skill degradation; which would suggest that immediately following training, providers would be more likely to remember this step in neonatal resuscitation. The purpose of this study is to determine if skills needed to evaluate the delivery of effective PPV are acquired in NRP training.

**Methods Used:** 41 interns underwent a comprehensive, simulation-based NRP course. Each intern then led the resuscitation of a stillborn neonate in the simulator. The scenario was scripted and standardized. Performance was videotaped and debriefed. 39 videos were available for review. Videos were evaluated to determine if the provider took corrective action when the heart rate did not improve: reapply mask, lift jaw forward, reposition head, check securions, open mouth, increase pressure if necessary.

**Summary of Results:** 8/39 (21%) of participants repositioned the head after positive pressure ventilation was implemented and there was no observed rise in heart rate.

**Conclusions:** Effective ventilation is the key to successfully resuscitating most compromised newborns; we have yet to determine how best to teach the cognitive and technical skills needed to evaluate the delivery of effective PPV. When we teach life-saving skills, we have to be guided by the outcome of our interventions. The lack of adherence to this step in the algorithm deserves further investigation; this may not be secondary to degrading of skill but rather in how we are teaching the cognitive and technical aspects of this step. This study highlights the importance of designing curricula to address specific, measurable learning objectives, using appropriate educational strategies to achieve those objectives, and measuring the effectiveness of our instruction.

**Session:** Neonatology - General II

**DISASTER PLANNING - TRIAGING RESOURCE ALLOCATION IN NEONATOLOGY**

R.S. Cohen¹, B. Murphy¹, T. Ahern², A. Hackel³ ¹Stanford Univ, Palo Alto, CA; ²Stanford Univ, Palo Alto, CA and ³USC Keck School of Medicine, Los Angeles, CA.

**Purpose of Study:** To develop a tool for rapid triage of Newborn Intensive Care Unit (NICU) patients in a regional disaster requiring the evacuation of 1 or more hospitals.

**Methods Used:** Review of the literature and tabletop exercises.

**Summary of Results:** NICUs need to be prepared for possible evacuation and transport of large numbers of NICU patients if 1 or more hospitals in a region are affected by a major disaster. Previously described methods for triage were not designed for this purpose, and do not apply to hospitalized neonates. We therefore developed and trialed a simple, resource-based system for rapid assignment of NICU patients to color-coded triage groups: “Triaging Resource Allocation In Neonatology” (figure TRAIN). This system can be applied readily during routine NICU rounds. It is designed for use on a regional basis as a standardized triage method for NICU patients. Assigning patients to resource-based triage groups as part of pre-planning facilitates rapid emergency evacuation. It also streamlines communication of patient needs and status, obviating the need for patient-by-patient evaluation during a disaster. Patients triaged “Blue” could be discharged rapidly. Those in “Black” could not be moved. Patients in “Red”, “Yellow”, or “Green” are easily prioritized for transport to NICUs with appropriate available resources.

**Conclusions:** A resource-based triage method, such as the one proposed, could be helpful when applied to all NICUs in a region, should a disaster require evacuating 1 or more NICU. We are putting TRAIN into use in NICUs in this region as part of our pre-planning strategy, and recommend other regions consider doing the same.
Session: Nephrology and Hypertension 299
REGRESSION OF ESTABLISHED LESIONS OF TYPE 2 DIABETIC NEPHROPATHY USING A PEPTIDE-DRUG
SB. Nicholas1, T. Cho1, J. Kim1, H. Kim2, N. Vaziri2 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2University of California at Irvine, Irvine, CA.
Purpose of Study: Diabetic Nephropathy (DN) accounts for ~50% of cases of end stage renal disease in the United States and consumes a large portion of our healthcare dollars. Indeed, therapeutic options, and an understanding of the mechanisms involved in causing regression of established glomerular lesions of DN are lacking. We prevented early DN lesions in type 2 genetically diabetic db/db mice by blocking the function of the fibronectin α5β1-integrin receptor with the non-immunogenic Arginine-Glycine-Glycine-Aspartate (RGD)-active vs. an RGE-control peptide. In mesangial cells, the active peptide activated anionis, and inhibited integrin-mediated ERK/MAPK both in vitro and in vivo, and ameliorated glomerular fibronectin, collagen I and IV and α5β1-integrin protein in vivo after 12 weeks. In this study, we demonstrated the effect of α5β1-integrin blockade using the RGD-peptide drug on established lesions of type 2 DN.
Methods Used: Aged diabetic db/db and non-diabetic db/m mice (age 21 weeks) with advanced lesions of DN were untreated or treated with 2 doses of active and control peptide-drug (3600µg/kg and 4800µg/kg) for 4 weeks. Initial and final plasma glucose and tail-cuff blood pressures were measured. Mice were placed in metabolic cages for 24h urine collection for albumin to creatinine (ACR) determination, kidneys were sectioned and protein was isolated for western blot analyses.
Summary of Results: There was a significant increase in plasma glucose and urine volumes in diabetic vs. non-diabetic mice (p<0.05). Aged diabetic db/db vs. non-diabetic db/m mice treated with active peptide-drug demonstrated a dose-dependent reduction in ACR, glomerular matrix accumulation, extracellular matrix proteins, markers of fibrosis, and oxidative stress signal transduction (p<0.05).
Conclusions: RGD-containing peptide-drug blockade of α5β1-integrin function in late stages of type 2 DN may potentially reverse overt proteinuria and reduce the risk of progression to ESRD.

Session: Nephrology and Hypertension 300
DEVELOPMENT OF A NOVEL RGD-VAULT NANOCAPSULE FOR DRUG DELIVERY AND INVESTIGATION OF SIGNALING MECHANISMS IN TYPE 2 DIABETIC NEPHROPATHY
TA. Brown-Bryan1,2, T. Cho1, J. Kim2, K. Norris3, V. Kickhoefer3, L. Rome3, SB. Nicholas1,2 1Charles Drew University, Los Angeles, CA; 2UCLA, Los Angeles, CA and 3UCLA, Los Angeles, CA.
Purpose of Study: Innovative therapies for diabetic nephropathy (DN), remain a major challenge. We identified a cyclized Arg-Gly-Asp (RGD)-containing peptide which prevented progression of early DN and caused regression of glomerular lesions in aged type 2 diabetic db/db mice. Albuminuria was reduced 50% and mesangial expansion decreased to non-diabetic db/m control levels. The peptide blocked α5β1-integrin-mediated primary mesangial cell (MC) adhesion to fibronectin (FN) ~50%. For specific targeting and efficient drug delivery, we designed a novel cyclized RGD-peptide with a free cysteine for packaging into vault nanoparticles, which are dynamic barrel-like structures in eukaryotic cells. Here, we investigate cell signaling, the in vivo effect of the cysteine-modified RGD-peptide with a free cysteine for packaging into vault nanoparticles, cysteine-modified and unmodified RGD-peptides blocked TGF-β, AKT, ERK/MAPK and STAT3 phosphorylation and ECM production, p<0.05. The modified RGD- vs. RGE-peptide normalized ACR in db/db mice, at doses 3 times lower than the unmodified RGD-peptide. The RGD-vault had a normal barrel-shape by EM.
Conclusions: Thus, the cysteine-modified RGD-peptide appears to greater potency than the unmodified RGD-peptide against adhesion of MC to FN, ECM production and early progression of DN. This may occur via activation of the AKT/STAT3 signaling cascade. The novel RGD-vaults may be a new class of non-immunogenic nano-drug delivery system with therapeutic potential in DN.

Session: Nephrology and Hypertension 301
INTERLEUKIN-33 (IL-33) IN CISPLATIN-INDUCED ACUTE KIDNEY INJURY (CISAKI)
C. Edelstein, A. Akcay, Q. Nguyen, Z. He, S. Faubel, A. Jani University of Colorado Denver, Aurora, CO.
Purpose of Study: We have demonstrated that caspase-1 is a mediator of CisAKI. Caspase-1 is activated in the “inflammasome”- the aim of the study was to determine the role of other inflammasome-activated proteins (IL-33, caspase-5) in CisAKI.
Methods Used: Mice were injected with Cisplatin (Cis) 25mg/kg and sacrificed on days 1, 2 and 3. BUN and Scr were elevated on Day 3.
Summary of Results: Caspase-5 activity (nmol/min/mg)was 11.2 in vehicle-treated (V) and 29.2 in CisAKI (P<0.01 vs. V, n=3). On immunoblot there was a three-fold increase in caspase-5 (47kDa) after Cis on days 1, 2 and 3 vs. V (P<0.05, n=3), Serum IL-33 (pg/ml) after Cis was 0 on day 1, 371 on day 2 (P<0.05 vs. day 1, n=4) and 59 on day 3 (P<0.05 vs. day 1, n=4). Whole kidney IL-33 (pg/mg) was 289 in V, 355 on day 1 after Cis, 407 on day 2 (P<0.05 vs. V) and 553 on day 3 (P<0.01 vs. V). On immunoblot of whole kidney there was a five-fold increase in IL-33 (22kDa) after Cis on days 1, 2 and 3 vs. V (P<0.05, n=3). To determine the source of IL-33 in the kidney, IF was performed. IL-33 was abundant in the endothelium in large and small blood vessels in both vehicle-treated and CisAKI. To determine if Cis induces IL-33 production in the endothelium, microvascular endothelial cells, treated with 10µM Cis, showed a two-fold increase in IL-33 protein vs. vehicle (p<0.05, n=4) on immunoblot analysis. We have previously demonstrated that there is macrophage infiltration in the kidney in CisAKI. On immunoblot analysis IL-33 was abundantly present in mouse peritoneal macrophages and RAW264.7 macrophages. IL-33 is an “alarm” that is released from injured cells to alert the immune system. IL-33 converts T helper 1 (Th1) to Th2 cells, Cis induces IL-33 and caspase-5 in kidneys on day 2 that precedes the increase in BUN and Scr on day 3, 3) an increase in IL-33 in endothelial cells. In conclusion, the function of IL-33 and other “inflammasomes” proteins in CisAKI merits further study.

Session: Nephrology and Hypertension 302
RAB26 FUNCTIONS IN THE RENAL EPITHELIAL PRIMARY CILIUM
BR. Peterson, H. Ward, A. Wandinger-Ness The University of New Mexico School of Medicine, Albuquerque, NM.
Purpose of Study: Primary cilia are specialized sensory structures that allow cells to mediate downstream signals in response to their extracellular environment. Inherited diseases including autosomal dominant retinitis pigmentosa, Bardet-Biedl syndrome, and polycystic kidney disease are manifestations of dysfunctional primary cilia. Rab proteins are regulators of membrane trafficking and intracellular signaling, with demonstrated roles of Rab8 and Rab11 in the transport of proteins to the primary cilium.

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Session: Nephrology and Hypertension 304
SUCCESSFUL TREATMENT OF BK VIREMIA WITH CIPROFLOXACIN IN PEDIATRIC RENAL TRANSPLANT RECIPIENTS
RA. Zaman, E.W. Tsai, M.H. Malekzadeh, H. Cheam, R.B. Ettenger
Mead Johnson Children’s Hospital, UCLA, Los Angeles, CA.

Purpose of Study: BK virus nephropathy affects 5% of pediatric renal allograft patients (pts). It is associated with graft dysfunction in 50% of affected pts and graft failure in 25%. BK viremia (BKV) precedes BK nephropathy. Currently, there is no agreed upon standard treatment. We aimed to report the safety and efficacy of ciprofloxacin (cipro) therapy on BKV in pediatric renal transplant pts.

Methods Used: We identified all cases of BKV and nephropathy in pediatric renal pts transplanted at Mattel Children’s Hospital, UCLA between January 2003 to September 2009. We followed BK quantitative PCR, renal biopsies, and side effects while on cipro treatment.

Summary of Results: Of 201 pediatric renal pts transplanted at our center, 10 developed BKV (incidence of 5%). Age at transplant ranged from 1–18 years old. 9 out of 10 of these pts had deceased donors. 7 out of 10 of these pts had induction therapy with daclizumab. PBts were maintained on steroid-based or steroid-free immunosuppression with tacrolimus and mycophenolate mofetil. Development of BKV ranged from 2–84 months post-transplant. 7 out of 10 of these pts developed BKV within the first year post-transplant. 4 out of 10 of these pts had acute graft rejection. 2 pts had BK nephropathy, and 1 pt had graft failure (due to noncompliance). Immunosuppression was decreased in 7 out of 10 pts. BKV in all of these pts decreased with cipro treatment. One patient had side effects of extended-spectrum beta-lactamases urosepsis and was switched to leflunomide. See Table.

Conclusions: In a case series of 10 pediatric renal transplant pts, we report successful reduction of BKV with cipro treatment with minimal side effects. No graft was lost due to BKV or nephropathy.

Characteristics of renal transplant pts developing BKV

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<th>Patient</th>
<th>Age at transplant (yr)</th>
<th>Sex</th>
<th>Treatment type</th>
<th>Induction</th>
<th>BK infection</th>
<th>Monitored post transplant</th>
<th>BK quantitative PCR (copies/mL)</th>
<th>BK nephropathy</th>
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Session: Nephrology and Hypertension 305
VITAMIN D INDUCES CELL DIFFERENTIATION BY DOWNREGULATING THE EXPRESSSION OF MEMBERS OF THE WNT SIGNALING PATHWAY IN MESENCHYMAL MULTIPOTENT CELLS
Jn. Arataza1, S. Sirad1, D. Vernet1, C. Norris1, 2 CDU, Los Angeles, CA; 1 UCL, Los Angeles, CA and 2 LA BioMed at Harbor-UCLA, Torrance, CA.

Purpose of Study: The VDR play an important role in the regulation of cell growth and cell fate. The Wnt signaling pathway is pivotal to gene expression, tissue development and controls cell renewal and lineage selection. We have previously shown that 1,25D induces the expression and nuclear translocation of VDR in our cell model limiting cell proliferation without increasing apoptosis. In this study we show that 1,25D promotes cell differentiation by down-regulating key family members of the Wnt signaling pathway potentially crucial mechanism in limiting CKD progression.

Methods Used: Cells primed with 5’-azacytidine (AZCT) were treated with and without 1,25D. Cell lineage markers were assessed by cytochemistry and PCR microarrays. The expression of genes related to the Wnt signaling pathway was analyzed by PCR microarrays. β-catenin and TCF4 expression was evaluated by ICC and western blot.

Summary of Results: Addition of 1,25D to the cell cultures induced an osteogenic cell lineage commitment characterized by increased expression of markers of osteoblastic differentiation such as: BMP1 (24h +2.45 and 4 days

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D1 (pression increases osteoblast differentiation and bone formation. Wnt family members such as frizzle receptors Fzd1 (Fzd5 (j2010 The American Federation for Medical Research loss disorders, CKD or various types of neoplasias.

A. Rassa 1,2, J. Lopez-Guisa 2, S. Collins 2, A. Eddy2

OBSTRUCTIVE NEPHROPATHY DECREASES THE PROGRESSION OF RENAL FIBROSIS IN

307 Session: Nephrology and Hypertension

308 ROLE OF IMPAIRED NRF2-KEAP1 PATHWAY IN CKD-INDUCED OXIDATIVE STRESS AND INFLAMMATION

ND. Vaziri, HJ. Kim University of California, Irvine, Orange, CA.

Purpose of Study: Oxidative stress and inflammation are constant features and major mediators of progression of chronic kidney disease (CKD). Nuclear factor E2-related factor-2 (Nrf2) confers protection against tissue injury by orchestrating antioxidant and detoxification responses to oxidative and electrophilic stress. While sources of oxidative stress and inflammation in the remnant kidney have been extensively characterized, the effect of CKD on Nrf2 activation and expression of its downstream gene products is unknown and was investigated.

Methods Used: Male Sprague-Dawley rats were subjected to 5/6 nephrectomy or sham operation and observed for 12 weeks. Kidneys were then harvested and Nrf2 activity and its downstream target gene products (antioxidant and phase II enzymes) were assessed. In addition, key factors involved in promoting inflammation and oxidative stress were studied.

Summary of Results: a confirmation of earlier studies the CRF rats exhibited increased lipid peroxidation, glutathione depletion, NF-kB activation, mononuclear cell infiltration and upregulation of MCP-1, NAD(P)H oxidase, cyclooxygenase-1 & 2, and 12-lipoxygenase in the remnant kidney pointing to oxidative stress and inflammation. Despite severe oxidative stress and inflammation, Nrf2 activity (nuclear translocation) was markedly reduced (~71%) whereas Nrf2 repressor, Keap1, was up-regulated (~96%) and products of Nrf2 target genes i.e. catalase (~22%), Mn-SOD (~15%), Cu/Zn-SOD (~32%), heme oxygenase-1 (~59%), NAD(P)H quinone oxidoreductase (~47%), glutamate-cysteine ligase catalytic subunit (~32%) were reduced in the remnant kidney.

Conclusions: Oxidative stress in the remnant kidney is compounded by a conspicuous impairment of Nrf2 activation and the corresponding antioxidant defense system.

Session: Nephrology and Hypertension

309 LOSS OF THE INTERSTITIAL PROTEIN VITRONECTIN DECREASES THE PROGRESSION OF RENAL FIBROSIS IN OBSTRUCTIVE NEPHIOPATHY

A. Rassa1,2, J. Lopez-Guia3, S. Collins2, A. Eddy2

University of Washington, Seattle, WA and 2Seattle Children’s Hospital and Research Institute, Seattle, WA.

Purpose of Study: Chronic kidney disease (CKD) is a major public health problem affecting approximately 11% of the US population and more than 50 million individuals worldwide. Several gene products of the thrombolytic cascade have been implicated in renal fibrosis. Plasminogen Activator Inhibitor-1 (PAI-1) and plasminogen are profibrotic. The urokinase Plasminogen Activator (uPA) has no effect on fibrotic outcome while its receptor (uPAR) attenuates fibrosis in the unilateral ureter obstruction (UDO) model of induced nephropathy. Both PAI-1 and uPAR bind the extracellular matrix glycoprotein Vitronectin (Vn) using two overlapping regions immediately adjacent to a single Arg-Gly-Asp sequence. The role of Vn in renal fibrosis has not been completely elucidated. The hypothesis of the present study is to examine the profibrotic effects of Vn in the UDO model on wild type (WT) and vitronectin knockout mice (Vn−/−).

Methods Used: Total renal collagen was measured after surgery at 7-, 14-, and 21-day intervals using a hydroxyproline assay and Picrosirius red collagen stain on sectioned kidneys. The relative expression of Vitronectin and Nephronecin (an ECM protein unique to mammalian kidneys and critical for development) were measured using semi-quantitative PCR (qPCR).

Summary of Results: The WT mice had significantly higher total collagen than the Vn−/− mice at 21 days (11.9% and 9.8%, respectively; P value = 0.035). Vitronectin expression was not detectable by qPCR at 21 days in both WT and Vn−/− mice. In contrast, Nephronecin was upregulated at 21 days in both WT and Vn−/− with respect to the 18s ribosomal gene.

Conclusions: The lack of Vitronectin expression in the WT cohort is most likely due to extensive damage to cells that produce Vn. The increased expression of Nephronecin could be associated with mechanisms of repair and proliferation similar to those seen in nephrogenesis. We can infer that these processes are induced during obstructive nephropathy to minimize the damaged caused by the progression of fibrosis. Further studies to corroborate this are necessary.

Session: Nephrology and Hypertension

310 EFFECTS OF END-STAGE RENAL DISEASE AND HEMODIALYSIS ON DENDRITIC CELL SUBSETS AND BASAL AND LPS-STIMULATED CYTOKINE PRODUCTION

MV. Pahl University of California, Irvine, Orange, CA.

Purpose of Study: Although bacterial infections have dramatically declined as the cause of death in the general population, they remain a major cause of mortality in patients with end-stage renal disease (ESRD). Moreover, the response to vaccination is profoundly impaired in this population. Dendritic cells (DC) are the major antigen presenting cells that bridge the innate and adaptive immune responses. Activation of DC by pathogens results in secretion of inflammatory cytokines and upregulation of co-stimulatory molecules. The activated DC prime naive T and B cells to the captured antigens.

Methods Used: Using flow cytometry, the number and phenotype of dendritic cell subsets were determined in pre- and post-dialysis blood samples from 20 ESRD patients maintained on hemodialysis. Ten normal individuals served as controls. In addition, the level of DC activation and their response to LPS stimulation were determined by assessing expression of co-stimulatory molecule, CD86, and antigen presenting molecule, HLA-DR, as well as production of TNFα, IFNγ, and IL-6.

Summary of Results: Compared to the control group the circulating dendritic cell count was significantly reduced in the ESRD patients before dialysis and declined further after dialysis. The reduction in pDC numbers was more striking than mDC. The magnitude of the LPS-induced upregulation of CD86 was comparable among the study groups as well as pre- and post-dialysis samples. However, LPS-induced TNFα production was significantly reduced in the post-dialysis samples with no significant difference in IL-6 and IFNα productions among the study groups and in pre- and post-dialysis samples.

Conclusions: ESRD results in significant DC depletion which is largely due to diminished Plasmacytoid DC subset. Hemodialysis procedure intensifies DC depletion and impairs LPS-induced TNFα production.

Session: Nephrology and Hypertension

311 MONITORING NON-COMPLIANCE AND GRAFT REJECTION IN PEDIATRIC RENAL TRANSPLANT PATIENTS USING VARIATION IN BLOOD IMMUNOSUPPRESSANT LEVELS

HE. Fernandez1, M. Hsia1, E. Tsai1, D. Gjertson2, MH. Malekzadeh1, RB. Ettenger3 1UCLA, Los Angeles, CA and 2UCLA, Los Angeles, CA.

Purpose of Study: Non-adherence is a major cause of graft rejection (rx) in renal transplant (tx) patients (pts). In adolescent liver tx pts, increased variation in tacrolimus (FK) trough levels correlates with increased acute rx. Preliminary data from 38 pediatric pts with deceased donor renal tx (DDRT)
supported this hypothesis. This study examines the correlation between graft rx and variation in FK and MMF trough levels.

Methods Used: 46 pts who underwent living related renal tx (LLRT) (n = 22) and DDRT (n=24) between 2002 and 2003 were included in this observational study, with average age of 13.7 ± 5.5 years old. 37 pts received steroid, 9 pts did not. 10 pts had biopsy-proven graft rx. Time to first rx episode averaged 3.7 ± 0.8 yrs post-tx. FK and MMF troughs levels were measured from 1–12 months post-tx.

Summary of Results: Median FK SD was 5.3 in pts with rx and 3.5 without rx. Since higher FK trough levels were correlated with higher SD (R2=0.17, p = 0.005), use of coefficient of variation (CV = SD/mean multiplied by 100%) eliminated this confounding effect. Median FK CV was 53.4% in pts with rx and 30% without rx. Two-sample Wilcoxon rank-sum test reveals median CV was higher in pts with rx than those without rx (p = 0.005). There was no difference in median FK SD and CV between DDRT and LLRT, or between steroid vs. no steroid. Median MMF CV was 51.9% in pts with rx and 45.1% without rx (p = NS).

Conclusions: These results confirm that higher FK CV correlates with increased risk for graft rx. MMF CV did not correlate with increased graft rx. Identifying a cut-off FK CV in a prospective study will be a next important step to determine its efficacy as a marker for non-adherence and graft rx.

Western Student Medical Research Forum
Student Scientific Session IV - Hematology/Oncology/Oncologic Surgery
1:30 PM
Friday, January 29, 2010

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery
310 EVALUATION OF THE EFFECTS HIP PROSTHETICS HAVE ON PROTON RADIATION THERAPY FOR PROSTATE CANCER
TB. Jeider1, DA. Bush2, JD. Slater2 1Loma Linda University; Loma Linda, CA and 2Loma Linda University Medical Center; Loma Linda, CA.

Purpose of Study: To evaluate the influence of hip prostheses in patients undergoing prostate cancer treatment with proton radiation therapy by comparing prostate and prostate plus seminal vesicle target treatment volumes along with analysis of dose-volume histograms for the bladder and rectum.

Methods Used: A retrospective analysis was conducted on 49 treatment plans for patients with a history of bilateral or unilateral hip arthroplasty who underwent prostate cancer treatment at Loma Linda Proton Radiation Therapy Center. Target treatment volumes for prostate and prostate plus seminal vesicle were compared using Mann-Whitney tests. Additionally, dose-volume histograms of the bladder and rectum for patients with a hip prosthesis who received any non-lateral beams were compared to 60 prostate cancer patients without a hip prosthesis who received only lateral beams using Mann-Whitney tests. A significance of α = 0.05 was used for all statistical tests.

Summary of Results: Patients with a history of hip arthroplasty have significantly larger volumes drawn for prostate and prostate plus seminal vesicle target treatment volumes than patients without a history of hip arthroplasty (p < 0.001 and p < 0.001, respectively). Any treatment plan that utilizes non-lateral radiation beam angles has significantly higher Cobalt Grey Equivalent (CGE) exposure to bladder and rectum tissues than plans that only use lateral-opposing beam angles (p = 0.014 or less for all p values). Treatment plans with non-lateral beam angles had up to twice the volume of bladder and rectum tissue exposed to 50% CGE than the control.

Conclusions: Proton radiation target treatment volumes drawn for patients with a history of hip arthroplasty encompass a significantly larger volume than patients without a prosthetic hip(s). This is most likely due to artifacts in planning images that obscure tissue boundaries and cause physicians to overestimate target volumes. Additionally, non-lateral proton radiation beam angles increase the exposure to surrounding tissue, especially to the bladder when oblique angles are utilized which could lead to increased treatment related toxicity.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery
311 EFFECTS OF ACUTE DIETARY MODIFICATION OF THE RATIO OF OMEGA-3 FATTY ACIDS TO OMEGA-6 FATTY ACIDS ON PLATELET FUNCTION: A PROSPECTIVE, PRELIMINARY STUDY
MJ. Matus, B. Bull, K. Hay, S. Aka Loma Linda University School of Medicine, Loma Linda, CA.

Purpose of Study: There is growing evidence that raising the ratio of Omega-3 to Omega-6 fatty acids will result in decreased platelet aggregation, decreased blood viscosity, and reduced thrombus formation. Western diets are significantly deficient in Omega-3 fatty acids with current ratios in the range of 1:10 to 1:30. This study evaluated potential changes in platelet aggregation times and the amount of time required to effect these changes by a daily ingestion of 5.2 grams of Omega-3 and limitation of dietary Omega-6 fatty acids.

Methods Used: One healthy adult male, after baseline platelet function was determined, consumed 1740 mg of Omega-3 fatty acids (J.R. Carlson Laboratories Inc.) three times a day and continued for 29 days. All known dietary sources of Omega-6 fatty acids were simultaneously eliminated. The diet consisted of salads (oil olive dressing), vegetables, and a modified Atkins high protein diet with no breads, baked or fried foods. The subject’s blood was drawn every third day. 450 μl of isotonic 0.025M CaCl2 solution was mixed with either: arachidonic acid 11.1 mg/ml (high dose AA), 5.5 mg/ml (low dose AA) or adenosine diphosphate 2.2 x 10^{-4} M (ADP). Sixty minutes after drawing, 150 μl of blood was added to each cuvette (10 x 75 test tube) and placed in a backlit, 37 C device that slowly rotated and rocked the cuvette (15 RPM). 1 mg of calcined diatomaceous earth (CDE) was added as a disclosure agent to make platelet activity visible. The end-point was aggregated platelets adhering to the cuvette wall.

Summary of Results: Using Boltzman sigmoidal regression, the end-points lengthened by 39% (ADP, 32%) (high dose AA), 30% (low dose AA), and 21% (CDE) respectively. There was no overlap between the 95% confidence limits for starting end-points and finishing end-points 29 days later.

Conclusions: Omega-3 consumption in adequate quantities coupled with minimization of Omega-6 intake results in significant lengthening of platelet aggregation end-points. The effect is first visible at 12 +/- 2 days and appears to be complete at 22 +/- 3 days. This suggests that acute dietary interventions have significant effects and that these effects are likely occurring at the megakaryocytic level.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery
312 IRREVERSIBLE ELECTROPORATION IN THE TREATMENT OF RABBIT VX2 LIVER TUMOR
MB. Totonchy1, EW. Lee1, V. Prieto1, D. Wong1, S. Dry2, CT. Loh1, ST. Kee1, 1UCLA, Los Angeles, CA and 2UCLA, Los Angeles, CA.

Purpose of Study: Irreversible electroporation (IRE) has gained increasing attention in the field of tissue ablation as a new minimally invasive surgical technique. The purpose of this study was to determine the effectiveness and safety of IRE in Rabbit VX2 liver tumor ablation and to present a radiopathologic correlation of IRE-induced liver tumor ablation.

Methods Used: For this study, 10 New Zealand white rabbits underwent IRE treatment of liver VX2 tumors and 10 others served as control. Size comparison between ultrasound and pathology, and histologic analysis of ablated vs. non-ablated tumors were investigated.

Summary of Results: In 2 weeks post-treatment, IRE decreased the size of tumor by 73–100% (p < 0.001) with no metastatic disease. Numerous lung and liver metastases were found in the control group. All 10 rabbits treated with IRE survived throughout the experiment without tumor burden or complications. H&E staining of IRE-treated tumors demonstrated a sharp demarcation between ablated and non-ablated areas. A positive TUNEL assay suggested involvement of apoptosis in the cell death process and positive CD30 immunostaining demonstrated stem cell involvement in the healing process of the IRE-treated area. Ki-67 immunostaining indicated complete destruction of cellular proliferating activity in IRE-treated tumors, while VEGF immunostaining showed complete preservation of blood vessels and bile ducts in all treated livers.
Conclusions: The results suggest that IRE is a novel non-thermal hepatic therapy which can eradicate hepatic tumors without damaging adjacent healthy tissue or critical structures. IRE was found to create focused complete cell death which results in hepatic regeneration with stem cell involvement.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery

313 INFLUENCE OF IMATINIB MESYLATE ON BONE MARROW-DERIVED DENDRITIC CELLS

E. Situ1, E. Katsanis2,3, N. Larmonier2,3 1University of Arizona College of Medicine, Tucson, AZ; 2Steele Children’s Research Center, University of Arizona College of Medicine, Tucson, AZ and 3University of Arizona College of Medicine, Tucson, AZ.

Purpose of Study: Primarily described as initiators and regulators of immune responses, dendritic cells (DC) may also be endowed with the capacity of directly triggering tumor cell death. This cytotoxic function is an atypical novel feature of these cells that may be used effectively in cancer immunotherapy. Imatinib mesylate has been reported to modulate DC killing potential in a dose- and time-dependent manner and may affect the differentiation of DC from bone marrow precursors, rendering them ineffective in eliminating tumor cells. Further studies are required to elucidate the molecular mechanisms underlying the modulation of DC by this drug and the possible significance of these findings in vivo as it relates to the promotion or inhibition of tumor growth.

Methods Used: DC were generated from Balb/c mouse bone marrow cultured in complete RPMI medium (Gibco/BRL) with GM-CSF and IL-4 (10 ng/ml each). On day 6, DC were selected by Magnetic Activated Cell Sorting (MACS, Miltenyi) using anti-CD11c antibody conjugated with microbeads and subcultured. Imatinib (10-5 M and 10-7 M) was added to the culture on day 0, 6, or 7. On day 8, DC were collected and co-cultured with 4T1 breast cancer cells (tumor cell:DC ratio = 1:5) and with LPS, which triggers DC killing activity. Tumor cell killing was then assessed by crystal violet assays.

Summary of Results: Exposure of DC to imatinib from day 7-8 does not affect their killing potential. Interestingly, reduced killing activity was observed when DC were pre-treated with imatinib (10-7 M and 10-5 M) from day 6 to day 8, resulting in a significant impairment of their tumoricidal activity. In addition, the presence of imatinib from day 0 and during the entire culture period resulted in the complete loss of DC killing potential.

Conclusions: Imatinib may modulate DC killing potential in a dose- and time-dependent manner and may affect the differentiation of DC from bone marrow precursors, rendering them ineffective in eliminating tumor cells. Further studies are required to elucidate the molecular mechanisms underlying the modulation of DC by this drug and the possible significance of these findings in vivo as it relates to the promotion or inhibition of tumor growth.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery

314 OTOTOXICITY AS A PREDICTOR OF OUTCOME IN OSTEOSARCOMA PATIENTS TREATED WITH CISPLATIN

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Purpose of Study: Currently almost all Osteosarcoma patients are treated with a chemotherapy protocol that includes Cisplatin. This platinum agent is known to cause irreversible ototoxicity in up to 60% of recipients. The objective of this study is to identify any correlation between cisplatin ototoxicity in osteosarcoma patients and their level of tumor response to this agent. We hypothesize that patients with no ototoxicity after induction therapy will show lower levels of tumor necrosis at the time of surgery (defined as under 90% necrosis), and secondly these patients upon completion of therapy will have a worse event free survival.

Methods Used: All individuals with a first diagnosis of Osteosarcoma before the age of 18 years and treated at BC Children’s hospital between 1990 and 2009 were retrospectively analyzed. The diagnosis of osteosarcoma was made based on histological examination of biopsy specimen’s. All chemo- therapeutic agents administered were captured and the total dose of cisplatin received was calculated. Audiology data that was captured throughout the course of treatment was also recorded, focusing on the baseline, week 12, end of therapy and current audiograms. Relapse was defined as a secondary progression of the initial tumor and/or the appearance of tumor at a distant site after the completion of therapy. Tumor response to cisplatin was determined by the percent necrosis, as assessed by the pathologist, at the time of surgery.

Summary of Results: 83 subjects were included in this study. Currently we have complete data for 32 subjects. The results thus far show an odds ratio of 5.727 with a 95% confidence interval of 0.2-120.8. Final results, including Kaplan-Meier Survival Graphs, will be presented at the meeting.

Conclusions: The early results of this study are intriguing, outlining a possible role for ototoxicity as a predictor of tumor response to therapy with cisplatin.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery

315 RECONSTRUCTION OF MALIGNANT MELANOMA RESECTION WITH ARTIFICIAL DERMAL SUBSTITUTE

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Purpose of Study: To describe an approach to reconstruction of malignant melanoma resection defects using acellular dermal replacement.

Methods Used: Four elderly patients with a mean age of 72 years underwent melanoma resection. The melanoma lesions were located on the face in 2 patients, the foot in 1, and the scalp in another. All diagnoses were made by biopsies, which demonstrated Clarke’s levels ranging from III to IV and Breslow levels from 0.65 to 4.6 mm. Co-morbidities included hypertension in all 4 patients, 1 of whom had a history of endometrial carcinoma (status post hysterectomy). Integra™ (Lifesciences Corp., Plainsboro, New Jersey) is an acellular and artificial dermal substitute used for reconstruction in the absence of natural dermis. After a wide local excision of the malignant lesion with clear margins, Integra™ was meshed to allow egress of fluid and applied to the wound bed with 4-0 chromic sutures. The average size of Integra™ sheets used was 71.2 cm2, ranging from 4 to 250 cm2. Appropriate skin grafts and dressings were applied to maximize healing and aesthetic outcome.

Summary of Results: In all 4 patients (100%), malignant melanoma resection defects with Integra™ placement demonstrated good adherence to the wounds without sign of infection. In 3 patients, a harvested full thickness skin graft was subsequently applied to the defect. The fourth patient did not require a skin graft as her wound completely healed with adequate coverage without complications. At 2 month follow up, no infection, hematomas, or skin graft or Integra™ failure occurred. All previous defects were completely healed without complications.

Conclusions: Our patients each showed successful Integra™ grafting on various parts of the body and face, exhibiting the versatility as to where it will be effective. Furthermore, its application was performed by different plastic surgeons, supporting the consistent results of this dermal matrix regardless of the surgeon. We recommend this technique for any resection defect with a viable wound bed and absent dermis as it has an absent complication rate in our series and acceptable aesthetic results.

Session: Student Session IV - Hematology-Oncology/Oncologic Surgery

316 HIV SEROSTATUS DOES NOT AFFECT EPIDERMAL ANAL CANCER OUTCOMES: A 15-YEAR RETROSPECTIVE STUDY

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Purpose of Study: HIV infection is a risk factor for epidermidal anal cancer (EAC), but the effect of HIV on EAC outcomes is unclear. The goal of this study was to examine the relationship between HIV status and EAC outcomes over the last 15 years.

Methods Used: We retrospectively reviewed all adults treated for invasive epidermoid carcinoma of the anus in our hospital system from January 1, 1994 to December 31, 2008. Sixty-three nine patients were treated. Forty-seven patients (75%) had primary chemoradiation, of whom 42 (89%) completed the planned radiotherapy. Fourteen patients (22%) underwent primary surgery, of whom 11 (79%) were treated by tumor excision and 3 (21%) by abdominoperineal resection. Two patients (3%) received radiotherapy alone. We used standard statistical tools to analyze HIV status and CD4 count (>200 cells/µL) for HIV+ patients with respect to demographics, tumor stage, treatment details, complications, disease-free survival, and overall survival.

Summary of Results: Forty-five patients (71%) were in complete remission after treatment, and 44 patients (70%) were alive at last follow-up. Kaplan-Meier estimates for disease-free and overall survival were 6.9 ± 1.0 years (95% CI: 5.1–8.7) and 9.3 ± 1.0 years (95% CI: 7.4–11.2), respectively. Significant differences between the HIV+ (N = 19) and HIV- (N = 44) cohorts were that the HIV+ cohort was younger (p < 0.0001), had less basaloid carcinoma (p < 0.01), had faster pack-years (p < 0.03), had higher incidence of anal condylomata (p < 0.01), and had less dermatitis during chemoradiation (p < 0.04). There were no significant differences in other demographic variables, treatment, complications besides dermatitis, or survival. In the CD4+ (N = 15) and CD4- (N = 4) groups, 0/10 patients were alive (p > 0.001), and had more Stage II disease than CD4+200 patients (p < 0.04). There were no significant differences in disease-free or overall survival.

Conclusions: HIV status did not affect anal cancer outcomes or therapeutic complications, except for an increased risk of dermatitis in HIV-negative patients undergoing chemoradiation. Low CD4 counts did not significantly affect outcomes in our study, but due to small sample sizes more data on these patients are needed.

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BREAST IMPLANT-ASSOCIATED T CELL ANAPLASTIC LARGE-CELL LYMPHOMA: CASE REPORT AND ESTABLISHMENT OF A NOVEL CELL LINE (TLBR-1)

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Purpose of Study: Primary lymphomas of the breast are very rare, representing 0.2–1.5% of breast malignancies, and over 95% of reported cases are of B cell origin. Recently, 31 cases of T cell lymphomas arising in association with textured breast implants have been reported worldwide. All cases have been classified as T-cell non-Hodgkin’s lymphomas, with an average patient age of 44.7 yrs (range 33–87yrs) and an average time from implant of 5.8yrs (range 1–28yrs). Patients received surgical, chemo, and/or radiation therapies, and except for one patient, remain disease free.

Methods Used: A new cell line designated TLBR-1 has been established from a tumor biopsy obtained from a patient in Australia using a fibroblast feeder layer and IL-2.

Summary of Results: Immunoperoxidase staining of the tumor biopsy specimen showed a CD30/CD4/CD8 co-expressing T cell population that was EMA+ and perforin/granzyme B+. Multiplex PCR of TCRγ genes showed monoclonal TCRγ rearrangement, suggesting a T cell origin. Pan T markers CD2/5/7, ALK-1, keratin AE1/AE3, CD20, CD56, and EBVISH were negative. After establishment and removal from the feeder layer, the non-adherent TLBR-1 cell line is IL-2 dependent and displays polymorphic cell shapes ranging from spherical to dendritic. Cell morphology examined on cytopsin preparations showed large cells with abundant cytoplasm and frequent mitotic figures. Surface staining by monoclonal antibodies showed that TLBR-1 is strongly positive for CD4/8, CD30, CD71, and CD26 expression, as well as antigen presentation-associated (HLA-DR+ CD80+ CD86+), IL-2 signaling (CD25+ CD122+), and NK/NKT cell (CD56+) markers. It has variable expression of T cell markers CD5/CD7/CD3-, adhesion (CD11c+ CD11b-), and myeloid (CD13+ CD14+ CD15+) markers. TLBR-1 lacks surface expression of B cell (CD10-CD19-CD20-CD21), dendritic cell (CD1a-), or stem cell (CD133-) markers. Cytogenetic analysis, transmission electron microscopy, and heterotransplantation studies in SCID mice are pending.

Conclusions: TLBR-1, a novel T cell ALCL, closely resembles the original biopsy and represents an important tool for studying this rare implant-associated breast lymphoma.

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HEAD AND NECK CANCER FOLLOWING SOLID ORGAN TRANSPLANTS

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Purpose of Study: The immunosuppressant medications taken by transplant patients help prevent organ rejection but often come at the cost of increased cancer rates. While the exact mechanism of increased cancer incidence is unknown, theories focus on the overall decreased surveillance and destruction of tumorigenic cells by the suppressed immune system and the possible carcinogenic nature of the drugs themselves. This retrospective study evaluates the clinical outcomes of aggressive head and neck cancer treatment of noncutaneous head and neck cancer, including free flap surgery and radiation, for solid organ transplant patients.

Methods Used: The study examines 26 solid organ transplant patients who underwent cancer treatment for noncutaneous lesions of the head and neck. Each of the patients underwent surgical excision and radiation.

Summary of Results: Five (19.2%) patients had a locoregional cancer recurrence after treatment. Three (11.5%) patients had a metastasis. Eighteen (69.2%) patients had no recurrence within the three year follow up. To date, 23 patients (88.5%) are alive with no evidence of disease, 1 patient (3.8%) is alive with evidence of disease, and 2 patients (7.7%) are deceased.

Conclusions: These results show a more favorable outcome for patients compared to previous literature, particularly when compared to patients who underwent surgery without postoperative radiation. Lower recurrence and increased survival rates were found when patients received aggressive cancer treatment involving a surgery and radiation combination. The use of extensive resection free flap reconstruction for noncutaneous cancer in addition to radiation is a viable treatment strategy for this growing patient population.
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PREDICTIVE MARKERS OF SPERM CRYOPRESERVATION SUCCESS IN MEN WITH CANCER
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Purpose of Study: Men who have been diagnosed with cancer often undergo radiation and chemotherapy. Such therapy is gonadotoxic and often causes temporary or permanent infertility. As a result, cryopreservation of sperm prior to therapy is recommended. Cryopreservation of sperm can also have a detrimental effect on a variety of sperm functions. This study evaluated standard semen analysis variables as well as pre-freeze and post-thaw semen quality of men prior to the onset of treatment.

Methods Used: Previously collected semen data (n=181) was analyzed from male cancer patients who have undergone treatment and sperm cryopreservation. Standard semen analysis variables such as sperm concentration, motility, total motile sperm count, sperm morphology, volume and pH were determined using standard laboratory protocols. Additional variables measured include rapid & linear motility, progressive motility, sperm recovery after purification, curvilinear velocity, straight-line velocity, lateral head deflection, leukocyte concentration, and immature germ cell concentration. Additional standard cryopreservation variables were assessed post-thaw to determine sperm motility and viability post-thaw.

Summary of Results: Sperm quality is found to deteriorate after cryopreservation. The population of patients that were the most severely affected are patients with leukemia, lymphoma, and testicular cancers. The most predictive marker of post-thaw semen quality is leukocyte concentration and sperm morphology. Patients that initiated chemotherapy prior to cryopreservation had an increased risk of morphological abnormalities.

Conclusions: Since cancer therapy in men already significantly impairs their reproductive potential, these men should be advised to cryopreserve semen before the onset of treatment. Since men with certain cancers have lower post-thaw viability it may be necessary to have more than one cryopreservation before the therapy begins.

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QUANTITATIVE CHARACTERIZATION OF MULTI-SIGNAL ACTIVATION OF CELLULAR RESPONSES IN MULTIPLE BIOLOGICAL SYSTEMS
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Purpose of Study: Current drug therapy views patients that have the same diagnosis as a homogenous group. However, multiple factors, including genetic and environmental variations, are thought to contribute to the large discrepancy in patient response to the same drug therapy. Thus, combination therapy may offer a huge improvement in overall patient response levels. In order to determine which combination may be most effective, we take a mathematical approach using artificial neural networks (ANN) to assess the effect of multiple drug combinations under different pathophysiological scenarios, such as non-small cell lung cancer (NSCLC) and Kaposi’s Sarcoma-associated Herpesvirus (KSHV).

Methods Used: Using in vitro cell culture models of NSCLC and KSHV, single and combination drug profiles were determined with respect to cell survival and transcription factor activity, respectively. Three drugs (AG490, indirubin-3’-monoxime, and U0126) were selected based on high tumor selectivity from over thirty clinically approved inhibitors in NSCLC. Cellular ATP level was used as a readout for cell survival and proliferation in NSCLC. Reactivation of KSHV was induced by a combination of bortezomib, db-cAMP, prostratin, and valproate. The activity of p38, p42/44, CREB, NF-kB, RBP-JK, and E2F transcription factors was measured using a dual luciferase assay at three different timepoints. To build the model, we used varying percentages of experimental datapoints to train the ANN to generate models for both cell lines. The remaining datapoints were used to test the accuracy of the model.

Conclusions: By taking a quantitative approach to characterize the effect of multiple inputs in three biological systems, we are able to reduce the size of drug combination studies in vitro. Ultimately, this research could potentially lead to the development of mathematical tools that can aid in the design of personalized drug therapy for cancer and viral infections.

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EFFECTS OF EPISODES OF TEMPORARY THRESHOLD SHIFT ON DISTORTION-PRODUCT OTOACOUSTIC EMISSIONS LEVEL/PHASE MAPS AND AUGMENTED DISTORTION-PRODUCT-GRAMS
S T. Purcell1, B. Stagner2, B. Lonsbury-Martin1-2, G. Martin1-2, Loma Linda University, Redlands, CA and 2 VA Loma Linda Healthcare System, Loma Linda, CA.

Purpose of Study: A temporary threshold shift (TTS) is a temporary change in hearing sensitivity that occurs after exposure to high sound levels. The extent of a TTS can be measured via distortion product otoacoustic emissions (DPOAEs), which are sounds produced by the cochlea in response to two pure-tone stimuli (labeled f1 and f2), which travel back out of the ear and can be measured via a microphone. These measurements can be evaluated using multiple techniques. Two such methods, the response level/phase (L/P) map and the augmented DP-gram (ADP-gram), allow the basal sources of emissions to be separated from the DPOAEs themselves. The ADP-gram uses an interference tone at 1/3 octave higher than the f2 tone, which causes cancellation of basal sources caused by the primary tones. It is presumed that the data obtained via current methods of TTS measurement is contaminated by basal source emissions, complicating the clinical use of these measures.

Methods Used: In an effort to measure the effects of TTS on L/P maps and ADP-grams, three normal-hearing rabbits were exposed to a pure tone stimulus of 102 dB SPL at 2.828 or 4 kHz for 10 minutes each. Immediately following this, ADP-grams were measured for the following hour. Subsequently, L/P maps were collected postexposure in order to observe the TTS effects and test the sensitivity of each measurement procedure.

Summary of Results: For equilevel primary tones, effects on the basal sources were seen over a broad range of test frequencies. Also, the DPOAEs recovered very rapidly, i.e., within ~24 hours. For the unequal level primary tones, it was observed that the ADP-gram was much more sensitive in measuring the extent of the TTS. These data supported the notion that the normal DP-gram is contaminated by basal sources, especially at the 60/55 dB SPL level, which is similar to a widely used primary-tone combination in the field of clinical audiology. The L/P map showed enhancement in the 2f1-f2 emission range due to the cancelation of basal emission sources.

Conclusions: The results suggest that the effects of TTS can be more accurately obtained by utilizing the newer ADP-grams and L/P maps, rather than the standard DP-gram that is used clinically.

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323
A PEDIATRIC RESEARCH CURRICULUM TO ENHANCE RESEARCH SKILLS OF POST-GRADUATE TRAINEES
Purpose of Study: Clinical Research is at the core of evidence-based practice, while Health Services Research, Knowledge Transfer and Practice Audit are key features to ensure good clinical practice. Pediatric residents and fellows must understand these disciplines and get involved in projects to acquire the knowledge, skills and competence in order to become better practitioners and engage in their own research projects. Our purpose is to develop, implement and evaluate a new research curriculum for pediatric trainees designed to improve research knowledge and skills.

Methods Used: The Research Curriculum has been in place for 2 years: 2008-09. It is offered to all new residents, sub-specialty residents and fellows. The curriculum consists of four components: 1) Formal Epidemiological Education (monthly) that includes presentations by faculty members followed by group discussion; each 4 hour session includes a presentation on health quality improvement/practice audit 2) The Residents’ Research Journal Club (monthly) is structured to introduce and review key research methodologies and address important pediatric issues; 3) The Research in Progress Forum (monthly) provides opportunities for residents to discuss research questions or ideas and seek assistance; 4) The Research Project is a key component that should culminate in conference presentations and publications.

Summary of Results: All curriculum components were evaluated on an ongoing basis. In Year 1 the new curriculum was well-accepted:1) Formal Education [91% Good or Very Good] 2) Journal Club [30% Excellent; 60% Very Good; 10% Good] 3) Research in Progress [13% Excellent; 38% Very Good; 25% Good]. In Year 2 overall evaluation was similar to the first year: 1) Formal Education [7.5% Excellent; 87.5% Good or Very Good] 2) Journal Club [12% Excellent; 59% Very Good, 29% Good].

Conclusions: This assessment indicates a demonstrable need and strong support for this tele-educational program through clinical research and practice audit. The second main objective is to develop interest for research and academic career. The evaluation of the research curriculum from trainees is encouraging.

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COLLABORATIVE GRAND ROUNDS THROUGH TELE-EDUCATION: AN INNOVATIVE, TRANSCULTURAL MEDICAL EDUCATION INITIATIVE

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Purpose of Study: Global Grand Rounds is a novel, learner-driven, international tele-educational exchange. This program results from evidenced-based curricular development that includes needs assessment, knowledge appraisal, and program evaluation. We hypothesize that faculty, residents, and medical students are interested in participating in Global Grand Rounds and that transcultural tele-education enhances education, cultural sensitivity, and clinical practice both locally (UC Davis) and abroad (Peking University).

Methods Used: We performed a comprehensive needs assessment of all UC Davis dermatology faculty, residents and rotating students. The assessment identified barriers, determined gaps in learning, and related participant experience to program design.

Summary of Results: The needs assessment revealed a high level of interest in international health (mean: 4.67, SE: 0.13, 95% CI: 4.39–4.93) and strong support for the concept of videoconferenced Global Grand Rounds (mean: 4.50, SE: 0.16, 95% CI: 4.18–4.88). One-hundred percent of participants reported they would attend (mean: 4.60, SE: 0.13, 95% CI: 4.32–4.88) and 80% would present or moderate (mean: 4.13, SE: 0.24, 95% CI: 3.63–4.64) a Global Grand Rounds videoconference. Residents were significantly more likely than faculty to agree or strongly agree that regular participation in grand rounds directly influenced their ability to provide improved patient care (p<0.03). Overall, grand rounds are well attended and highly regarded for their educational value (80% attend more than two-thirds of the conferences/year, and 67% report the educational value as ‘high’ or ‘very high’).

Conclusions: This assessment indicates a demonstrable need and strong support for this tele-educational program. Utilization of pre-defined, outcome-based evaluation measures will provide an objective assessment of the program’s impact on our students, residents and the dermatologic community. Video-based Global Grand Rounds may be an effective, relatively low-cost adjunct to established learning methods to enhance continuing education, while building constructive relationships between academic institutions from different nations.
Session: Student Session V - Health Care Research/Surgery
327 NEW SYNTHESIS METHODS OF NOBLE METAL NANOCLUSTERS FOR APPLICATION IN NANOMEDICINE
J. Krol, M. Malecki Western University of Health Sciences, Pomona, CA.
Purpose of Study: Awareness of the role played by nanoparticles in medicine, biotechnology, pharmacy, and public health is growing rapidly (www.airnow.gov). Currently, research is being conducted in the use of nanoparticles as drug delivery systems, contrast agents, and even as a means to detoxify polluted ground water on a large scale. In this study, we report a new method of synthesizing nanoparticle clusters of noble metals.
Methods Used: The manufacture, microfiltration, and functionalization of nanoparticles consisting of noble metals face two major difficulties: the inherent poor chemical reactivity of noble metals and the presence of contaminating by-products. To address these problems, we developed a novel technology: a titanium-sapphire laser generating pulses of 1.1μJ at 1030nm wavelength. The beam was focused onto targets consisting of pure gold or palladium, which were mounted into the chambers filled with deionized, double-distilled water with electrical resistance above 18 MΩM. The outlets and inlets allowed for gentle pooling of nanoparticle production. The generated nanoparticles were isolated via gradient ultracentrifugation and/or were fractionated by increasing g-force spins. The nanoparticles were analyzed for purity using electron beam x-ray crystallography and energy dispersive x-ray spectroscopy.
Summary of Results: Our method resulted in high yields of very pure gold and palladium nanoparticles. High purity of gold and palladium samples was determined based on crystal lattices of gold atoms showing single or multiple crystal arrangements. Mono-elemental composition was demonstrated with energy dispersive x-ray spectroscopy in the form of the single element specific peaks within the spectra.
Conclusions: The novel method, which we developed, allowed us to generate and purify nanoparticles of gold and palladium. This technique opens new avenues of using nanoparticles in medicine, public health, environmental health, and bioengineering.

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328 ECONOMIC FACTORS IN THE PRACTICE OF ANESTHESIA
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Purpose of Study: This systematic literature review was conducted to investigate appropriate ways to reduce costs associated with anesthesia care.
Methods Used: Between Mar-Sep 2009, medical databases were repeatedly searched to identify papers on economic factors published since 1995, associated with medical centers within developed countries. Wholesale drug acquisition costs for the University of Washington Medical Center were also compared to article data to provide a current perspective.
Summary of Results: Anesthesia medications comprise a significant portion of hospital pharmacy budgets and are under direct scrutiny of hospital administrators seeking savings in the current economic environment. This literature review found that the highest drug waste was associated with total intravenous anesthesia (TIVA), which includes the administration of propofol with remifentanil, alfentanil, or fentanyl. The overall expense of TIVA protocols remains 4 times higher than the cost of administering isoflurane, with remifentanil, alfentanil, or fentanyl. The overall expense of TIVA protocols remains 4 times higher than the cost of administering isoflurane, with remifentanil, alfentanil, or fentanyl.
Conclusions: There is potential for significant savings by shifting to isoflurane from TIVA protocols.

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329 ALCOHOL AND MUSCULOSKELETAL INJURY: THE EFFECTS OF ALCOHOL ON RECOVERY FROM FRACTURES AND DISLOCATIONS
ND. Ford1, S. Bazargan1, DE. Fish2, D. Pan1 1Charles Drew University of Medicine and Science/ David Geffen School of Medicine at UCLA, Los Angeles, CA and 2David Geffen School of Medicine at UCLA, Los Angeles, CA.
Purpose of Study: To assess the role of alcohol misuse in length of hospital stay, rate of infection, and rate of re-operation amongst patients recovering from fractures and dislocations.
Methods Used: This was a retrospective analysis of the California Hospital Discharge Data. ICD-9 codes were used to search the California Hospital Discharge Data (1991–2000). These codes were used to identify skeletal fractures and joint dislocations, procedures involving open and closed reduction of fractures, and post-operative infections. For alcohol misuse, patients with ICD-9 codes for abuse or acute intoxication, acute intoxication with dependence, and addiction were included in the study. Various statistical tests including descriptive statistics, chi-square and t-tests, and multivariate analyses were employed to analyze the associations between each predictor and outcome variables.
Summary of Results: Alcohol misuse was identified in 3.4% (n = 28,013) of our sample. Using multivariate logistic regression we were able to identify a statistically significant relationship between alcohol misuse and each of the outcome variables. Patients diagnosed with an alcohol misuse experienced a significantly greater length of hospital stay (OR 2.20, CI: 2.14–2.26, p = .001), rate of re-operation (OR 1.53, CI: 1.49–1.57 p = .001), and rate of infection (OR 1.99, CI: 1.76–2.25 p = .001) as compared to patients with no alcohol related recovery from fractures or dislocations (F/Ds).
Conclusions: Alcohol misuse may play an inhibitory role in the healing process amongst patients recovering from F/Ds through increasing the length of hospital stay, rate of re-operation, and rate of infection. In the future we intend to revisit our data set and further break down our analysis to identify upper vs. lower extremity fractures as well as region of limb fractured.

Western Student Medical Research Forum
Student Scientific Session VI - Community Health (International)
1:30 PM
Friday, January 29, 2010

Session: Student Session V - Community Health (International)
330 HOW DOES PARTICIPATING IN AN INTERNATIONAL PROJECT AFFECT STUDENTS’ PERCEPTION ON PROJECT SUSTAINABILITY?
D. Wadiwa, J. Jansen, S. Turvey, K. Kang, V. Kapoor University of British Columbia, Vancouver, BC, Canada.
Purpose of Study: To determine the impact of participation in a student driven international project on students’ perception on project sustainability.
Methods Used: The 23 UBC students that participated in the Global Health Initiative (GHI) projects were surveyed. The surveys collected information from students regarding perception of project sustainability ranked on a scale of 1 to 10 prior to the global health project participation and upon return from the project. The survey also collected qualitative information on project sustainability by asking the question: “How did you ensure the sustainability of your project?”
Summary of Results: Quantitative Results:
On average, a 69.8% relative increase in the perception of project sustainability was observed after participating in the project. In addition to the increase in perception on project sustainability, participants also graded the importance of sharing their experiences with others. The average importance of sharing project experience was ranked 8.60 on a 10 point scale.

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Overall, GHI project participants reported an increase in their views on project sustainability together with a weighting on the importance of sharing experiences thus transferring knowledge.

Qualitative Results:

Although participant responses were quite assorted there was a common theme to the answer of the sustainability question on the survey. Project participants planned to certify sustainability of their project via knowledge transference and a careful recruitment process to ensure that the incoming team for the year of 2010 shares the vision of the project alongside ambition to see the project develop. Additionally, the participants were confident with the community’s ability to continue the project successfully. The community involvement was varied depending on the project.

Thus, the underlying objective to enhance project sustainability was through community commitment and the recruitment of a team for follow up and further development for the upcoming year.

Conclusions: Through the partaking in GHI projects, students’ perception of project sustainability was SIGNIFICANTLY increased and this correlated with the desire to share and transfer knowledge to others in order to allow the sustainability to continue.

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NUTRITIONAL AWARENESS AND EMPOWERMENT IN INDIA: TEACHING FOOD MULTIMIX PREPARATION IN A FOOD FESTIVAL SETTING

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Purpose of Study: Proper nutrition is important for improving the immune system, preventing weight loss and wasting, and ensuring compatible food drug absorption in HIV patients. Food multimix is a nutrient-rich flour made from local ingredients. The ingredients are designed to be accessible and affordable. Recipes developed using multimix are high the calories and protein important for HIV patients. A food festival was organized to educate patients about nutrition and empower them with a recipe for making multimix.

Methods Used: Patients in the antiretroviral therapy (ART) center at the Namakkal Government Hospital were surveyed about their food accessibility, typical meals and multimix experiences. Responses from the survey were used to design the food festival. The food festival occurred over the span of six days in the ART center for patients coming to pick up their monthly supply of medication. Health education consisted of group discussions given by the nutritionist and charts outlining daily recommended nutritive allowances, nutritious values of common Indian foods, and multimix preparation. Volunteers prepared 4–5 recipes using multimix for patients to sample. Also, a cooking competition was held to engage patients in healthy and affordable cooking. Attendees of the festival offered comments in a feedback book.

Summary of Results: Over 400 patients and family members received nutritional education and sampled multimix recipes during the festival. Seven patients participated in the cooking competition. Most patients enjoyed the multimix dishes and many wrote down preparation instructions and nutritional information. All of the suggestions in the feedback book were positive. A few patients told staff members that they did not like the taste of multimix.

Conclusions: The project met the goals of disseminating nutritional awareness and teaching multimix preparation to HIV patients. Just as important, conducting the event gave local NGOs a vehicle to collaborate, ally and exchange ideas. Printed and electronic copies of the educational material were left with the local organizers, who are interested in continuing the food festival in the future. Further work is needed to address the specific nutritional needs of patients receiving ART and to include the general hospital population.

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ESTABLISHMENT OF HIV CHRONIC CARE FACILITY IN RURAL KENYA

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Purpose of Study: In 2009, four medical students who are members of Global Initiative for Village (GIVE) travelled to Kenya to assess the health services of a rural community outside Kisumu. Despite a high prevalence of HIV, access to basic HIV services remains absent in the local Health Centre. In order to improve the delivery of HIV services to the community, GIVE facilitated collaboration between local Health Centre staff and municipal and provincial institutions.

Methods Used: Preliminary meetings with Health Centre nurses and support staff and the Kisumu Municipal Officer of Health (MOH) were held in order to assess the current situation and mobilize all pertinent institutions. Population and disease statistics were obtained, organized and submitted as a formal proposal to the Provincial Antiretroviral Therapy Office. GIVE organized the following basic requisite items of an HIV care facility: an on-site clinical officer (CO), availability of opportunistic infection prophylaxis, transportation to the nearest blood laboratory for CD4 measurement, and a follow-up process for HIV+ individuals. To facilitate nursing staff training in HIV chronic care, GIVE collaborated with Aphia II Nyanza, a USAID-funded NGO.

Summary of Results: The response of the Health Centre staff, the MOH, and most importantly, the community, was overwhelmingly positive. Nurses were motivated to receive training in HIV management and Aphia II Nyanza supported the MOH in providing a full-time CO. Community consultation prompted project ownership and served to mobilize and sensitize the community to HIV care. GIVE gained valuable insight into the politics and development of health projects and forged important relationships with local government officials. Since its establishment by GIVE in 2008 the local HIV Voluntary Counseling and Testing Centre has seen a 23% HIV+ test rate. The overall test positive rate at the Health Centre, including tuberculosis patient testing is 34%.

Conclusions: Through collaboration with the community and the local government GIVE hopes to establish a sustainable HIV Chronic Care Facility to serve the local HIV+ population. Currently, initial training has been completed, and nursing staff is able to provide basic prophylaxis, preventative treatment, and follow-up for HIV+ individuals; however, they are forced to refer patients to larger facilities for ARV therapy.

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GLOBAL INITIATIVE FOR VILLAGE EMPOWERMENT (GIVE): ACHIEVING SUSTAINABILITY AND CONTINUITY WITH STUDENT-LED INTERNATIONAL AID WORK IN THE FACE OF HIGH MEMBERSHIP TURNOVER

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Purpose of Study: GIVE is a student run organization that has been implementing projects to alleviate poverty and promote public health in rural Kenya for four years. Our vision is one of sustainability in these projects but the nature of the group has made this difficult to achieve. Membership turnover has been very high while projects have developed slowly over time causing much of the progress to be lost in the subsequent generations of students. The goal of the study was to achieve continuity by developing a system by which projects can be developed adequately and passed on seamlessly from one generation of students to the next. With this novel approach GIVE believes that continuity will be maintained in the face of high member turnover.

Methods Used: The sustainability of projects was assessed with a qualitative approach looking at the survival, achievements and community involvement of projects over the past four years. Success was defined as projects continuing to run at one year follow up. Membership has been tracked over time to record turnover as well as specific project involvement. The results of membership tracking within a project were then compared with the assessment of the project.

Summary of Results: It was found that in order for a project to be sustainable, each group member must be involved in that project for a minimum of two years.

Conclusions: GIVE has seen many successes and failures during the short existence of the organization. Effective projects with a focus on sustainability must be managed for a minimum of two years. It is recommended that other student-led aid organizations establish a similar mandate. For most effective management, members must spend one year planning a project, followed by implementation of the project on the ground, and finally a second year planning the follow up for the project and training new members. GIVE’s experience has demonstrated that projects are best facilitated on the ground by members who have previously visited the site followed by those who
received adequate training from members who previously visited the site. This simple concept is overlooked by many who seek change. The structure of our organization encourages participants to make a longer term commitment which aid in achieving the aforementioned goals.

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A GROWING NEED: USING A MULTI-PRONGED COMMUNITY BASED APPROACH TO TREAT CHILDHOOD ANEMIA IN THE INDIAN HIMALAYAS

L. Ching1, M. Suen1, S. Brkanovic1, E. Hendren1, K. Ghang1, A. Lam1, T. Nguai1, S. Rose1, S. Skitch1, N. Taha1, G. Tansley1, L. Bornais2, V. Kapoor1
1University of British Columbia, Vancouver, BC, Canada and 2UBC, Vancouver, BC, Canada.

Purpose of Study: Childhood anemia and malnutrition is associated with poor health and impaired cognitive development, impacting academic performance and subsequent work productivity in adulthood. In this study we assess the effectiveness of a multi-factorial community driven intervention to reduce the burden of this disease on a rural student population in the Spiti Valley, India.

Methods Used: Annual school-based health screens were implemented in a population of ethnically Tibetan children (ages 4 to 16) in which hemoglobin (Hb) levels were calculated with a HemoCue Hb Photometer. Results were adjusted for age, gender and altitude based on WHO guidelines. In partnership with the community, a four-pronged approach was employed comprising of (1) school-wide iron-supplementation (2) screening and treatment of helminth infections (3) promotion of general student health through hygiene/nutrition education and sanitation infrastructure (4) the construction of solar-powered greenhouses to increase winter consumption of vitamin-rich, green leafy vegetables. Follow-up nutrition analysis of school diet was conducted in 2009.

Summary of Results: In 2008, Hb screens showed a very high prevalence of anemia at 78.3% (mean Hb = 132.6 g/L, n = 384) and blood smears indicated a mixed multifactorial etiology suggestive of both iron and global micronutrient deficiencies (folate, B12). The multi-prong intervention resulted in a marked reduction in the prevalence of anemia with 2009 values at 71.3% (mean Hb = 141.1 g/L, n = 416). Health screens showed a concurrent reduction in helminth infection (5.6% to 2.7%) but still indicated signs of vitamin deficiency in 20.4% of children (a finding supported by the results of dietary/meal analysis). Greenhouses reported harvests into February, extending the availability of fresh produce in the region by 4 months.

Conclusions: In the Spiti Valley, malnutrition and anemia are major health concerns due to a constellation of local factors. This multi-faceted community partnership approach has expected promising reductions in the prevalence of anemia and nutrient deficiency in the target population, and demonstrates a sustainable model for easing the burden of disease in rural settings.

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TOBACCO AND ALCOHOL USE IN THE SPITI VALLEY REGION OF NORTHERN INDIA

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1University of British Columbia, Vancouver, BC, Canada and 2Kaillash Institute of Nursing & Para-Medical Sciences, Noida, India.

Purpose of Study: Tobacco and alcohol use are major public health issues that cause substantial morbidity and mortality in communities worldwide. The current study assessed the prevalence of tobacco and alcohol consumption among adults living in the Spiti Valley region of northern India. Currently, there is no data available regarding the epidemiology of tobacco and alcohol consumption in this community.

Methods Used: Sixty-four adults within the Spiti Valley completed an interview regarding their tobacco and alcohol use. Interviews were conducted with the collaboration of nursing students fluent in the local language. Tobacco use items were derived from the WHO Global Adult Tobacco survey. Alcohol use items asked about typical consumption patterns and the occurrence of problems as a result of alcohol use.

Summary of Results: Rates of tobacco use were consistent with levels reported in studies conducted in other parts of India. Among male participants, 54% were current smokers and 34% regularly used smokeless forms of tobacco. Females reported substantially less tobacco use. Alcohol use was common among the current sample. The rates of alcohol consumption were substantially higher than those reported in a recent Indian national survey. In the current study, the majority of males (76%) were current drinkers and rates of alcohol consumption were also high among females (50%). Heavy patterns of alcohol use were also relatively common with many respondents reporting daily consumption patterns. Many drinkers in the sample reported experiencing negative consequences as a result of their alcohol consumption.

Conclusions: This study indicates that tobacco and alcohol use are significant public health issues in the Spiti Valley. Rates of alcohol consumption and alcohol-related problems are particularly high compared to those found in other parts of India. There is significant concern among residents about the negative effects of tobacco and alcohol consumption on community well-being. The results of this survey will be used as an initial step towards developing a community based-approach to reducing the negative health effects of tobacco and alcohol consumption in the Spiti Valley.

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COMPARING SURVEY DATA FROM THE LAST 3 YEARS ON GLOBAL HEALTH PROJECTS' INFLUENCE ON THE UNDERSTANDING OF GLOBAL HEALTH AND SOCIAL RESPONSIBILITY AMONG PARTICIPANTS

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Purpose of Study: UBC Students’ Global Health Initiative organizes international health projects involving undergraduate medical students as well as students from other faculties. Each year, GHI evaluates how participating in its projects influences students’ awareness and understanding of global health and social responsibility. The purpose of this study is to compare the results from the last three years.

Methods Used: Self-reported prior- and post-trip knowledge were compared using absolute percentage change for four response variables graded on a 0 to 10 scale: cross-cultural communication, project development, project sustainability, and community collaboration. Additionally, student impressions of the sustainability of their project, their attitudes on the importance of knowledge transfer and their overall experience with the project were all recorded. These variables were also graded on a 0 to 10 scale—with 0 being the lowest outcome and 10 being the highest. The averages were taken for each of these parameters.

Summary of Results: With the cross cultural communication parameter, there was an increase of 16.6% in 2007(n = 9), 17.3% in 2008(n = 30), and 18.9% in 2009(n = 23). The project development parameter increased 23.3% in 2007, and 27.8% in both 2008 and 2009. In terms of project sustainability, knowledge values rose 21.2% in 2007, 26.0% in 2008 and 20.0% in 2009. Finally, in terms of community engagement, an increase of 22.2% was seen in 2007, 22.3% in 2008, and 29.0% in 2009. Participant impressions of the sustainability of their project averaged 8.0 in 2007, 7.6 in 2008, and 7.2 in 2009. The importance of knowledge transfer averaged 9.3 in 2007, 9.2 in 2008, and 8.5 in 2009. Finally, the overall experience averaged 8.8 in 2007, 8.9 in 2008, and 8.6 in 2009.

Conclusions: Responses from GHI’s projects over the last three years show similarities: while thoughts on sustainability, knowledge transfer and the experience have fallen slightly in the last year, they still remain high. Furthermore, cross-cultural communication has been the lowest scoring parameter each year, while project development knowledge remains the highest scoring. These findings will help GHI refine its skill-building workshops for project members to work on weakness and build on strengths.

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ANALYSIS OF MACRO AND MICRONUTRIENT DEFICIENCIES IN A RURAL HIMALAYAN COMMUNITY

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1University of British Columbia, Vancouver, BC, Canada; 2University of British Columbia, Vancouver, BC, Canada.

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Purpose of Study: To assess levels of nutrient deficiency in order to evaluate previous health projects run by the Global Health Initiative (GHI) team and to create a list of recommendations to address chronic health problems at a rural boarding school.

Methods Used: Using anthropometric measurements (weight and height - based on World Health Organization [WHO] standards), clinical signs and symptoms and a Hemocue B analyzer, the population was assessed for stunting/wasting, micronutrient deficiency and anemia. A nutrition analysis of the school meals was conducted using a weekly menu, food stock records and Daily Recommended Intake (DRI) values.

Summary of Results: The nutrition/health screen found that 20% of the population showed signs of micronutrient deficiency, 20% is stunted (based on Indian growth charts), and 71% is anemic. The dietary assessment showed student meals are adequate in calories and carbohydrates but inadequate in dietary fat, high biological value (HBV) protein, iron, folate, zinc and B12.

Conclusions: Short growing seasons and snowfall leave Rangrik cut-off from fresh food for seven months per year. Additionally, government funding for school meals remains less than 10US$ monthly per student. Crops from seven greenhouses (planned) will help mitigate micronutrient deficiency. Anemia through year round vitamin rich vegetable availability (previously impossible in the community). Stunting prevalence, a broader nutritional issue, must be curbed through additional school meal funding. These nutritional issues are not unique to Munsel-Ling. While some factors remain geographical, this interdisciplinary model combining health, nutrition and policy work can be highly effective in increasing food security in any marginalized community.

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EFFECTIVENESS OF COMMUNITY HEALTH CARE WORKERS IN THE PREVENTION OF DIARRHEA IN RURAL KENYA

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Purpose of Study: To evaluate the effectiveness of a community health care worker (CHW) program in educating the local population on water treatment using a flocculant-disinfectant and on the treatment of diarrhea with oral rehydration solution and zinc.

Methods Used: Surveys were conducted to evaluate the impact of the CHW program on household water treatment, diarrhea treatment, and diarrhea prevalence in children less than five years of age.

Summary of Results: The point prevalence of diarrhea was reduced by 1.3% (10.9% to 9.6%) with a relative risk reduction of 12.4%; the rate of flocculant-disinfectant use increased by 7% (0% to 7%); and the use of oral rehydration solution increased 6 fold (from 3.5% to 22%).

Conclusions: A volunteer community health care worker program can be implemented in a short amount of time resulting in local changes in water purification habits and diarrhea treatment, but the effect of diarrhea prevalence was small and not significant.

Effectiveness of Community Health Care Workers

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<th>odds ratio</th>
<th>95% CI</th>
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<td>appropriate water treatment use</td>
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<td>1.5</td>
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<td>appropriate diarrhea treatment use</td>
<td>44%</td>
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Session: Student Session VI - Community Health (International) 339 THROUGH THEIR EYES: USE OF PHOTOVOICE TO EMPOWER BOYS IN A UGANDAN ORPHANAGE

M. Sanghera1, Y. Wang1, N. Radziminski1, D. Roccamatisti1, W. Jang1, WQ. Cannon1, F. Gagnon1, M. Kagoda2, A. Kasangaki2, K. Kiproti2, A. Kizito2, AJ. Macnab1

1UBC/BC’s Children’s Hospital, Vancouver, BC, Canada and 2Makerere University, Kampala, Uganda.

Purpose of Study: Organizations caring for orphans and street youth in Africa aim to provide a safe and stable environment, promote school and community involvement and to rehabilitate and reintegrate the well-being of the children they care for. As part of a joint Ugandan/Canadian University partnership we offered a photo-voice project to one representative organization in Kampala. Photo-voice is a validated and creative method of aiding subjects to voice and discuss issues of concern.

Methods Used: Photo-voice involves participatory research. The organization’s director outlined the purpose and invite boys to participate. Follow-up interviews with the investigator - the remainder were encouraged to do the same with the organization’s leaders. All boys were enthusiastic about participation, took pictures successfully, and clearly found the medium an enjoyable way to tell their story. The pictures were also compiled into a group scrapbook with blank pages to allow the boys write descriptions or thoughts in their own words.

Conclusions: Photo-voice provides a creative method for enabling self-expression of issues of personal and social relevance. The successful participation of 20 Ugandan AIDS orphans and street youth in this pilot project suggests the methodology could be more widely applied in this environment. The scrapbook concept is novel and provides opportunities for future individual or group discussions on themes and issues of importance.

Session: Student Session VI - Community Health (International) 340 COMMUNITY RESPONSE TO ALCOHOL ABUSE IN YARMAG SUDDISTRICT OF ULAANBAATAR CITY, MONGOLIA

CR. Huntington University Washington School of Medicine, Seattle, WA.

Purpose of Study: Alcohol abuse has reached epidemic proportions in Mongolia, especially in urban areas. Yarmag subdistrict is one ger district of the capital city, where many rural herders have come to live. Community members believe the effects of poverty and unemployment make ger districts more susceptible to alcohol abuse. The goal of this project was to initiate community-based interventions to reduce harm from alcohol in Yarmag.

Methods Used: Using a community focus group and interviews, the project targeted two groups in Yarmag—(1) teenagers who are statistically at very high risk for alcohol abuse and (2) family physicians who see patients of all ages affected by alcohol abuse and alcoholism. 1. Teens were chosen by the Yarmag social worker for participation in a community workshop. A series of interactive sessions was planned, including time to brainstorm ideas to curb alcohol abuse in youth populations. 2. The project also targeted three family physicians and one resident working at a Yarmag family medicine clinic. Translations of the WHO’s Alcohol Use Disorders Identification Test (AUDIT) and additional material on alcoholism and alcohol abuse were offered to all providers. The necessity and effectiveness of early diagnosis and intervention for patients was discussed. Two Mongolian medical students served as translators and consultants for project design.

Summary of Results: 1. A small group of teenagers came to the first session and expressed a general sense of helplessness concerning alcohol abuse in their community. In a second meeting, teens decided not to continue the sessions. 2. Physicians were pleased with the AUDIT questionnaire. They stated that early diagnoses would be easier with the AUDIT’s scoring system and wanted to incorporate this knowledge into a school education program for October.

Conclusions: The impact of the project depends entirely on the physicians trained. If they increase their screening and intervention efforts as a result of new resources and discussions, it may result in less alcohol abuse among patients. Alcoholism in Mongolia is a vast problem with cultural, historical, genetic, socio-economic, and political factors. Future progress for reducing harm from alcohol will require an increase in political will, more funding, and changes in societal attitudes.
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IMPLEMENTING A SUSTAINABLE HEALTH EDUCATION CURRICULUM FOR THE CHILDREN OF A REMOTE COMMUNITY IN THE INDIAN HIMALAYAS

Purpose of Study: To build upon existing health education projects established by Global Health Initiative (GHI) students and to create a sustainable curriculum for a boarding school in the Spiti Valley region of Northern India.

Methods Used: GHI students oversaw several steps in the design and implementation of the health curriculum to ensure continuity. These included: 1) identification of major health issues through health screens, surveys, and community observation; 2) ongoing meetings with school and community leaders to design an appropriate curriculum; 3) provision of teaching material (resources, posters and teaching outlines) to teaching staff; 4) active involvement in leading lessons from the curriculum; 5) formation of a teaching partnership with local nursing students; 6) promotion of student involvement and ownership of the curriculum through creating posters and reinforcing behavioural changes in the younger students.

Summary of Results: To address the health issues identified, a health education syllabus was created. Topics included hand washing, tobacco, skin infections, oral hygiene, nutrition and water. In 2009, 420 students were provided lessons from each of these topics. Two hand washing stations were constructed and new toothbrushes were distributed to reinforce the lessons provided. The success of the project has been measured by changes in hygiene, specifically an increase in frequency of hand washing and wound cleaning, and the use of more appropriate drinking water sources.

Conclusions: GHI has run health projects at Munsel-Ling School in the Indian Himalayas since 2007. The community approached the 2008 GHI team requesting a health care curriculum to encourage practical applications of basic hygiene and health knowledge. By having teachers and nursing students take part in the curriculum, we can empower the community to take a more active role in health education. The teachers and nurses can provide continual learning as they incorporate the health curriculum into their daily lesson plans. With a successful program in place, the school can act as a model for change for other schools in the Spiti Valley; additionally students can continue to build healthy habits long after GHI has left the community.

Session: Student Session VII - Community Health 342
LOW COST NUTRITION IN GLENIDGE, MT: ONE LESS BOX IN THE GROCERY CART
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Purpose of Study: To show that a homemade version of a commonly consumed boxed meals is more nutritious without significant increase in cost or preparation time.

Methods Used: Glenidge, MT is the seat of Dawson County, whose inhabitants work primarily in Railroad and Agriculture and are of a lower socioeconomic status than average for the state. The county has among the highest rate of diabetes in Montana. Diet choices that are low in saturated fat and sugar, and high in fiber and nutrients help prevent obesity and associated conditions like diabetes and heart disease. Yet people of low income frequently choose lower quality boxed food at the supermarket because it is convenient and inexpensive.

Informal polling at the grocery store was undertaken to determine what boxed foods are popular in Glenidge. Then a homemade recipe for the shopper’s favorite, Hamburger Helper, was developed using Internet recipe resources. The nutritional information, convenience, and cost of boxed hamburger helper were compared to the homemade alternative. Samples of the homemade version and a pamphlet with recipes and information on cost, nutrition, and convenience were distributed during peak shopping time at the local grocery store.

Summary of Results: The homemade version of hamburger helper contained 90% of the calories, 75% of the saturated fat, 750% of the fiber and 5% of the sodium, took 5 minutes longer to prepare, and was the same cost as the boxed equivalent. Seventy samples and 40 pamphlets were handed out.

Conclusions: Low cost but nutritious food choices are possible using the resources of a rural grocery store. Using common ingredients to make a homemade version of hamburger helper achieved significant changes in the nutrient content of a common boxed food. Modifying a popularly consumed food may be an effective way to encourage more nutritious diet. To continue this research, similar comparisons for other prepared foods should be done and made available to the public.

Session: Student Session VII - Community Health 343
STRATEGIES FOR PREVENTION OF CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES IN HIGH SCHOOLS: A FORMATIVE ASSESSMENT
S. Farnsworth, A. Kong, A. Sussman UMN School of Medicine, Albuquerque, NM.

Purpose of Study: Using an adaptation of a community-based participatory research process, we collected formative research data on interpersonal, intrapersonal, institutional, community, and policy level factors that may be used to create a school-wide cardiovascular disease and type 2 diabetes prevention program in high schools to support students in improving nutrition and physical activity.

Methods Used: Six high schools with school-based health centers, with a student population greater than 500 and servicing a predominantly Hispanic student population were recruited. Formative data were collected through each school’s School Health Advisory Council (SHAC). Additional semi-structured interviews with eight parents of overweight/obese (OW/OB) high school students and seven OW/OB students were completed to identify areas for school improvement. A survey based on formative results was created to assess specific strategies within identified school areas for change with regards to acceptability, feasibility and sustainability. SHAC members completed the survey. Quantitative data were analyzed using descriptive statistics while qualitative data were evaluated using an iterative analytic process for thematic identification.

Summary of Results: Key areas identified for change by SHACs include: school policy/systems, school meals programs, competitive foods/beverages, health education, physical education, physical activity, staff wellness, and before/after school programs. Among parents interviewed, 6 were female, mean age was 45 years, and ethnic/racial distribution was 1 Hispanic, 1 Native American, 1 Non-Hispanic white and 1 other. Among students, 4 were female, mean age was 16 years, and ethnic/racial distribution was 4 Hispanics, 2 African Americans and 1 Non-Hispanic white. Key themes identified by respondents for school improvement include: lack of healthy food options, infrequent curriculum/extra-curricular physical activity opportunities and inadequate exposure to health/nutritional information through classroom experiences. Key strategies identified as most feasible, acceptable and sustainable by SHAC members include: marketing campaign to promote nutritious snack/food choices, after school program for students/parents/school staff to engage in non-competitive physical activity aimed at lifelong healthy living, yearly taste tests of healthy foods that reflect a variety of cultures, and community linkages to physical activity opportunities.

Conclusions: Parents and students identified challenges in having access to healthy foods, opportunities for physical activity in the schools and inadequate exposure to health/nutritional information through classroom experiences. High schools were open to creating a healthier environment but strategies to address improvement received varying levels of support.
Purpose of Study: Due to the advancement of medical technology the majority of pediatric cancer patients will survive. The end of cancer treat-
ment does not mean the end of cancer care. Most pediatric cancer survivors are not aware of the risk for late effects nor the treatment they received. The objectives of this study were to characterize the educational services provided by Community Based Organizations (CBOs) specifically for pediatric and young adult cancer survivors. Data obtained will be used to develop a tar-
ged educational intervention (peer navigation) for adolescent and young adult (AYA) childhood cancer survivors.

Methods Used: A convenience sample of 8 CBOs located within California were recruited. Participants completed a 13-item fixed-item response ques-
tionnaire regarding survivorship services provided, prior to an in-depth interview. Quantitative analysis was performed using Excel. In-depth, key informant interviews were transcribed verbatim using “Transcriber Soft-
ware”. Transcripts were loaded into ATLAS.ti to assist in the management of the systematic coding. Qualitative analysis was performed using the Grounded Theory Method. After reviewing the coded data, major themes were then identified.

Summary of Results: The majority of CBOs provided educational material on the possible side effects of treatment and information on where survivors should go to receive their follow-up care. The information least provided by CBOs was educational material on a plan for primary care after cancer treat-
ment and health insurance accessibility.

Conclusions: Community Based Organizations which serve the AYA cancer survivor community support the development of a peer navigator educational intervention. Key elements of the educational intervention include the timing of the intervention to follow the end of cancer treatment and to incorporate sensitivity to the culture of the AYA community. Future research will in-
corporate these findings from the CBOs into the development of the peer navigator intervention and test the acceptability within the AYA survivor population.

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DISASTER AND MASS CASUALTY PREPAREDNESS IN EUREKA, MONTANA
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Purpose of Study: In rural Eureka, Montana, 5000 people rely on two medical clinics for healthcare. The three nearest hospitals are 50 to 70 miles away. Patients requiring substantial emergency care must be transported to a hospital by private vehicle, ambulance or ALERT helicopter flight. The community lacks a disaster plan, but is preparing for a mock mass casualty. The purpose of this project was to contribute to disaster and mass casualty preparedness by identifying community needs and resources, and creating tools to assist the community in disaster planning.

Methods Used: Observation of community medical issues and discussion with local healthcare providers and Emergency Medical Services (EMS) identified the need for disaster/mass casualty planning in Eureka. Emergency medical care is a major concern due to hospital distance, limited resources, and current lack of a community plan. Literature review revealed the basis of rural disaster planning to be integration of community resources, cooperation among healthcare providers and EMS, and communication systems. These priorities led to identification of external resources, design of a resource survey tool and an emergency contact system for clinic staff as well as fa-
cilitating dialogue among healthcare providers, EMS and regional hospitals.

Summary of Results: Communication with a hospital disaster officer iden-
tified external resources, which were summarized for disaster planning. A resource survey tool was designed to assess the ability of office-based med-
ical practices to assist in a disaster. The EMS medical director will use the survey to identify clinic resources, highest level of care, number of patients to receive care and staff available for the clinic on scene at a disaster. It may be reproduced for similar rural communities to use. An emergency contact system was designed for clinic staff and the proposal was submitted to the clinic office manager for its implementation.

Conclusions: Small rural communities like Eureka pose unique challenges to disaster/mass casualty planning, requiring cooperation among EMS and providers. This project enabled local EMS to identify resources through interaction with clinics using the survey tool, and helped clinics to implement basic emergency communications. These steps will assist with themock mass casualty and the eventual development of a community-wide disaster plan.

Session: Student Session VII - Community Health 347
EMERGENCY MEDICAL KIT FOR AFONIKA, AK
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Purpose of Study: The Old Believer (OB) Community of Afognak Island, AK is a small self sufficient, Russian Orthodox community. Emergencies on Afognak Island have occurred related to childbirth, accidental trauma and acute sudden illness in which physicians in Kodiak have been contacted by telephone for medical advice because travel to town has been impossible due to weather. The purpose of this project was to strengthen the relationship between the OB community and a Kodiak physician by designing an emergency medical kit unique for the community. The majority of the kit will be used only under directions from a physician via telephone. A community member will receive limited first aid training covering kit contents and wound care and will manage kit use.

Methods Used: OB members were interviewed about the community health needs and barriers to medical care. In collaboration with a Kodiak physician, a community leader, local pharmacies and professional literature, an emer-
gency kit was compiled based on parameters of cost, safety and efficiency. The community paid for the kit. Color-coded inventory sheets for the contents of the kit were created and five information pages on wound care and suture technique were adapted from the guide Where There Is No Doctor by David Werner. A logbook to track kit usage, relevant phone numbers and full information sheets for prescription medications were included. Two informal trainings were conducted with the community leader on kit use, basic first aid, and wound repair including suture technique.

Summary of Results: This project resulted in the development of a medical kit. Antibiotics, analgesics, first aid, suture supplies and tools were included. The final kit cost was $180. The two training sessions with the community leader were successful; she gained proficiency with suture technique, vital signs, bleeding control and verbally agreed to contact a physician prior to administration of any prescription medications included in the kit.
Session: Student Session VII - Community Health 348

DEVELOPMENT AND EVALUATION OF A SPORTS MEDICINE-BASED CURRICULUM FOR ELITE PRE-PROFESSIONAL BALLET DANCERS

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Purpose of Study: To assess the feasibility and effectiveness of a sports medicine-based educational intervention for elite pre-professional ballet dancers.

Methods Used: 4 week prospective observational study conducted at the Maple Conservatory of Dance in Irvine, CA. 23 dancers aged 14–21(m = 16.48) attended four 1.5 hour educational sessions addressing hip anatomy, biomechanics, and injury etiology, prevention and rehabilitation techniques. The concept of “turnout,” a cornerstone physical skill of ballet, was a key focus. A quasi-experimental design evaluated dancers’ knowledge by a written pre-test and post-test. Comments from dance faculty on the application of skills to daily work were gathered in interview format.

Summary of Results: Prior to the course, 78.3% of the dancers reported experiencing hip pain in the past, and 40% stated they were “somewhat unhappy” with their turnout. Although post-test scores were only marginally higher than pre-test scores (p = 0.15), all 23 dancers demonstrated increased knowledge of hip anatomy, biomechanics, injury etiology/prevention/treatment at the end of 4 weeks. Dance faculty noted a marked increase in focus on areas central to core hip function in the ballet technique as a result of the information presented in the workshops. Participants under age 17 may have attended the pilot workshop in the antecedent 4 week period in which the same curriculum was taught, but for which a formal analysis was not conducted. Dancers participating in the pilot session correctly answered 70 of 75 questions in an informal final session of the workshop. When separately analyzing older first time attendees (n = 5), their scores improved significantly (p = 0.026) whereas the scores of the younger dancers remained relatively constant.

Conclusions: Elite pre-professional ballet dancers can learn about hip anatomy, biomechanics, injury treatment and prevention within an established summer dance intensive program. Most importantly, we demonstrated that integration of a sports medicine program into ballet training is feasible and facilitates students’ understanding of the core function of the hip and pelvis in dance and the origin of hip turnout to facilitate injury prevention.

Session: Student Session VII - Community Health 349

BIRTH SPACING EDUCATION IN THE HISPANIC COMMUNITY OF OTHELLO, WASHINGTON

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Purpose of Study: The birthrate in Adams County, in which Othello is the largest city, is over twice that of Washington State as a whole. The population is 63.8% Hispanic. Motherhood is an important cultural value and still addressing health concerns. Empowering a partnership through a community leader provides a direct conduit for the development of culturally competent care.

Conclusions: Beyond providing a tangible medical kit, this project aimed to establish an evolving dialogue between the Othellean community and a physician whose respect for the community’s cultural and religious autonomy while still addressing health concerns. Empowering a partnership through a community leader provides a direct conduit for the development of culturally competent care.

Method: Through conversations with physicians, nurses and clinic staff, the local Washington State Migrant Council’s daycare center was identified as the venue in which the target population could be most effectively reached. A literature review showed that many women would like help in planning the spacing of their children and prefer information given in a discussion format with both mothers and fathers present. An informal discussion was arranged at the daycare’s next parent’s meeting. Washington State’s First Steps Program, which has been shown to improve adverse outcomes associated with insufficient birthing intervals, was identified as an effective yet underutilized program within the community that families could be referred to. Informational packets discussing contraceptive options were provided in Spanish.

Summary of Results: Seventy-three parents attended the discussion. Both men and women participated through sharing their personal stories and discussing how child bearing has affected their lives. One audience member discussed what services the First Steps program had provided her. After the event was over 13 women picked up informational packets on contraception.

Conclusions: Parents who attended the discussion acknowledged that sufficient care has not been taken in their community in regards to family planning. Resources are available in the community and were presented as effective means of ameliorating the problem. Increased education and awareness of both the problem and the available solutions may have helped a few families to take more control over the planning of their families. With increased education on birth spacing I believe many more families could be helped.

Session: Student Session VII - Community Health 350

FAMILY PLANNING AND BIRTH CONTROL FOR LATINAS IN MOSES LAKE, WASHINGTON

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Purpose of Study: Latinas in Moses Lake have a high risk of unintended pregnancy. These women commonly experience their first pregnancy at a young age and continue to have many children due to poor understanding of birth control options. This project was intended to further the education of Hispanic women with regard to effective birth control options for the purpose of spacing out children through culturally and educationally appropriate methods.

Methods Used: Observing clinicians, social workers, and outreach coordinators identified a community need involving birth control for Latinas. In order to present educational material in a culturally friendly way, a family planning approach to birth control was used. Instead of presenting birth control methods as a means of preventing pregnancy, patient interactions and educational handouts were aimed at presenting birth control methods as a means of family planning for spacing out children.

Summary of Results: A simple family planning brochure was developed for Hispanic women in both English and Spanish to be distributed in clinician offices and through Maternity Support Service visits. Patient education was also achieved through individual consults with patients presenting to the clinic for obstetric visits. One on one interviews were conducted to determine the knowledge patients had regarding birth control options after delivery. Options previously unknown to patients were discussed. In the context of timing for future children patients were very responsive to the idea of birth control other than condoms and permanent sterilization, which were the most widely understood methods pre-consult. The patient interactions received positive feedback, as did the informational brochure. The brochure can be reprinted for future use.

Conclusions: The women at the Moses Lake Community Health Center recognize the need for and benefit of effective, nonpermanent birth control methods for family planning. Many informational resources are available for birth control, but the education and assimilation levels of most Hispanic women in the community limit their knowledge of birth control. Birth control methods need to be presented in a culturally sensitive manner related to family planning, and all of the options for birth control need to be covered in office visits in order to achieve widespread success.
Conclusions: The OI Registry has recruited members from around the world providing a large amount of data for future research, networking researchers and patients to promote research projects. It provides a large amount of self-reported information that is useful in descriptive analyses. Limitations include being self-reported, lack of smoking status, alcohol use, diagnostic tests and timing of treatments compared to fractures. Diagnosis of type is often by clinical characteristics but adding diagnostic tests may increase accuracy of type reporting, particularly with new OI types V-VII. Bone density scans were reported in 58.2–72.7% of members, varying by age and gender. Not all members may have access to healthcare that includes DEXA machines, which may be significant if these members also do not receive treatment for undiagnosed low bone density, warranting future research. We anticipate the OI database will grow as more clinicians and researchers become aware of it and OI patients access it. This registry is likely to be a platform for additional observational studies of OI patients and for recruitment into trials.

Summary of Results: Among 1,138 US members, the mean age was 32.0 (SD 17.5) for women and 25.7 (SD 19.3) for men. Women 18 years or older were 49.7% of the population; Men 18 years or older 20.3%; boys 15.5%; and girls 14.5. OI Type I is most represented (46.1%). A majority reported an OI type without reporting having received a diagnostic test for OI. 50.3% report no fractures before birth. The majority of all types report ability to walk unaided. Type I OI was more closely associated with a walk unaided response than any other OI type.

Purpose of Study: Addressing eating habits through food education in Stevenson, WA

Methods Used: A community discussions with healthcare providers, the emergency medical services coordinator, the high school principal, and the county sheriff was conducted along with clinical observations. Obesity and its associated health conditions were chosen as the target to address. A literature review was conducted to confirm a correlation with food label education. Food props from the grocery store were used as examples in educating the community to choose healthy food options. Cooking classes and cooking demonstrations throughout the community were receptive and interested. An electronic copy of the brochure was left with the project. The project reached around 100 people. The local population was supportive of the project. The project reached around 100 people. The local population was receptive and interested. An electronic copy of the brochure was left with the Rock Creek Clinic for future reproduction.

Summary of Results: The community members were supportive of the project. The project reached around 100 people. The local population was receptive and interested. An electronic copy of the brochure was left with the Rock Creek Clinic for future reproduction.

Conclusions: The project reminded people the tools and discretion they hold to eating healthy. After completing the project, it appears that healthy people were drawn to the booth and its information while people who didn’t make healthy diet a priority were not interested. Therefore the target population was probably not adequately reached. It is difficult to measure the effectiveness of the booth, brochures, and demonstrations but approximately 8% of the population was exposed to the message. To significantly influence the obesity trends in Stevenson, people will need to be exposed to healthier food options. Cooking classes and cooking demonstrations throughout the year to encourage new recipes could gradually change the daily menu in the households of Stevenson to healthier options.

Purpose of Study: CDFMC has many immigrant Latina women in their Ob patient panel. These patients may experience numerous barriers to receiving quality care. Social isolation and lack of access to resources are risk factors for postpartum depression (PPD). When these risk factors are addressed in the antepartum period, the incidence of PPD may be reduced. An intervention was designed to address barriers to care among these women in their 3rd trimester. The intervention provided an opportunity for the expectant mothers to form social networks, learn parenting skills and family planning options.

Methods Used: Multiple sources of information were queried to understand the problem of PPD. A literature review, observation of Ob visits and discussions with health care providers indicated a need for increased social support, family planning and access to parenting skills classes in Spanish. Latina patients due in the next 3 months were identified. An event was planned and patients received invitations via 4 points of contact. The intervention was conducted in Spanish and rotated patients through 4 stations, each provider staffed. The 4 stations were: calming baby, adjusting to life with a newborn, family planning and infant care. Primagravidita mothers were matched with multigravida mothers. Participants were surveyed to join postpartum support groups.

Summary of Results: Of the 23 patients invited, 14 attended with 13 additional children. 4 healthcare providers and 1 interpreter facilitated stations. Each woman rotated through 4 stations for a total of 56 small group discussions. Participants made new relationships, learned to swaddle, shush and care for their newborns and began thinking about pregnancy prevention. Gifts relevant to the postpartum period were distributed, including bath supplies, condoms and swaddling blankets. 70% of the guests indicated interest in new mother support groups, which are being planned by clinic.

Conclusions: Interventions in the antepartum period may reduce PPD risk factors in women facing social isolation and barriers to services. Discussions are underway to repeat the intervention quarterly at CDFMC. Women who meet in the antepartum intervention will continue together in new mother support groups. Interest in educational intervention is high among Latina OB patients and therefore new intervention models must be created in Spanish that are sustainable.
Session: Student Session VIII – Surgery 355

COMPARISON OF ROBOTIC RADICAL PROSTATECTOMY OUTCOMES IN PATIENTS WITH AND WITHOUT PREVIOUS RENAL TRANSPLANTATION

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Purpose of Study: To evaluate the initial series of robotic radical prostatectomy (RP) in patients with previous renal transplantation.

Methods Used: We retrospectively identified all patients who had undergone RP for localized prostate cancer between 2005 and 2008 at a single institution (n = 227). Patients with a prior renal transplant were compared to patients with normal renal function. A four-arm robotic configuration was utilized in all patients. Port placement was modified in prior transplant patients by placing the assistant on the side opposite from the transplant and moving the conventional robotic ports to avoid trauma to the graft. Preoperative demographics, perioperative parameters, and postoperative outcomes were compared using a t-test for continuous variables and chi-square test for categorical variables.

Summary of Results: In comparing the patients with renal transplants to those with normal renal function, there was no difference in ASA score, Gleason score, BMI, EBL, complications, and oncologic results. The renal transplant patients were younger (51 vs. 62.5 years, p = 0.03). The mean operative time was statistically longer for renal transplant recipients (400 vs. 257 min, p < 0.07). This was due to extensive abdominal adhesions from prior peritonitis and increased difficulty in obtaining access to the pelvis. The renal transplant cohort (n = 2) had statistically higher creatinine level due to one patient having two previous nonfunctional renal transplants prior to surgery. The PSA was undetectable in both patients and similarly both were continent at short-term follow-up.

Conclusions: RP is feasible in patients with a prior renal transplant. This study provides the initial series of RP in renal transplant recipients. As a secondary endpoint these patients were compared to those with normal renal function. Although technically more challenging, RP may be performed with acceptable morbidity and early oncologic outcomes similar to other prostate cancer patients.

Session: Student Session VIII – Surgery 356

REGIONAL VARIATION AND TRENDS IN ANTERIOR LUMBAR INTERBODY FUSION

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Purpose of Study: Patients with lumbar radiculopathy requiring surgery may be treated with anterior lumbar interbody fusion (ALIF). This study explores the regional trends and variations for the use of instrumentation, graft, surgical microscope, and neuropsychiologic monitoring during ALIF operations.

Methods Used: An orthopaedic patient database (PearlDiver Inc.) was used to conduct a retrospective review of ALIF patients, examining the use of autograft, allograft, intervertebral cage, instrumentation, intraoperative microscope, and neuropsychiologic monitoring. Data were evaluated by region and year.

Summary of Results: 6,894 patients in the database underwent ALIF surgery from 2004-Quarter-1 through 2007-Quarter-4. There were 468 (6.8%) patients from the Northeast, 1,186 (17.1%) from the Southeast, 3,348 (48.6%) from the South, 1,513 (16.7%) from the West, 4,066 (59.0%) single-level ALIF patients, and 2,828 (41.6%) multi-level ALIF patients. Autograft, allograft, intervertebral cage use rose over 2004-2007 from 30.9%–4.7%, 20.3%–22.0%, and 92.5%–85.7% respectively. 3,067 patients (44.5%) received instrumentation. More multi-level ALIF patients (49.4%) received instrumentation than single-level ALIF patients (41.1%). 577 (8.4%) patients had ALIF surgery performed with the aid of an intraoperative microscope. Over 2004–2007, microscope usage increased from 6.2%–10.1%, being highest in the West (14.2%) and lowest in the Northeast (4.3%). Neurophysiologic monitoring was used for 1,911 patients (27.7%). Neurophysiologic monitoring rates rose from 22.7%–33.3%, being highest in the South (36.5%) and lowest in the Midwest (13.1%).

Conclusions: ALIF procedure technique varies across region and year. Future studies hopefully will elucidate the reasons for this variability, further determine the operating trends, and determine if differing complication rates for different techniques exist and have clinical significance.

Session: Student Session VIII – Surgery 357

PYODERMA GANGRENSUM OF THE FINGER IN A PEDIATRIC PATIENT: A UNIQUE CASE AND CHALLENGING DIAGNOSIS

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Case Report: A 14 year old Hispanic girl with a history of ulcerative colitis presented to our hospital with a one day history of fever, facial edema, and lesions of the left long finger and scalp. Presumed to be abscesses, these lesions were drained in the emergency department. Admitted for further debridement, parenteral clindamycin and Rifampin were begun. A left hand X-Ray showed significant soft tissue swelling with no evidence of osteomyelitis or septic arthritis. Laboratory studies demonstrated elevated ESR, CRP, anemia, hypoalbuminemia, and leukocytosis.

On 8/16/09, a debridement of the distal radial left long digit phalynx was performed, releasing purulence. Warm saline-hydrogen peroxide soaks and dressing changes were begun. On the second postoperative day, despite changing antibiotics to vancomycin and cefotaxime, the patient’s fever reached 102.7 degrees F with worsening edema and cellulitis of the debrided digit. A second operation of the digit was performed on 8/18/09 with placement of a temporary irrigation catheter into the flexor sheath for saline and lidocaine flushes. At this point, she was on a 5-antibiotic regimen. A biopsy of the left long finger obtained showed focally ulcerated skin, subjacent tissue necrosis, and neutrophil infiltration into the dermis.

On 8/21/09, a diagnosis of pyodermagangrenosum was entertained and all antibiotics discontinued. Pimecrolimus 1% cream was applied during dressing changes and all flushes discontinued the following day. Parenteral infliximab was begun with cefazolin, and methylprednisolone was initiated with subsequent disruption of fever and resolution of digital edema. By the fourth day of steroid therapy, a taper was indicated by improving range of motion of the digit, decreased swelling, and a lack of tenderness. Four weeks after surgery, the digit was greatly improved with the exception of dry gangrene at the tip, which was allowed to autoamputate. Full range of motion of the PIP and MCP joints was no longer limited by pain and restored. This is the first reported incidence of digital pyodermagangrenosum in a pediatric patient in which elevated ESR and CRP leukocytosis and fever were evidenced.

Session: Student Session VIII – Surgery 358

A CADAVERIC STUDY OF THE CERVICAL SYMPATHETIC CHAIN AND GANGLIA: POTENTIAL CLINICAL APPLICATIONS

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Purpose of Study: Discrepancies in the description of the detailed anatomy of the cervical sympathetic trunk (CST) could be a cause of complications in surgical procedures of the cervical vertebral column and spine. Inadvertent damage to the CST is a potential risk during a treatment of cerebral vasospasm following subarachnoid hemorrhage as anesthetic is injected at the superior cervical ganglion (SCG) to interrupt sympathetic action at cerebral blood vessels, resulting in vasodilation, improved cerebral perfusion, and alleviating neurological symptoms. The goal of this cadaveric study was to increase the understanding of the anatomical details of the CST, specifically the length of the sympathetic chain, the number and locations of identifiable ganglia, the ganglia’s dimensions, and their spatial relationships to the vertebral artery, an easily identifiable clinical landmark.

Methods Used: Detailed dissections of the neck and upper thorax regions were performed to expose the CST in 20 neck specimens from 10 embalmed human cadavers. The specimens were analyzed using Adobe Photoshop CS3 to trace the sympathetic chain, ganglia, and vertebral artery and to measure all pertinent lengths and distances. The data was analyzed using R statistical software.

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Session: Student Session VIII – Surgery
359 SCARLESS MICROPORRT AUGMENTED RESTORATION OF TRIANGULATION (SMART) SURGERY: A NEW SURGICAL PARADIGM
ND. Krupp, DJ. Greene, P. Mahdavi, J. Chamberlin, KY. Ebrahimi, D. Baldwin Loma Linda School of Medicine, Loma Linda, CA.
Purpose of Study: Laparoendoscopic single-site surgery (LESS) and Natural orifice transluminal endoscopic surgery (NOTES) produce excellent cosmetic outcomes, but are technically challenging with steep learning curves. These challenges have limited their application in urologic surgery. The objective of this study was to test the feasibility of a novel surgical paradigm for minimally invasive surgery that produces a scarless outcome and restores the fundamental principles of triangulation.
Methods Used: Two SMART nephrectomies (Scarless Microporrt Augmented Restoration of Triangulation) were performed in the porcine model. A single 2.5 cm umbilical incision was placed and three additional 2 mm ports were placed in a diamond configuration. Specialized instruments were developed which were passed intra-abdominally and assembled at the umbilicus; thereby providing the functionality of a 5 mm or 10 mm instrument with only a 2 mm skin incision. A pinhole camera was brought in through the umbilical incision but suspended and directed with a 2 mm shaft thereby allowing optimal camera positioning. Only hilar ligation and renal entrapment required use of the umbilical port. All other portions of the case including camera visualization, dissection, cauterization, retraction and suction were able to be performed through 2 mm ports using SMART technology.
Summary of Results: Two porcine SMART nephrectomies were completed with no complications and minimal blood loss. Mean operative time was 99 minutes (82, 115 minutes). The restoration of triangulation made this technique easy to learn and subjectively improved surgeon comfort compared to LESS.
Conclusions: SMART represents a new paradigm for scarless minimally invasive surgery. Application of SMART technology could simplify and improve the acceptance for LESS and NOTES.

Session: Student Session VIII – Surgery
360 TEMPORARY RIGID FIXATION OFFERS BENEFITS OVER THE TRADITIONAL METHOD OF MAXILLOMANDIBULAR FIXATION IN SECURING THE OCCLUSION IN MANDIBLE FRACTURES
BS. Lee, G. Machado, W. Wong, M. Martin Loma Linda University School of Medicine, Loma Linda, CA.
Purpose of Study: Maxillomandibular fixation (MMF), a commonly used method to secure the occlusion in simple mandible fractures, is found to be a lengthy procedure that entails the risk of blood-borne disease transmission. In our retrospective clinical study, a new method of intra-operative temporary rigid fixation (TRF) and dynamic occlusal assessment followed by definitive rigid fixation was used, eliminating the need for the traditional method of MMF.
Methods Used: Clinical and radiographic outcomes were evaluated in a series of 57 consecutive non-comminuted, non-angle fractures of the mandible.
Summary of Results: The overall complication rate was 3.8% (2 patients); non-union in one patient, and numbness of the lower lip in another patient. Pre-morbid occlusion was accomplished in 100% of patients, as determined in the post-operative clinic. No patient required revision of fixation for malocclusion or instability. From this study the TRF technique is found to be more effective in securing the occlusion than the MMF technique as it expedites the procedure, avoids health risks, allows the dynamic evaluation of intercuspal, excursive relations, and protrusive relations before fixation, and also prevents iatrogenic lingual tilt in the coronal plane and lingual splay in the axial plane.
Conclusions: The TRF technique is recommended for practitioners of all experience levels since subsequent conversion from TRF to an MMF- established jaw relation is simple, in case a pre-morbid occlusion is not easily confirmed once TRF is applied.

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361 PROSPECTIVE COMPARISON BETWEEN TWO EXPERIMENTAL NEEDLESCOPIC SUCTION DEVICES
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Purpose of Study: Recent technological advances in minimally invasive surgery have included techniques designed to leave no scar, including laparoendoscopic single-site surgery and needlescopic surgery. A major limitation of needlescopic surgery is the absence of a reliable needlescopic suction device (NSD). The purpose of this study was to compare the ability of two experimental NSDs to suction fluids with varied viscosities and to specifically determine suction rate and clogging time.
Methods Used: A 2 mm diameter hollow core suction apparatus was created that would provide suction through a 2 mm needlescopic port. A second device incorporating a larger diffusion tip that could be assembled internally was also created. The ability of these two devices to suction saline, a mixture of blood (hematocrit 38%), and saline in porcine intestine was compared in vitro. The amount of fluid suctioned per minute was compared between the two tips for the saline, blood, and intestine solutions. The time until suction obstruction was recorded. A student t-test was run to compare flow rates and time to obstruction in 10 separate trials per NSD.
Summary of Results: When tested against normal saline, the conventional single tip NSD suctioned at a rate of 924 cc/min, whereas the diffusing tip NSD suctioned at a rate of 886 cc/min (p = 0.006). In the blood solution, the single tip NSD suctioned at a rate of 820 cc/min vs. the diffusion tip NSD at a rate of 811 cc/min (p = 0.04). In the porcine intestine solution, the single tip NSD suctioned at a rate of 15.0 cc/min with all trials clogging after an average of 2 sec (range 0–7 sec), while the diffusion tip NSD suctioned at a rate of 536 cc/sec and never completely clogged. No clogging was observed in the saline or blood solution.
Conclusions: The suction rate of the conventional simple tip needlescopic device was slightly greater (1–4%) than the diffusion tip in the saline and blood solutions. However, in the intestine solution the simple NSD clogged almost instantaneously, whereas the diffusion tip NSD never completely clogged. Although the diffusion tip had a slightly decreased overall suction rate, it does not become completely obstructed with fat. Future efforts to improve needlescopic suction with high viscosity fluids are necessary.
isolated small intestinal segments of Sprague-Dawley rats, and the springs were deployed to allow expansion intraoperatively. The rats were followed on X-Ray at 24 hours post-op and regularly thereafter.

**Summary of Results:** Higher force springs showed early and consistent perforation at or near the ends of the springs. Lower force springs did not show immediate perforation but often revealed spring curvature during elongation and delayed perforation seen on follow-up X-Ray.

**Conclusions:** Although many types of wire and springs can be made, the springs designed so far have been unable to successfully lengthen small bowel over the course of many weeks, and instead have expanded to their relaxed length immediately, suggesting that the bowels cannot withstand the force applied by the spring. Further research will be needed to determine whether such springs may be used for lengthening of the small bowel. Use of even lower force springs or assistive devices may be necessary to elongate the bowel without perforation.

**Session:** Student Session VIII – Surgery 363

**PRE-OPERATIVE SERUM ALBUMIN LEVEL AS A RISK FACTOR FOR POST-OPERATIVE COMPLICATIONS IN VENTRAL HERNIA REPAIR**


**Purpose of Study:** Roughly 100,000 incisional hernia repairs (IHRs) are performed annually in the USA. Though there have been improvements in suture material and closure technique over the years, the recurrence of IH has not diminished. One reason for this may be that less-carefully studied patient-specific biological factors may influence wound healing after IHR. Past studies have looked at smoking and diabetes as risk factors for post operative wound complications in IHR. Preoperative nutritional status, however, has not been explored in a diverse group of patients undergoing IHR with mesh, such as those cared for at our academic medical center. In this study, it is determined whether there is an association between serum albumin level and postoperative complications in IHR patients.

**Methods Used:** Charts of 247 patients undergoing IHR at an academic medical center from 2003 through 2009 were reviewed for operation, technique, recurrence, complications, relevant laboratory values and patient demographics. Data was analyzed with the two-tailed Fisher exact test.

**Summary of Results:** Of the charts reviewed, 82 IHRs had sufficient details for analysis. Complications were grouped into 3 separate categories: bowel (including iatrogenic bowel injury, ileus, bowel obstruction, adhesion formation, enterocutaneous fistula), wound (including pain and erythema, scar contraction, skin necrosis, wound/mesh infections, hematoma), and recurrence. The only significant difference in average albumin level was the level between the group with no complications (3.41 g/dL) and the group with bowel-related complications (2.28 g/dL). (P = 0.02).

**Conclusions:** Understanding patient-specific risk factors can improve management of IHRs. Establishing that preoperative nutrition is an important factor in determining the postoperative health of an IHR patient may suggest that these patients require adequate nutrition prior to surgery. This would decrease postoperative bowel-related complications such as ileus, bowel obstruction, or enterocutaneous fistulae. These results hold promise for improved IHR patient management in the future, and will be further explored as more data are accrued.

**Session:** Student Session VIII – Surgery 364

**EARLY EXPERIENCE OF THE MARGRON FEMORAL STEM IN TOTAL HIP ARTHROPLASTY AT GREATER LOS ANGELES VETERAN’S ADMINISTRATION HOSPITAL**

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**Purpose of Study:** We performed an early review of a novel femoral stem recently released and withdrawn from the US market. The Margron (Portland Orthopedics, Sydney, Australia) is an uncemented femoral stem that employs differential thread pitch technology and HA coating for femoral fixation. We sought to identify any early complications with this product, specifically aseptic loosening and need for revision surgery.

**Methods Used:** 51 consecutive Margron total hip arthroplasties performed at the West Los Angeles Veterans Association Hospital from March 25, 2004 to October 26, 2007. All were performed by a single attending senior surgeon through a posterior approach. 14 hips were lost to follow-up. Of the 37 patients (4 female, 33 male, average age 61), 28 hips had osteoarthritis, 5 had osteotetrosis, 2 had post-traumatic arthritis, and 1 had rheumatoid arthritis. Metal on metal bearings were employed. Average follow-up was 18 months (range 6 months–46 months).

**Summary of Results:** At latest follow up, 2/37 stems had exhibited radiographic signs of subsidence and aseptic loosening with clinical pain. Both went on to revision surgery (23 and 21 months after index surgery) and were found to be grossly loose. No intraoperative or postoperative femoral fractures were noted.

**Conclusions:** We report a 5% rate of early aseptic loosening in a recently released femoral stem device utilizing a novel method for femoral fixation. This is a concerning rate of failure in light of the extremely low historical rate of aseptic loosening for modern, uncemented femoral stems. Our results coincide with the Australian registry which shows a 3 fold increase of revision surgery at 5 years with the Margron stem vs conventional stems. We recommend that more clinical data be compiled before determining of the Margron stem is safe for clinical use.

**Session:** Student Session VIII – Surgery 365

**CHOLECYSTECTOMY FOR ACUTE CHOLECYSTITIS AT NIGHT DOES NOT RESULT IN ADVERSE OUTCOMES**

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**Purpose of Study:** The purpose of our study was to determine whether the outcomes of laparoscopic cholecystectomy, the most frequently performed procedure by surgical residents, were affected by the time of operation.

**Methods Used:** A retrospective review of all laparoscopic cholecystectomies at Harbor-UCLA Medical Center for acute cholecystitis by the Acute Care Surgery residents was performed between 1/1/2002-3/31/2009. Data collected include patient age, ethnicity, gender, length of hospital stay as well as need for intensive care, time of operation, need for intraoperative cholangiogram (IOC) and endoscopic retrograde cholangiopancreatography (ERCP). A comparison was performed of cholecystectomies performed in the first 16 hours of the typical resident on call day (6AM-10 PM) and the last 8 hours of a resident on call day (10 PM-6AM). Outcome measures were complications, bile duct injury, need to convert to an open operation, and mortality.

**Summary of Results:** A total of 1337 patients with acute cholecystitis received laparoscopic cholecystectomy. 1019 patients received the operation between 6AM–10PM (Period 1), and 265 patients received the operation between 10PM–6AM (Period 2). When comparing the two time periods, the median age was similar between the two groups (37 vs. 36) and there were a similar proportion of females (74.1% vs. 79.2%). The majority of patients were Hispanic (86.2% vs. 85.7%). The median length of hospital stay was also similar (5 vs. 4 days). Approximately 16% of patients required conversion to an operation and this was equal in the two groups. With respect to the outcomes, there was a similar rate of complications for the two periods (2.6% vs. 3.4%). One percent of patients in the Period 1 had a bile duct injury vs. 0.4% in Period 2 (p = 0.5). There was only one mortality in the total patient population.

**Conclusions:** The findings of the study suggest that in the current duty hour era, laparoscopic cholecystectomy performed at night, by residents working beyond 16 hours does not affect outcomes. The new recommendations by the IOM to further decrease duty hours is unlikely to result in improvement in outcomes of this frequently performed operation.

**Cardiovascular III Concurrent Session 8:30 AM Saturday, January 30, 2010**

**Session:** Cardiovascular III 366

**GLUCAGON-LIKE PEPTIDE-1 ATTENUATES POST-RESUSCITATION MYOCARDIAL MICROCYCULATORY DYSFUNCTION**

AN. Beneze1, BB. Dokken1,2, MK. Teache1, RW. Hillwig3, KB. Kerm1

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**Coronary Flow Reserve (CFR)** indicates abnormal myocardial microcirculatory function since these swine intracoronary administration of 60 mcg adenosine. In this study, low CFR technique of intracoronary Doppler flow measurements before and after arrest and at 1 and 4 hours post-resuscitation, was measured using a standard infusions of either GLP-1 (American Peptide, 10 pM/kg/min) or an equalous circulation, animals were blindly randomized to post-resuscitation GLP-1 treated swine when compared to the control group.

**Conclusions:** Post-resuscitation GLP-1 infusion following cardiac arrest significantly improves CFR when compared to placebo-treated animals.

<table>
<thead>
<tr>
<th>Coronary Flow Reserve (CFR)</th>
<th>Pre-Arrest</th>
<th>PR 1 HR</th>
<th>PR 4 HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.6 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>GLP-1</td>
<td>2.6 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.3 ± 0.1*</td>
</tr>
</tbody>
</table>

PR = Post-resuscitation. All data are mean ± SEM. *P < 0.05 vs controls

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**MOLECULAR MECHANISM OF HEME OXYGENASE-1 INDUCTION BY STATINS**

S. Schulz-Geske, FS. Kalish, H. Zhao, HJ. Vreman, RJ. Wong, DK. Stevenson Stanford University School of Medicine, Stanford, CA.

**Purpose of Study:** Statins are widely used for their lipid-lowering effects, which is mediated by inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. Beyond these effects, beneficial cholesterol-independent actions of statins have also been described. We and others have previously shown that statins induce the antioxidant enzyme heme oxygenase-1 (HO-1) in vitro and in vivo, but the mechanism of this induction has not yet been fully elucidated. Bach1, a heme-sensitive transcriptional factor, has been reported to suppress the HO-1 gene. This study addresses the hypothesis that statins induce HO-1 differentially and that an inactivation of the repressor Bach1 is the mechanism by which statins upregulate HO-1.

**Methods Used:** NIH3T3 HO-1-luc (HO-1-luc) cells, stably transfected with the full-length HO-1 promoter, driving expression of the reporter gene luciferase (luc) and NIH3T3 cells, stably expressing Bach1 shRNA (shB), were incubated with 25 and 50µM Simvastatin (SV), Lovastatin (LV), Atorvastatin (AT), and Rosuvastatin (RV) for 6 and 24h. Promoter activity was measured by bioluminescence imaging in HO-1-luc cells. HO-1 mRNA, HO-1 protein, and HO-1 activity was determined in HO-1-luc and shB cells after 1-24h of incubation with 25µM SV or RV by qRT-PCR, Western blot, and gas chromatography, respectively.

**Summary of Results:** All statins studied activated the HO-1 promoter after 6h incubation. SV and RV showed the strongest potency to activate the HO-1 promoter (see Table). SV and RV significantly increased HO-1 mRNA, HO-1 protein, and HO activity in both cell lines. Although SV had the strongest effect on the HO-1 promoter of all statins tested, RV was more effective in inducing HO-1 mRNA and protein as well as HO activity. Compared to HO-1-luc cells, there was a slightly lower, but not significant, induction of HO-1 in shB cells after incubation with SV and RV.

**Conclusions:** We conclude that statins differentially induce the HO-1 promoter, but this induction does not appear to be directly mediated via Bach1. The exact role of Bach1 in statin-induced HO-1 expression needs to be further elucidated.

**Fold Induction (mean±SD) of HO-1 Promoter Activity**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>SV</th>
<th>LV</th>
<th>AV</th>
<th>RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.5±0.1*</td>
<td>1.3±0.0*</td>
<td>1.2±0.2*</td>
<td>1.3±0.1*</td>
</tr>
<tr>
<td>24</td>
<td>1.1±0.1</td>
<td>1.2±0.1</td>
<td>1.1±0.2</td>
<td>1.1±0.2</td>
</tr>
</tbody>
</table>

*P < 0.05

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**DRUG REDISCOVERY: GLYBENCALAMIDE EXHIBITS THROMBOSOME RECEPTOR-DEPENDENT ANTITHROMBOTIC ACTIVITY**

HJ. Ting, F. Khassaeh Western University Hospital Health, San Marino, CA.

**Purpose of Study:** While proper platelet function is a vital component of hemostasis, inappropriate activation of platelets contributes to occlusive disorders such as myocardial infarction and ischemic stroke. One axis of platelet activation involves the synthesis of the lipid mediator thromboxane A2 (TXA2), which operates by binding to its seven-transmembrane receptor (abbreviated as TPR) on the platelet surface. Although this signaling pathway is a clearly established component of thrombogenesis, there are currently no TPR antagonists available for clinical use; and aspirin remains the sole agent targeting this pathway. However, prolonged usage of aspirin is associated with multiple adverse effects, and so there is still considerable interest in developing alternative TPR antagonists. Unfortunately, there are several profound obstacles in translating novel drug discovery into a clinical therapeutic. One solution to these limitations is to investigate new uses for currently prescribed drugs, an approach termed “drug rediscovery”. In the course of pursuing this approach we noticed that the sulfonlurea, glybenclamide, appears to possess several of the pharmacophores known to exist in the well-characterized TPR antagonist SQ29,548. Thus, we predicted it would interact with TPRs (and exhibit antplatelet/antithrombotic activity).

**Methods Used:** See Results

**Summary of Results:** It was found that glybenclamide: 1) inhibited human platelet aggregation induced by the TPR agonist U46619 (1µM) and the TXA2 precursor arachidonic acid (0.5mM), concentration-dependently (1-10µM); 2) displaced SQ29,548 from its binding sites; 3) lacked any detectable effects on aggregation stimulated by 15µg ADP, or the thrombin receptor activating-peptide 4 (40µM); 4) failed to raise cAMP levels; 5) selectively (at 10mg/kg) blocked mouse TPR-mediated aggregation, under ex vivo settings; 6) prolonged (at 10mg/kg) the tail bleeding time in mice; and 7) prolonged (at 10mg/kg) the time for occlusion in a mouse carotid artery thrombosis model.

**Conclusions:** These findings indicate that glybenclamide exerts inhibitory effects on platelet function by specifically interacting with TPR, and exhibits antithrombotic activity. Thus glybenclamide, or a rationally designed derivative, has the potential to be applied in the management of thrombotic disorders.

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**HYPOXIA MIMETIC, COBALT CHLORIDE, MEDIATES C-AMP RESPONSE ELEMENT BINDING PROTEIN DOWN-REGULATION IN CONDITIONED VASCULAR SMOOTH MUSCLE CELLS**

I. Braw1,2, L. Knaub1, J. Reusch1,2, 1 UC Denver, Aurora, CO and 2VAMC, Denver, CO.

**Purpose of Study:** Pulmonary arterial hypertension (P AH) is a proliferative vasculopathy characterized by pathologic findings including intimal hyperplasia and medial hypertrophy of the small pulmonary arteries and arterioles. It is known that vascular endothelial cells (EC) produce chemokines that regulate smooth muscle cells (SMC) phenotype. The transcription factor CREB (cAMP Response Element Binding Protein), is essential to SMC function, maintaining cellular quiescence. It is also known that chronic
hypoxia induces vascular SMC proliferation, but the exact cellular mechanism(s) are incompletely understood particularly when considering EC and SMC crosstalk. CREB down-regulation has been demonstrated in animal models of PAH, but in cultured SMC exposed to hypoxia responses have been variable. We sought to generate a consistent model of SMC hypoxia in vitro, by using previously reported hypoxia-mimetic cobalt chloride (CoCl2). We hypothesize that EC interaction with SMC in the context of hypoxia, cobalt chloride, would lead to consistent CREB down-regulation.

**Methods Used:** Primary EC were serum-deprived for 24 hrs, then exposed to CoCl2 (200 & 600μM) for 24-48 hrs. Serum-deprived SMC were exposed to EC-conditioned media or CoCl2 directly for 24 hrs. Protein extracts were prepared and Western blot analyses were performed and assess the content of target proteins- CREB, HIF 1α (Hypoxia Inducible Factor 1-alpha) and CK2 (Casein Kinase 2).

**Summary of Results:** CoCl2 induced a dose dependent increase in HIF 1α protein in EC and SMC treated with EC-conditioned media. No significant change in HIF 1α protein was observed in SMC following direct exposure to CoCl2. A dose-dependent loss of CREB and phosphorylated-CREB and CK2 was demonstrated in SMC following treatment with EC-conditioned media. In SMC, CoCl2 induced production of reactive oxygen species (ROS) was variable, in contrast exposure to EC-conditioned media consistently elevated ROS production.

**Conclusions:** This data suggests that EC and SMC crosstalk enhances the hypoxic phenotype induced by CoCl2, manifested by increased HIF 1α stability, down-regulation of CREB protein and enhanced ROS production.

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**UTILITY OF EXERCISE TREADMILL TESTING FOR PREDICTING PROGNOSIS IN LOW-INTERMEDIATE RISK WOMEN PRESENTING WITH CHEST PAIN**

B. Chatterton1, D. Chang3, L. Baker1, J. Calkins2, E. Amsterdam1

**UCD School of Medicine, Sacramento, CA; 2Kaiser, Sacramento, CA and 3UCLA, Los Angeles, CA.**

**Purpose of Study:** Current literature suggests that exercise treadmill tests (ETT) yield a high rate of false positive results in women. Because of this limitation, more accurate but higher cost methods, such as stress imaging, have been advocated for initial evaluation for coronary artery disease (CAD) in women. Therefore, we reviewed our results in a large cohort of women who underwent ETT as the initial test for detection of CAD.

**Methods Used:** We included all women with no history of CAD and normal resting electrocardiograms (ECG) who received ETT (Bruce protocol) for evaluation of chest pain at the University of California, Davis, Medical Center from September 1996 to October 2003. Data included cardiac risk factors (RF), degree of exercise-induced ST depression, and functional capacity (METs) on ETT. The Social Security Death Index was queried to obtain follow-up all-cause mortality.

**Summary of Results:** The study group included 1,971 women aged 21–86 yrs (avg. 53 yrs). The majority (1,136, 57.6%) had a low cardiac risk profile (0-1 RF) and 835 (42.4%) had ≥2 RF. There were 331 (16.8%) positive (POS) tests for ischemia (≥1.0 mm ST depression), 1,523 (77.3%) negative (NEG) tests, and 117 (5.9%) non-diagnostic (NonDx) tests. Follow-up interval was 6-13 yrs (avg. 8.5 yrs) during which all-cause mortality was 3.6% (n = 12, 0.4%/yr) in POS group, 3.3% (n = 51, 0.4%/yr) in NEG group and 12.0% (n = 14, 1.4%/yr) in NonDx group. Mortality was significantly higher in the NonDx group versus the POS and NEG groups (p < 0.05). Mortality was unrelated to magnitude of ST depression. However, functional capacity was 8 METs in survivors and 6 METs in those who died (p < 0.05).

**Conclusions:** The rate of positive ETT in women with no prior history of cardiac disease, normal ECG, and a low-intermediate risk profile was not excessive. Long term all-cause mortality was related to functional capacity and number of cardiac risk factors. Survival was not related to ischemic ST depression, but ETT was an effective method for determining prognosis in low-intermediate risk women with normal resting ECGs and no prior history of cardiac disease.
Left ventricular pseudoaneurysm is a rare and potentially fatal mechanical complication of an acute myocardial infarction. Case series have demonstrated that the symptoms at presentation when ventricular pseudoaneurysm is discovered are variable. We present a case of a 71 year-old male with a past history of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease who presented for further evaluation of a six-week complaint of shoulder pain. The onset of the discomfort coincided with a recent fall and with the physical activity of moving furniture. This was initially diagnosed as musculoskeletal pain and treated symptomatically. At subsequent evaluation changes on electrocardiogram prompted further investigation by echocardiography. At the time of echocardiography the patient was discovered to have a narrowed mouthed thin walled left ventricular defect located at the posterior wall. Subsequent evaluation with contrasted computed tomography confirmed the diagnosis of left ventricular pseudoaneurysm. Coronary angiography revealed three- vessel coronary artery disease. The patient then underwent successful three- vessel coronary artery bypass and patch repair of his left ventricle. This case reinforces the need for a high index of suspicion when evaluating diabetic patients in the clinic and demonstrates the utility for multiple imaging modalities when evaluating patients with this life threatening condition.

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RARE BUT LIFE THREATENING MASS OF THE RIGHT ATRIUM: A CASE REPORT
T. Randhawa1,2, M. Ratliff1,2 1UNM Medical Center, Albuquerque, NM and 2Albuquerque VA Medical Center, Albuquerque, NM.

Papillary fibroelastomas are identified incidentally during transthoracic echocardiograms, and few found during cardiac surgeries for other reasons. Despite their benign histology, they can lead to death due to coronary or cerebral embolization or cause severe valvular dysfunction. Literature search showed only 5 previous case reports of rare and life threatening tumor in the right atrium. This report describes the case of a 64 year old male, found to have a right atrial, frond-like mass, attached to the endocardium by a short pedicle during MV repair. Complete resection of the mass was performed and histology confirmed the diagnosis. Surgical resection of the symptomatic tumor is recommended with only rare reports of recurrence.

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PILOT STUDY TO DEVELOP GUIDELINES FOR EVALUATION OF PEDIATRIC CARDIOMYOPATHY
D. Sureka, J. Bernstein Stanford University Hospitals, Palo Alto, CA.

Diagnosing the cause of pediatric cardiomyopathy is challenging due to its etiological heterogeneity. Priority is given to the identification of treatable disorders such as Pompe disease and conditions with predictable co morbidities or high recurrence risk. Evaluative guidelines exist but have not been validated by clinical studies. Our goal is to develop a diagnostic algorithm by identifying clinical and laboratory findings associated with an identifiable cause of cardiomyopathy.

Methods Used: Retrospective chart review was performed on all cases of pediatric cardiomyopathy seen by the Genetics service over a nine year period.

Summary of Results: Twenty-four of fifty-two subjects had an identifiable cause of cardiomyopathy categorized as: primary cardiac, metabolic, storage, syndromic or infectious. Of the five patients with metabolic disease, two had fatty acid oxidation defects and three had mitochondrial disease. All patients with metabolic disease presented with hyperammonemia, hypotonia, weakness or lactic acidosis. Five of six patients with a storage disease had an elevated creatine kinase (CK). The sixth patient did not have CK testing. Karyotype and testing for glycosylation disorders were not diagnostic in any of our cohort.

Conclusions: Preliminary study results indicate a thorough history and physical exam can direct laboratory evaluations resulting in efficient diagnosis. Metabolic labs and CK effectively screened for treatable conditions. Findings of hypotonia, weakness, hyperammonemia and lactic acidosis were associated with the presence of an identifiable disorder. In the face of negative metabolic screening labs and one of the above features, additional work up is indicated including evaluation for mitochondrial disease. An elevated CK should prompt further evaluation for Pompe disease.
hypothese that a normal CK is a negative predictor of infantile Pompe disease.

We propose a stepwise evaluation of cardiomyopathy with initial screening designed to detect treatable conditions. The presence or absence of clinical features will direct further diagnostic evaluation. Expansion of our cohort to include all diagnoses of pediatric cardiomyopathy at our institution will serve to validate our initial findings, and assess if absence of specific markers is a negative predictor of disease.

**Endocrinology II**
Concurrent Session
8:30 AM
Saturday, January 30, 2010

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A CASE OF CONGENITAL HYPOPARATHYROIDISM WITH PERSISTENT HYPERCALCEMIA—WHAT GIVES?
M. Garimella, K. Colleran, MR. Burge, MF. Bouchonville, P. Hassett, G. Comerci
University of New Mexico, Albuquerque, NM.

**Case Report:** A 51 year old woman with congenital hypoparathyroidism was admitted to the hospital for evaluation of persistent hypercalcemia.

The patient was diagnosed early in life and had been on lifelong calcitriol and vitamin D replacement. Recent treatment consisted of Calcitriol 0.25 mcg 3 days a week and calcium carbonate 500 mg three times a day. She had a history of bipolar disorder, and often increased medication doses when she “felt poorly”. In 2003, a diagnosis of milk alkali syndrome was made when she was admitted with hypercalcemia (Calcium=22.2 mg/dL; Ref. Range = 8.5–10.5 mg/dL), metabolic alkalosis, and acute renal failure. Similar presentations occurred over the next several years, prompting her psychiatrist to assume control of her medications. This was successful in keeping her out of the hospital for an extended period of time. Over recent months, however, her serum calcium level again began increasing, requiring interventions with intravenous fluid hydration with temporary improvement. A presumptive diagnosis of hyperparathyroidism due to surreptitious ingestion of medications was entertained.

In September 2009, she was admitted for hydration and observation. Endocrinology consultation noted that her calcium remained high and 1,25-(OH) D levels continued to rise despite discontinuing her calcium and calcitriol supplements (see Table). Evaluation demonstrated a normal SPEP and UPEP, negative PTHp, and an ACE level of 104 U/L (Ref. Range = 9–67 U/L). A PET scan showed extensive lymphadenopathy concerning for lymphoma. A subsequent CT scan revealed peri-bronchovascular nodules in the upper lobe and mediastinal adenopathy. A bronchoscopic biopsy showed non-caseating granulomas consistent with sarcoidosis.

**Conclusions:** To our knowledge this is the first reported case of sarcoidosis occurring in a patient with congenital hypoparathyroidism and chronic renal dysfunction secondary to medullary calcinosis from recurrent milk alkali. We will discuss the nuances of calcium dysregulation seen with these disorders.

---

**Table 1:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Calcium (8.5-10.5 mg/dL)</th>
<th>1,25-OH Vit D (15-75 pg/mL)</th>
<th>1 PTH (12-72 pg/mL)</th>
<th>Creatinine (0.6-1.0 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/06/08</td>
<td>11.2</td>
<td>37</td>
<td>8</td>
<td>2.46</td>
</tr>
<tr>
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<td>12.2</td>
<td>59</td>
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<td>3.37</td>
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<tr>
<td>09/11/09</td>
<td>11.0</td>
<td>81</td>
<td></td>
<td>2.79</td>
</tr>
</tbody>
</table>

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378
TESTOSTERONE LEVELS AND SUBJECTIVE AND OBJECTIVE SEXUAL FUNCTION IN WOMEN WITH HYPOPITUITARISM
J. Scott1, E. Zuckerbraun1, M. Lee1, M. Morgan2, A. Rapkin2, TC. Friedman3, Charles Drew University, Los Angeles, CA and 1David Geffen School of Medicine, UCLA, Los Angeles, CA.

**Purpose of Study:** The psychological and physiological role of testosterone in women sexual function remains poorly understood. Cross-sectional studies have not found a correlation between subjective sexual function and measurements of testosterone. Women with hypopituitarism have severely diminished ovarian and adrenal androgen production and thus represent an excellent model to study the consequences of androgen deficiency.

**Methods Used:** Total testosterone, objective sexual function (blood flow and somatosensory thresholds) and the subjective Female Sexual Function Index (FSFI) were measured in 29 women with documented hypopituitarism (median age 40.6 ± 9.4 years, BMI 30.1 ± 5.1 kg/m2) and 29 healthy volunteers (median age 28.3 ± 8.4 year, BMI 23.6 ± 4.2 kg/m2) in an IRB-approved study.

**Summary of Results:** Total testosterone levels were markedly diminished among women with hypopituitarism (4.74 ± 4.3 ng/dL) compared to normal volunteers (37.0 ± 22.4 ng/dL, p < 0.0002). Patients had significantly lower sexual functioning in all domains of the FSFI compared to controls. In patients and controls together, higher levels of testosterone were significantly correlated with higher levels of sexual functioning in all domains (desire, orgasm, satisfaction, arousal, lubrication, pain, less), and total FSFI. Quantitative somatosensory testing showed that after controlling for age, patients have similar vibration, cold and heat detection compared to controls. Only lower vaginal heat sensation was significantly correlated with higher levels of testosterone. Genital blood flow was similar between patients and controls and was not correlated with testosterone levels. Depression and fatigue correlated with low testosterone levels.

**Conclusions:** Testosterone deficiency in women with hypopituitarism leads to impairment in subjective, but not objective sexual function. Testosterone more likely affects central (brain) rather than peripheral processes. Genital sensation and genital blood flow are probably not testosterone-mediated. These data provide compelling rationale for placebo-controlled, randomized trials of testosterone replacement in women with hypopituitarism.

---

**Table 1:** Treatment groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Placebo</th>
<th>Testosterone</th>
<th>Anastrazole/T</th>
<th>Dutasteride/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Ovaril antagonist</td>
<td>acyline</td>
<td>acyline</td>
<td>acyline</td>
<td>acyline</td>
</tr>
<tr>
<td>Testosterone</td>
<td>T gel</td>
<td>T gel</td>
<td>T gel</td>
<td>T gel</td>
</tr>
<tr>
<td>Enzyme inhibitor</td>
<td>-</td>
<td>anastrazole</td>
<td>dutasteride</td>
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</table>
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EXPERIMENTALLY-INDUCED TESTOSTERONE DEFICIENCY RAPIDLY INCREASES SERUM INSULIN AND INSULIN RESISTANCE IN NORMAL MEN
CN. Snyder, JK. Amory, WJ. Bremner, ST. Page University of Washington, Seattle, WA.

Purpose of Study: The effect of sex steroids on insulin resistance has implications for male cardiovascular health. Low testosterone levels have been linked epidemiologically to decreased lifespan. Insulin resistance may precede diabetes and predict an increased risk of cardiovascular disease. We determined the effect of experimentally-induced testosterone deficiency on insulin resistance in normal men.

Methods Used: In a pilot study, eight healthy men, with an average age of 38 (range 28-50), were treated with the potent gonadotropin-releasing hormone (GnRH) antagonist acyline at a dose of 300 µg/kg subcutaneously on Days 0 and 14. Fasting serum hormones, chemistries and lipids were measured at baseline and after 28 days of testosterone deficiency.

Summary of Results: Experimentally-induced testosterone deficiency significantly increased fasting plasma insulin levels but not fasting plasma glucose levels between Day 0 and Day 28. Consequently, HOMA IR was significantly increased and QUICKI was significantly decreased, indicating increased insulin resistance. Both leptin and adiponectin were significantly increased at Day 28.

Conclusions: This study demonstrates that an increase in insulin resistance occurs within 28 days in normal men with experimentally-induced testosterone deficiency. This occurred without a change in BMI. Decreased testicular hormone levels could act through increased insulin resistance to increase cardiovascular risk.

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ACTIVATION OF TOLL-LIKE RECEPTOR 2 INDUCES TNF-α CYTOKINE RELEASE, ENDOPLASMIC RETICULUM STRESS AND METABOLIC TRANSCRIPTS EXPRESSION IN OBESE HUMAN ADIPOSE TISSUE
EC. Cheang1, M. Metcalf2, A. White3, RW. O’Rourke1,2, * Oregon Health and Science University, Portland, OR and 1Oregon Health and Science University, Portland, OR.

Purpose of Study: Obesity is associated with a state of chronic systemic inflammation that has been implicated in the pathogenesis of many co-morbid conditions including insulin resistance and visceral fat accumulation. Toll-like receptors (TLRs) are known to be the central mediators of inflammation in many pathological mechanisms; however, their role in adipose-based inflammation in obese individuals is poorly understood.

Therefore, the purpose of this study was to investigate the role of TLRs stimulation in regulating cytokines expression, Endoplasmic reticulum stress (ERS) gene and metabolic gene transcriptions in obese human adipose tissues.

Methods Used: Stromal vascular fraction lymphocytes (SVF) were collected from the visceral adipose tissue (VAT) of 8 obese patients undergoing bariatric surgery. TLR-stimulated SVF in vitro culture was studied with the ELISA for identifying cytokines expression such as TNF-α, IL-6, IL-10 and MCP-1. RT-PCR was also done to characterize the metabolic stress response and ERS genes transcription at the transcript level.

Summary of Results: 1. TNF-α cytokines production increased significantly in obese human SVF treated with TLR2 agonist stimulation (374.2 ± 66.9 pg/ml) vs. untreated control (298.0 ± 51.8 pg/ml), *p < 0.011. However, no other significant difference in IL-6, IL-10 and MCP-1 cytokines expression was found in response to other TLR ligands stimulation. 2. Human VAT SVF stimulated with TLR-2 agonist showed a statistically significant up-regulation of ERS gene expression including HSP47 (1.29 ± 0.14; *p < 0.030) and PERK (1.30 ± 0.18; *p < 0.034) as well as a statistically significant increase in metabolic gene expression including JNK (1.30 ± 0.17; *p < 0.031).

Conclusions: For the first time, this study demonstrates the TLR2 ligand regulates TNF-α, a pro-inflammatory cytokine expression in human AT SVF. Activation of TLR2 also significantly up-regulates ER stress and JNK genes transcription in human AT SVF. Although more patient samples are needed to confirm the results, the study gives us insights for how the TLR2 ligand regulates adipose tissue inflammation, which plays an important role in obesity-related diseases.

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ANALYSIS OF 25-HYDROXY VITAMIN D3 AND D1 IN HUMAN SERUM BY 2 DIMENSIONAL LC-MS/MS
JA. Ray1, MM. Kushnir1, AL. Rockwood1,2, AW. Meikle1,2,3, * Oregon Institute for Clinical and Experimental Pathology, Salt Lake City, UT; 2University of Utah, Salt Lake City, UT and 3University of Utah, Salt Lake City, UT.

Purpose of Study: Vitamin D deficiency is known to have diverse effects ranging from ostomalacia to auto immune disorders. The status of Vitamin D is assessed by measuring 25-hydroxy vitamin D (25OHD). Commercial immunoassays for 25OHD suffer from interferences. Our goal was to develop a rapid, sensitive and specific LC-MS/MS method for quantifying 25OHD in human serum.

Methods Used: 100 µL serum aliquots were spiked with internal standard and proteins were precipitated. The samples were filtered and analyzed by LC-MS/MS using two-dimensional chromatographic separation. MRM transitions monitored for 25OHD1 and 25OHD2 were 413/337 and 401/365 respectively. The analysis time was 6.5 min.

Summary of Results: Total imprecision for the method was less than 9.8%. Limit of quantitation and detection for 25OHD1 and 25OHD2 were 1.0 and 0.5 µg/L, respectively. The method was linear up to 1000 µg/L for both analytes. The observed mean recoveries in samples spiked pre-filtration were 91% and 98%, and post-filtration were 106% and 109% for 25OHD1 and 25OHD2, respectively. No interference was observed with structurally similar steroids.

Demin regression equation for comparison with Chemiluminescent Immunoassay (CLIA) method was CLIA = 1.09* LC-MS/MS + 2.4, n = 371, r = 0.788, S<sub>CV</sub> = 6.8. Comparison with commercially available LC-MS/MS methods were LC-MS/MS<sub>ref</sub> = 1.03*LC-MS/MS<sub>ref</sub> + 0.5 (r = 0.991, S<sub>CV</sub> = 1.66) and LC-MS/MS<sub>ref</sub> = 1.045* LC-MS/MS<sub>ref</sub> - 1.1 (n = 91, r = 0.960, S<sub>CV</sub> = 3.2), for 25OHD2 and 25OHD2, respectively. Concentrations of 25OHD in NIST (National Institute for Standards and Technology) standard SRM 972 were found to be between 2-10% of the target values.

Conclusions: The present LC-MS/MS method is free from interferences. Large scatter in comparison with CLIA suggests cross-reactivity in CLIA. Comparison with commercially available LC-MS/MS methods suggests the need for using an LOQ of 1 µg/L for 25OHD2 and 25OHD2. By avoiding the use of dehydrated ions of 25OH2 and 25OHD2 as the molecular and product ions commonly used in LC-MS/MS methods, this method provides more specific MRM transitions that results in improved sensitivity.
Purpose of Study: Levotirothroxine (LT4) therapy is used to suppress TSH production in patients with papillary thyroid cancer (PTC) near-total thyroidectomy (Ttx), to attenuate TSH stimulation of residual normal and malignant thyroid tissue. Serum thyroglobulin (Tg), a protein released from thyroid-derived tissue, is routinely measured to monitor for persistent disease in these patients because levels correlate with tissue mass when TSH is suppressed. There is no current consensus on the optimal degree of TSH suppression, however. One study suggests that TSH suppression <0.4 mL/L does not produce further decreases in serum Tg levels. Given the ability of 2nd generation Tg assays to detect Tg at 0.1ng/dL, we hypothesize maximal serum Tg suppression occurs at TSH <0.1mIU/L.

Methods Used: Retrospective study of serum Tg values in low-risk PTC patients with Ttx at LAC+USC for malignancy, diagnosis of PTC without evidence of extrathyroidal spread, and Tg antibody negativity. All serum Tg tests were performed using a 2nd generation immunometric assay. Patient Tg values (n = 212) were analyzed within 4 TSH groups: 1) undetectable-0.05; 2) 0.05-0.49; 3) 0.1-0.49; 4) 0.5-3.5mIU/L. (normal range). Patient charts were reviewed for clinical hyperthyroidism.

Summary of Results: Median Tg values for groups 1 to 4 were 0.13, 0.15, 0.13, 0.165 ng/dL, respectively. There was a statistically significant difference in median serum Tg among the TSH suppression groups (p < 0.001). Pairwise comparisons found a statistically significant difference in median serum Tg between TSH suppression groups 1 (TSH < 0.05) and 4 (TSH 0.5–3.5) (p = 0.0053), and a trend towards a significant difference between groups 2 and 4. Evidence of clinical hyperthyroidism was not different among the groups.

Conclusion: Suppressive doses of LT4 therapy to achieve TSH levels <0.5 mIU/L may be justified in low-risk PTC patients without evidence of persistent disease. Power may have been insufficient to detect differences between groups 2 and 4. Similar trends may exist in high-risk PTC patients. Prospective studies are warranted to further evaluate the effect of TSH suppression on Tg in both populations.

Session: Endocronology II

384 EFFECT OF HUMAN ISLET AMYLloid POLYPEPTIDE ON AUTOPHAGY IN PANCREATIC BETA-CELLS

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Purpose of Study: Type 2 diabetes (T2DM) is characterized by a deficit in β-cell mass, increased β-cell apoptosis and amyloid deposits derived from islet amyloid polypeptide (IAPP) that has the propensity to form toxic oligomers. We previously found that β-cells from human IAPP transgenic rats (HIP rat), used as a model for T2DM, display an accumulation of ubiquitinated proteins independent of a proteasome impairment. Also, ubiquitinated proteins were recently reported to be degraded by the proteasome or the lysosome-dependent process, autophagy. In this study, we addressed the following: 1) Does h-IAPP affect autophagy in β-cells? 2) Does stimulation of autophagy rescue β-cells from h-IAPP-induced apoptosis? 3) Does inhibition of lysosomal degradation exacerbate h-IAPP-induced apoptosis?

Methods Used: We used isolated islets from wild type (WT) and HIP rats, and rat insulinoma cells (INS) transfected with h-IAPP adenovirus. Autophagy was assessed by immunoblotting for LC3-II, a marker of autophagosome formation, and for p62, an ubiquitin-binding protein, which interacts with LC3-II, allowing lysosomal degradation of polyubiquitinated proteins and itself. Levels of p62 mRNA were evaluated by real time quantitative RT-PCR. Autophagy was stimulated with rapamycin. Lysosomal degradation was inhibited with E64-d/pepstatin A. Apoptosis was evaluated by immunoblotting for the active form of caspase-3.

Summary of Results: We detected a ~2-fold increase in LC3-II and p62 protein levels in HIP rat islets in comparison to WT. Though p62 protein level increased, p62 mRNA level did not. We also detected agglutination of p62 in HIP rat β-cells. These data suggest a defect in lysosomal degradation in cells from h-IAPP transgenic rats. To determine how the expression of h-IAPP induced apoptosis in β-cells. Here, we found stimulation of autophagy with rapamycin decreased h-IAPP-induced apoptosis, whereas inhibition of lysosomal degradation exacerbated h-IAPP-induced apoptosis in INS cells.

Conclusions: Alteration of protein degradation system and β-cell apoptosis induced by misfolded h-IAPP in T2DM models may, at least in part, be mediated by deficiency in lysosomal degradation.

Session: Endocrinology II

385 EFFECT OF INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 REPLACEMENT ON GONADOTROPIN RELEASING HORMONE-ANTAGONIST INDUCED MALE GERM CELL APOPTOSIS IN INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 KNOCKOUT MICE: NEW INSIGHTS INTO REGULATION OF GERM CELL PROGRAMMED CELL DEATH

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Purpose of Study: Apoptosis in male germ cells can be induced by GnRH antagonist (GnRH-A) in rodents and primates. We have recently shown that intratesticular injection of Insulin-like Growth Factor Binding Protein (IGFBP)-3 peptide can also trigger male germ cell apoptosis in the rat and IGFBP-3 knockout (KO) mice are resistant to GnRH-A induced testicular germ cell apoptosis. To further study the role of IGFBP-3 in male germ cell apoptosis, we examined the incidence of germ cell apoptosis in GnRH-A-treated IGFBP-3 knockout mice with or without IGFBP-3 peptide replacement.

Methods Used: Adult (38–43 week-old) male wild type (WT n = 5) and IGFBP-3 KO (n = 13) mice were studied. Groups of WT (n = 2–3) and IGFBP-3 KO mice (n = 3–4) were treated with a single sc injection of vehicle or GnRH-A (acyline 20 mg/kg BW). An additional group of GnRH-A-treated IGFBP-3 KO mice received an intratesticular injection of a synthetic IGFBP-3 peptide at day 13 and 14 post-GnRH-A. Animals were sacrificed at day 15. TUNEL was used to detect apoptotic germ cells. IGFBP-3 expression was demonstrated by western blotting (WB).

Summary of Results: Compared with wild type animals, IGFBP-3 knockout mice demonstrated significant resistance to GnRH-A induced germ cell apoptosis. Local replacement of IGFBP-3 peptide into the testis was able to sensitize germ cells to apoptosis triggered by GnRH-A treatment. Exogenous IGFBP-3 was detected in the mitochondrial fractions of IGFBP-3 KO animals by WB after intratesticular injection of IGFBP3 peptide.

Conclusions: IGFBP-3 plays an important role in male germ cell apoptosis. Mitochondrial enrichment of IGFBP-3 in the testis can be achieved by local injection of the IGFBP-3 peptide.

Session: Endocronology II

386 TESTICULAR HYPERTHERMIA DECREASES RNA HELICASE DDX4 EXPRESSION IN APOPTOTIC GERM CELLS

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Purpose of Study: We and others have previously demonstrated that 1) testicular hyperthermia induced germ cell apoptosis mainly occurs at the early and late stages of the seminiferous epithelia cycle in rat testes; 2) germ cell specific RNA helicase DDX4 (Yas/ Mvh) is expressed in pachytene spermatocytes and round spermatids that are most susceptible to heat-induced apoptosis; 3) RNA helicase DDX4 is one of the major components of the chromatoid body in late spermatocytes and round spermatids; 4) DDX4 Knockout mice are infertile with spermatogenic arrest at zygotene of the chromatoid body; 5) Recent evidence suggests that the chromatoid body is involved in translational regulation in the microRNA pathways of germ cell development. Thus, we hypothesize that increased testicular temperature may alter DDX4 expression and in turn interfere the microRNA pathways leading to germ cell apoptosis. The objective of this study is to determine the role of DDX4 (a germ cell specific evolutionarily conserved RNA Helicase) in the regulatory mechanism of heat induced germ cell apoptosis in rat testis.

Methods Used: Groups of 5 rats were used as control or received mild testicular hyperthermia. Wet heat treatment was performed with submerging rat scrotum containing testes in water bath at 43°C for 15 minutes. Testes samples were obtained at 30 minutes, 2 hours, 4 hours, 6 hours, and 12 hours after heat exposure. TUNEL Assay detected germ cell apoptosis. Western Blot and immunohistochemistry assessed DDX4 expression.

Summary of Results: DDX4 is specifically localized in pachytene spermatocytes and round spermatids in adult rats. Decreased DDX4
expression in heat susceptible germ cells at early and late stages was observed as early as 2 hours preceding the DNA fragmentation in apoptotic germ cells occurring at 6 hours after heat exposure.

**Conclusions:** 1) Decreased testicular specific DDX4 expression disrupting RNA processing in translational regulation contributes to heat-induced germ cell apoptosis; 2) DDX4 is an early germ cell specific responder to heat stress in rat testis; 3) DDX4 may be a candidate target for male contraceptive development.

**Session: Endocrinology II**

**387**

**MICROTUBULE-ASSOCIATED SERINE/THREONINE KINASE 205 IS A NONRECEPTOR ACTIVATOR OF HETEROTRIMERIC G PROTEINS**

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**Purpose of Study:** G-protein coupled receptors are essential for transducing signals from the extracellular environment of a cell and initiating an intracellular response via activation of heterotrimeric G proteins. Microtubule Associated Serine/Threonine Kinase 205 (MAST205) was previously discovered as a novel receptor-independent activator of heterotrimeric G-proteins. Studies in Saccharomyces cerevisiae demonstrated that MAST205 interacts with the heteromeric G protein subunit Gq. Based on these findings, we hypothesize that the kinase domain of MAST205 is responsible for interacting with Gq.

**Methods Used:** Site-directed mutagenesis was used to create two kinase dead mutants by substituting methionine for each of two lysine residues in the kinase domain. The mutants were tested in a yeast strain that lacks a GPCR and contains a human Gq subunit. A growth assay was used to study G-protein signaling in yeast transformed with both wild-type MAST205 and the kinase dead mutants. Yeast were grown on media lacking histidine, adenine, and containing varying concentrations of the histidine synthesis inhibitor 3-amino-1,2,4-triazole. MAST205 was fused to yellow fluorescent protein and expression in yeast confirmed by microscopy.

**Summary of Results:** Wild-type MAST205 signaled well (growth on 5mM 3-AT) whereas the kinase-dead mutants did not signal (no growth on 1 mM 3-AT) despite similar levels of expression. These findings demonstrate a role for the kinase activity of MAST205 in its ability to interact with Gq.

**Conclusions:** The results are relevant because it has been well known that Gq interacts with Na/H exchanger. In addition, it has also been shown that MAST205 inhibits Na/H exchanger NHE 3. Future studies will focus on determining whether the MAST205-Gqi interaction contributes to inhibition of NHE 3 or Gqi-Na/H exchanger interactions.

**Session: General Internal Medicine and Aging**

**389**

**THERMOSENSITIVE BIODEGRADABLE POLYMERIC DRUG DELIVERY SYSTEM TO THE EYE**

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**Purpose of Study:** Poly(N-isopropylacrylamide) (pNIPAAm) is a thermo-sensitive polymer that undergoes a reversible phase transition from liquid state at ambient temperature to solid at 32°C. The purpose of this study is to characterize an innovative polymer composition integrating pNIPAAm of a predefined molecular weight (MW) with biodegradable polyester as a platform for sustained drug release within the eye.

**Methods Used:** Polymer samples were synthesized from NIPAAm monomers and polycaprolactone (PCL) based macro-initiators, and characterized with rheometry. In vitro cytotoxicity and live-dead assays were applied to ensure polymer biocompatibility with NIH 3T3 fibroblast cultures. A 20% pNIPAAm solution was saturated with Norfloxicin antibiotics at 25°C, and drug release studies were performed at 37°C with release rates measured using UV-Vis spectrophotometry. In a pilot study, polymer-drug solutions were injected with a 25G needle into the sub-conjunctival space and in the anterior chamber of New Zealand white rabbit (NZW) eyes (n = 3), followed by monitoring of eye inflammation and drug release to the anterior chamber.

**Summary of Results:** Rheometrical measurements of the polymer’s liquid phase transition showed a sharp increase of the storage modulus (G') near 32°C. Cytotoxicity assays demonstrated good tolerance of the cells after three days of growth over pre-heated polymer. Polymer was loaded with drug and injected with a syringe and 25G needle at 25°C, followed by solidification in less than 10 seconds at 32°C. This phase transition was reversible with lowered temperature. The in vitro drug studies showed an initial burst release within the first 48 hours, followed by steady drug release levels for 3 weeks. In vivo the polymer depots caused an initial moderate inflammation that was resolved after one day, and showed a burst release of drug within the first 4 hours and steady levels over the next 2 weeks.

**Conclusions:** Novel biodegradable thermosensitive polymers have been developed and initial studies demonstrate the feasibility for sustained drug delivery in the eye. Further development is indicated to optimize phase transition kinetics and delivery strategy suitable for clinical application.

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**EVIDENCE THAT ENDOGENOUS INSULIN-LIKE GROWTH FACTOR-1 ATTENUATES ENDOXOTOXIN INDUCED CACHEXIA**

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**Purpose of Study:** Cachexia - inflammatory wasting of lean muscle mass - causes morbidity and mortality in many common diseases, including cancer and advanced renal, hepatic and cardiac disease. Cachexia increases proteolysis while decreasing myogenesis leading to net muscle catabolism. Reduced serum insulin-like growth factor-1 (IGF-1) - a key anabolic hormone - may contribute to cachexia, since exogenously administered IGF-1 can reduce skeletal muscle loss. We hypothesized that endogenous muscle IGF-1 acting as a paracrine factor actively opposes cachexia by inhibiting proteolysis and up-regulating pro-myogenic anabolic signals.

**Methods Used:** Two experiments were performed utilizing subepithelial endotoxin (100ng/gLPS ip) injections to induce cachexia in C57/B6 mice. In Experiment 1 animals were sacrificed 4, 22, and 44 hours after LPS treatment and tissues harvested. In Experiment 2 IGF-1 signaling was blocked during endotoxin-induced cachexia by administering an IGF-1 receptor neutralizing antibody (40mg/kg A12 ip) one day prior to LPS. Animals were sacrificed 22 hours after LPS treatment and tissues harvested. Body composition was analyzed using quantitative magnetic resonance (QMR) and skeletal muscle gene expression was evaluated using quantitative PCR of proteolytic (Atr-1, MuRF1), IGF-1, and myogenic MRF family (MyoD, MRF4, Myf5, Myogenin) genes.

**Summary of Results:** In Experiment 1, maximal induction of proteolytic gene expression occurred 22h after endotoxin administration. Skeletal muscle IGF-1 and MRF family (MyoD, Myf5, Myogenin) mRNA expression decreased significantly at 4h, but IGF-1 and MRF family (Myf5, MRF4) gene expression was significantly elevated at 22h. In Experiment 2, A12 significantly decreased the expression of MRF family genes (Myf5, Myogenin) while increasing expression of proteolytic genes.

**Conclusions:** These results demonstrate that endogenous IGF-1 signaling is activated in muscle during cachexia and attenuates proteolytic pathway gene expression while increasing expression of myogenic genes. Increasing muscle IGF-1 signaling may be a novel treatment paradigm for cachexia.

**Session: General Internal Medicine and Aging**

**390**

**MORGELLONS DISEASE: ANALYSIS OF A POPULATION WITH CLINICALLY CONFIRMED MICROSCOPIC SUBCUTANEOUS FIBERS OF UNKNOWN ETIOLOGY**

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**Purpose of Study:** Morgellons disease is a controversial illness in which patients complain of stinging, burning and biting sensations under the skin.
Unusual subcutaneous fibers are the unique objective finding. The etiology of Morgellons disease is unknown, and diagnostic criteria have yet to be established. Our goal was to identify prevalent symptoms in patients with clinically-confirmed subcutaneous fibers in order to develop a case definition for Morgellons disease.

Methods Used: Patients with subcutaneous fibers observed on physical examination (designated as the fiber group) were evaluated using a data extraction tool that measured clinical and demographic characteristics. The prevalence of symptoms common to the fiber group was then compared to the prevalence of these symptoms in patients with Lyme disease and no complaints of skin fibers.

Summary of Results: The fiber group consisted of 122 patients. Significant findings in this group were (1) an association with tick-borne diseases and hypothyroidism; (2) high numbers from two states, Texas and California; (3) high prevalence in middle-aged Caucasian women; and (4) an increased prevalence of smoking and substance abuse. Although depression was noted in 29% of the fiber patients, pre-existing delusional disease was not reported. After adjusting for non-specific symptoms, the most common symptoms reported in the fiber group were: crawling sensations under the skin; spontaneously-appearing, slow-healing lesions; hyperpigmented scars when lesions heal; intense pruritus; seed-like objects, black specks or “fuzz balls” in lesions or on intact skin; fine, thread-like fibers of varying colors in lesions and intact skin; lesions containing thick, tough, translucent fibers that are highly resistant to extraction; and a sensation of something trying to penetrate the skin from the inside out.

Conclusions: This study of the largest clinical cohort reported to date provides the basis for an accurate and clinically useful case definition for Morgellons disease.

Session: General Internal Medicine and Aging

THE IMPACT OF METFORMIN ON VITAMIN B12 LEVELS IN SUBJECTS WITH TYPE 2 DIABETES

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Purpose of Study: The 2009 American Diabetes Association’s Standards of Medical Care recommend metformin as a first-line therapy for Type 2 diabetes (DM2). Studies have suggested that metformin disturbs the Ca-dependent uptake of the B12-IF complex in the ileum resulting in B12 deficiency. With over 20 million people with DM2 in the U.S. and 40 million metformin prescriptions written in 2008 alone, a large population is at risk of B12 deficiency and it’s sequelae including neurological deficits. The purpose of this pilot study is to characterize the relationship of metformin exposure to hypovitaminosis B12.

Methods Used: 50 veteran subjects, mean age 60 yrs [95% CI, 57–63] and mean time on metformin 5.4 yrs [95% CI, 0.4–12], were assessed during one study visit. Demographics, medical history and dietary information were obtained and BMI was calculated. Subjects were categorized by length of metformin exposure: ≤ 2, 2–4, 4–6, and > 6 years. Subjects were also categorized by ‘mg-years’ (daily dosage x years on drug), which quantified their overall exposure to metformin, similar to the ‘pack-years’ notation used to quantify smoking exposure. These groups were then correlated with B12, Ca++, PO4, and Mg2+ levels.

Summary of Results: In this pilot study, there was a significant difference in the primary endpoint of B12 levels in subjects taking metformin compared to a random sample of 500 veterans (349.1 pg/mL [95% CI, 306–393] vs. 530.9 pg/mL [95% CI, 489–573], P = .0065). 29% of subjects in this study had clinically low B12 values. This is significant compared to the B12 values of 500 random subjects, with only 11.5% having clinically low B12. Regression analysis of B12 and ‘mg-years’ was performed, indicating that 5.93% of B12 variability could be predicted by the length of metformin exposure, however due to the limited sample size this trend did not reach statistical significance (P = .99).

Conclusions: This study showed vitamin B12 levels in our study population of veterans with DM2 treated with metformin were significantly lower compared to a random sample of the veteran population. The results of this pilot study indicate a need for further research on the detrimental effects of metformin on B12 levels. This information is essential and can provide a wide impact on the care of people with DM2.
was not significantly changed at TG > 150 mg/dl. Our results suggest that adequate control of glycaemia and weight may improve diabetic dyslipidaemia. Non-HDL, but not calculated LDL, is a useful therapeutic target at TG >150mg/dl. This study is limited to the predominance of elderly male patients.

mean lipid profile, A1c, BMI by triglyceride classification

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Session: General Internal Medicine and Aging
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RESERPINE FOR PRIMARY HYPERTENSION
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Purpose of Study: To investigate the dose-related effect of reserpine on blood pressure, heart rate and withdrawals due to adverse events.

Methods Used: Systematic review of randomized controlled trials comparing reserpine to placebo in patients with primary hypertension. The databases CENTRAL, EMBASE, and MEDLINE were searched. We also traced citations in the reference sections of the retrieved studies.

Summary of Results: Of 242 studies, 4 trials met our inclusion criteria and were analyzed quantitatively. The results of this systematic review indicate that reserpine has a statistically significant hypotensive effect on systolic blood pressure as first-line agent (weighted mean difference -7.92, 95%CI -14.05, -1.78). It also lowers diastolic blood pressure (-4.15, 95% CI -9.19, 0.90), mean arterial pressure (-7.87, 95% CI-16.86, 1.11) and heart rate (-5.70, 95% CI -21.74, 10.34) but these results were not statistically significant. Rauwolfa, an alternative Rauwolfia serpentina alkaloid to reserpine, seemed to reduce diastolic blood pressure (-10.00, 95% CI -14.44, -5.56) and heart rate (-6.00, 95% CI 9.84, -2.16) with statistical significance. Withdrawals due to adverse effects were not reported in the included trials and as such could not be quantified. The dose-response data are weak and trials with more inclusive dosage range are lacking. As well, parallel placebo controlled data on the various Rauwolfia serpentina alkaloids and the whole root are also lacking to draw conclusive evidence.

Conclusions: The evidence shows that reserpine monotherapy is effective in reducing systolic blood pressure in primary hypertension. It also lowers diastolic blood pressure, mean arterial pressure and heart rate, but these results were not statistically significant compared to its systolic blood pressure lowering effect. However, we could not make definite conclusions as the sample size from these randomized controlled trials was small. For the same reason, a dose-response pattern could not be established.

Session: Hematology and Oncology II
396
INCREASED STABILITY OF ANTI APOTOTIC PROTEINS IN BREAST CANCER CELLS RENDERS THEM RESISTANT TO CYCLOHEXIMIDE INDUCED APOPTOSIS
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Purpose of Study: Breast cancer is a poorly understood complex and heterogeneous disease. Evasion of apoptosis is one of the key properties of cancer cells. The purpose of this study is to elucidate potential mechanisms by which breast cancer cells may evade stress-induced apoptosis using cycloheximide (CHX) as an apoptotic insult.

Methods Used: A panel of normal mammary epithelial (MCF10A, HMLE) and breast cancer cell lines MCF-7, MDA-MB-231 and MDA-MB-468 were treated with CHX (100µg/ml). Apoptosis was measured by fluorometric analysis of caspase-3 activity and TUNEL assay. Anti-apoptotic proteins as well as their ubiquitinated forms were detected by western blot analysis. Immunoprecipitation was performed to examine the associations between E3 ligase and anti-apoptotic proteins.

Summary of Results: In normal mammary epithelial cells CHX induced mitochondria-mediated apoptosis and a 20-fold increase in caspase-3 activity was detected, while breast cancer cells were found to be resistant to CHX-induced apoptosis. We find increased stability of Bcl-2 and Mcl-1 in breast cancer cell lines, which is in sharp contrast to their short half-life in mammary epithelial cells. MG-132, an inhibitor of ubiquitin- proteosome degradation machinery was found to attenuate CHX-induced apoptosis in normal mammary epithelial cells. While the levels of ubiquitinated Bcl-2 and Mcl-1 and their proteosomal degradation increased with CHX treatment in normal mammary epithelial cells, while reduced levels of ubiquitinated proteins were detected in breast cancer cells. While the expression and protein of mule, the mammary epithelial cells, while reduced levels of ubiquitinated proteins were detected, while breast cancer cells were found to be resistant to CHX-induced apoptosis. We find increased stability of Bcl-2 and Mcl-1 in breast cancer cell lines, which is in sharp contrast to their short half-life in mammary epithelial cells. MG-132, an inhibitor of ubiquitin- proteosome degradation machinery was found to attenuate CHX-induced apoptosis in normal mammary epithelial cells. While the levels of ubiquitinated Bcl-2 and Mcl-1 and their proteosomal degradation increased with CHX treatment in normal mammary epithelial cells, while reduced levels of ubiquitinated proteins were detected in breast cancer cells. While the expression and protein of mule, the E3 ligase for Mcl-1, was comparable in normal and transformed cells, its association with Mcl-1 was detected only in normal mammary epithelial cells. Our studies therefore, provide an insight into the mechanisms by which breast cancer cells might evade apoptosis, through increased stability of anti-apoptotic proteins.

Conclusions: Anti-apoptotic proteins are resistant to ubiquitin-mediated degradation in breast cancer cells compared to normal mammary epithelial cells. Therapeutic interventions designed to increase ubiquitination of key apoptotic proteins in breast tumor might reduce tumor burden.
Session: Hematology and Oncology II

397 THERAPEUTIC EFFECTS OF TARGETING INTEGRIN α4β1 IN ITS MECHANISM OF ACTION

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Purpose of Study: Part 1: We treated mice bearing subcutaneously injected Lewis lung carcinoma (LLC) tumors and mice that spontaneously develop breast cancer (PyMT model) with a small molecule inhibitor of integrin α4β1. We wanted to determine if targeting integrin α4 in tumor models has therapeutic effect. Part 2: We recently found that integrin α4β1 is involved in lymph node lymphangiogenesis, or the development of new lymphatic vessels, of which lymphatic endothelial cell (LEC) migration is an essential step. Previous work in our lab showed that PI3-kinase γ activates integrin α4β1 in myeloid cells. To understand the mechanism of how integrin α4β1 is activated we are exploring the role of PI3-kinase α and PI3-kinase γ in LECs.

Methods Used: Part 1: We treated mice bearing subcutaneously injected Lewis lung carcinoma (LLC) tumors and mice that spontaneously develop breast cancer (PyMT model) with a small molecule inhibitor of integrin α4β1. Part 2: We stimulated LEC migration and in vivo lymph node lymphangiogenesis with VEGF-C in the presence of chemical inhibitors to PI3-kinase α and PI3-kinase γ.

Summary of Results: Part 1: Mice treated with the integrin α4 inhibitor have significantly decreased tumor volume and weight in the LLC model and decreased tumor burden in the spontaneous breast cancer model. Examination of tumors in the PyMT model shows a significant decrease in both blood vessel and macrophage infiltration in the treated group compared to the control group. Part 2: Chemical inhibitors to PI3-kinase α, not PI3-kinase γ, block VEGF-C stimulated LEC migration and inhibit in vivo lymph node lymphangiogenesis.


Part 2: PI3-kinase α regulates LEC migration and potentially activates integrin α4β1 in LECs.

Session: Hematology and Oncology II

398 DISCOVERY OF CANCER GENE-MICRONORA REGULATORY NETWORKS IN CANCER

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Purpose of Study: Cancer is a disease of somatic mutation. Genes recurrently mutated in cancer, such as TP53 and KRAS, are implicated as drivers of tumorigenesis. MicroRNAs (miRNAs), a class of small, non-coding, post-transcriptional repressors, have been recently found to play important roles in the regulatory networks of many cancer genes and frequently exhibit altered expression in cancer. We have developed a systematic approach correlating miRNA expression with cancer gene mutation status to discover new regulatory network interactions. Once validated, these interactions represent possible targets for highly-specific cancer therapies.

Methods Used: Cancer gene somatic mutation data and miRNA expression data derived from 714 Sanger Cancer Genome Project cell lines were obtained from the Welcome Trust Sanger Institute and Broad Institute, respectively. A total of 34 cancer genes and 582 miRNAs were analyzed. For each cancer gene, in each cell line, the cancer cell lines were classified into mutant and wild-type groups based on presence or absence of non-synonymous mutations in the gene. Expression of each miRNA was compared between the two groups using Student’s t-tests. To minimize bias introduced by tissue-specific miRNA expression, cell lines were classified by tissue of origin and histology into 36 tumor groups and two types of analyses were performed with respect to these groups: 1) a tumor-specific analysis in which expression levels were compared only within tumor groups and 2) an aggregated analysis in which expression levels were standardized with respect to each tumor group’s wild-type expression level prior to comparison across tumor groups.

Summary of Results: In the tumor-specific analysis, we identified 80 significant cancer gene-miRNA correlations (FDR < 0.01) representing 13 distinct cancer genes and 65 miRNAs within 13 different tumor groups. In the aggregated analysis, we identified 50 cancer gene-miRNA correlations (FDR < 0.01), six of which overlapped with the tumor-specific analysis, representing 9 distinct cancer genes and 45 miRNAs. Our results reinforce interactions such as TP53-miR-34a and VHL-miR-210 which have been previously validated by experiment.

Conclusions: We present a novel approach for the discovery of global regulatory interactions in cancer. Once validated, these interactions represent possible targets for highly-specific cancer therapies.

Session: Hematology and Oncology II

399 FAST NEUTRON RADIOTHERAPY IN THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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Purpose of Study: Malignant pleural mesothelioma (MPM) is a fatal disease lacking standardized treatment. We describe the use of fast neutron radiotherapy in MPM patients referred to the Department of Radiation Oncology at the University of Washington Medical Center.

Methods Used: Retrospective chart review of MPM patients receiving fast neutron radiotherapy treatment from 1980 to 2008. Dates of death were ascertained from patient record or by search of Social Security Death Index.

Summary of Results: A total of 31 MPM patients (27 male, 4 female) received fast neutron radiotherapy as part of their treatment regimen. Median age at diagnosis was 59.7 years (range 46.6–72.3). Brigham stage at presentation was as follows, Stage I: 13, Stage II: 1, Stage III: 8, Stage IV: 2. Seven cases did not have staging information available. Sixteen cases were of epithelial histology, 2 sarcomatoid, 2 mixed or biphasic and 11 cases lacked histologic classification. Eighteen patients received Fast neutron radiotherapy as a component of trimodality treatment which included surgery and chemotherapy. The most common surgery performed was extrapleural pneumonectomy (69.2%) and the most common chemotherapy regimen was a combination of cisplatin, methotrexate and vinblastine (45.8%). The mean radiation dose was 17.2 neutron Gray (range: 8.8–20.4). Median overall survival was 18.2 months (range 0.9–73.3) with no patients currently alive. One patient receiving radiotherapy alone as a palliative measure died during treatment. One patient was unable to tolerate radiotherapy and stopped before completing treatment. On univariate analysis, Brigham stage at presentation was a significant predictor of survival (p = 0.004). No significant differences in survival were observed when comparing patients who received trimodality treatment compared to those who did not. Additionally, no significant impact on survival was observed by histology or chemotherapy regimen, though strata were small.

Conclusions: Fast neutron radiotherapy may be utilized in the management of MPM patients. However, compared to studies utilizing conventional radiotherapy, there was no improvement in outcome even when used in a trimodality regimen.

Session: Hematology and Oncology II

400 OUR EXPERIENCE WITH 72 PATIENTS ON WHOM WE DETECTED ENDOMETRIAL BLOOD FLOW ON DOPPLER TRANSVAGINAL EXAMINATION - A CORRELATIONAL STUDY BETWEEN SONOGRAPHY AND PATHOLOGY


University of California, Davis, Sacramento, CA

Purpose of Study: Uterine cancer is the most common malignancy of the female reproductive system with currently 40,100 new cases and 7,470 deaths reported annually in the United States. Imaging plays an important role in screening for endometrial abnormalities and identifying those that require further evaluation with endometrial biopsy. Currently, transvaginal ultrasound using endometrial thickness parameters is the imaging modality of choice to initially evaluate women with post- or peri-menopausal and intermenstrual uterine bleeding. Given the known role of angiogenesis in tumor growth, the evaluation of tissue vascularization with color flow Doppler may be useful in the prediction of endometrial vascular changes that occur in polyps and malignancies. Here, transvaginal ultrasound with color Doppler is correlated to endometrial biopsy in pre- and postmenopausal women with variable endometrial thickness.

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Methods Used: In this retrospective study, specimens obtained from endometrial aspiration, dilation and curettage or hysterectomy were correlated to previous transvaginal ultrasound exams and examined with color Doppler flow. There were 138 women included in the study, 83 premenopausal and 55 postmenopausal.

Summary of Results: Premenopausal women had detectable blood flow in 76% of polyps and in the sole malignancy while postmenopausal women had detectable flow in 56% of polyps and 60% of malignancies. Irrespective of endometrial thickness, premenopausal women with positive flow were 3 times more likely to harbor a polyp compared to those without. Premenopausal women with thin endometria had detectable flow in 77% of polyps, while most biopsies were benign in those without flow (91%). Premenopausal women with thick endometria had detectable flow in 75% of polyps and in the sole malignancy. Postmenopausal women with thin endometria had detectable flow in 67% of polyps but flow was absent in the sole malignancy. Postmenopausal women with thick endometria had positive flow in 50% of polyps and 75% of malignancies.

Conclusions: Color Doppler adds additional value to the ultrasound examination for detecting endometrial abnormalities.

Session: Hematology and Oncology II

401 ARE THERE AGE DIFFERENCES IN THE CANCER SURVIVORSHIP EXPERIENCE?

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Purpose of Study: Given that there are over 12 million cancer survivors in the United States and this number is expected to rise, a closer look at the long-term psychological and physical effects of cancer treatment is increasingly important. To facilitate this research, the UCLA-LIVESTRONG Survivorship Center of Excellence has established a Cancer Survivor Registry (CSR) that began recruitment in early 2009.

Methods Used: The CSR survey includes extensive medical, demographic, quality of life, psychological, and behavioral questionnaires. We examined responses to the MOS 36-Item Short Form Health Survey (SF-36), Center for Epidemiologic Studies Depression Scale (CES-D), Fatigue Symptom Inventory (FSI), and Pittsburgh Sleep Quality Index (PSQI) questionnaires completed as of 7/09. We hypothesized there would be different outcomes based on current age (survivors < 50 years vs. ≥ 50 years).

Summary of Results: Data from only 57 cancer survivors over the age of 18 are available. An updated analysis with over 90 respondents will be reported at the meeting. The two age groups were similar in gender, education, and time since diagnosis, but differed in type of cancer. Mean time since diagnosis was 11.5 years. Compared to survivors over the age of 50, younger survivors reported more severe depression (38.5% vs. 12.9% with CES-D scores ≥ 16, p = 0.026), more severe fatigue (FSI mean score of 18.08 ± 15.98 vs. 9.13 ± 10.43, p = 0.019), and showed a trend towards worse sleep quality (53.8% vs. 35.4% with PSQI scores > 5, p = 0.164). Younger survivors reported some SF-36 subscale scores that were significantly worse than age-matched controls. Specifically, they differ on the General Health Perceptions scale (a mean of 58.86 ± 24.12 vs. control mean of 75.87 ± 17.86, p = 0.002) and Vitality scale (a mean of 51.68 ± 25.53 vs. control mean of 62.42 ± 19.43, p = 0.042).

Conclusions: Younger cancer survivors report greater depression and fatigue than older ones. They report poorer general health perceptions and lower energy level than age-matched controls. Greater attention to management of symptoms of depression, fatigue, and sleep is warranted and may improve quality of life in younger cancer survivors.

Methods Used: Groups of adult C57/B16 mice with a targeted disruption of Angiopoietin-2 expression (Ang2−/−) and exhibiting defective lymphatic function were compared with wild-type controls (Ang2+/+). Mice were genotyped, weighed and anesthetized and GFP-marked B16-F10 murine melanoma cells were mixed with PBS and injected subcutaneously into the dorsum of the left ear with approximately 250,000 B16-F10 murine melanoma cells and observed for 23 days. At sacrifice, Evans blue dye was injected subcutaneously into the left ear to observe draining lymphatic vessels from the ear to the cervical lymph node. The primary tumor was excised and measured, as well as the sentinel lymph node, lungs and any other gross metastases.

Summary of Results: Primary tumor incidence was 62% (n = 8/13) in Ang2+/+ and 93% (n = 14/15) in Ang2−/−, with average primary tumor size being 4.9mm3 ± 2.30 (X ± SE) in Ang2+/+ and 13.5mm3 ± 7.75 (X ± SE) in Ang2−/−. Secondary cervical tumor incidence was 77% (n=10/13) in Ang2+/+ and 60% (n = 9/15) in Ang2−/−, with average secondary tumor size being 1585mm3 ± 705.5 (X ± SE) in Ang2+/+ and 816.7mm3 ± 227.6 (X ± SE) in Ang2−/− mice. Additionally, there were no lung metastases in Ang2+/+ compared to 23% (n = 3/13) in Ang2−/−.

Conclusions: These findings suggest that intact functional lymphatic vessels play a facilitative role in lymphogenous tumor dissemination but perhaps not in primary tumor growth. Primary tumors within Ang2−/− were in general larger than the primary tumors of Ang2+/+. This interesting finding needs to be confirmed by further study. It is possible that limited lymphogenous spread within Ang2−/− mice forces tumor cell grouping, which may provide selective pressure stimulating primary tumor growth. Nonetheless, the overall effect of defective lymphatic growth and transport seems to have an inhibitory effect on melanoma spread and thus may have therapeutic potential.

Session: Hematology and Oncology II

404 THE EFFECT OF KNOCDED DOWN ONCOSTATIN M EXPRESSION ON HIF1α IN MOUSE MAMMARY TUMORS

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Purpose of Study: Oncostatin M (OSM) is an interleukin-6 cytokine. Its 1986 discovery excited many in the scientific community, as in vitro studies revealed its ability to inhibit cancer cell proliferation and thus led many to believe in its promise as a chemotherapeutic agent. However, though it decreases proliferation, OSM has been shown to enhance the metastatic phenotype. This project aims to attempt clarification of the role of this agent in a mouse model of human breast cancer. Namely, our goal is to correlate OSM expression with that of hypoxia inducible factor 1 alpha (HIF1α), a transcription factor known to enhance angiogenesis and metastasis.

Methods Used: Work in our laboratory points to hypoxia inducible factor 1 alpha as a mediator of OSM’s upregulation of vascular endothelial growth factor (VEGF), a major pro-angiogenic growth factor. Western blots completed in our lab have correlated the expression of OSM with that of HIF1α, a significant correlation in that distant metastases exhibit greater activity of genes responsive to the HIF1α transcription factor than non-invasive tumors. This research aims to correlate OSM expression to HIF1α expression in vivo via immunohistochemistry. Mouse mammary tumor tissue was stained with primary antibody against either OSM or HIF1α; a secondary antibody-horseradish peroxidase conjugate and DAB chromogen was used to facilitate visualization.

Summary of Results: Preliminary data showed that mice who received cancer cells with knocked down OSM exhibit diminished HIF1α expression as detected by immunohistochemistry. However, further blinded analysis revealed no significant difference in staining between the two groups, indicating that our experiment did not successfully prove an in vivo correlation between OSM and HIF1α.

Conclusions: Further optimization of the immunohistochemical methods may elucidate a greater difference in staining. If still no distinction is detectable, it is possible that the hypoxia inherent in many advanced tumors occurs to such a degree that it obscures the effect that reduced OSM expression may have on the expression of the HIF1α transcription factor.
Purpose of Study: Venous thromboembolism (VTE) is a complication of gynecologic surgery that has been attributed to the postoperative state and the presence of malignancy. A previous study of 262 patients who did not receive sequential compression devices (SCDs) or pharmacologic VTE prophylaxis demonstrated a 9.6% incidence of VTE in patients operated on for benign neoplasms and a 35% incidence in those operated on for malignant neoplasms. We sought to determine the difference in the frequency of VTE, defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), between these two groups in our patient population who did receive SCDs and/or pharmacologic VTE prophylaxis.

Methods Used: A chart review was performed on 156 patients who underwent gynecologic surgery at the University of New Mexico Hospital. Seventy-eight patients with benign lesions were matched with 78 patients with malignant lesions. These groups were compared for differences in clinical characteristics, procedures performed, type of VTE prophylaxis used, and the frequency of VTE using Fisher’s exact test or chi-squared test for categorical variables and t-test for continuous variables.

Summary of Results: Data showed no significant difference in the frequency of VTE between benign and malignant groups (1.26% vs. 3.85%, p = 0.067). The two groups had no difference in measured clinical characteristics except for an increased mean body weight in the malignant group (81.3 vs. 73.8 kg, p = 0.024). The malignant group did see more frequent usage of all types of VTE prophylaxis (93.6% vs. 82.1%, p = 0.0479), including either sequential compression devices and/or pharmacologic anticoagulation.

Conclusions: Our results found no difference in the frequency of postoperative VTE between the two groups and also found a decrease in the overall frequency of VTE when compared to the reference study. This suggests that the use of SCDs and pharmacologic prophylaxis equalized the risk of postoperative VTE between patients with benign and malignant neoplasms and substantially decreased the overall risk of VTE in both groups.

Immunology and Rheumatology II
Concurrent Session
8:30 AM
Saturday, January 30, 2010

Session: Immunology and Rheumatology II
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MONOCYTE CHEMOTACTANT PROTEIN (MCP)-1 IS REQUIRED FOR LIVER REGENERATION
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Purpose of Study: The liver is the only internal organ capable of regeneration following an insult like viral infection or surgical resection. Liver regeneration is driven by the coordinated expression of cytokines and growth factors that stimulate proliferation in the remnant liver. Monocyte chemotactant protein-1 (MCP-1 or CCL2) is a chemokine that recruits monocytes, as well as lymphocytes and hepatic stellate cells, to sites of inflammation in the liver. In other model systems, elevated levels of MCP-1 are associated with increased hepatic inflammation and fibrogenesis, assuming inactivation of MCP-1 attenuates liver injury and fibrosis. The purpose of this study was to determine how MCP-1 contributes to liver regeneration elicited by surgical PH.

Methods Used: Following partial hepatectomy (PH) in which 70% of the liver is surgically resected, MCP-1-/-(knockout) mice and wild type controls were euthanized at time points 0, 24, 36, and 48 hours. To detect proliferation, mice were pulsed with BrdU (50 mg/kg) two hours prior to euthanasia at desired time points post-PH. Remnant liver tissue was formalin-fixed for immunohistochemical staining or homogenized for western blot (WB) analysis.

Summary of Results: Based on BrdU-incorporation, hepatocyte proliferation in MCP-1 knockout mice was three-fold lower than in wild type mice at 36 and 48 hr PH. Decreased proliferation in MCP-1 knockout mice was confirmed by decreased expression of PCNA and cyclin A WB in the regenerating liver, which coincided with increased expression of p27Kip1. Levels of the prostaglandin synthesis enzymes Cox-2 and PGES-1 were also increased in MCP-1 knockout mice.

Conclusions: These findings suggest that MCP-1 is required for optimal liver regeneration to occur and that, in the absence of MCP-1, hepatocytes fail to progress to S phase of the cell cycle. Future studies will determine if diminished regeneration in MCP-1 knockout mice results from impaired recruitment and activation of monocytes that produce cytokines necessary for the priming phase of liver regeneration. Moreover, they will explore the relationship between MCP-1 and prostaglandin signaling during regeneration.

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PROTECTIVE ANTI-CANCER VACCINES ELICIT TUMOR-INFLITRATING LYMPHOCYTES WHICH EXPRESS A SPECIFIC CDR3 MOTIF
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Purpose of Study: Cancer is currently a leading cause of death for which curative therapy is largely unavailable. Cancer immunotherapies, including tumor vaccines, comprise a new strategy to combat such diseases. One approach is to immunize patients with peptides that mimic tumor-surface antigens to augment the natural anti-tumor T cell response. These antigenic peptides, or mimotopes, elicit T cells that cross-react with the endogenous tumor antigen. Using the CT26 tumor model in mice, we showed that mimotope vaccination increases the quantity and efficacy of tumor-antigen-specific CD8+ T cells. In addition, we observed a correlation between prophylactic protection from tumor growth and the systemic presence of tumor-specific T cells expressing a particular amino acid motif on the antigen-binding CDR3β loop of their T cell receptors (TCR). Our current study tests the hypothesis that T cells with this CDR3β motif naturally infiltrate established tumors and are amplified after mimotope vaccination. Future studies will determine if these T cells have higher affinity for the tumor antigen, thus furthering understanding of the molecular interactions leading to improved anti-tumor responses and bringing us closer to a goal of effective cancer vaccine design.

Methods Used: We isolated tumor-infiltrating lymphocytes (TIL) from mice that were unvaccinated, vaccinated with endogenous tumor antigen, or vaccinated with a protective mimotope. Mimotope vaccines consist of baculovirus-infected insect cells engineered to express mimotope + MHC Class I. We immunized the mice and transplanted CT26 tumor cells subcutaneously. The tumors were harvested once they were palpable, and tumor-specific CD8+ TIL were sorted using FACS. We sequenced the TCR of TIL and analyzed them for the presence of the CDR3β motif.

Summary of Results: TCR from TIL elicited by protective mimotope vaccines expressed the CDR3β motif with increased frequency compared to TIL from unvaccinated mice.

Conclusions: T cells which contain this CDR3β motif naturally migrate to the tumor and are amplified by the mimotope vaccine. Their increased presence with protective vaccination suggests an important role for these T cells in improving anti-tumor immunity.

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MICROCHIMERISM IN DOWN SYNDROME
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Purpose of Study: Bidirectional traffic of cells across the placenta results in the establishment of small numbers of allogeneic cells known as fetal microchimerism (in the mother) and maternal microchimerism (in the child). Microchimerism has been associated with certain classic autoimmune diseases and protection from cancer - both features of Down Syndrome (DS). The carriage of a DS fetus is associated with increased concentrations of circulating fetal cells and long-term medical risks for the mother such as Alzheimer’s disease. The hypothesis tested is that microchimerism associated with DS has long-term health consequences for both mother and child. In this pilot study, we report the frequency and quantity of maternal microchimerism in individuals with DS, and fetal microchimerism in their mothers.

Methods Used: Total genomic DNA was isolated from peripheral blood mononuclear cells from volunteers with DS (proband, PB) and their mothers (mothers of proband, MPB). PB and MPB were genotyped at the DRB1, DQA1 and DQB1 loci to identify non-shared alleles. In circumstances where HLA alleles were shared, genotyping was performed for other polymorphic genes: AT3, GSTP1, GSTM1, and TG. Utilizing a panel of quantitative-PCR assays targeting DRB1, DQA1, DQB1, or non-HLA polymorphisms to
detect chimeric DNA, the prevalence and quantity of either fetal or maternal microchimerism was determined. For comparison, healthy individuals without DS or pregnant women were selected from a well characterized shared resource cohort.

Summary of Results: Of the 16 DS pairs typed for HLA and non-HLA alleles, 14 PBs and 12 MPBs were informative for at least one gene for which a quantitative PCR assay was available. Maternal microchimerism in DS PB and control PB was 21.4% and 9.8%, respectively; odds ratio of 2.5 (95% CI, 0.37–17). Fetal microchimerism in DS MPB and control MPB was 25% and 21.7%, respectively; odds ratio of 1.2 (95% CI, 0.17–8.0). Concentrations of fetal and maternal microchimerism were similar between cases and controls.

Conclusions: Long-lasting microchimerism was detected in pregnancies affected by DS. The pilot data here demonstrate more frequent maternal microchimerism in DS PB. Because of long-term consequence to both the mother and child in a pregnancy affected by DS, future studies are warranted.

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X-LINKED ANDROGEN RECEPTOR GENE POLYMORPHISM IN MALES WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Purpose of Study: The gender bias (males: females = 1:8) in systemic lupus erythematosus (SLE) led to the hypothesis that a CAG repeat polymorphism in the androgen receptor (AR) gene, with the capacity to modulate androgen-dependent gene transcription, may increase the risk of developing SLE, and/or the severity of SLE.

Methods Used: Thirty-five male SLE patients, who enrolled in the genetic study, met diagnostic criteria for SLE, and had complete medical records, were scored for disease severity using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), a standard, validated damage instrument. These 35 patients, as well as 136 unaffected control men, were genotyped to determine the length of a CAG repeat (from 12 to 27 repeats), which resulted in a polyglutamine tract in exon 1 of AR. A short CAG repeat (<17) confers enhanced transactivation function of the androgen receptor product in vitro. The number of CAG repeats was tested either as a continuous or dichotomized (≤17 vs. >17) variable for association with SLE and disease status. Logistic regression was used to assess the relationship between SDI, CAG repeats, and other clinical variables including age of onset, disease duration, and cumulative steroid dose.

Summary of Results: The number of CAG repeats was not associated with SLE susceptibility, but showed a trend toward longer CAG repeats being associated with a younger age of disease onset (p = 0.13). The number of CAG repeats was inversely correlated with SDI (r = −0.38, p = 0.028), indicating that patients with fewer CAG repeats tended to have more severe damage from their disease. Other than shorter CAG repeat length (<17) (p = 0.038), none of the clinical variables described above was significantly associated with high SDI in these 35 male patients.

Conclusions: These data suggest that, in males who have SLE, short CAG repeats in the androgen receptor gene may be a risk factor for developing more disease damage, while long CAG repeats may be protective. More studies are needed to replicate these findings in larger cohorts. The identification of biomarkers for disease damage has prognostic significance for SLE patients, and may lead to early interventions.

Session: Immunology and Rheumatology II

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CCR7 EXPRESSION IN PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS B CELLS

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Purpose of Study: Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease characterized by hypergammaglobulinemia that leads to inflammation resulting in a significant rate of morbidity and mortality. B cells play a major role in the pathogenesis as they are in part responsible for the autoantibody production. Yet, little is understood about their dysregulation and participation in SLE (Arce E, et al., J Immunol., 167:2361). Recent reports have suggested that Epstein-Barr Virus (EBV) may induce SLE (Harley JR, James JA; Bull NYU Hosp # Dis., 64:45). CCR7 is a chemokine receptor with a role in trafficking T cells and B cells to secondary lymphoid organs. CCR7 has been theorized to be upregulated by EBV (Yoshida R, et al., J Biol Chem., 272:13803). In order to better understand EBV’s role with SLE and the migration patterns of B cells in the disease process, we investigated the expression of the marker CCR7 in pediatric SLE subjects and in healthy controls.

Methods Used: Flow cytometry was used to analyze whole blood samples from 26 pediatric SLE subjects and 8 healthy controls.

Summary of Results: CCR7 expression in pediatric B cells expressing CCR7 was 38.6% and 5.3% in SLE subjects and in healthy controls, respectively. The standard deviations (s.d.) were 27.1% and 4.9%. The mean absolute amount of B cells expressing CCR7 was 348.3 and 46.3 in subjects and in controls, respectively. The s.d. were 312.1 and 44.7.

Conclusions: The fold increase in CCR7 expression in B cells in pediatric SLE subjects suggests that B cells of SLE subjects follow a variant migration pattern. Also, to some extent this data supports the idea that EBV may be involved in the development of SLE. However, the large s.d. suggests that EBV may only be involved in a selected population of SLE subjects and other factors are likely at play.

Session: Immunology and Rheumatology II

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PLASMA REGULATES MONOCYTE PROGRAMMED DEATH LIGAND-1 EXPRESSION IN JUVENILE LUPUS

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Purpose of Study: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibodies and deficient phagocytic activity by monocytes (Mo). The course of SLE alternates between the flare, or active state, and the remission, or inactive state. The flare state of SLE has been correlated with loss of Programmed Death Ligand-1 (PD-L1) expression on Mo. PD-L1 is a critical regulator of the immune response. It controls effector T lymphocytes to maintain immune tolerance and protect tissues from immune-mediated damage. Dysfunctions of the PD-L1 pathway have been reported in various autoimmune diseases, including SLE, rheumatoid arthritis, and Grave’s disease. We hypothesized that plasma from SLE patients contains soluble factors that regulate PD-L1 expression in Mo.

Methods Used: 9 patients aged 8 to 17 were studied, along with 4 age-matched healthy controls. Peripheral blood mononuclear cells (PBMC) were incubated for two days with plasma obtained from either healthy donors or SLE patients. The expression level of PD-L1 on Mo was assayed by four-color flow cytometry. Cytokines were assayed in plasma samples and PBMC culture supernatants by Luminex cytokine assay.

Summary of Results: An average of 61% of Mo from SLE patients in flare expressed PD-L1 compared to 71% of Mo from healthy donors. Plasma from healthy donors induced PD-L1 expression in SLE flare Mo by 38% compared to plasma from patients with active disease (p < 0.05). SLE flare plasma did not downregulate PD-L1 expression in healthy Mo. We detected decreased levels of TNF-α in SLE PBMC culture supernatants compared to healthy PBMC. Blocking TNF-α in healthy plasma with a specific monoclonal antibody inhibited PD-L1 upregulation in SLE Mo.

Conclusions: Lupus flare plasma does not contain factors that can inhibit PD-L1 induction in Mo. In contrast, the plasma of lupus patients in a flare state is missing soluble factors that are required for PD-L1 expression in Mo. TNF-α is a soluble inducer of PD-L1 expression in Mo and may be a key regulator in lupus. Further understanding of the mechanism of PD-L1 dysregulation in SLE could lead to new treatments and clinical assays to develop more specific treatments for SLE patients.

Session: Immunology and Rheumatology II

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B-CELL LYMPHOMA IN JOB SYNDROME OF HYPER-IgE AND RECURRENT INFECTIONS

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Purpose of Study: The autosomal dominant Job syndrome of Hyper-immunoglobulin E and recurrent infections is a rare primary immunodeficiency characterized by high serum levels of IgE, recurrent severe staphylococcal and fungal infections, skeletal anomalies, unusual...
facies and altered inflammatory responses. With the discovery of mutations in the STAT3 gene in the majority of the cases of Hyper-IgE syndrome, it is now possible to make a molecular diagnosis of this disease. Both primary and secondary immunodeficiencies are thought to predispose one for development of malignancy. Several cases of lymphoid malignancies have been reported in Job syndrome patients, but the reason for this increased risk or its association with particular STAT3 mutations is yet to be determined. Here we report a 48-year old male with Job syndrome of hyper-IgE and recurrent infections who presented with a parotid mass that was identified as a diffuse large-B cell lymphoma.

Methods Used: Immunohistochemical stains were used to characterize the lymphoma. We have used a PCR-based high-resolution DNA-melting assay followed by targeted sequencing to scan selected exons of the STAT3 gene for mutations.

Summary of Results: Immunohistochemical stains highlighted scattered small T lymphocytes and large atypical B cells strongly positive for CD20 in the parotid mass biopsy. We have scanned for mutations in the proband and two of his affected children as well as 11 unaffected family members and determined that the mutation arose in the proband and it was transmitted to two of his four children. The mutation identified leads to R382Q change in the DNA-binding domain of STAT3 protein. We have found no mutations in STAT3 in any of the unaffected family members.

Conclusions: Job syndrome is associated with increased risk of lymphoma. The mechanism of lymphomagenesis is not known. With the discovery of mutations in the STAT3 gene we can now determine genotype-phenotype associations and investigate the molecular pathogenesis of lymphoma development in Job syndrome of Hyper-IgE and recurrent infections.

Session: Immunology and Rheumatology II

412 MARKED INCREASES IN BOTH PROINFLAMMATORY AND DOWN-REGULATORY CYTOKINE CONCENTRATIONS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Purpose of Study: Multiple sclerosis (MS) is a progressive autoimmune disease resulting in demyelination of the central nervous system. The inflammatory nature of MS is evident by the increased infiltration of macrophages, monocytes, and T-cells surrounding acute and active-chronic plaques, which suggests the participation of immunoregulatory cytokines. The purpose of this study was to determine if there are differences in cytokines and other inflammatory markers in serum from 647 diagnosed MS (24% male, mean age 47.2 ± 12.1y; 76% female, mean age 48.8 ± 11.7y) and 109 age and sex matched normal controls.

Methods Used: We utilized an in-house developed multiplexed immunosay to simultaneously assess the serum concentrations of 13 cytokines inflammatory markers including IFN-γ, IL-1β, 2, 4, 6, 8, 10, 12, 13, TNF-α, IL-2, and soluble CD40 ligand in the patient and control groups.

Summary of Results: Significant increases in cytokine concentrations between MS patients and normal controls were found for 1) TH1 cytokines; IFN-γ (mean 5.7 vs 0.2 pg/ml, p = 0.002) and IL-2 (mean 7.3 vs 1.6 pg/ml, p = 0.0005); 2) Pro-inflammatory monokines; IL-1β(mean 35.9 vs 13.5 pg/ml, p = <0.0001), and TNF-α (mean 2.5 vs 1.3 pg/ml, p = 0.01) as well as 3) TH2 regulatory cytokines; IL-4 (mean 2.8 vs 0 pg/ml, p = <0.0001) and IL-13 (mean 5.7 vs 0.8 pg/ml, p = <0.0001).

Conclusions: The profiling of cytokines in MS may help to identify the mechanisms involved in this common, progressive, autoimmune neurological disorder which could possibly lead to new methods of treatment employing cytokine or cytokine receptor blocking agents, or anti-inflammatory cytokines.

Session: Immunology and Rheumatology I

413 MAGNETIC RESONANCE IMAGING AND BRAIN HISTOPATHOLOGY IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Purpose of Study: Magnetic resonance imaging (MRI) often demonstrates brain lesions in neuropsychiatric systemic lupus erythematosus. The present study compared post-mortem histopathology with pre-mortem MRI in NPSLE.

Methods Used: 200 subjects with NPSLE were studied prospectively with MRI over a 10-year period during which 22 subjects died. In 14 subjects, a brain autopsy with histopathology that permitted direct comparison with pre-mortem MRI was successfully obtained. Surface anatomy was used to determine the approximate location of individual lesions.

Summary of Results: Pre-mortem MRI findings in fatal NPSLE were small focal white matter lesions (100%), cortical atrophy (64.3%), ventricular dilatation (57.1%), cerebral edema (50%), diffuse white matter abnormalities (42.9%), focal atrophy (35.7%), cerebral infarction (28.6%), acute leukoencephalopathy (25%), intracranial hemorrhage (21.4%), and calcifications (7.1%). Microscopic findings in fatal NPSLE included global ischemic changes (57.1%), parenchymal edema (50%), microhemorrhages (42.9%), glial hyperplasia (42.9%), diffuse neuronal/axonal loss (35.7%), resolved cerebral infarction (33.0%), microthromboemboli (28.6%), blood vessel remodeling (28.6%), acute cerebral infarction (14.3%), acute macrohemorrhages (14.3%), and resolved intracranial hemorrhages (7.1%). Cortical atrophy and ventricular dilatation seen by MRI predicted brain mass at autopsy (r = −0.72, p = 0.01, and r = −0.77, p < 0.01, respectively). Cerebral autopsy findings, including infarction, cerebral edema, intracranial hemorrhage, calcifications, cysts, and focal atrophy were also predicted accurately by pre-mortem MRI.

Conclusions: Brain lesions in NPSLE detected by MRI accurately represent serious underlying cerebrovascular and parenchymal brain injury on pathology.

Session: Immunology and Rheumatology II

414 COMPARISON OF DIAGNOSTIC ACCURACY OF QUESTIONNAIRE AND AUTOANTIBODY TESTING FOR UNDIAGNOSED INFLAMMATORY ARTHRITIS IN SEQUENTIAL HEALTH FAIR SCREENS

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Purpose of Study: This study compared the results of health fair screens in 2008 and 2009 to determine reproducibility of diagnostic accuracy of questionnaire and autoantibody testing for undiagnosed inflammatory arthritis (IA).

Methods Used: Free Colorado health fair screening for IA for those without prior diagnosis was offered in 2008 and 2009. Screening included: demographic data, Connective Tissue Disease Screening Questionnaire (CSQ, which assesses self-reported symptoms of IA) and rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) testing. At all 2008 and selected 2009 screening sites subjects also had limited joint exam, and ≥2 swollen joint was designated as IA. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated for CSQ (≥3 positive responses, highly specific for IA in prior studies) and/or RF/CCP testing for IA on exam.

Summary of Results: In 2008 and 2009, 601 and 962 subjects were screened (including exam), respectively. Mean age of subjects in each year was ~58. In 2008, 14% of subjects had IA on exam versus 9% in 2009 (p < 0.05). Other results are presented in the table.

Conclusions: Compared to 2008, 2009 CSQ and RF/CCP testing for IA had decreased sensitivity and PPV, increased specificity and a similar NPV. Only specificity was statistically significantly different (non-overlapping CL). Broadly similar PPV/NPV in 2008/2009 suggest that health fair screening with CSQ and RF/CCP testing without joint exam may be useful for identifying...

*Results of Health screening in 2008 and 2009

<table>
<thead>
<tr>
<th>Subject</th>
<th>2008 (N=601)</th>
<th>2009 (N=962)</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
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*Results for diagnostic accuracy are reported as percentages with 95% confidence limits (CL)
Session: Immunology and Rheumatology II

415 IDENTIFYING ENVIRONMENTAL FACTORS & THEIR ROLE IN THE DEVELOPMENT OF PSORIATIC ARTHRITIS

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Purpose of Study: To identify and characterize the environmental factors that contribute to the development of PsA.

Methods Used: In this case control study, a questionnaire was administered to cases (Psoriatic Arthritis, PsA) and controls (Psoriasis, Ps). All PsA patients were recruited from the University of Toronto PsA Clinic and were recently diagnosed (<7 yrs) by a rheumatologist using the CASPAR criteria. All Ps patients were recruited from a longitudinal University of Toronto Ps cohort study, and were previously diagnosed by a dermatologist (arthritis ruled out by a rheumatologist). We compared the environmental events that occurred prior to arthritis onset between cases and controls since 1999. This included: occupational tasks, physical activity, psychological stressors, vaccinations, infections, and physical injury. Ps patients were assigned arthritis reference dates for statistical comparison purposes.

Summary of Results: 119 PsA patients were compared to 119 Ps patients. The mean ages were 46 and 48 years old (s = 12.8 & 13.8), with 43% & 40% females, respectively. Data analysis included univariate analysis, expressed in odds ratios (OR), confidence intervals (CI), and p-values. The environmental events associated with an increased risk of developing PsA are: Lifting Cumulative Loads >100lb/hr (OR = 3.22, 95% CI = 1.65,6.31, p = 0.0006), Any Injuries Except Road Traffic Accidents or Fractures (OR = 2.67, 95% CI = 1.30,5.47, p = 0.01), and Any Severe Infection (ie: prescribed antibiotics & hospitalized, OR = 5.72, 95% CI = 1.22,26.89, p = 0.03). Other trends correlating to increased PsA risk are: Any Infection (ie: prescribed antibiotics) (OR = 1.64, 95% CI = 0.92,2.93, p = 0.09), and Pushing Cumulative Load >200lb/hr (OR = 1.98, 95% CI = 0.98,3.97, p = 0.06).

Conclusions: Certain tasks, injuries, and infections were identified to increase the risk of developing PsA from Ps. The clinical applications may include: designing diagnostic tools, and implementing preventative or non-medical therapeutic recommendations to minimize the risk of developing PsA. Future steps involving further statistical analysis will determine the significance of hormonal exposures, lifestyle factors, and other traumatic events.
Purpose of Study: Intrauterine growth restriction (IUGR), one of the most common disease states of newborns, predisposes infants to a variety of diseases including bronchopulmonary dysplasia (BPD) and vitamin A deficiency (VAD). Vitamin A, or retinoic acid (RA), acts via retinoic acid receptors, α, β, and γ (RARα, RARβ and RARγ, respectively) to effect gene transcription. The role of the RARs is vital for normal lung development as demonstrated by knockout mice. However, the effect of IUGR on RAR gene expression and retinoic acid levels has not been well elucidated. We therefore hypothesized IUGR would decrease RAR gene expression and serum retinoic acid levels, and would adversely affect lung architecture at critical stages of rat lung development.

Methods Used: We used a vascular model of IUGR in the rat and measured mRNA and protein levels of RARα, RARβ and RARγ using standard methods. Measurements were performed at 3 ages - day 0 (D0), day 6 (D6) and day 21 (D21) of life. We used immunohistochemistry (IHC) to evaluate localization of RARs. High performance liquid chromatography was used to measure serum RA levels, and morphometric analysis was incorporated to assess quantitative architecture changes in the rat lung.

Summary of Results: IUGR significantly decreased gene expression of RARα in both sexes and RARβ in males only at D0, the saccular stage of rat lung development. At D6, the alveolar stage of rat lung development, IUGR significantly decreased mRNA levels of RARγ without changing protein abundance. Contrary to our hypothesis IUGR actually increased gene expression of RARγ at D21, a time of waning lung development. The noted changes in gene expression caused by IUGR occurred in the absence of any changes in serum levels of retinoic acid or RAR localization at D6 or D21, or quantifiable thickenings in lung architecture at any of the ages.

Conclusions: We conclude that IUGR decreases expression of RARα, RARβ and RARγ at critical stages of rat lung development and does so in the presence of normal serum retinoic acid levels. As hypothesized, effects of IUGR showed gender specificity, and males appear to be more adversely affected. We speculate that IUGR results in prenatally reprogramming, the effects of which alter retinoic acid signaling pathways.

Session: Neonatal Pulmonary II

ALVEOLAR SIMPLIFICATION PERSISTS IN THE LUNG OF PRETERM LAMBS FOLLOWING 3 DAYS OF MECHANICAL VENTILATION AND 10 WEEKS OF RECOVERY

MJ. Dahl, JM. Alvord, CA. Blair, ZM. Wang, L. Dong, A. Wint, MJ. McCoy, R. McKnight, DM. Null, BA. Yoder, RH. Lane, KH. Albertine University of Utah, Salt Lake City, UT.

Purpose of Study: Preterm (PT) neonates who develop neonatal chronic lung disease (CLD) have alveolar simplification and frequently long-term consequences, such as recurrent respiratory problems. The underlying mechanisms that lead to long-term consequences are unknown. To begin to investigate long-term consequences, we modified our PT lamb model of neonatal CLD to deliver the preterm lambs earlier in gestation, wean them from ventilation support, and let them recover for ~3 months, which is equivalent to ~2 years postnatal age in humans. We hypothesized that alveolar simplification and molecular changes will persist in the lung of preterm lambs following 3d of MV and 10–11 weeks of recovery.

Methods Used: Pregnant ewes were given dexamethasone before delivery of PT lambs (~128d gestation [equivalent to ~28wk gestation in humans]; term ~150d). The PT lambs were intubated, given surfactant, managed by MV for 3d, weaned to nasal CPAP for 3d, and weaned from ventilation support and lived for 10–11wk more (PT weaned). Control lambs were born at term gestation (~3 wks after the PT lambs were delivered) and lived for 8wk more (T+8wk control). Lung tissue was analyzed by morphometry, and immunoblot for apoptosis (cleaved caspase 3) and proliferation (PCNA).

Summary of Results: At 10–11wk of postnatal age, weaned PT lambs had significantly thicker alveolar walls (~20%, p < 0.05; n = 3/group) compared to T+8wk controls. Greater airspace wall thickness could result from increased accumulation of cells in the airspace walls, such as interstitial cells. To begin to assess this possibility, we measured apoptosis (cleaved caspase 3) and cell proliferation (PCNA) by immunoblot. Although not significantly different, a trend was evident for more cell turnover, evident as more cleaved caspase 3 (~45%) and PCNA (~35%) protein abundance in the PT weaned group compared to T+8wk controls.

Conclusions: A brief period of MV has long-term consequences on structural development of the lung. One structural consequence is greater thickness of the airspace walls. We speculate that greater thickness results from altered balance between apoptosis and cell proliferation among cells that constitute the airspace walls. (HL62875, HL56401, HD41075, CHRC).

Session: Neonatal Pulmonary II

RESUSCITATION DECREASES mRNA OF EARLY RESPONSE GENES IN THE DEVELOPING RAT LUNG

TR. Carroll, M. Fitzhugh, E. O’Brien, K. Albertine, R. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: Preterm neonates frequently require positive pressure ventilation (PPV). Those that receive little more than resuscitative PPV are generally expected to do well and suffer no adverse consequences from their brief exposure to PPV. However, recent studies have demonstrated that even gentle ventilation strategies increase biomarkers of lung injury during critical periods of lung development. What is unknown is how PPV as a resuscitative measure, during critical periods of lung development, affects biomarkers of lung injury. We hypothesized that PPV would increase biomarkers of early lung injury during a critical stage of lung development.

Methods Used: We applied PPV to rats at postnatal day 6 (P6), corresponding to the alveolar stage of rat lung development. Rat pups were either exposed to room air without ventilation, 15 minutes of hyperoxia (30% FiO2) without ventilation, or 15 minutes of hyperoxia with ventilation at a tidal volume (Vt) of 6–8 ml/kg. mRNA levels of Early response gene1 (EGR1), Connective tissue growth factor (Ctgf), Cysteine-rich 61 (Cyr61) and Amphiregulin (Areg) were measured in rat lung. We used ANOVA to detect differences between test groups and sex-matched controls.

Summary of Results: Hyperoxia affected no change in mRNA levels of any of these genes with one exception; there was a significant decrease (p < 0.05) in mRNA levels of Ctgf in males as compared to sex-matched, room air controls. PPV with FiO2 of 30% significantly decreased (p < 0.05) the mRNA levels of EGR1 (both sexes), Ctgf (males), Cyr61 (both sexes) and Areg (females).

Conclusions: In contrast to previous work on preterm lambs during the saccular period of development, we found that PPV, as a resuscitative measure, significantly decreases early biomarkers of lung injury during the alveolar stage of lung development. Specifically EGR1 - a biomarker of early inflammation, Ctgf - a promoter of mesenchymal cell proliferation, Cyr61 - a promoter of endothelial cell proliferation, and Areg - a promoter of epithelial proliferation. We speculate that brief resuscitative measures initiate a cascade of changes in gene expression, which may affect pulmonary development by altering inflammatory and proliferative processes long after the resuscitative efforts.

Session: Neonatal Pulmonary II

VITAMIN A THERAPY REDUCES IGF-1 PROMOTER 2 mRNA LEVELS IN THE LUNG OF CHRONICALLY VENTILATED PRETERM LAMBS

MJ. McCoy, D. Metcalfe, B. Metcalfe, B. Beck, X. Ke, RA. McKnight, L. Dong, MJ. Dahl, DM. Null, B. Yoder, RH. Lane, KH. Albertine University of Utah, Salt Lake City, UT.

Purpose of Study: The molecular basis of neonatal chronic lung disease (CLD) is not known. A molecule that is implicated is insulin-like growth factor-1 (IGF-1) because its expression is involved in lung development and greater in the lung of mechanically ventilated (MV) preterm infants and lambs with neonatal CLD. Our studies using preterm lambs also indicate that alveolar formation is improved by using nasal CPAP instead of MV, and the improvement is associated with lower IGF-1 expression in the lung. Several studies have shown that vitamin A (VitaA) therapy during MV also improves alveolar formation. Whether this beneficial effect of VitaA therapy on alveolar formation is related to altered expression of IGF-1 is not known. We hypothesized that VitaA therapy reduces IGF-1 expression in the lung. To test this hypothesis, we used VitaA gain-of-function and loss-of-function approaches.

Methods Used: PT lambs were delivered at 131d gestation (term ~150d), intubated, given surfactant, and managed for 3d. Ovine sequences were
cloned to design probes for IGF-1 promoter 2. Real-time RT-PCR was used to quantify mRNA levels in preterm lambs managed by MV, VitA+MV, retinoic acid receptor antagonist+MV (RAR antagonist+MV), nasal CPAP (positive outcome preterm control), or RARs antagonist+nasal CPAP.

Summary of Results: Airspace walls were significantly thinner in the VitA+MV, RARx agonist+MV, and nasal CPAP groups (−30%, p<0.05 for n = 3/group) compared to the MV alone and RARx antagonist+nasal CPAP groups. IGF-1 promoter 2 mRNA expression, relative to GAPDH mRNA expression, was ~50% lower (not significant) in the VitA+MV, RARx agonist+MV, and nasal CPAP groups compared to the MV alone and RARx antagonist+nasal CPAP groups.

Conclusions: VitA therapy reduces IGF-1 promoter 2 mRNA levels in lung. This reduction is associated with thinner airspace walls. Because IGF-1 is a mitogen, we speculate that reduced levels of IGF-1 expression during VitA therapy contributes to attrition of interstitial cells from the airspace walls. The mechanism for attrition appears increased apoptosis of interstitial cells, as we have shown in preterm lungs managed by nasal CPAP (Reburn, AJRCCM 2008).

Session: Neonatal Pulmonary II

422 MAINTAINING PHENOTYPIC EXPRESSION IN CULTURED TYPE II CELLS OF ADULT HUMAN LUNG

PL. Balland1, JW. Lee2, X. Fang3, C.J. Chapin3, L.W. Gonzales3, V. Kolla3, MA. Matthay1, 2UCSF, San Francisco, CA; 3UCSF, San Francisco, CA; UCSC, San Francisco, CA and 4CHOP, Philadelphia, PA

Purpose of Study: Alveolar type II cells have multiple functions including surfactant production and fluid clearance that are critical for normal lung function. Precocious differentiation of type II cells occurs in cultured fetal lung epithelial cells treated with dexamethasone plus cAMP/xanthine (DCI). We hypothesized that DCI treatment would maintain phenotypic properties of adult type II cells in culture.

Methods Used: Type II cells were isolated at 95% purity from 5 adult human lungs and cultured 5d on collagen-coated plates in serum-free medium:DCI. Gene expression was assessed by DNA microarray (Affymetrix U133A), qPCR, immunostaining and Western analysis.

Summary of Results: Freshly isolated cells were >95% viable and had high levels of surfactant proteins (SP)-A/B/C. During control culture, expression levels decreased ~2-fold for 6.9% of expressed genes including 21 genes related to surfactant and numerous genes of immune response. Large decreases in mRNA content occurred for PGC (SP-B, 25-fold) and SP-C (14-fold), and d-s control cells contained fewer lamellar bodies. DCI treatment during culture increased 316 mRNA ≥1.5-fold (range 1.6- to 10-fold) compared to control cells, representing ~4% of expressed genes; 40% of these genes were also hormone-induced in previous studies with fetal cells. Highest induction (≥10-fold) occurred for PGC, ZBTB16, DUOX1, PLUNC and CIT. 15 genes related to surfactant were induced (PGC, PLAG1/0/1B, SFTPc, FASN, FABP5, LPL, FADS1, CEBPD, SFTPB, SFTPD, ADFP, SCD, SFTPA, and LDLR). Induction of selected genes was confirmed by qPCR and/or Western analysis. DCI-treated cells contained lamellar bodies that were positive for SP-B and DCI-LAMP 25 genes that were induced in both fetal and adult cells, including 6 genes related to surfactant, also had decreased expression during control culture and thus are candidates for hormonal regulation in vivo.

Conclusions: Exposure of adult human type II cells to glucocorticoid and cAMP during culture maintains expression of surfactant-related and other genes. Surfactant production and other type II cell functions may be modulated by hormones in vivo in response to stress, injury or disease.

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423 EFFECT OF MATERNAL FOOD RESTRICTION ON FETAL RAT LUNG DEVELOPMENT

J. Corral, A. Karadag, R. Sakurai, JS. Tonday, VK. Rehan Harbor-UCLA, Torrance, CA

Purpose of Study: The biomolecular effects of intrauterine growth restriction on the developing lung can be elucidated by studying elastin deposition and eNOS mRNA expression (a marker for lung damage) when rat pups are food-restricted during gestation. Measuring lung function provides an ideal tool to examine how it effects the lung as the intrauterine growth-restriction (IUGR)-exposed pup grows. We hypothesized that IUGR lungs have a different elastin expression and long-term decreased pulmonary function. As a secondary measure, we evaluated whether one of the biomarkers of lung injury, eNOS, would increase in the IUGR lung as well.

Methods Used: We used a well-studied rat model of maternal food restriction (MFR) during gestation to produce IUGR pups. Rat dams 10 days 10 days into pregnancy were divided into ad lib fed controls and food-restricted dams that received 50% of standardized laboratory diet. The latter served as the IUGR model. After delivery, pups were compared at postnatal days 1, 21, and 9 months. The lungs underwent Western blotting using GAPDH as a standard for study of effects on elastin and eNOS expression. Immunohistochemistry (IHC) was used to demonstrate differences at the alveolar level between pups whose mothers’ had been allowed ad lib feeds and those whose mothers’ food was restricted. Using methacholine challenge, differences in pulmonary function between the 2 groups was studied at the 3 designated ages by looking at pulmonary resistance and compliance.

Summary of Results: At postnatal day 1 and 9 months of age elastin expression was increased in IUGR lung when compared to controls (p ≤ 0.05), eNOS mRNA expression was also increased at postnatal day 21 and 9 months of age (p ≤ 0.05), with corresponding morphometric changes demonstrated by IHC. Compared to controls, the MFR group had no significant change in pulmonary resistance, but did have significantly decreased pulmonary compliance at 9 months (p ≤ 0.05 vs control, n = 4).

Conclusions: Maternal food restriction alters lung function in the offspring. These results suggest that lungs in the MFR offspring were not only stiff, but were also hyperresponsive to methacholine challenge. Elastin, an important extracellular matrix protein and mediator of elastic recoil of the lung, was found to be altered, thus providing a potential explanation for how IUGR decreases lung function.

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424 INTRAUTERINE GROWTH RESTRICTION ALTERS EXPRESSION OF GENES INVOLVED IN L-ARGININE METABOLISM IN THE LUNG

DT. Malleske, M. Campbell, X. Yu, C. Callaway, R. McKnight, K. Albertine, R. Lane University of Utah, Salt Lake City, UT

Purpose of Study: Intrauterine growth restriction (IUGR) predisposes the newborn to diseases that may persist into adulthood, such as pulmonary hypertension. Alterations in nitric oxide (NO) production and vascular development mediated by Nitric Oxide Synthase (NOS) and Arginase are described in infants, children and adults with pulmonary hypertension. Specifically, increased arginase activity influences pulmonary vascular resistance by reducing NO production and inducing vascular remodeling through increased cell proliferation and collagen deposition. During normal development, endothelial NOS (eNOS) expression is relatively constant in fetal, newborn and adult lung whereas arginase 2 expression and total arginase activity is highest in the fetus and decreases post-natally. Arginase 1 is expressed at low levels at all stages. This relationship, which maintains a high pulmonary vascular resistance (PVR) in the fetus and allows the transition to reduced PVR after birth, may be disrupted by IUGR. We hypothesize that lungs from IUGR animals will have increased arginase gene expression which persists with maturation.

Methods Used: Pregnant, time-dated Sprague-Dawley rats at day 19 of gestation (term is 21.5 days) were anesthetized and bilateral uterine artery ligation was performed (IUGR group). At term gestation the rats were anesthetized and the pups delivered by Caesarian section. Pups were euthanized and tissues were harvested at postnatal days 0 (D0) and 21 (D21). Levels of mRNA from whole lung were determined for eNOS, arginase I and arginase II.

Summary of Results: IUGR reduced eNOS (P = 0.02), arginase 1 (P = 0.08) and arginase 2 (P = 0.10) mRNA levels in D0 males vs. controls. At D21, IUGR males had equivalent eNOS and arginase 2 mRNA levels, but increased arginase 1 (P = 0.02) mRNA levels vs. controls. IUGR females had reduced arginase 2 (P = 0.04) mRNA levels at D0 and no mRNA differences vs. controls at D21.

Conclusions: IUGR affects NOS and arginase mRNA levels differently in male and female rats. We speculate that IUGR males are at greater risk for developing pulmonary hypertension compared to IUGR females. This is consistent with observed frequency and severity of pulmonary hypertension among human IUGR male infants.

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IMPROVED PULMONARY FUNCTION AND EXERCISE CAPACITY FOR EXTREMELY LOW BIRTH WEIGHT CHILDREN BORN IN THE 1990S COMPARED TO THOSE FROM THE 1980S
H. Kilbride1,2, C. Castor3, M. Gelatt1,2, K. Teson1, R. Sabath1,2, Children’s Mercy Hospitals & Clinics, Kansas City, MO and 3University of Missouri Kansas City SOM, Kansas City, MO.
Purpose of Study: To assess pulmonary function and exercise capacity of children who were born extremely low birth weight (ELBW) and treated with surfactant compared to a cohort cared for in an earlier era without surfactant.
Methods Used: Pulmonary function and treadmill testing were performed on 13 children, 12 to 15 years old, who had been born during 1993–1995 with birth weights of 801 grams and treated with surfactant. Findings were compared with those previously obtained on children of the same birth weight born during 1983-1989, before surfactant treatment was available (Kilbride et al, J Pediatr 2003;143:488). Group differences were determined by two-tailed t tests.
Summary of Results: There were no group differences in gender or race. Those from the recent period were tested at an older (12.9 vs 11.1 years, P = .001) and tended to be heavier and taller. Pulmonary function test results were comparable between groups except for FEV1, which was higher on average for more recent survivors. Oxygen consumption measures, an estimate of exercise capacity, were significantly greater for children in the more recent cohort, compared to those from the 1980s. These values for the ELBW children of the 1990s were no different from the normal weight comparison group from the earlier study.
Conclusions: These preliminary data would suggest mild improvement in pulmonary function and significant improvement in exercise capacity for ELBW children born in the surfactant era compared to those from an earlier era.
ELBW Groups

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426
LATE DOSES OF SURFACTANT IN VENTILATED PREMATURE INFANTS: A PILOT STUDY
R. Ballard1, R. Keller1, J. Merril2, L. Palermo3, W. Truong4, R. Steinhorn5, R. Ryan6, E. Eichenwald7, D. Durand2, S. Courtney8, D. Black9, P. Ballard1, UCSC, San Francisco, CA; 2CHO, Oakland, CA; 3UCSF, San Francisco, CA; 4CMH, Kansas City, MO; 5CMH, Chicago, IL; 6WCHOB, Buffalo, NY; 7BCM, Houston, TX and 8Stony Brook UMC, Stony Brook, NY.
Purpose of Study: Extremely low gestational age newborns requiring mechanical ventilation after 7 days of age have > 70% incidence of bronchopulmonary dysplasia (BPD), and 2/3rds of these infants experience episodes of surfactant dysfunction secondary to deficiency of surfactant protein (SP)-B (Merrill, Peds Res. 2004). Treatment with inhaled Nitric Oxide (inO) increases survival without BPD (Ballard R, New Engl J Med 2006, 2007) but does not abolish surfactant dysfunction. We hypothesized that late doses of surfactant plus inO would improve surfactant function and decrease occurrence of BPD.
Methods Used: We enrolled infants <30 wk GA who required mechanical ventilation and were receiving inO at 7–14 d in a multicenter, randomized, blinded pilot Trial Of Late Surfactant (TOLSURF) and treated with up to five additional doses of surfactant (Infusurf) or sham administration over 3 wk.
Summary of Results: Between 208 and 6/09, 60 infants at 9 hospitals were enrolled with mean BW of 693 ±114 g, GA of 25.4 ± 1.3 wk, and 58% male. 7 infants (12%) died before 36 wk. 70% of the infants remained intubated and received all 5 doses per protocol. During 259 doses of study drug (or sham) only 4 (1.5%) infants had significant bradycardia, 4 required re-intubation and 1 infant required resuscitation. The mean respiratory severity score (RSS–MAP X FiO2) was 3.1 at study entry and decreased or was unchanged 2 h after each of 5 dosing procedures. There were no episodes of pneuomothorax, pulmonary hemorrhage or worsening of a PDA.
Conclusions: We conclude that late administration of surfactant is safe and tolerated well by intubated premature infants. Tracheal aspirate samples are being evaluated for the interaction of inO with surfactant. A large multicenter study (TOLSURF) to evaluate clinical outcome is underway.

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PREVENTION OF PERINATAL NICOTINE EXPOSURE-INDUCED ALTERATIONS IN AIRWAY CONSTRICITION BY PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA (PPARy) AGONIST ROSIGLITAZONE
J. Liu, R. Sakurai, JS. Torday, VK. Rehan, L.A. Biomed, Torrance, CA.
Purpose of Study: To determine the effects of PPARy agonist on perinatal nicotine exposure-induced alterations in 1) mesenchymal markers of tracheal constriction and 2) tracheal constriction responses.
Methods Used: Pair-fed pregnant Sprague Dawley rat dams received nicotine (diluent), Nic (1 mg/kg, sc.), and Nic (1 mg/kg, sc.) + a PPARy agonist Rosiglitazone (RGZ) (3 mg/kg, i.p.) in 100 µl volumes daily from e6 until the pups were 21-day old. Pups were delivered spontaneously and breast-fed ad libitum. At postnatal day 21, the pups were sacrificed and tracheas were collected for both mRNA and protein expression, and tracheal tension studies.
Summary of Results: Compared to control, with perinatal Nic exposure, mRNA or protein expressions of the mesenchymal markers of tracheal constriction such as α-smooth muscle actin (α-SMA), calponin, collagen 1 and 3 were significantly increased. Tracheal constriction responses were also significantly increased as compared with control after perinatal Nic exposure. Concomitant treatment with RGZ blocked the Nic-induced alterations in both tracheal constriction marker expression and constriction responses.
Conclusions: Alternations in upper airway function in a rodent model of perinatal Nic exposure were blocked by concomitant administration of RGZ. We speculate that perinatal smoke exposure-induced asthma in offspring can be effectively prevented by PPARy agonists. Disclosure: Supported by grants from the NIH (HL75405, HD051857, HD058948) and the TRDRP (15IT-0250 and 17RT-0170).

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CARCINOEMBRYONIC CELL ADHESION MOLECULE 6 IN PREMATURITY INFANT AND ADULT LUNG FLUID
C. Chapin1, N. Bailey2, P. Ballard1, UCSF, San Francisco, CA and 2CHOP, Philadelphia, PA.
Purpose of Study: Carcinoembryonic cell adhesion molecule 6 (CEACAM6) is a glycosylated, GPI-anchored protein in epithelial cells found in a variety of organs where it participates in innate immune defense and promotes tumorigenesis. Recently, we described developmental and hormonal regulation of CEACAM6 in cultured human fetal lung epithelial cells. In the current study we examined levels and surfactant association of CEACAM6 in lung fluid of premature infants and adults.
Methods Used: Tracheal aspirates were obtained from ventilated premature infants at one day (n = 8) or two weeks (n = 29) of life. Adult bronchial alveolar lavage was obtained from cadaver lungs (n = 7). Large aggregate (LA) surfactant was isolated by centrifugation, and protein and phospholipid (PL) were measured. CEACAM6 content was determined by Western and immunoblot blot and normalized to total fluid protein or surfactant PL. Association with surfactant was determined using KBr density gradient centrifugation of LA surfactant.
Summary of Results: Total CEACAM6 of tracheal aspirate was low in d-1 premature infants and levels increased 4-fold over the next 2 wks to adult levels. Western analysis of CEACAM6 revealed three isoforms at 90, 60 and 50 kDa likely representing variable glycosylation. In supernatants, 90 kDa CEACAM6 was similar (66% and 74% of total) for d-1 infants and adults and less for d-14 infants (35%, p < 0.05). For all groups the 90 kDa form represented >80% of CEACAM6 in the surfactant pellet. The concentration of CEACAM6 in the surfactant pellet of adult and d-14 infants was 3.9 ± 0.9% and 2.2 ± 1.9% of PL by weight, respectively, similar to surfactant protein (SP)-B. To examine the affinity of CEACAM6 for surfactant we performed

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density gradient centrifugation of LA surfactant; 100% of CEACAM6 was recovered along with a similar amount of SP-A. Western blot analysis was used to examine levels of Prdm1 and Prmt5 expression in undifferentiated ESCs.

**Summary of Results:** Prdm1 and Prmt5 proteins are expressed by undifferentiated ESCs prior to PGC formation. Prdm1 is expressed in both nucleus and cytoplasm, while Prmt5 expression is enriched in the cytoplasm. To evaluate whether Prdm1/Prmt5 expression is regulated by specific epigenetic or post-transcriptional mechanisms in undifferentiated ESCs, Western blot was performed in ESCs null for microRNA processing enzyme Dicer1 in line with the endogenous. Study results indicate that Prdm1 and Prmt5 expression in ESCs is governed by an as yet unidentified molecular process.

**Conclusions:** Prdm1 and Prmt5 are already poised to differentiate towards PGCs in vitro once the appropriate signals are provided. Future studies will evaluate whether Prdm1 and Prmt5 exist as a complex upon PGC formation in vitro, and which downstream targets are repressed to enable PGC formation.

**Session:** Neonatology - Developmental Biology

**431 EPITHELIAL-SPECIFIC DELETION OF APC ALTERS CELL FATE DETERMINATION DURING LUNG DEVELOPMENT**

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**Purpose of Study:** Bronchopulmonary dysplasia (BPD) is a debilitating disease among premature infants. Normal lung morphogenesis is interrupted, as evidenced by the attenuation of alveologenesis and vasculogenesis. The Wnt signaling pathway, mediated via β-catenin, plays a key role in cell proliferation and cell fate determination during development. In the absence of Wnt signal, Adenomatous Polyosis Coli (APC) forms a destruction complex and inhibits β-catenin activity. The role of APC in lung development is unknown. The current study was designed to address this knowledge gap by examining the consequences of inactivating the APC gene via a Cre-LoxP approach, specifically in lung epithelial cells.

**Methods Used:** Nkx2.1 is a marker of lung epithelial cell identity. We used the Nkx2.1-cre to drive recombination in Apcre;LoxP mice. Double-transgenic Nkx2.1-cre; Apcre;LoxP embryos were sacrificed at different stages of development. The lungs were analyzed by Western blot and immunohistochemistry.

**Summary of Results:** APC is expressed in normal developing lungs. APC is co-localized with markers for smooth muscle, ciliated and neuroendocrine cells, but not Clara and basal cells. In mutant lung epithelial cells, immunofluorescent staining and western blot confirmed a significant decrease in APC and a commensurate accumulation of β-catenin. Phenotypically, the APC mutant lungs showed abnormal dilation of the distal airways and formation of polyps within the bronchiolae. The polyps lacked both β-TUBULIN and Nkx2.1 expression, which indicate the loss of lung epithelial cell lineage.

**Conclusions:** Epithelial-specific deletion of APC leads to accumulation of β-catenin and distinct phenotypic changes in developing lungs with loss of pulmonary cell identity. Further studies are underway to delineate the mechanism in which APC controls lung development.

**Session:** Neonatology - Developmental Biology

**432 IN UTERO NICOTINE EXPOSURE DISRUPTS GLOBAL PARATHYROID HORMONE-RELATED PROTEIN SIGNALING**

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**Purpose of Study:** Background: The molecular mechanism(s) underlying increased predisposition to fibrosis in organs following pre- or postnatal exposure to smoke is poorly understood. Parathyroid hormone-related protein (PTHrP), an epithelial autocrine/paracrine secreted protein, drives specific epithelial-mesenchymal interactions which are critical for normal development and homeostasis in organs. Nicotine-induced disruption of PTHrP
Intrauterine growth restriction (IUGR) is associated with altered lung development in the human and rat. One regulator of lung development is the transcription factor, PPARγ. We have previously demonstrated that IUGR reduces levels of PPARγ mRNA and protein in neonatal male and female rat lungs. A recently identified target of PPARγ is the histone lysine methyltransferase, Setd8, an enzyme that places a methyl group on lysine (K)20 of histone (H)4. Importantly, Setd8 places this mark on histones associated with the PPARγ gene. Despite the importance of PPARγ in the dysregulation of lung development in IUGR, the mechanism driving changes in Setd8 is unknown. We hypothesize that IUGR decreases mRNA and protein levels of Setd8 in male and female rat lungs at birth, independent of gender. Furthermore, the reduced level of Setd8 protein in IUGR occurs at the neonatal age, results in a reduction of Setd8 and thus reduced levels of H4K20Me on the PPARγ gene. We speculate that the IUGR induced reduction in PPARγ gene expression is driven by a feedback loop of Setd8 protein, which further reduces the level of transcript in the IUGR setting.

Methods Used: IUGR was induced by bilateral uterine artery ligation in rat dams at E19 of gestation. Real-time RT-PCR and western blotting were used to measure Setd8 mRNA and protein respectively in the lungs of IUGR and control offspring at birth. Chromatin immunoprecipitation (ChIP) was used to assess H4K20Me levels at various positions along the PPARγ gene in the same samples.

Summary of Results: Analysis thus far has evaluated mRNA and protein levels of PTHrP in PND 1, PND 7, and PND 21, following which various organs including lungs, liver, kidneys, were extracted, and snap frozen in liquid nitrogen for RT-PCR and Western analysis studies.

Conclusions: In utero nicotine exposure affects offspring PTHrP signaling globally, probably explaining the increased predisposition to fibrosis following smoke exposure during pregnancy. This effect is blocked by the concurrent administration of PTHrP agonist and PPARγ antagonist. Importantly, IUGR reduces PTHrP mRNA levels and protein expression at 14 days of age. We speculate that reduced PTHrP signaling in the neonatal rat lung, results in a reduction of Setd8 and thus reduced levels of H4K20Me on the PPARγ gene, independent of gender. Furthermore, the reduced level of Setd8 protein, in IUGR occurs at the neonatal age, results in a reduction of Setd8 and thus reduced levels of H4K20Me on the PPARγ gene. We speculate that the IUGR induced reduction in PPARγ gene expression is driven by a feedback loop of Setd8 protein, which further reduces the level of transcript in the IUGR setting.

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433 IUGR DECREASES mRNA AND PROTEIN LEVELS OF HISTONE METHYLTANSFERASE SETD8 IN CONJUNCTION WITH REDUCED H4K20ME IN THE NEONATAL RAT LUNG
L. Joss-Moore, Y. Wang, C. Callaway, X. Yu, R. McKnight, R. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: Intrauterine growth restriction (IUGR) is associated with altered lung development in the human and rat. One regulator of lung development is the transcription factor, PPARγ. We have previously demonstrated that IUGR reduces levels of PPARγ mRNA and protein in neonatal male and female rat lungs. A recently identified target of PPARγ is the histone lysine methyltransferase, Setd8, an enzyme that places a methyl group on lysine (K)20 of histone (H)4. Importantly, Setd8 places this mark on histones associated with the PPARγ gene. Despite the importance of PPARγ in the dysregulation of lung development in IUGR, the mechanism driving changes in Setd8 is unknown. We hypothesize that IUGR decreases mRNA and protein levels of Setd8, and that this will be associated with reduced H4K20Me on the PPARγ gene in the neonatal rat lung.

Methods Used: IUGR was induced by bilateral uterine artery ligation in rat dams at E19 of gestation. Real-time RT-PCR and western blotting were used to measure Setd8 mRNA and protein respectively in the lungs of IUGR and control offspring at birth. Chromatin immunoprecipitation (ChIP) was used to assess H4K20Me levels at various positions along the PPARγ gene in the same samples.

Summary of Results: Results are IUGR as % of Control ± SEM. IUGR reduced levels of Setd8 mRNA in male and female rat lungs at birth (male: 73.0 ± 7%*, female: 63.2 ± 4%**). IUGR also decreased protein levels of Setd8 in male and female rat lungs at birth (male: 48.9 ± 3%** female: 58.7 ± 17%**). Consistent with reduced levels of Setd8, IUGR also reduced the amount of H4K20Me in exon 4 of the PPARγ gene in males and females (male: 73.5 ± 12%, female: 62.1 ± 9% *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001). We conclude that IUGR reduces levels of Setd8 in the neonatal rat lung, independent of gender. Furthermore, the reduced level of H4K20Me observed on the PPARγ gene in IUGR is consistent with reduced levels of Setd8 protein. We speculate that the IUGR induced reduction in PPARγ in the rat lung, results in a reduction of Setd8 and thus reduced H4K20Me on the PPARγ gene. We further speculate that this produces a feedback loop by which rat lung PPARγ levels are further reduced in the setting of IUGR.

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434 IUGR ALTERS CANNABINOID RECEPTOR-1 MRNA LEVELS IN MALE JUVENILE AND ADULT RAT BRAINS
N. Mitchell, L. Joss-Moore, M. Hale, Y. Wang, X. Yu, C. Callaway, X. Ke, R. McKnight, R. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: Humans and animals born IUGR are at an increased risk for metabolic abnormalities as adults, such as obesity and Type 2 diabetes mellitus, with males being more severely affected than females. However, the molecular mechanisms underlying these abnormalities are unclear. One system recently implicated in obesity and metabolism is the endocannabinoid (EC) system. Obese humans and animals have increased EC system activity. Administration of cannabinoid receptor-1 (CB1) agonists has led to increased food intake and fat storage, while use of CB1 antagonists has led to decreased food intake and weight loss. Despite the link between the EC system and the metabolic abnormalities seen in IUGR, the effects of IUGR on the EC system are unknown. We therefore hypothesize that IUGR will alter the expression of CB1 in rat brains, and that these differences will be gender-specific.

Methods Used: Bilateral uterine artery ligation at day 19 of gestation (term=21.5) was used to induce IUGR. Rats were born spontaneously, culled to litters of 6, and raised with the dams until day 21, at which time the animals were either sacrificed or raised until day 120. We used real-time RT-PCR to analyze mRNA levels of Cnr1 in both IUGR and control rats, and Western blots were used to analyze protein levels of CB1. Food intake was measured from day of life 35 until day 120.

Summary of Results: IUGR significantly decreased Cnr1 mRNA levels in D21 males to 47 percent (+/−12) of controls (p < 0.05), but did not affect levels in D21 females. IUGR did not affect CB1 protein levels in either sex at D21. IUGR significantly increased Cnr1 mRNA levels in D120 males to 325 percent (+/−1) of controls (p < 0.0001), but did not affect levels in females. At day 120, IUGR females ate 15% less than control females, and IUGR males ate 4% less than control males.

Conclusions: IUGR affected Cnr1 mRNA levels in a developmentally and gender specific manner. We speculate that the increase in Cnr1 mRNA levels at D120 will correlate with protein results at D120. We also speculate that the increase in Cnr1 mRNA, despite no increase in average food intake, suggests that metabolic abnormalities seen in IUGR are not CNS driven, but rather caused by IUGR’s effects peripherally, such as in adipose tissue and/or the liver.

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435 MATERNAL DIABETES MELLITUS ALTERS DNA METHYLATION OF THE HEPATIC IGF-1 GENE
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Purpose of Study: Prenatal maternal diabetes mellitus increases the risk of postnatal morbidity in humans and rats. These morbidities include erratic adipogenesis and insulin resistance, both of which are regulated by hepatic IGF-1. Previous studies demonstrate that maternal diabetes decreases the postnatal hepatic IGF-1 mRNA levels and alters histone methylation and acetylation associated with the IGF-1 gene in an age and gender specific manner. However, it is unknown whether DNA methylation is similarly affected. We hypothesized that maternal diabetes in the rat alters postnatal IGF-1 DNA methylation.

Methods Used: To test this hypothesis, pregnant rats were given streptozotocin (STZ) on day 13 of pregnancy. Maternal glucose levels were monitored with insulin injections. Livers were harvested on postnatal days 1 (DOL 1) and 21 (DOL 21) from pups of both STZ and sham (CON) maternal rats. DNA methylation quantified using bisulfite sequencing at 12 sites in promoter 1 (−528, −523, −470, −302, −260, −231, −143, −86, −31, −29, −13 and −22) and 6 sites in promoter 2 (−231, −142, −133, −112, −70 and −41).

Summary of Results: In promoter 1, no change was seen at DOL 1. However, maternal diabetes caused hypermethylation at sites −260 and −143 in females at DOL 21. At DOL 1 in promoter 2, maternal diabetes caused hypomethylation of site −112 in males, hypomethylation of site 70 in females, and a trend toward significance of hypermethylation at site −112 in females, with no change at DOL 21.
Conclusions: Maternal diabetes alters hepatic IGF-1 DNA methylation of promoters 1 and 2 in an age and gender specific manner. These findings are intriguing because they are consistent with other studies on KLF-1 in IUGR demonstrating that DNA methylation of the hepatic IGF-1 gene is affected by prenatal conditions. We speculate that by altering DNA methylation of the hepatic IGF-1 gene, maternal diabetes affects IGF-1 gene expression in adulthood.

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EFFECTS OF MATERNAL FOOD RESTRICTION ON FETAL LUNG ALVEOLAR EXTRACELLULAR MATRIX DEPOSITION AND LONG TERM PULMONARY FUNCTION IN EXPERIMENTAL RAT MODEL

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Purpose of Study: We hypothesized that IUGR lungs have a different elastin expression and long term decreased pulmonary function. As a secondary measure, we hypothesized that one of the biomarkers of lung injury, alpha-SMA, would increase in the IUGR lung as well.

Methods Used: We used a well-studied rat model of maternal food restriction (MFR) during gestation to produce IUGR pups. Rat dams that were 10 days into pregnancy were divided into controls that were allowed ad lib feeds and compared to food-restricted dams that received only 50% of standardized laboratory diet. The latter serving as the IUGR model. After delivery, the pups from each litter were compared at postnatal days 1, 21, and 9 months. The lungs were isolated and underwent Western blotting using GAPDH as a standard for study of effects on elastin and alpha-SMA expression. Immunohistchemistry (IHC) was used to demonstrate differences at the alveolar level between pups whose mothers' had been allowed ad lib feeds and those whose mothers’ food was restricted. Using methacholine challenge, differences in pulmonary function between the 2 groups was studies at the 3 various ages by looking at pulmonary resistance and compliance.

Summary of Results: At postnatal day 1 and 9 months of age elastin expression was increased in IUGR lung when compared to controls (p ≤ 0.05, n = 4). Alpha-SMA expression was also increased at postnatal day 21 and 9 months of age (p ≤ 0.05) with corresponding morphometric changes demonstrated on IHC. Compared to controls, the MFR group had no significant change in pulmonary resistance, but did have significantly decreased pulmonary compliance at 9 months (p ≤ 0.05 vs control, n = 4).

Conclusions: Maternal food restriction alters lung function in the offspring. These effects persist in the MFR lungs in the MFR offspring were not only evident, but were also hyperresponsive to methacholine challenge. Elastin, an important extracellular matrix protein and mediator of elastic recoil of the lung, was found to be altered, thus providing a potential explanation that IUGR decreases lung function.

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KRUPPEL-LIKE FACTOR 4 EXPRESSION IN DEVELOPING HUMAN SKIN

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Purpose of Study: Infants born prematurely run a greater risk of developing infections and dehydration due to the underdevelopment of the epidermis. Kruppel-like factor 4 (KLF-4) is a transcription factor involved in fetal skin barrier acquisition. In animal studies, absence of KLF-4 results in underdeveloped skin and decreased barrier protection against dehydration, resulting in renal failure and premature death. We examined KLF-4 expression in human fetal skin from 15 weeks to 24 weeks gestational age to determine if expression increases during gestation, and to evaluate changes in expression after normoxic stimulation.

Methods Used: Total RNA was isolated from samples of human fetal skin from 15 to 24 weeks gestational age. RNA was isolated, quantified spectrophotometrically, checked for lack of degradation via gel electrophoresis, and reverse transcribed. The resulting cDNA was used in real-time PCR reactions with primers and probes for KLF-4. Data were normalized using GAPDH in duplex reactions, and analyzed by unpaired t-tests and ANOVA.

Summary of Results: KLF-4 expression was detected in all samples tested. KLF-4 expression increased significantly with increasing gestation (p < 0.001). Expression was 20 to 30-fold greater in the higher gestation ages tested (21–24) than in the lower ages (15–18; p < 0.01, 15–18 versus 21–24).

Conclusions: KLF-4 was expressed in all fetal skin tested, and was expressed in significantly greater quantities in higher gestational ages. We speculate that the expression of KLF-4 increases significantly following extremely preterm birth and that KLF-4 is associated with the rapid maturation of skin after premature delivery of extremely low birth weight infants. Experiments are currently being performed (data pending) in which fetal skin is exposed to 24 hours of normoxia (somewhat mimicking conditions of premature birth), and KLF-4 expression is determined.

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ERYTHROPOIETIN ENHANCES GROWTH IN DEVELOPING RETINAL CELL CULTURES

K. Sanchez, S. McConaghy, RK. Ohls University of New Mexico, Albuquerque, NM.

Purpose of Study: While adult and animal studies have reported neuroprotective effects of erythropoietin (Epo), there has been limited evaluation of the effects of Epo on growth and differentiation of cells in the developing human retina. We investigated the effects of Epo on fetal retinal cultures, and hypothesized that, similar to its neuroprotective effects, Epo would increase total cell number, increase expression of antiapoptotic genes, and decrease expression of apoptotic genes.

Methods Used: Human fetal retinal samples were collected between 16 and 24 weeks of gestation. Cell suspensions were created and plated at 105 cells/mL. Cells were grown in culture with 0, 0.1, 1, or 10 U/mL Epo for 5 days. Cell phenotypes were identified histologically and cell counts performed. Cells were then plated in triplicate and total RNA isolated and quantified spectrophotometrically. RNA was reverse transcribed and quantitative PCR performed using primers and probes to identify Bax and Bcl gene expression. GAPDH was used as an internal control in duplex reactions.

Summary of Results: Absolute cell counts increased significantly over baseline when no growth factors were added, and cell numbers increased with increasing gestation (p < 0.02). Cell counts increased with increasing Epo concentrations: without growth factors added, cell counts increased approximately 2 fold over 5 days. With the addition of 0.1 U/mL Epo there was a significant increase in cell numbers over cultures without Epo (p = 0.05). The addition of either 1 or 10 U/mL Epo resulted in even greater increases in cell number (p = 0.02, 0 versus 1; p = 0.001, 10 versus 0). There was no significant difference in cell number between 1 and 10 U/mL Epo. In addition, there was no significant difference in responsiveness to Epo over the gestational ages tested. Compared to Bcl expression measured in cells cultured without Epo, Bcl expression increased 83%, 90%, and 98% in cells cultured with 0.1, 1, and 10 U/mL Epo, respectively. There was no significant difference in Bax expression.

Conclusions: Epo significantly stimulated cell growth of human fetal retinal cells in dose dependent fashion. The expression of the antiapoptotic gene Bcl significantly when cells were cultured with Epo.

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ACCURACY OF PULSE OXIMETRY READINGS FROM DIFFERENT SITES IN NEWBORN: A PROSPECTIVE STUDY

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Purpose of Study: Pulse oximeters are routinely used in the neonatal Intensive care unit (NICU) for oxygen saturation (SpO2) monitoring. The typical sites for the pulse oximeter probes are over the palm or sole of newborns. However, in sick newborns clinicians often use other sites, such as, the wrist and ankle to obtain measurements of oxygen saturation. Accuracy of the measurements obtained from these sites has not been validated. We investigated whether SpO2 measurements at the wrist or ankle are comparable to SpO2 measured at the palm or sole in the NICU.

Methods Used: In this prospective study, we obtained simultaneous SpO2 readings from the ipsilateral palm and wrist, or sole and ankle to validate the accuracy of the readings from these sites. The Masimo pulse oximeter was used (Masimo Radical-7). Neonates admitted to NICU requiring monitoring were enrolled. Neonates weighing > 4500 g or infants with multiple congenital anomalies were excluded. Regression analysis was performed to
determine the relationship between paired measurements. The mean and SD of the paired differences were also calculated.

Summary of Results: 60 patients were enrolled in this study: birth weight 2369 ± 993 g, range 450–3910 g; gestational age 34.2 ± 4.1 weeks, range 25–40 weeks; median postnatal age 2.5 days, 25th–75th percentiles 1–6 days. There was a good positive correlation between paired measurements; correlation coefficients (r) and corresponding p values were as follows: 1) Right Palm SpO2 (%) 98.8 ± 1.6 and Right Wrist SpO2 98.8 ± 1.6, r = 0.88, p < 0.001 (n = 55 patients, 165 pairs); 2) Left Palm SpO2 (%) 99.2 ± 1.2 and Left Wrist SpO2 99.1 ± 1.2, r = 0.84, p < 0.001 (n = 56 patients, 168 pairs); 3) Right Sole SpO2 (%) 99.5 ± 0.8 and Right Ankle SpO2 99.3 ± 1.0, r = 0.73, p < 0.001 (n = 57 patients, 171 pairs); 4) Left Sole SpO2 (%) 99.4 ± 1.2 and Left Ankle SpO2 99.3 ± 1.2, r = 0.76, p < 0.001 (n = 60 patients, 180 pairs).

Conclusions: Our results show that the wrist and ankle can be used as alternative sites to measure SpO2 in the NICU. There is a stronger correlation between the palm and wrist SpO2 readings compared to the sole and ankle. The wrist appears a better alternative site for pulse oximeter probe placement when the palm or sole are not available.

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440 TUBERCULOSIS IN THE NEWBORN

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Case Report: We report a case of disseminated tuberculosis in a 29 day-old female infant.

Introduction: Tuberculosis (TB) in the infant is rare, and usually presents nonspecifically (fever, upper respiratory tract symptoms). Once infected, up to 40% of infants develop active TB.

Case report: A 38-week female was born by vaginal delivery to a G2P2 30-year-old. Baby had low birthweight (2.3kg) but otherwise was well and went home with mom. Prenatal tests were negative, including PPD. Baby presented at 29 days with mild respiratory distress and fever. Mother had cough and fever. The initial chest x-ray showed bilateral nodular infiltrates. Baby was admitted and progressed to respiratory failure. She was then transferred to our hospital for possible ECMO (extra-corporeal membrane oxygenation). She was placed on VA ECMO for cardiorespiratory failure. Broad spectrum antibiotics were started (meropenem, vancomycin and fluorconazole). All infectious testing, including viral assays, were negative. The mother’s symptoms had resolved. Notable physical examination findings were persistent hyperpermia of the hands and feet (despite poor central perfusion) and significant progressive hepatomegaly. Abnormal labs included: BUN 290 with normal creatinine, direct bilirubin 32mg/dl, pancytopenia, high LDH (3667units), high ferritin (9000units), high IL2 (35794units), and absent Natural Killer cell function. With suspicion of hemophagocytic lymphohistiocytosis (HLH), chemotherapy was started (etoposide, dexamethasone). After which, the patient worsened significantly. Care was withdrawn on day of life 59. Autopsy results demonstrated disseminated tuberculosis with complete destruction of the lungs and invasion of the liver and bone marrow. There was no evidence of HLH. The mother was found to have active TB.

Discussion: Tuberculosis is endemic in many regions of the world. The failure of a patient to respond to conventional therapies, especially in the case of fever, respiratory failure and hepatosplenomegaly in the neonate, should lead the care-provider to consider TB.

Neuroscience II

Concurrent Session

8:30 AM

Saturday, January 30, 2010

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441 DOES PREDATORY SCENT STRESS INCREASE THE LIKELIHOOD OF LATER DEVELOPMENT OF POST TRAUMATIC STRESS DISORDER?

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Purpose of Study: With a lifetime prevalence in the general U.S. population of 8–9% Post Traumatic Stress Disorder (PTSD) is an important clinical diagnosis with a major economic impact. The hallmark of this diagnosis includes the experience or perception of a life threatening event which lead to a cluster of clinical symptoms. To date, PTSD has proved a difficult disease to treat and the development of an animal model would be advantageous. The goal of our study was to determine if predatory odor exposure increased the susceptibility for developing PTSD in adulthood in an animal model.

Methods Used: PTSD in mice was induced using predatory rat odor exposure as the life threatening event. Following odor exposure, odor exposed and control mice underwent behavioral testing on elevated plus maze. Anxiety was measured via time spent in seconds in the open arms as well as overall locomotion between the arms.

Summary of Results: There was a significant effect of PTSD treatment condition F(1,28) = 19.356, p < 0.0001 indicating that the odor exposed spent less time in the open arms than control mice. A post hoc t-test showed that this was true both for day 1 t(14) = 2.14, p = 0.049 and on day 2 of testing t(14) = 3.9, p < 0.001.

Conclusions: We found that predatory exposed mice spent less time in the open arms in the elevated plus maze. This finding is consistent with anxiety behavior. These results suggest that the predatory odor mouse model may prove useful for exploring treatments for PTSD.

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442 DEVELOPMENT AND CHARACTERIZATION OF A MOUSE MODEL OF POSTTRAUMATIC STRESS DISORDER

N. Anast, KK. Caldwell University of New Mexico, School of Medicine, Albuquerque, NM.

Purpose of Study: The lifetime prevalence rate of Post Traumatic Stress Disorder (PTSD) is estimated to be 8–9%. Efforts to better understand the pathophysiological changes underlying PTSD, and the mechanisms by which exposure to traumatic events produce these changes, may rely on the use of animal models.

Methods Used: Using a predator-odor exposure design, we developed an animal model of PTSD using adolescent male mice that demonstrates both the anxiety and depressive symptoms of PTSD. Male mice at postnatal day 30–42 were divided into two groups. The treatment group was exposed to soiled female rat bedding for 10 minutes and the control group was exposed to clean unsoiled bedding for 10 minutes. The mice were all reexposed to clean unsoiled bedding 14 days later. Characterization of the model included the effects of predator odor exposure on learned helplessness and open field/novel object behaviors.

Summary of Results: Odor-exposed mice demonstrated an overall increase in the mean escape latency and number of escape failures as compared to controls in the learned helplessness test. However, a bimodal distribution of the data was noted with one subset of animals displaying a reduction in escape latency and failures while the other subset displayed increases in these measurements. No differences between odor-exposed mice and control mice were demonstrated in open field and novel object testing.

Conclusions: The predator-odor exposure model of PTSD used in this study fulfills the five criteria for evaluating animal models of PTSD. This mouse model should be a useful tool in testing hypotheses about the neural mechanisms underlying PTSD and future studies aimed at pharmacologic treatment of PTSD.

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443 EFFECT OF TOBACCO SMOKE ON LEARNED ALCOHOL CONSUMPTION IN C57BL/6 MICE

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Purpose of Study: Two of the most abused drugs in the United States, alcohol and tobacco, are often co-abused. Alcoholism is nearly ten times more common among smokers than among nonsmokers. Human studies, although difficult to control, suggest that nicotine increases alcohol consumption. Research on rats and mice demonstrated mixed results; some studies reported that nicotine increased alcohol consumption while others showed decreased consumption. Cigarette smoke can be considered to be a more appropriate model than nicotine alone, because the smoke includes...
other chemicals that may affect alcohol consumption in addition to nicotine. For example, two of these other constituents include monoamine oxidase (MAO) inhibitors, which increases alcohol tolerance in mice, and acetaldehyde, which increases alcohol consumption in C57BL/6 mice.

**Methods Used:** Phase I: C57BL6 male mice (4–5 wk old) were conditioned to drink alcohol using the sucrose method. Over a 2-week period, sucrose was gradually reduced and alcohol concentration increased until the mice were drinking 7.5% alcohol only. Phase II: The mice were either placed into a control no-smoke chamber or into a smoking chamber for 6 hours per day for two weeks. The experimental group of mice (n = 19) were exposed to environmental tobacco smoke that was a mixture of sidestream and mainstream tobacco smoke from denicotinized cigarettes for the first week, and cigarettes with nicotine levels comparable to those commercially available for the second week. The control group (n = 12) received no smoke in an adjacent chamber. Immediately after the 6-hour period in the chamber, the control and experimental groups were given 2-hour access to the 7.5% alcohol.

**Summary of Results:** Following the smoking condition, the experimental group had a 5% decrease in body weight while the control group showed a 12% increase in weight, which was a significant difference between the groups. However, the experimental and control groups showed no significant differences in alcohol consumption after the smoke exposure period.

**Conclusions:** These data do not support the hypothesis that exposure to cigarette smoke increases alcohol consumption in C57BL6 mice under these conditions. Supported by VA Merit Review and NIH-NIAAA grants.

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**RAPID AND SIGNIFICANT INDUCTION OF VEGF EXPRESSION IN HUMAN MENINGIOMA UNDER HYPOXIC CONDITIONS**

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**Purpose of Study:** Meningiomas enjoy a rich vascular supply, driving therapeutic interest in inhibitors of vascular endothelial growth factor (VEGF). However, there has been no quantitative analysis of in vivo VEGF expression by meningioma, the presence of constitutive versus inductive expression, or the kinetics of in vitro response to hypoxia.

**Methods Used:** To quantify in vivo VEGF expression, we developed a protocol to determine direct ex vivo intratumoral VEGF levels. Fresh explants of intracranial tumors, including meningioma (n = 9), low-grade glioma (LGG;n = 6), glioblastoma (n = 7), and metastasis (n = 3) were snap frozen for protein extraction and VEGF quantification by ELISA. In parallel, fresh meningioma explants were reduced to single-cell suspension and cultured. Culture purity, as determined by dropout of CD45+ macrophages, was confirmed by flow cytometry. Low-passage lines were sequentially cultured under normoxic and hypoxic conditions. Hypoxia induction of VEGF and termination of VEGF expression following return to normoxia were assayed by ELISA.

**Summary of Results:** In vivo VEGF levels were significantly lower in meningioma (mean 47.4 +/- 243.9 ng/mg protein) than in LGG (140.1 +/- 66.1 ng/mg), metastasis (1104.2 +/- 505.3 ng/mg), or glioblastoma (2042.0 +/- 1282.9 ng/mg). VEGF levels in short-term meningioma cultures under hypoxia were confirmed by flow cytometry. Low-passage lines were sequentially cultured under normoxic and hypoxic conditions, hypoxic induction of VEGF and termination of VEGF expression following return to normoxia were assayed by ELISA.

**Conclusions:** As expected, rich vascularity results in comparatively low VEGF expression by meningioma, and its expression appears largely inducible, as opposed to constitutive. However, VEGF expression increases aggressively and dramatically in response to hypoxia; return to normoxia results in a slow attenuation to baseline levels. These findings warrant vigilance with anti-VEGF therapies, as drug withdrawal may result in induced tumor hypoxia without parallel VEGF antagonism, driving transiently high levels of VEGF and subsequent neovascularization.
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EFFECTS OF THE NON-STEROIDAL ESTROGEN RECEPTOR MODULATOR STX ON GUINEA PIG MEAL PATTERNS AND FEEDING BEHAVIOR

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Purpose of Study: Loss of the gonadal steroid estrogen during reproductive senescence has long been associated with a disruption in homeostatic processes. Although estrogen replacement therapy serves as a viable method in combating these irregularities, it is not without an increased risk of breast and uterine cancer. Recent evidence, however, has shown a newly synthesized non-steroidal STX compound as a plausible alternative to estrogen, ultimately leading to the restoration of homeostatic function devoid of uterine growth that may be indicative of cancer. We hypothesize that STX would act analogous to estradiol in terms of stabilizing some of the post-menopausal effects, specifically energy homeostasis. This study aims to determine the effects of STX on feeding behavior and meal patterns in gonadectomized female and, for comparison, male guinea pigs.

Methods Used: Gonadectomies were performed with the subjects under ketamine-xylazine (33 and 6 mg/kg, respectively, s.c.) anesthesia, alongside intra-abdominal implantation of Data loggers to monitor core body temperature. Guinea pigs underwent 4 days of post-operative recovery, 3 days of acclimation in the automated feeding chambers, and 7 days of behavioral monitoring, during which animals were weighed and injected daily with either 150ul of STX or its vehicle at 8:00 am. Food and water were available ad libitum. Daily and hourly intakes, as well as meal size, frequency and duration, were measured and stored for offline analysis.

Summary of Results: STX-treated animals exhibited a 5-10g decline in daily intake as indicated by a diminished nocturnal feeding response, with no change in uterine mass. Experimental data also indicated a sex difference in the effects of STX on meal pattern, with STX decreasing meal duration in males and decreasing meal frequency in females. Data shows that males are more responsive to STX, whereas females show greater adaptability near the end of the 24 hr cycle.

Conclusions: STX clearly mimics the effects of estrogen in altering energy metabolism and attenuating weight gain, without the proliferative effects on peripheral reproductive organs. This suggests that STX may be more suitable than estrogen for hormone replacement therapy during menopause.

Session: Neuroscience II 448

MECHANISMS UNDERLYING ASTROCYTOSIS FOLLOWING SCIATIC NERVE INJURY

Y. Liu, M. Xu, C. Chavkin
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Purpose of Study: Neuropathic pain is a widespread debilitating condition that has been challenging to treat. Partial sciatic nerve ligation (pSNL) in mice is a commonly used model for studying chronic pain, performed by tightly ligating approximately one-third to one-half the diameter of the nerve. Previous research has shown that pSNL results in dynorphin-dependent kappa opioid receptor activation, which subsequently leads to astrocyte proliferation in the ipsilateral dorsal horn of the spinal cord. Induction of neuropathic pain is linked to this astrocytosis; however, the underlying cellular processes are unclear. The goal of this study is to investigate the role of p38 mitogen-activated protein kinases (MAPks) in mediating neuropathic pain.

Methods Used: Our experiments used GFAP-CreERT2/p38αlox/lox conditional knockout (CKO) mice, which selectively excised p38α in astrocytes following tamoxifen administration. 4 wild type (WT) and 4 CKO mice were given intraperitoneal tamoxifen injections once daily for 7 days. On day 5 of injections, all mice were anesthetized with pentobarbital, and pSNL surgeries were performed on the right limbs. Behavioral pain responses were assessed on days 2, 4, and 6 following pSNL by measuring paw withdrawal latencies using Hargreaves test for thermal hyperalgesia, and von Frey hair test for mechanical allodynia. On day 7 after pSNL, the mice were intracardially perfused with paraformaldehyde. Immunohistochemical staining of the dorsal horn of the lumbar spinal cord was performed using glial fibrillary acidic protein (GFAP), p38α, and phospho-p38 antibodies.

Summary of Results: Compared to WT, CKO mice showed longer ipsilateral paw withdrawal latencies in both Hargreaves and von Frey hair tests on all three behavioral test days. Additionally, CKO mice showed recovery, as early as the second test day, while WT mice continued to demonstrate significant hyperalgesia and allodynia on all three test days. Immunostaining of the spinal cord showed an increase in phospho-p38 and in GFAP + p38α double-labeling in the ipsilateral dorsal horns of WT mice, but not in CKO mice.

Conclusions: CKO mice showed decreased astrocyte proliferation in the ipsilateral dorsal horn of the spinal cord, and lower levels of mechanical allodynia and thermal hyperalgesia, suggesting a role for the p38 MAPK pathway in astrocyte activation and neuropathic pain.
Purpose of Study: Angelman Syndrome (AS) is a rare genetic neurological disorder characterized by severe mental retardation, microcephaly and inappropriate laughter. The syndrome is caused by mutations in the maternal ub3a gene coding for the protein E6-AP, an E3 ubiquitin ligase. This study attempts to show that the neurological phenotype in AS is associated with morphological changes in cultured mouse hippocampal neurons that exhibit imprinted expression of Ub3a gene.

Methods Used: To quantify the morphological changes in the cultured cells we measured the number of dendrites per cell as well as the dendritic diameter. A reduction in dendritic size and number would significantly impact the processing capacity of hippocampal neurons. To accomplish this analysis we explored cell staining via microinjection. Microinjection can be used to deliver dyes directly into the cell, providing a clear picture of neuronal morphology without interference from neighboring cells. Wild-type and mutant ub3a hippocampal neurons were injected with a fluorescent dye (DiO) and images were collected using a confocal microscope. A quantitative analysis of dendrite size and number was performed using MetaMorph® imaging software.

Summary of Results: The results of the MetaMorph® analysis showed a 39% decrease in dendritic number (n > 20, p < 0.001) and a 45% decrease in dendritic diameter (n > 90, p < 0.001) in hippocampal neurons from mice with Ub3a maternal deletion as compared to wild-type mice. Furthermore, neurons with maternal Ub3a deletion showed a significant decrease in number and size of dendritic spines, a small membranous protrusion from a dendrite that constitutes the post-synaptic portion of a synapse.

Conclusions: The changes in morphology seen in these hippocampal neurons indicate that Ub3a/E6-AP plays a key role in dendritic growth and maturation. Further research focused on dendritic spine morphology in vivo may provide evidence that Ub3a/E6-AP has an essential role in synaptic development. Additionally, continued optimization of the microinjection delivery system is ongoing with the goal of delivering fluorescently tagged cDNA constructs that code for the ub3a gene as well as genes coding for proteins CamKII and RhoA that are hypothesized to interact with E6-AP with hopes of visualizing protein-protein interactions.

Session: Neuroscience II 451

EVALUATING GLOBAL HYPOXIC-ISCHEMIC BRAIN INJURY IN ADULTS USING PROTON MAGNETIC RESONANCE SPECTROSCOPY

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Purpose of Study: Few studies have been published involving the use of proton MR spectroscopy (MRS) in determining hypoxic-ischemic injury (HII) in adults. The purpose of this study is to evaluate changes in brain metabolites of adult patients who have sustained HII.

Methods Used: We performed a retrospective chart review of 113 adult patients who were evaluated with proton MRS from 2002 to 2009 early after injury for suspected HII to the brain. Single voxel proton MRS was performed in the mid-occipital grey matter (OGM) of the brain in an 8 cc volume. The following metabolite levels were measured: N-acetylaspartate (NAA; a neuronal marker), creatine (Cr; marker for energy metabolism), choline (Cho; marker for cell membrane disruption), myo-inositol (Ins; astrocyte marker and osmolyte), and lactate (Lac; marker for anaerobic glycolysis). Metabolite ratios were calculated and presence of Lac was increased in HII patients indicating neuronal loss or dysfunction and can be used as a marker to evaluate the extent of HII injury. Future studies will compare early metabolic findings to long term outcome.

Pulmonary and Critical Care II
Concurrent Session 8:30 AM Saturday, January 30, 2010

Session: Pulmonary and Critical Care II 452

SURROGATE CONSENT FOR RESEARCH INVOLVING INCAPACITATED ADULTS: LEGAL & ETHICAL CONSIDERATIONS

T. Stone University of Texas Health Science Center at Tyler, Tyler, TX.

Purpose of Study: Elucidate federal, state and international laws and relevant ethical principles that govern the use of surrogates (or third parties such as proxies or legally authorized representatives) to provide consent for research on behalf of decisionally incapacitated adults.

Methods Used: Statutes, regulations, court cases and related ethics codes and legal material of U.S. and international jurisdictions were abstracted and analyzed to determine their implication for the use of surrogate consent for research involving decisionally impaired adults.

Summary of Results: Federal, state and international laws address the use of surrogates to provide consent for research on behalf of decisionally impaired adults. Federal regulations and European Union directives expressly defer to state or local laws to determine the precise conditions under which investigators may seek surrogate consent and surrogates may exercise consent authority. However, the handful of state laws which explicitly permit surrogates to exercise consent authority for research vary significantly. Similar inconsistent laws are being considered in several states. In other states, such explicit laws do not exist. Consequently, investigators, IRBs and research sponsors may attempt, as evidenced by investigations conducted by the Office for Human Research Protections (OHRP), to incorporate the permissibility of involving decisionally impaired adults in research from state laws that pertain to surrogate consent to medical treatment generally. Absent direct clinical benefit to subjects provided by proposed research that is consistent with medical practice, state and local laws on surrogate consent to treatment are unlikely to provide surrogates with the legal authority to exercise consent to research on behalf of decisionally impaired adults.

Conclusions: More specific policies should be developed and implemented by research institutions, IRBs, and research sponsors which would conform to their applicable state and local laws and prevailing ethical norms that address the use of surrogates to provide consent for research on behalf of decisionally impaired adults. Investigators and IRBs should be provided with appropriate related training and guidance. Model policy guidance and practice pointers are provided for investigators and research review committees for this purpose.

Session: Pulmonary and Critical Care II 453

CASE SERIES OF COCCIDIOIDOMYCOSIS IN CRITICALLY ILL INFANTS AND CHILDREN

N. Puranik1, R. Hernandez1, R. Dimand1,2 1UCSF-Fresno, Fresno, CA and 2Children’s Hospital Central California, Madera, CA.

Purpose of Study: Coccidioidomycosis (Cocci) is a fungal infection endemic to California’s San Joaquin Valley. Most patients usually present with influenza-like illness, and less than 2% develop disseminated disease. According to California Dept of Public Health’s analysis of cases (2000–2007), the incidence of reported Cocci cases (5/100,000) and hospitalizations (1.2/100,000) in children 0–19 years of age was low, when compared to other age groups. Although there are sporadic case reports of Cocci in critically ill children, this is the first case series of Cocci in the Pediatric Intensive Care Unit (PICU). This series describes the clinical course of patients admitted to the PICU at Children’s Hospital Central California (CHCC) over a 7 year period.

Methods Used: A retrospective chart analysis of patients with a confirmed diagnosis of Cocci with serology, culture and/or histopathology, who were in the PICU at CHCC from 2003–2009.

Summary of Results: 8 patients (9 admissions) admitted to PICU from 2003–09; of total 550 Cocci cases at CHCC(1.6%). Average age was 11.8 years
with SD of 7 yrs; range 0.25–20 yrs. 7 patients had pulmonary disease, and 1 had CNS dissemination. 5 of 8 patients were previously healthy; 1 with chronic liver disease (long-term ventilation period), 1 had asthma (no support), 1 with prior pulmonary Cocci (no initial PICU admission). 5 of 8 patients with initial diagnosis & treatment of Community Acquired Pneumonia (CAP); All 5 admitted to PICU for impending respiratory failure; 4 needed vent support. 5 of 8 patients required mechanical ventilation, with an average of 13.2 days with SD 9.2 days; range 3–28 days. 2 of 8 patients required intotropes; 1 and 4 days. Average LOS was 10 days with SD of 10 days; range 2–23 days. Average 8 days from initial symptoms to Cocci treatment was 19.75 days, with SD of 9.5days; range 5–20 days. All 8 had good outcome.

Conclusions: Based on data reviewed, of all inpatients with Cocci, the need for PICU admission for Cocci is uncommon (1.6%). Pulmonary Cocci was much more common than CNS Cocci. Subtlety of presentations was demonstrated by nearly three weeks (19.8 days) from first symptomatology to initiation of Cocci treatment, likely from initial CAP diagnosis in outpatient setting or on admits. Even in the case of multiple chest/mediastinal abscesses, good outcomes were achieved.

Session: Pulmonary and Critical Care II 454
UNIQUE RAT STRAIN SURVIVES BREATHING PURE OXYGEN, EXERCISES AND LIVES LONGER: POSSIBLE ROLE FOR HEAT-SHOCK PROTEINS AND REDUCED INFLAMMATION
JJ. Repine1, AC. Tan2, CJ. Beehler3, K. Crader1, ND. Elkins1, J. Vina4, JP. Singer1, PD. Blanc1,2, EH. Yelin3, G. Sanchez4, C. Iribarren4, MD . Singer1, PD. Blanc1,2, EH. Yelin3, G. Sanchez4, C. Iribarren4, MD .

Methods Used: We used Affymetrix GeneChip Rat Genome 230 2.0 arrays to measure lung mRNA before and after hyperoxia for ~52 h. Raw microarray signal intensities were extracted using MA5 algorithm of Affymetrix Power Tools. Gene probe sets were collapsed based on maximum signal values and signal intensities were extracted using MAS5 algorithm of Affymetrix Power Tools. Significance Analysis of Tools. Gene probe sets were collapsed based on maximum signal values and signal intensities were extracted using MAS5 algorithm of Affymetrix Power Tools. We used the Function, Living, Outcomes, and Work (FLOW) cohort study of adults with COPD to assess the joint impact of systemic disease, the effects of non-pulmonary dysfunction on physical health have not been clearly characterized. We sought to evaluate the impact of respiratory and lower extremity muscle function on exercise capacity and lower extremity function in patients over a broad range of COPD severity.

Methods Used: We used the Function, Living, Outcomes, and Work (FLOW) cohort study of adults with COPD to assess the joint impact of limited respiratory and lower extremity muscle strength on validated measures of submaximal exercise performance (Six Minute Walk Test [6MWT]) and lower extremity function [Short Physical Performance Battery (SPPB), poor function defined as the lowest quintile of the SPPB]. The MicroRPM Respiratory Pressure Meter (Micromedical Ltd, Rochester, Kent, UK) was used to evaluate measures of respiratory muscle function (maximum inspiratory pressure [IP] and dynamometry (MicroFet2 dynamometer (Saemmmons Preston, Bolingbrook, IL) was used for manual muscle testing of the quadriceps, a key muscle used in ambulation.

Methods Used: All intubations performed in the ED at an urban, academic Level 1 Trauma Center from 1 July 2007 to 30 June 2009 were analyzed in this observational study. The two videolaryngoscopes included in this study were the GlideScope® and the CMAC®. After each intubation was performed, a survey form was completed by the operator. Data was collected on success, number of attempts, Cormack-Lehane (CL) view, lens fogging (LF), lens contamination (LC), and number of difficult airway predictors (DAPs). LF was rated on a 10 cm visual analog scale (VAS) with 0 = no fog and 10 = completely fogged. LC was graded as none, mild, moderate, or severe. Descriptive statistics were used to compare success rates, performance characteristics, and performance, characteristics, and number of DAPs. A p-value of <0.05 was considered to be statistically significant.

Summary of Results: DL was the initial device chosen in 56.6% (533/942) of cases, where as a videolaryngoscope was chosen in 35.8% (377/942). The cases in which VL was the initial device chosen, 82.5% (278/337) were performed with the GlideScope® and 17.5% (59/337) with the CMAC®. See table for DL vs. VL comparison results.

Conclusions: VL had a statistically significant higher first attempt success rate than DL. In addition, VL was able to obtain a grade I or II CL view more often than DL. VL provided a view of the airway with only minimal LF and very little LC. The difference in ultimate success rate between the two modalities was not statistically significant. Despite being used in cases with more DAPs, VL was superior to DL in terms of first attempt success rate and performance characteristics.

Success Rates and Performance Characteristics of DL vs. VL

Methods Used: All intubations performed in the ED at an urban, academic Level 1 Trauma Center from 1 July 2007 to 30 June 2009 were analyzed in this observational study. The two videolaryngoscopes included in this study were the GlideScope® and the CMAC®. After each intubation was performed, a survey form was completed by the operator. Data was collected on success, number of attempts, Cormack-Lehane (CL) view, lens fogging (LF), lens contamination (LC), and number of difficult airway predictors (DAPs). LF was rated on a 10 cm visual analog scale (VAS) with 0 = no fog and 10 = completely fogged. LC was graded as none, mild, moderate, or severe. Descriptive statistics were used to compare success rates, performance characteristics, and number of DAPs. A p-value of <0.05 was considered to be statistically significant.

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Conclusions: VL had a statistically significant higher first attempt success rate than DL. In addition, VL was able to obtain a grade I or II CL view more often than DL. VL provided a view of the airway with only minimal LF and very little LC. The difference in ultimate success rate between the two modalities was not statistically significant. Despite being used in cases with more DAPs, VL was superior to DL in terms of first attempt success rate and performance characteristics.

Session: Pulmonary and Critical Care II 456
RESPIRATORY AND SKELETAL MUSCLE STRENGTH: IMPACT ON EXERCISE PERFORMANCE AND LOWER EXTREMITY FUNCTION IN COPD

Purpose of Study: Although COPD is increasingly recognized as a systemic disease, the effects of non-pulmonary dysfunction on physical health have not been clearly characterized. We sought to evaluate the impact of respiratory and lower extremity muscle function on exercise capacity and lower extremity function in patients over a broad range of COPD severity.

Methods Used: We used the Function, Living, Outcomes, and Work (FLOW) cohort study of adults with COPD to assess the joint impact of limited respiratory and lower extremity muscle strength on validated measures of submaximal exercise performance (Six Minute Walk Test [6MWT]) and lower extremity function [Short Physical Performance Battery (SPPB), poor function defined as the lowest quintile of the SPPB]. The MicroRPM Respiratory Pressure Meter (Micromedical Ltd, Rochester, Kent, UK) was used to evaluate measures of respiratory muscle function (maximum inspiratory pressure [IP] and dynamometry (MicroFet2 dynamometer (Saemmmons Preston, Bolingbrook, IL) was used for manual muscle testing of the quadriceps, a key muscle used in ambulation.

Summary of Results: In our cohort (n = 1,202; mean age 58.2 ± 6.2 years; 57% female) the mean FEV1 was 1.79 ± 0.79 liters. Those in the highest quartile of combined MIP and quadriceps strength comprised the referent category (i.e., the most favorable group); the lowest quartile of combined strength was tested as the highest risk category. Relative to those with most favorable status, those with low MIP and low quadriceps strength manifest a large reduction in 6MWT capacity (~120 meters; 95%CI 148 to 92 meters) and a nearly ten-fold greater odds of poor lower extremity function (OR 9.38; 95% CI 4.4–22).

Session: Pulmonary and Critical Care II 455
A COMPARISON OF VIDEOLARYNGOSCOPY TO DIRECT LARYNGOSCOPY FOR EMERGENCY DEPARTMENT INTUBATIONS
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Purpose of Study: To compare the success rates and performance characteristics of videolaryngoscopy (VL) to direct laryngoscopy (DL) for the intubation of emergency department (ED) patients.

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Conclusions: Reduced respiratory and lower extremity muscle strength is associated with markedly impaired exercise capacity and greater likelihood of poor function. Our findings highlight the possibility that earlier attention to muscle weakness could be an important component of disability prevention in patients with a broad range of COPD severity.

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457
RED BLOOD CELL TRANSFUSION IN PEDIATRIC TRAUMA PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT: PRACTICE EVALUATION

L. Shobab1, P. Skippen2, G. Krahn1, S. Butterworth3

Purpose of Study: Recent evidence in adults suggests a restrictive approach to blood transfusion is safe in intensive care patients, however there is little evidence about this transfusion strategy in children. This study evaluates the use red blood cell transfusion in the critically injured pediatric patient population.

Methods Used: A 5 year (2004–2009) retrospective review of all patients admitted with the diagnosis of trauma to a tertiary pediatric intensive care center (PICU) was undertaken. Characteristics of transfused patients included: age, PRISM score (pediatric illness severity score), pre-transfusion haemoglobin and lowest systolic blood pressure 6 hours prior to transfusion. Number of transfusions, age of blood and cross match status were recorded. Outcomes included length of stay, nosocomial infection, multigorgan dysfunction and mortality. Rates of blood transfusion during first 3 years vs. latter 2 years were compared as was number of transfusions per patient. Descriptive statistics were used.

Summary of Results: 383 trauma patients were admitted to the PICU, 107 received a blood transfusion. Patients were on average 8.4 years old with a median number of transfusion per patient. 65% vs. latter 2 years were compared as was number of transfusions per patient.

Conclusions: Approximately 25% of critically injured children were transfused with blood and nosocomial infection and multigorgan dysfunction were relatively common. These children received multiple transfusions, yet in close to one third the pre-transfusion haemoglobin level was greater than 90 in 27% of this group, 80% had normal systolic blood pressure. Transfused patients received an average of 3.2 blood transfusions, which were 19 days old, of which 92% were cross matched. Median length of hospital stay was 13 days, nosocomial infection developed in 40%, multigorgan dysfunction in 72% and mortality was 10%. Blood was transfused in 24% in the first 3 years compared to 28% more recently; median number of transfusions per patient for both time periods was 2. There was no difference in pre-transfusion haemoglobin thresholds between 2004–2007 and 2008–2009 patients.

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IMMUNOPATHOLOGICAL CHANGES IN THE LUNGS OF SARIN EXPOSED RATS

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Purpose of Study: Organophosphorus compounds that serve as nerve agents are among the most lethal chemical toxins known to mankind. Because of its vaporization properties, the nerve agent sarin is among the most lethal chemical toxins known to mankind. Because of its vaporization properties, the nerve agent sarin is most likely chemical agent for a war/terrorist setting. Although the lethality of sarin results primarily from respiratory failure, the effects of sarin on lung responses are poorly understood.

We hypothesize that sarin inhalation stimulates the production of proinflammatory cytokines and chemokines in the lung that trigger leukocytic emigration into the lung. To address this hypothesis, we determined the cytokine/chemokine milieu of the lung at various times after exposure F344 rats to 1-2 LD50 sarin inhalation.

Methods Used: 1) Sarin Exposure: Because the proposed studies were designed to assess sarin-induced acute lung injury, animals were exposed via nose-only inhalation to ~1-2 LD50 (4-8 mg/m3) sarin. Analysis was carried out on 4-6 surviving animals and p values of < 0.05 were considered significant. 2) Bronchoalveolar lavage fluid (BALF) were used to determine chemokine/chemokine composition by ELISA. BAL cells were cytospun to examine differential cell count. Lungs were fixed and tissue sections were stained with hematoxylin and eosin (H&E) and graded for inflammation. To visualize apoptosis, lung sections from control rats and sarin treated rats were stained for a Terminal Uridine Deoxynucleotidyl Transferase DUTP Nick End Labeling (TUNEL) assay using an Apoptosis Detection Kit. 3) Lung RNA was extracted and tested cytokines and chemokines by qPCR analysis. Generally, qPCR is carried out with a Qiagen qPCR kit according to manufacturer’s directions.

Summary of Results: Histopathologically, one can see that sarin inhalation caused either partial or total detachment of the epithelial cell layer in the alveoli. This is further supported by the observation that sarin induced a dramatic increase in the number of epithelial cells in the BAL. Moreover, BALF cytokine/chemokine levels, including eotaxin, IL-2, TNF-α, and IL-1β are significantly altered.

Conclusions: Inhalation of sarin at 1-2 LCD50 disrupts the epithelial lining of the rat alveolar cells that is likely to disrupt gas exchange and promote lung inflammation and respiratory failure.

Session: Pulmonary and Critical Care II
459
NECROTIZING ENTEROCOLITIS IN TERM INFANTS: A CASE SERIES

J. McDermott1,2, M. Fruzza1, B. Diament1,2, UCSF Fresno, Fresno, CA and 1Children’s Hospital Central California, Madera, CA.

Purpose of Study: Necrotizing enterocolitis is a serious infection of the gastrointestinal tract occurring predominantly in preterm neonates. About 10% of the time, NEC occurs in term infants. While the pathophysiology is unclear, it can be related to infection, compromise to gut blood flow, or congenital heart disease. We report on two term neonates with no known predisposing factors for their presentation and course of NEC.

Methods Used: Case #1: A 5 day old male presented with direct hyperbilirubinemia at birth, mom was GBS+ with ROM~18-20 hrs, adequately treated with antibiotics; he received an initial 48 hours of antibiotics. According to parents, he was doing well at home. He was referred to the ER for worsening jaundice and transferred to our tertiary Children’s Hospital. Here, he quickly decompensated; abdominal X-rays showed portal venous air and pneumatisis intestinals in small bowel, colon, and stomach. In the PICU, mechanical ventilation, triple antibiotics and bowel rest was started; he quickly improved, with no portal venous air, pneumatisis intestinalis, or perforation evident in the next 24 hours. Hepatocellular enzymes were essentially normal. After 2 weeks of gut rest, he had a bloody mucoid stool; after 3 weeks, a lengthy colonic stricture was found. At no time was acidosis, renal or hepatic impairment noted.

Case #2: A 28-day old male presented with fever and respiratory distress. Shortly after transfer to the tertiary Children’s hospital, he worsened, requiring intubation and mechanical ventilation. Several days after clinical improvement, he developed a tense, distended abdomen; abdominal X-rays showed areas suspicious for pneumatisis intestinalis. Despite negative lateral decubitus abdominal X-rays, four colonic perforations were discovered by urgent exploratory laparotomy, needing a subtotal colectomy.

Summary of Results: (see conclusions)

Conclusions: Although classically described in premature infants, NEC is rare in term infants with their etiology and course unclear. For example, in case #1, massive pneumatisis including stomach wall, small and large intestine with air in liver and spleen appeared much worse than the clinical picture. Various interventions have been proposed to help decrease the incidence of NEC; however, we need to identify those infants at increased risk for NEC in order to intervene.

Session: Pulmonary and Critical Care II
460
SUBPLEURAL CYSTS IN CHILDREN WITH DOWN SYNDROME

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Purpose of Study: Autopsy and radiologic case series have identified subpleural cysts in children with Down syndrome since 1986. Although rarely described in pediatric literature, reports have focused on the association of these cysts in children with Down syndrome and congenital
Methods Used: We present 3 cases of children with Down syndrome, CHD, and subpleural cysts who are followed in pulmonology clinic.

Summary of Results: VA is a 6-year-old girl with Down syndrome and a history of patent ductus arteriosus (PDA) who was evaluated for reactive airway disease at age 4. A chest radiograph at that time showed round lucencies in the right upper lobe. MW is an 8-year-old boy with Down syndrome, repaired PDA, and complete atrioventricular septal defect. He was hospitalized for pulmonary coccidioidomycosis. NL is a 4-year-old boy with Down syndrome, PDA, and mild pulmonary hypertension. On routine chest radiograph, he had cyst-like lucencies in his lungs. All three children had subsequent chest CT scans which showed round, peripheral cysts bilaterally.

Conclusions: Our cases support the association between Down syndrome, subpleural cysts and CHD. Healthcare providers should be aware of this association and that chest CT is the imaging of choice. In addition to possibly worsening pulmonary hypertension, these cysts may cause a spontaneous pneumothorax. However, these cysts have not shown clinical significance to date in our 3 patients. The children remain stable in room air with normal oxygenation and stable echocardiograms. We continue to monitor them with routine clinic visits, serial chest CT scans, and echocardiograms. The utility of screening patients with Down syndrome and CHD remains in question. Further studies involving a larger population of patients with Down syndrome are needed.
trauma, and subchondral infection. The use of Bone Morphogenetic Proteins (BMP) in bone fusion and spinal arthrodesis continues to increase in frequency due to its ability to reduce the potential number of non-unions. Therefore, it is important to determine if BMP implantation is a safe and effective treatment for resistant non-unions and failed arthrodesis in a long-term setting.

Methods Used: An IRB-approved, retrospective cohort analysis was conducted on 56 patients (33 female, 23 male; median age = 47) that were administered hBMP for the treatment of resistant non-unions (51) and failed arthrodesis (5) between 1987 and 1998 at UCLA Medical Center. All patients had previously failed methods of fracture treatment, including iliac crest bone graft. Radiology reports, post-operative surgery reports, and physical examination reports were assessed, and the following endpoints were measured: 1) rate of fusion failure, 2) allergic reaction to hBMP, 3) post-operative infection, and 4) malignancy, up to the point of the patients last follow-up visit (median = 51 months; range = 2-256 months). The non-unions consisted of 34 femurs, 5 humeri, 5 tibias, 3 carpal bones, 2 ulnae, 1 radius, and 1 clavicle.

Summary of Results: 30/56 (69%) went on to achieve successful osseous union following revision surgery with hBMP implantation. 25/6 (3.5%) acquired a post-operative infection at the implant site, that required additional surgery. There was no incidence of malignancy or allergic reaction to hBMP noted in these studies. Overall, 48/56 (86%) of patients did not suffer from any adverse event associated with hBMP implantation.

Conclusions: hBMP implantation retains its high level of safety and efficacy for the treatment of resistant non-unions and failed arthrodesis in a long-term setting. It is important to assess other comorbidities and risk factors that impact the safety and efficacy profile of hBMP. Due to the high level of morbidity and costs associated with revision surgery, the use of hBMP can revolutionize management of non-unions and failed arthrodesis.

Session: Surgery II
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EVALUATION OF ACELLULAR DERMAL MATRIX IN BREAST RECONSTRUCTION
JT Tieman1, JP Agarwal2, LA Anderson2 1University of Arizona College of Medicine, Tucson, AZ and 2University of Utah, Salt Lake City, UT.

Purpose of Study: Breast cancer patients have multiple options following mastectomy, with implant based reconstruction being one of the more common. Two different acellular dermal matrices are available, and are used to create a pocket for placement of the implant. While their use has been shown to be safe in breast reconstruction, no studies have compared them to each other with regards to complication rates, or effects of radiation on incorporation rates.

Methods Used: Female patients ages 18-80, opting for breast reconstruction at the Huntsman Cancer Center in Utah, are study eligible. Patient data is collected and recorded in stages. Stage 1 is from time of expander placement to final reconstruction. Stage 2 is from final reconstruction to two months post-op, while stage 3 follows patients for two years. The first surgery is expander and dermal matrix placement. Patients follow a standard routine of care, with complications and progress recorded at routine visits. To allow for integration and revascularization of the matrix, the removal of expanders and final reconstruction does not occur before 3 months after initial surgery.

Outcome data is patient satisfaction, histological data from punch biopsies taken at surgeries, as well as clinical evaluation of matrix to characterize its incorporation. The clinical findings are correlated with the pathologic features and evaluated and will be compared statistically.

Summary of Results: At this point in the study, we are able to report on the stage 1 data and some stage 2 data. The data thus far does not indicate that there are any differences in the rate of complications between the two matrices, which would support our hypothesis. Additionally, there is no difference in the rates of incorporation between those patients receiving radiation and those who do not; however, there is a tighter capsule in those patients who received radiation. This may prove to translate into a higher rate of capsular contracture. There is also some preliminary data to indicate increased complication rates in patients with a history of smoking.

Conclusions: This study will offer an extremely important insight into the proper timing of clinical treatment, and whether or not matrices should be used on patients undergoing radiation.

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FLUOROCROME ANALYSIS OF RADIgenic BONE DAMAGE: A SEARCH FOR AN ANIMAL MODEL OF OSTEO RADIONECROSIS OF THE MANDIBLE
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Purpose of Study: To use fluorochrome analysis in an animal model of post-extraction radiogenic bone damage in order to provide a foundation for a histomorphometric definition of ORN of the mandible and better investigate its molecular pathogenesis. Evaluation of the molecular defects seen in radiogenic bone damage can lead to a more complete understanding of ORN, and thus, more targeted therapies that may help cure or even prevent this debilitating disease.

Methods Used: Ten male (56 day old) Sprague-Dawley rats (7 experimental, 3 controls) were subjected to either 20Gy-advanced High Dose Rate (HDR) Brachytherapy or sham radiation to their left mandible. All animals underwent immediate extractions of all three left molars. Fluorochromes were injected intraperitoneally at specific time intervals (0d, 9d, and 26d post-extraction). Animals were sacrificed at 14d and 28d post-extraction and mandibles were removed for fluorochrome analysis.

Summary of Results: The fluorochrome labeling patterns in our model are highly suggestive of cell necrosis occurring in the extraction site. Lack of any second label (demeclocycline, orange) in the extraction sockets, yet present in the lamellar inferior rim of the radiated mandibles, can be explained by the absence of any active bone metabolism in the extraction site and suggests earlier osteogenic cell death after radiation. Fluorescent microscopy also demonstrated significantly reduced bone mineralization of irradiated lamellar cortical bone at 28days post-irradiation (1.50 μm/μm2 compared to 4.63 μm2/ day for controls, P = .0027).

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SONOGRAPHIC EVALUATION OF THE SUPRASPINATUS TENDON: AT REST, AND IN THE CRASS AND MODIFIED CRASS POSITIONS

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Purpose of Study: Sonography has been proven to be highly valuable for the evaluation of the rotator cuff. Positioning of the shoulder is crucial to accurate and thorough evaluation of the rotator cuff tendons. The Crass and Modified Crass positions are the most common positions used in research and in the clinic for the evaluation of the supraspinatus, but the differences they evoke have never been quantified. Our study is aimed at determining the differences in length and thickness of the supraspinatus tendon evoked by the crass and modified crass position from resting values in normal shoulders, in order to determine clinical relevance of each position.

Methods Used: The sample population consisted of 50 asymptomatic volunteers with no history of shoulder pathology (25 M aged 19-32, and 25 F aged 21-31). Sagittal and transverse dimensions were imaged at rest and in both positions. Length measurements were taken from the lateral most edge of the acromion to the highest point on the humerus. Thickness values were taken by measuring the thickness 1cm proximal from the rotator cuff interval.

Summary of Results: Both positions expose more of the supraspinatus tendon to visualization than what is seen at rest, and both positions stress the tendon as evidenced by a decrease in tendon thickness. However, no statistically significant difference was seen between the length of the tendon exposed by the two positions (t = .4 for females, t = .31 for males) or the change in thickness between the two positions (t = .24 for females, t = .19 for males). Additionally, we recorded an average thickness value of 5.1 mm, SD .53 mm, which differs from the established literature value of 6 mm.

Conclusions: In terms of length of supraspinatus tendon exposed and amount of tension applied based on the change in thickness, the two positions do not generate different dimensions in the tendon. In light of the fact that the Crass position is quite difficult to assume when someone has shoulder pain, we advocate that the modified Crass position is sufficient for the evaluation of the supraspinatus tendon. Additionally, the value of 5.1mm that we recorded should replace the previous standard of 6mm.

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USING COLLAGEN SCAFFOLDS ON TRANSPLANTATION SITES TO FACILITATE INCREASED CELLULAR VIABILITY OF HFF1 FIBROBLAST CELLS

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Purpose of Study: The purpose was to identify methods to enhance viability of islet cells transplanted into the portal vein of recipients suffering from chronic pancreatitis and diabetes. Current methods of islet cell portal vein implantation have led to complications such as Portal Vein Thrombosis (PVT), hyperglycemia, and drug toxicity. This study looked into alternative viable sites for islet cells to grow. Use of collagen scaffolds could enhance islet cell docking since ECM can bind easily with collagen matrix. Collagens were used as substitutes for islet cells and seeded on regular and electrospun collagen to test their binding efficacy to collagen surfaces.

Methods Used: Manufactured slides of collagen scaffolds were used as a bed for HFF1 Fibroblast seeding. Two types of collagen were used. One consisted of electrospun collagen (SPL2, an electrostatically modified Type I collagen) and the other of regular, unaltered Type I collagen (SPL1). Seeding of fibroblasts was carried out at 1.42 x 105 cells/cm2 at a total scaffold seeding area of 36.72 cm2. When cells were seeded, they were incubated at 37°C, 5% CO2. Medium used was modified MCDB, changed every 3 days.

Summary of Results: Data show successful cellular growth with these scaffolds. Using an Alamar Blue viability assay two days after incubation, there were positive signs of cellular growth. The two collagen scaffolds, SPL1 and SPL2, demonstrated near equal efficacy in facilitating fibroblast proliferation. SPL1 scaffolds had a final cell count of 29,044 cells/well compared to SPL2 scaffolds with 26,916 cells/well. SPL2 mimicked better the physiological conditions of an actual human dermis. The slight discrepancy between cell counter numbers could be associated with the modified medium used.

Conclusions: Collagen scaffolds as a base for cellular growth appear to be a promising tool for surgical transplantation. Observation of positive growth patterns with HFF1 fibroblasts on collagen suggests that other cell types, particularly islet cells, could be seeded on these same scaffolds. With SPL2, viability of islet cells can be sustained through efficient binding between SPL1 and ECM. This scaffold, in conjunction with a conducive bodily site (e.g., omental pouch), could serve as a highly suitable environment for enhanced islet cell growth and function.
on pediatric patients as part of their technical surgical training during a 2 month rotation. For each procedure, the resident was the principal operator, with the attending surgeon assisting. Technical feedback was given by the attending surgeon to the resident by reviewing the videotape footage with them. A second video was taken of the resident performing the same procedure after the performance feedback session. Residents were not given specific feedback on their sharps handling technique. Assessment of safe and unsafe sharps handling was determined based on the Association of Perioperative Nurses and the American College of Surgeons guidelines. Resident safety performance was assessed in three areas: personal sharps tasks, passage of sharps and verbal notification regarding sharps. For residents with a second procedure video-taped, safety performance was compared between the 2 procedures. Descriptive statistics were employed.

**Summary of Results:** Data was collected from 19 surgical residents’ videos: 4 plastic surgery and 15 general surgery. Residents safely performed sharps tasks, passed sharps and verbally notified about sharps an average of 66.3%, 91.5% and 10.6% of the time respectively. Eight residents had a second hernia repair videotaped. In comparing the second to the initial video, residents demonstrated a 10.5% increase in safe personal sharps tasks, a 3.9% increase in safe passing of sharps and a 16.6% decrease in verbal notification about sharps. One of the current techniques for posterolateral corner reconstruction is the dynamic PLT-PFL reconstruction. However, the importance of the position of the PLT-PFL junction and the angle between the two tendons when considering a reconstruction of the posterolateral corner, the dynamic nature of the position of the PLT-PFL junction and the angle between the two structures must be considered.

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**KINEMATICS OF THE POSTEROLATERAL CORNER OF THE KNEE: A CADAVERIC STUDY**

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**Purpose of Study:** To quantify the detailed kinematics of the posterolateral corner of the knee for the purpose of developing a strategy for anatomical reconstruction.

**Methods Used:** Five human cadaveric knees were investigated using a custom testing system. Specimens were dissected leaving the quadriceps and hamstring muscles and the capsule intact except for that covering the posterolateral corner. The popliteal tendon (PLT) and the popliteofibular ligament (PFL) were marked using No. 0 black silk and small metal screws for digitizing. Muscle loads were set at 10N for the quadriceps, 4N for the hamstring and 0.8N for the popliteus tendon to represent residual tension. All measurements were made at neutral, external and internal tibial rotation at 0, 30, 60 and 90 degrees of knee flexion using a Microscribe 3DLDX (Revware Inc, Raleigh, NC). Paired t-test was used for statistical analysis with p < 0.05.

**Summary of Results:** Across all flexion angles the PLT-PFL junction moved laterally-superiorly-anteriorly 6.4 ± 1.0mm with tibia ER and medially-inferiorly-posteriorly 5.9 ± 1.6mm with tibia IR. The angle between the PLT and the PFL was increased 15.0 ± 2.3° with tibial ER and decreased 9.5 ± 3.5° with tibial IR. The angle between the PFL and the fibula axis on the sagittal plane increased 14.6 ± 1.4° with tibia ER and decreased 10.7 ± 0.4° with tibia IR.

**Conclusions:** One of the current techniques for posterolateral corner reconstruction involves fixing the PLT and PFL grafts to the posterior wall of the tibia. However, our study showed that this point moves with tibial rotation. The angle between the PLT and PFL and the angle between the PFL and fibula both increase with tibia ER and decrease with tibia IR. Therefore, when considering a reconstruction of the posterolateral corner, the dynamic nature of the position of the PLT-PFL junction and the angle between the two structures must be considered.

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**HIGH-DEFINITION VIDEO-ENDOSCOPY: A FUNCTIONAL ASSESSMENT OF IMAGE QUALITY**

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**Purpose of Study:** High-definition (HD) video technologies have been widely adopted in recent years, replacing standard-definition (SD) technologies in endoscopic instrumentation. The HD technologies have significantly higher pixel resolution at a greater cost than SD technologies. However, more clinically relevant measures of spatial image resolution, color discrimination, and contrast sensitivity have not yet been tested in HD endoscopic instrumentation. The goal of this study is to assess these objective measures of image quality in HD versus SD video-endoscopic units.

**Methods Used:** Participants (n = 18) were shown images on a monitor and tested psychophysically with the Farnsworth-Munsell 100-Hue test, Farnsworth-Munsell total error scores for color discrimination were significantly better with the HD unit than the SD unit (88.3 ± 27.0 sec vs 98.9 ± 32.7 sec; p = 0.043). Farnsworth-Munsell total error scores for color discrimination were significantly better with the HD unit than the SD unit (91 ± 58 vs 119 ± 51; p = 0.005). Finally, half of participants obtained equal contrast sensitivity test scores on HD and SD units; 39% obtained greater contrast sensitivity scores on HD instrumentation, and 11% performed better on the SD unit.

**Conclusions:** HD video-endoscopic instrumentation may provide improved color discrimination and contrast sensitivity, as compared with SD instrumentation. Despite the higher pixel resolution of HD units, performance on a clinically relevant measure of spatial image resolution was similar with HD and SD units in this experimental design. These results justify further investigation into the clinical significance of HD video-endoscopic instrumentation.

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**THE ROLE OF MORPHOLOGY OF THE FIRST METATARSAL IN THE SURGICAL TREATMENT OF THE ADOLESCENT BUNION**

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**Purpose of Study:** Several studies have investigated the role of various osteotomy techniques in the outcome of hallux valgus correction. The shape of the first metatarsal has not been extensively discussed with regard to its importance in surgical correction of bunion deformities. The specific aim of this study is to investigate the theory that morphology of the first metatarsal plays a role in the outcome of hallux valgus corrective surgery.

**Methods Used:** This is a retrospective study of radiographs of patients who underwent metatarsal osteotomies for bunion deformity from 1993 and 2001. Preoperative and postoperative radiographic parameters were measured which included 1st metatarsal (MT) length, 1st MT head width, intermetatarsal angle, and hallux valgus angle. For comparison, radiographic measurements were recorded in patients with similar demographics who did not have bunion deformities.

**Summary of Results:** Twenty-six patients underwent thirty-two metatarsal osteotomies for bunion deformities of which thirteen were distal osteotomies and nineteen were proximal. There were nineteen females and seven males with an average age of 15.2 years old. Fifty-five normal foot radiographs of patients with similar demographics were reviewed. The width of the first metatarsal head was found to be proportional to the length of the first metatarsal (correlation coefficient of 0.734). When plotting the shape of the metatarsal (as a length/width ratio) against the angular correction of the osteotomies there was no significant correlation between the shape of the metatarsal and the amount of angular correction achieved postoperatively. Results of this study confirm that the width of the first metatarsal is proportional to its length. There was no indication that surgical correction of metatarsals that were relatively short and wide was more likely to produce favorable radiographic angular correction.

**Significance:** Understanding the impact of morphology on outcome of hallux valgus correction may help guide selection of appropriate surgical candidates as well as selection of appropriate surgical approach. While no correlation was found between the shape of the first metatarsal and the
amount of angular correction achieved, further research directions are considered.

**Western Student Medical Research Forum**

**Student Scientific Session IX - Behavior and Development/Community Health**

8:30 AM
Saturday, January 30, 2010

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**Session: Student Session IX - Behavior and Development/Community Health**

**SEXUAL HEALTH ATTITUDES AND BEHAVIOR AMONGST ACCULTURATED YOUNG SOUTH ASIAN AND MIDDLE EASTERN FEMALES**

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**Purpose of Study:** To examine personal, perceived parental attitudes, and religiosity in association with sexual behavior and preventive health amongst acculturated young South Asian and Middle Eastern women.

**Methods Used:** Study is a cross-sectional, self-administered anonymous web-based survey. Survey collected socio-demographic information, sexual behaviors, preventive health maintenance, and risk factors for STIs. The survey included a question about willingness to participate in a future focus group interview. Frequency distributions were obtained for all study variables. Measures of personal and familial sexual health attitudes and religiosity were compared with sexual behavior and preventive health outcomes. Chi-square tests were used to compare the distributions of categorical variables and t-tests were used to compare the means of continuous variables.

**Summary of Results:** Degree of religiosity did not significantly predict personal attitudes, sexual behaviors, or reproductive health care maintenance. However, there was a significant relationship between how much influence religion has on the way one chooses to act and spend time each day and more conservative personal attitudes towards sexuality (p = 0.01). History of clinical breast exam is significantly correlated with personal attitudes towards sexuality, independent of religiosity (p = 0.03). This association shows more conservative personal attitudes relating to not having had a clinical breast exam in the past year. History of pelvic exams is significantly correlated with the mother’s perceived attitude toward sexual activity, independent of religiosity (p = 0.006). This association shows more conservative perceived maternal attitudes towards sexuality relating to a lack of pelvic exam and cervical cancer screening in the past 3 years.

**Conclusions:** These results suggest personal and mother’s perceived attitudes more strongly influence preventive health care maintenance, specifically clinical breast exams and cervical pap smears, respectively. Religiosity did not show correlations to health behavior in this study. Pending focus group data will hopefully help to elucidate and correlate the motivations and barriers to accessing care and making health-related decisions.

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**Session: Student Session IX - Behavior and Development/Community Health**

**NON-PHARMACOLOGICALLY INDUCED REWARDS AND ANHEDONIA: A STUDY OF SKYDIVERS**

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**Purpose of Study:** There is evidence that people who participate in intense activities such as skydiving experience more anhedonia than the general population. We hypothesize persons participating in skydiving have higher than normal levels of anhedonia as measured by the SHAPS scale as compared to a control population. They will have higher scores on all three BAS scales, and lower on the BIS scale.

**Methods Used:** Participants were given a survey which contained the following: The SHAPS Scale measures the current state of anhedonia. It consists of 14 items with answer choices “Definitely Agree, Agree, Disagree, and Definitely Disagree”, each of which correlate to a point value 1-4. A higher score is indicative of a higher state of anhedonia. BIS/BAS Scales are considered highly relevant in determining reward seeking tendencies. The scales consist of 20 items which are then broken down into the Behavioral Inhibition System Scale (BIS; 7 items), and the Behavioral Approach System scale (BAS; 13 questions). The BAS is further broken down into 3 subscales, Fun Seeking (BAS Fun; 4 Items), Reward Responsiveness (BAS Reward; 5 items), and Drive (BAS Drive; 4 items). The survey also included general information such as sex, age, number of jumps, number of years in the sport, and wingloading of parachute.

**Summary of Results:** The skydiving group was found to have significant differences from the control group in all categories except BAS Drive. No difference was found between the two skydiving groups in all categories except BAS Reward Responsiveness. BAS Reward Responsiveness was found to have a statistically significant difference from the original study with a p value of less than .005.

**Conclusions:** The hypothesis that the skydiving group would be significantly higher in BAS and SHAPS was confirmed with the exception of BAS reward responsiveness and BAS Drive. It will be important in the future to attempt to correlate these scores to both time in the sport and jump numbers to see if there is a dose response relationship.

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**Session: Student Session IX - Behavior and Development/Community Health**

**REDUCING STUDENT BURNOUT AND STRESS UTILIZING WEB-BASED INTERVENTIONS**

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**Purpose of Study:** A review of literature reveals that stress and burnout is prevalent in healthcare professions. Some literature suggests that depression and disengagement in the first year of medical school is predictive of psychological morbidity later in training, including satisfaction and health, attrition from the field, and patient care. Considering the difficulties inherent in changing work hours and student time constraints, we developed a web-based randomized control trial using self-administered stress reduction interventions. In addition, we will look at the relationship between locus of control (LOC) and the effectiveness of our interventions. LOC refers to an individual’s expectations as to where control over external events resides. Literature suggests that an internal LOC, the belief that one has some individual control over external events, correlates with preventative health behaviors, thus LOC may be predictive of the population of students that will respond best to these interventions. While inconclusive, the literature also suggests a gender difference in LOC and burnout rates. From data collected, we will clarify and analyze burnout rate discrepancies between genders and their correlation with LOC.

**Methods Used:** 300 health sciences students at the University of Colorado will be randomized into a control, relaxation, or cognitive behavioral therapy (CBT) group. The relaxation group will employ an MP3 guided imagery relaxation exercise. The CBT group will employ a downloadable CBT-based problem solving worksheet. Participants will complete their web-based intervention 3 times/wk for 3 months, with compliance, burnout level, and LOC being assessed at 1 week, 1 month, 3 months, and 6 months. Burnout will be assessed using the MBI, while LOC will be assessed using the Levenson IPC scale.

**Summary of Results:** We hypothesize that web-based stress reduction will decrease burnout by 20% in health sciences students at 3 months, as measured by the Maslach Burnout Inventory (MBI). A internal LOC may predict responses to these interventions and contribute to gender differences in burnout prevalence.

**Conclusions:** Stress and burnout have implications for future patient care. Due to the time constraints of medical training programs, this study will offer web-based interventions designed to offer flexibility, ease, and confidentiality for reducing student burnout.
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477 INVESTIGATING THE ROLE OF PERFECTIONISM IN EATING DISORDER SUBTYPES
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Purpose of Study: Eating disorder manifestation is complex and multifaceted. Past research has determined that perfectionism plays an integral role in maintaining, and perhaps developing, eating disorders. Perfectionistic individuals are compulsive and driven to achieve the “ideal body.” Patients with eating disorders have elevated self-oriented and socially-prescribed perfectionism scores as compared to controls and other psychiatric disorders. Maladaptive perfectionism scores can predict eating disorder severity, and those patients with lower scores have a better response to treatment and outcome at follow-up. While some features of anorexia nervosa (AN) and bulimia nervosa (BN) may overlap, necessitating the eating disorder not otherwise specified (EDNOS) category, certain features of personality may differ between BN and AN. For example, patients with AN tend to be persevering, rigid, inflexible, and perfectionistic, while BN tend to be disorderly, elevated, and impulsive. Patients with AN score higher on perfectionism measures than those with BN and this transition from AN to BN is often perceived by the patient as a failure to meet perfectionistic self-standards, with individuals with BN tending to be dramatic, excitable, and disorderly, and those with AN tending to be persevering, rigid, inflexible, and perfectionistic. The current literature was reviewed regarding the subject of tobacco use and bipolar disorder. While the relationship between certain mental illnesses, especially schizophrenia and depression, has been well documented and studied, patients with bipolar disorder have very high rates of smoking; however, this relationship is less well studied. The increased rate of smoking is one cause of increased morbidity and mortality in patients with bipolar disorder compared to the general population. The purpose of this project is to review the current literature on the subject of tobacco use and bipolar disorder, possible explanations for the increase in smoking rates among this population, studies on smoking cessation programs in this group and areas for future research.

Methods Used: The current literature was reviewed regarding the subject of tobacco use and bipolar disorder.

Summary of Results: The literature review revealed that there is an increased prevalence of smoking among bipolar patients with rates ranging from 30.1% to 70%. Only one very small randomized-controlled trial of five patients was found regarding nicotine cessation. This trial used bupropion for smoking cessation; however, only two of five patients completed the trial. There have also been a few case reports in which varenicline induced mania or worsened psychosis when used for smoking cessation. There have been no studies of nicotine withdrawal symptoms, readiness to change, reasons for smoking or topography in this population.

Conclusions: Nicotine use is very high in patients with bipolar disorder. There is much work to be done learning more about the association between nicotine and bipolar disorder, especially in terms of cessation programs.

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479 ADAPTIVE MECHANISM MATURITY IN RELATION TO ANXIETY AND DEPRESSION SYMPTOM SEVERITY IN CANCER PATIENTS
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Purpose of Study: In response to a cancer diagnosis, patients react to the stress of their illness with anxiety. While psychological mechanisms (ego defense mechanisms) provide adaptive strategies, some are reportedly more effective than others in managing symptoms of anxiety. This study hypothesized that cancer patients with Immature adaptive styles would report more severe anxiety symptoms than those with Mature mechanisms. Based on previous work, a secondary hypothesis proposed that adaptive style immaturity would be significantly related to depression symptom severity.

Methods Used: In this IRB approved study, patients (n = 31), after ruling out delirium and severe pain syndromes, completed two symptom severity scales (the Beck Depression Inventory and the Hamilton Anxiety Scale) and a measure of adaptive mechanism maturity (the Defense Style Questionnaire). All gave informed consent and completed the scales as outpatients while receiving chemotherapy for a variety of cancer diagnoses. The final sample included 14 females and 17 males ranging in age from 27 to 81 (mean 59.9 ± 11.9). To test the hypothesis, Pearson’s r assessed the scale scores for association with probability set at 0.05.

Summary of Results: Contrary to the primary hypothesis, Immature defense mechanism endorsement did not correlate significantly with anxiety symptom severity (r = 0.27, p = 0.14). However, the data suggested a trend towards significance in this as well as in an inverse association between anxiety severity and the ratio of Mature/Immature style endorsement (r = -0.26 p = 0.15). While we observed a significant relationship between anxiety and depression severity scores (r = 0.59, p < 0.001), only depression appeared to correlate with Immature adaptive mechanism endorsement (r = 0.36, p = 0.04).

Conclusions: Although non-significantly correlated, the hypothesis correctly predicted the direction of the trends relating adaptive style maturity endorsement to anxiety severity. This may reach significance in a larger sample. On the other hand, the secondary hypothesis was correct in predicting a significant correlation between depression severity and Immature adaptive styles. These data suggest that targeted interventions towards Immature adaptive styles could potentially ease depression severity, and perhaps anxiety symptoms, in patients with cancer.

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480 ACTIVITY SCHEDULING AS A CORE COMPONENT OF EFFECTIVE CARE MANAGEMENT FOR LATE-LIFE DEPRESSION
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Purpose of Study: Activity scheduling has been established as a core component of evidenced-based treatment for late-life depression in primary care. We examined intervention records from 906 participants in the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial, the largest depression study for older adults to identify activity scheduling strategies used in the context of successful depression care management (CM).

Methods Used: Observational mixed methods analysis of 4,335 CM session notes from 597 participants in the intervention arm of the IMPACT trial. We performed qualitative analyses of CM notes documenting specific activities. Grounded theory methodology was used to identify categories of activities addressed in sessions and descriptive statistics were used to identify patient and care manager factors associated with specific activities and to examine associations between specific activity categories and depression outcomes at 12 months.
Summary of Results: Through iterative review 29 distinct categories of activities were identified. Activities were also differentiated into either ‘social’ or ‘solitary’ categories. The vast majority of patients discussed at least one social and one solitary activity during their course of treatment. Sessions most commonly focused on activities related to physical activity / exercise (32%), followed by medication management (22%), and active (19%) and passive (14%) activities. Patients with lower education levels had fewer but more detailed CM notes. Women and participants with less education were more likely to be engaged in social activities to help others. We observed greater variation in activities related to care manager than to patient characteristics.

Conclusions: Older primary care patients in CM for depression worked on a wide range of social and solitary activities. Overall, medication management, health and other medically-related activities dominated the range of activities, likely reflecting the high level of chronic medical illness in this group. CMs were a stronger predictor of variations in activities than patient factors.

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481 SUSTO AND POST-TRAUMATIC STRESS DISORDER: ETHNOPHARMACOLOGICAL AND PHARMACOLOGICAL TREATMENTS
AY. Hunt University of Washington School of Medicine, Seattle, WA.
Purpose of Study: Pre-Colombian illness Susto (Spanish for ‘fright’) is present throughout Latin America and the United States. Susto and Post-traumatic Stress Disorder (PTSD), despite being distinct cultural illnesses, appear following a traumatic or frightening experience and share the following symptoms: disturbed sleep or dreams, feelings of sadness, lack of motivation to perform daily tasks, lack of self-worth, detachment from others, irritability, and an exaggerated startle response. Pharmacological and ethnopharmacological treatments exist for PTSD and Susto. These treatments are typically accompanied by cognitive therapies: counseling in the biomedical model, and rituals in the folk medicine model. This literature review seeks to compare the ethnopharmacological and pharmacological treatment effectiveness for both illnesses in adult Hispanic and non-Hispanic white patients.

Methods Used: Systematic literature review.

Summary of Results: In vitro assays show that Mayan plants used to treat Susto have GABA, receptor activity, a target of benzodiazepenes, which are also used in the treatment of PTSD. Mayan healers use some plants to treat both epilepsy and Susto. In vitro assays of these plants show relevant activity on epilepsy drug targets (GABA-transaminase inhibition). Interestingly, epilepsy drugs are used in the treatment of PTSD and constitute an active area of research. Additional articles report healer consensus on plants/plant families used to treat Susto. Despite the relatively large number of published studies of Susto, none document the effectiveness of treatment in human patients.

Selective serotonin reuptake inhibitors are the pharmacological treatment of choice for PTSD, but no controlled trials were found to evaluate treatment effectiveness for Hispanic patients despite evidence that pharmacological effects may vary across ethnicities.

Conclusions: Given the relative newness of the PTSD diagnostic criteria with respect to the classic studies on Susto, further research may prove the two illnesses mutually inform one another with respect to underlying neurophysiology, drug development, and culturally competent patient care. Hispanic mental health care disparities and refractory PTSD both merit inquiry that could enhance the care and quality of life for Hispanic and non-Hispanic populations dealing with trauma and distress.

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482 TEENAGE PRESCRIPTION DRUG ABUSE IN DARRINGTON, WA
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Purpose of Study: Darrington is a community of 1,500 people 75 miles Northeast of Seattle. The town is experiencing a rising problem in prescription drug abuse, especially among teenagers. There have been multiple, potentially fatal, recent drug overdoses and an increased prevalence of drug trafficking and use at the schools.

In a 2008 survey conducted by the Darrington school district, 16.7% of eighth graders reported use of Ritalin without a doctor’s orders and 20% reported use of pain killers to get high. Among high school seniors, 22.2% admitted to using pain killers to get high. It has been found that the earlier an adolescent or teenager uses prescription drugs for non-medical purposes, the more likely an individual is to develop a lifetime drug addiction.

A community based project was implemented in order to raise awareness and educate the community on methods of identifying and preventing teenage prescription drug abuse.

Methods Used: A search of the professional literature, using PubMed, was conducted to discover the underlying basis and prevalence of teenage prescription drug abuse. A local teenager with a history of prescription drug abuse was interviewed to solicit her thoughts on the causes of the rise in prescription drug abuse, the methods of drug diversion, and the perceived effectiveness of school-based drug education programs. Finally, a presentation and open discussion forum was held with the physician of Darrington clinic, school district officials, and local law enforcement officers. Input from these sources was incorporated into an informational brochure and a newspaper article.

Summary of Results: 500 copies of the brochure were distributed to parents of all children in the school district, and made available at the local family resources center, the Darrington clinic, and the law enforcement office. In addition, an article describing the prescription drug abuse problem was published in the local newspaper.

Conclusions: Teenage prescription drug abuse is a national problem of all socioeconomic classes. As a small, rural community, Darrington is disproportionately affected by this problem compared to larger communities. Although prescription drug abuse remains a significant problem in Darrington, the meeting facilitated an open dialogue concerning the issue, and compelled leaders of the community to pursue solutions to the problem beyond the scope of this project.

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483 DEPRESSION IN PREMEDICAL UNDERGRADUATES
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Purpose of Study: Medical students and physicians are exposed to unique pressures that render them vulnerable to increased rates of depression, an illness which can impair quality of life and predispose to numerous medical and psychiatric sequelae. These same types of pressures also plague premedical undergraduates who work long hours to become competitive for medical school admission. However, far less is known about their risk for depression. Do the seeds of depression faced by medical students and physicians begin in medical school, or can they be traced back to premedical training? We attempt to answer this question by assessing the severity of depressive symptoms in premedical students compared to other undergraduates.

Methods Used: We invited all undergraduate biology majors at UC San Diego to participate in a web-based survey. Subjects were also recruited through Experimentrix, a UC San Diego psychology research recruitment program. The survey consisted of demographic and clinical based questions such as gender, ethnicity, age, major, graduation date, premedical status, perceived financial strain, and past, current, and family history of major depression. We used the Patient Health Questionnaire (PHQ-9) to assess depressive severity.

Summary of Results: 647 premedical and 1495 non-premedical undergraduates completed the questionnaire. Premedical students were more likely to meet symptomatic criteria for major depression and exhibit greater depression severity than non-premedical students despite no differences in past or family histories of major depression. Female premedical students exhibited greater depression severity than female non-premedical students and males. Hispanic premedical students, in particular, had higher rates of depression than other premedical students and Hispanic non-premedical students. Finally, we found a substantial discrepancy between the number of students with major depression based on PHQ-9 criteria and the number actually carrying a clinical diagnosis of major depression.

Conclusions: These findings underscore the importance of recognizing the unique strains and mental health consequences of a premedical curriculum,
especially for women and certain minority ethnic populations. Further research must be done with the intention of identifying opportunities for prevention and early intervention which may provide significant public health payoffs in the long run.

Session: Student Session IX - Behavior and Development/Community Health

ENCOURAGING YOUTH SUN SAFETY AT A PUBLIC POOL IN GLENSHAW, MONTANA

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Purpose of Study: Residents of rural Glasgow, Montana (pop. 2922) are at an elevated risk for developing skin cancers. Since Glasgow’s economy is agriculturally focused, the population spends a greater time outdoors. At Glasgow’s primary care clinic, many elderly residents present with both benign and malignant skin lesions from a lifetime of sun exposure. Since prevention is most effective in childhood and adolescence, the project aimed to improve sun safety behavior in children who frequent the Glasgow public pool by collaborating with parents and with lifeguards.

Methods Used: Preventing childhood sun damage was the focus of a project initiated after noting the frequency of patients with skin damage and observing sunburned adolescent patients. The Glasgow public pool was chosen as an inherently sun unsafe location which drew the targeted age groups. A literature review was used to determine appropriate intervention methods. Outreach included meeting with lifeguards and parents and encouraging them to be role models of sun-safe behavior. A written quiz about sun safety, developed from the primary literature, was taken by parents. Discussions emphasized childhood sun safety and how role models can encourage sun-safe behavior. Posters with safety tips were posted at the pool, and an article on sun safety ran in the weekly Glasgow Courier.

Summary of Results: The pool’s nine lifeguards were given current information about sunscreen labels and usage. Twenty-eight parents took the sun-safe quiz and were educated about safe behavior. Half of the parents were unaware that the most of lifetime skin damage occurs before age twenty. Parents who reported putting sunscreen on their children but not themselves were educated on their behavior-modeling potential. Handouts were distributed to parents to reinforce the information discussed.

Conclusions: The sun-safety education program enacted at the Glasgow Public Pool targeted an at-risk population. Speaking with lifeguards and parents about skin cancer risk and sun damage increased awareness of the importance of sunscreen, hats and long sleeves. The quiz highlighted areas where parents’ knowledge was lacking. Speaking with both groups about proper sun safety increased the chance that the children will develop positive sun behavior and lower their lifetime skin cancer risk.

Session: Student Session IX - Behavior and Development/Community Health

PATHOLOGICAL GAMBLING IN WENATCHEE, WASHINGTON: PREVALENCE AND ACCESS TO CARE

JW. Redinger University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Wenatchee is a city of 30,000 people in central Washington with access to a major hospital, two general care clinics, and several specialty clinics. The community has numerous gambling venues including card rooms, bingo halls, and a major casino. Gambling addiction is a debilitating psychological disorder that positively correlates with physical proximity to gambling venues and has a bimodal age distribution, suggesting a high incidence of pathological gambling in a city with a significant number of residents above age 65 (15.0%) and between ages 15-25 (14.8%). This study seeks to assess the rate of problem gambling in the Wenatchee area and the effectiveness of primary care provider (PCP) efforts to address this community health issue.

Methods Used: PCPs at Columbia Valley Community Health (CVCH), a low-income area clinic, were interviewed to assess currently diagnosed pathological gamblers (PGs) and PCP efforts to counsel PGs. Field interviews were conducted with local gamblers, Gamblers Anonymous (GA) members, the CVCH director of behavioral counseling, and a casino floor manager to assess local resources for addiction counseling.

Summary of Results: Within the Wenatchee and East Wenatchee city limits, state gambling licenses have been granted to 20 pull-tab establish-
Methods Used: An NIH grant provided the penitentiary with doses of Twinrix®, a bivalent vaccine against Hepatitis A and B, but funding cuts left the facility without a delivery mechanism. A literature review validated the need for preventing Hepatitis in correctional settings with education and immunization. Due to the lack of vaccine, inmates were encouraged to continue the series if released from prison before completion. Inmates who started the vaccine elsewhere were offered continuing doses as needed. Injections were administered intramuscularly and patients were scheduled for 1- and 6-month boosters.

Summary of Results: A successful pilot immunization campaign was initiated with 92% of approached inmates (36/39). An additional 9 vaccine doses were given to individuals to continue a previously initiated Twinrix® series. Only 3 inmates refused, generally citing fear of needles. The nursing staff will employ this method to implement a continuous vaccination program.

Conclusions: When properly educated about the risks and benefits of being immunized most inmates opted to participate in the vaccination program, protecting not only themselves but the community at-large. A major challenge is finding an efficient delivery system, but this approach provides a viable solution.

Session: Student Session X - Community Health/Infectious Disease/ Metabolism, Lipids and Diabetes

490 CREATING LOCALLY APPROPRIATE HIV/SEXUALLY TRANSMITTED INFECTION OUTREACH MATERIALS: AN ACTIVITY TO EMPOWER PERUVIAN MEN WHO HAVE SEX WITH MEN AND TRANSGENDERED OUTREACH WORKERS

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Purpose of Study: Because they are marginalized by larger society, men who have sex with men (MSM), and transgendered community members are less likely to use health services and more likely to engage in risky behaviors. This leads to increased rates of sexually transmitted infections (STI) and HIV in this population. To combat this, the Alberto Barton Clinic in Callao, a suburb of Lima, employs MSM/Transgendered outreach workers as community educators. These workers identified the lack of materials as a barrier to conducting effective work. As a result, locally appropriate reusable outreach materials were created to empower outreach workers and to make them more effective in their role.

Methods Used: After observing MSM/Trans outreach workers, focus sessions were held to discuss their roles, and challenges. This was followed by a discussion of how their work could be supported. The group decided that a portable, visual aid would best enhance their outreach sessions. Workshops were held to determine its contents. Upon construction of the visual aid, the outreach workers were briefed in its use and educational sessions were conducted in the community.

Summary of Results: The flip chart consisted of 27 colored sheets with pictures and information on male and female infections with herpes, pubic lice, genital warts, gonorrhea, chlamydia, syphilis, and HIV. Also covered were modes of transmission, proper use of a condom, and the importance of treatment. Eleven outreach workers were briefed on use of the flip chart and it was used in an educational session. At this session the outreach worker was noticeably more confident than at previous sessions. 18 community members participated in the session and appeared engaged and enthusiastic. A drawback of the aid was that it ended up being quite heavy, which may limit its portability. Materials cost $100 USD and were paid for by the UW IHO Project Fund.

Conclusions: Provision of visual aids is a relatively inexpensive way to empower outreach workers and enhance knowledge of STIs/HIV. However, additional work needs to be done to improve the acceptance of MSM/Trans individuals within society. It is only when we are able to combat the social injustice this community faces that we can truly begin to address their health concerns.

Session: Student Session X - Community Health/Infectious Disease/ Metabolism, Lipids and Diabetes

491 EFFECTIVENESS OF COMMUNITY HEALTH WORKERS IN THE PREVENTION OF MALARIA IN MACHAKOS, KENYA

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Purpose of Study: To evaluate the effectiveness of community health workers (CHWs) focusing on knowledge about malaria and the use of insecticide treated nets (ITNs) in children under five.

Methods Used: A questionnaire, adopted from the Kenyan Demographic Health Survey, was conducted in August, 2007 by Kenyan health officials and served as the baseline data for this study. In March, 2008, using this survey, researchers and translators visited homes in nine villages questioning families with children less than five years of age. The two main questions addressed...
the knowledge about malaria and the practice of correctly using ITNs. A sample size of 500 children with an 80% power to detect a difference of 4.7% between the null hypothesis and the alternative hypothesis was calculated using a two-sided Chi-square test with continuity correction and a significance level of 0.05. In order to assure random sampling with proportional sizes, sub-locations were sorted, randomized and then selected from a spreadsheet. Data from the initial and follow up survey were compiled by the field researchers using a standard database program, EpInfo. Data cleaning and analysis was completed using SAS and EpInfo statistical software. Due to the potential correlation among children within the same household, the generalized estimating equation approach for repeated measures was used. In this case, ITN was the dependent variable and time was the independent variable with a target sample size of 119 homes.

Summary of Results: 267 surveys were compiled for the pre-intervention knowledge assessment and 340 in the post-intervention analysis. 81% of the families surveyed correctly knew the cause for malaria before the study and 93% after the CHW intervention (p < 0.01). 265 surveys were compiled for correct ITN usage before the CHW intervention and 340 in the post-intervention analysis. 70% of the surveys had and correctly used mosquito nets before the intervention study and 88% after the CHW intervention (p < 0.01).

Conclusions: Implementation of a Community Health Worker program significantly increases the knowledge of malaria and the use of ITNs.

Session: Student Session X - Community Health/Infectious Disease/ Metabolism, Lipids and Diabetes
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PREDICTORS OF POOR OUTCOMES AMONG TUBERCULOSIS PATIENTS IN COASTAL KENYA

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Purpose of Study: Kenya has recently been identified as having the 13th highest tuberculosis (TB) burden globally, with over 130,000 new cases and 24,000 TB related mortalities reported annually. More than half of all new TB infections occur in HIV-seropositive individuals in Kenya. Using Ministry of Health data, collected from a large provincial hospital on the coast of Kenya, we sought to evaluate factors associated with poor outcomes and treatment failures.

Methods Used: Baseline patient characteristics, co-morbid conditions, treatment regiments and outcomes from 273 sequential patients were abstracted and analyzed. A waiver was obtained from the IRB at the University of Washington School of Medicine, Los Angeles, CA.

Summary of Results: Males accounted for 61.6% of the patients with available data and most (88.1%) were between 18-65 years of age. HIV status was reported for 88.3% of individuals and almost half of these individuals were HIV-1 infected (41.7%). Most individuals had pulmonary TB (79.6%) and almost half of these were smear negative (41.6%). Treatment outcomes were reported in 77% of all records. When compared with HIV uninfected individuals, HIV-1 co-infected individuals were 4.8 times more likely to experience poor treatment outcome (death, treatment failure or default from clinic) (p < 0.001). In addition, negative initial sputum microscopy was associated with a 3.2 fold increase in poor treatment outcomes in all patients (p = 0.032) and a 13.7 fold increase in HIV co-infected patients (p = 0.001).

Conclusions: Despite relatively modest HIV-1 prevalence rates in coastal Kenya (7.9%) compared to Nairobi (9%) and Nyanza Province (15.3%), HIV-1 co-infected individuals appear to account for a substantial proportion of TB cases in this cohort. In addition, HIV-1 and TB co-infected individuals appear to be at considerable risk of poor outcomes, particularly when initial sputum smears are negative. It is unclear whether the higher rate of treatment failure and death is due to poorer responses to TB treatment or to failure to diagnose alternative illness in these individuals. Improved TB diagnostics, treatment and retention in care are needed to improve outcomes in Kenya, particularly among HIV-1 co-infected individuals.

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RENAL VOLUME DETERMINED BY COMPUTED TOMOGRAPHY

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Purpose of Study: Radiologic determination of renal size is a critical step in establishing a differential diagnosis in renal parenchymal disease. Renal length is currently used to measure renal size, but there is a broad push toward three-dimensional, quantitative techniques.

Methods Used: Thirteen patients from our institution who received multiple computed tomography (CT) scans (average = 20.8, range 5 to 45) for symptoms unrelated to renal disease were identified retrospectively. CT scans were performed at 120 kV with slice thickness of 5 mm up to 10 mm. Left kidney (LK) and right kidney (RK) volumes were assessed by hand segmentation (window = 400 HU, level = 30 HU) on 253 scans. The effect of contrast medium (iohexol-350 and iodoxanol-320) on kidney volume was evaluated.

Summary of Results: The mean LK and RK volumes were 179.1 ± 39.7 [standard deviation] cm³ and 172.7 ± 37.1 cm³, respectively. The LK and RK volumes for each patient fluctuated proportionally over time by an average of 48.0 cm³ and 47.4 cm³. In response to contrast medium, the mean increase in LK volume was 8.6 cm³, or 4.9% (p = 0.00009), and the mean increase in RK volume was 9.1 cm³, or 5.2% (p = 0.0004). The anticipated LK and RK volumes, volume relationships between LK and RK, and relationships between kidney volumes of men and women were reinforced.

Conclusions: The findings emphasize the utility of CT as a three-dimensional, quantitative tool not only for the assessment of normal physiologic volume fluctuations, but also in the diagnosis of pathologic changes to the renal parenchyma.

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ALTERED EXPRESSION OF ENZYMES INVOLVED IN NITRIC OXIDE PRODUCTION IN ISLETS FROM DIABETIC MICE

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Purpose of Study: Endothelial cell dysfunction occurs in diabetes and contributes to microvascular disease. A major function of the endothelial cell is production of nitric oxide (NO), which involves the cofactor tetrahydrobiopterin (BH4). BH4 deficiency is associated with endothelial dysfunction in several tissues in diabetes. However, BH4 synthetic enzyme expression has not been previously examined in pancreatic islets. Thus, we sought to determine whether these two regulatory enzymes are present in islets and whether their levels are altered in diabetes.

Methods Used: We used MS-1 and β-TC3 cells (immortalized mouse islet endothelial and islet β-cells, respectively) and C57BL/6J mouse islets to determine the presence of GTPCH and DHFR mRNA and protein using real-time PCR and western blot, respectively. Islets were isolated from db/db diabetic mice at two time points during the course of diabetes: 8 (fasting glucose = 385mg/dl) and 16 weeks (fasting glucose = 395mg/dl), and compared to age-matched db/+ controls (fasting glucose = 190mg/dl at 8 and 160mg/dl at 16 weeks; n = 6–8 per group).

Summary of Results: GTPCH and DHFR mRNA and protein were present in MS-1 cells, β-TC3 cells, and mouse islets. In db/db mouse islets, GTPCH mRNA levels at both 8 and 16 weeks were reduced by 40% compared to age-matched db/+ controls (p < 0.05). DHFR mRNA was increased 2-fold in db/db mouse islets at 8 weeks compared to db/+ controls (p < 0.05), but levels did not differ at 16 weeks.

Conclusions: GTPCH and DHFR are present in islets, occurring in both β- and endothelial cells, and their expression is altered in db/db mice. This differential expression may contribute to endothelial dysfunction in the islet in diabetes.

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DIABETES AND HEARING IMPAIRMENT AMONG AFRICAN AMERICANS AND HISPANICS IN THE UNITED STATES

SK. Grisby, KE. Wolf, M. Bazargan Charles Drew University of Medicine and Science, Los Angeles, CA.
The lens epithelium of HAR transgenic animals demonstrated a width for comparison of cell density. Two zones are functionally defined within the lens epithelium, the mitotically active Germinative Zone (GZ) and the less proliferative Center Zone (CZ).

Summary of Results: The Tg lens epithelium demonstrated a decrease in the percentage of BrdU/DAPI staining within the GZ as compared to nTg (N = 5). All animals received intraperitoneal injections of BrdU one hour prior to euthanasia and eye dissection. Immunohistochemistry was performed on the epithelial flat mounts for BrdU incorporation (as an indicator of S phase of mitosis) as well as DAPI for reference of total nuclei. Cell counts were performed visually. Images were overlaid with a grid consisting of boxes measuring 50 pixels in width for comparison of cell density. Two zones are functionally defined within the lens epithelium, the mitotically active Germinative Zone (GZ) and the less proliferative Center Zone (CZ).

Conclusions: The lens epithelium of HAR transgenic animals demonstrated a decrease in the number of cells in S phase in both the Germinative and Center Zones. Paradoxically, the cell density was increased among the transgenic epithelia within the germinative zone. This is suggestive that apoptosis, in addition to cell proliferation may be inhibited by over expression of HAR. As the transparency of the lens is contingent upon the precise degradation of cellular contents of the inward compacting epithelium, these findings suggest a possible pathway by which HAR mediates cataract formation.

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LENS EPITHELIUM PROLIFERATION OF ALDOSE REDUCTASE TRANSGENIC MICE
G. Zablocki, P. Ruzycki, M. Petrash University of Colorado School of Medicine, Aurora, CO.

Purpose of Study: The pathogenesis of Diabetic Cataract formation is incompletely understood and is a key factor to the morbidity incurred by diabetes. Previous research has identified the enzyme Aldose Reductase (AR) as a key player in cataract formation in the setting of Diabetes. The following experiment used mice transgenic for the expression of Human Aldose Reductase (HAR) within the lens epithelium in order to further study the role of HAR in the lens.

Methods Used: In order to characterize the proliferative state of the epithelium, lens of 19 day old HAR transgenic animals (Tg) (N = 5) were compared to age matched non-transgenic controls (nTg) (N = 5). All animals received intraperitoneal injections of BrdU one hour prior to euthanasia and eye dissection. Immunohistochemistry was performed on the epithelial flat mounts for BrdU incorporation (as an indicator of S phase of mitosis) as well as DAPI for reference of total nuclei. Cell counts were performed visually. Images were overlaid with a grid consisting of boxes measuring 50 pixels in width for comparison of cell density. Two zones are functionally defined within the lens epithelium, the mitotically active Germinative Zone (GZ) and the less proliferative Center Zone (CZ).

Summary of Results: Low-frequency of mild or greater severity: Mean age of hearing impairment were 55.7 compared to 41.2 without hearing impairment (p < 0.0001). 7.7 percent of African-Americans compared to 12.7 percent of Hispanics had hearing impairment (p < 0.0001). 7.5 percent of African-Americans compared to 10.9 percent of Hispanics had hearing impairment (p < 0.0001). 66.2 percent were men compared to 33.8 percent female that reported hearing impairment (p < 0.0001). Of those with hearing impairment 16.6 percent reported a diagnosis of diabetes (p < 0.0001). 45.1 percent of those who reported hearing impairment had an educational level greater that high school (p < 0.0001).

High- frequency of mild to greater severity: Mean age of hearing impairment were 53.8 compared to 37.0 without hearing impairment (p < 0.0001). 7.5 percent of African-Americans compared to 10.9 percent of Hispanics had hearing impairment (p < 0.0001). 66.2 percent were men compared to 33.8 percent female that reported hearing impairment (p < 0.0001). Of those with hearing impairment 12.2 percent reported a diagnosis of diabetes (p < 0.0001). 49.4 percent of those who reported hearing impairment had an educational level greater that high school (p < 0.0001).

Conclusions: Those who reported a diagnosis of diabetes also reported an increased prevalence of hearing impairment. Hispanics had higher prevalence of hearing impairment compared with African Americans. Those with higher education levels had higher prevalence of hearing impairment. More men than women reported a hearing impairment. These findings were consistent in both low-frequency of mild or greater severity and high- frequency of mild to greater severity.

Session: Student Session XI - Surgery

8:30 AM
Saturday, January 30, 2010

Session: Student Session XI - Surgery

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EVALUATION OF RISK COMMUNICATION IN THE FIELD OF ELECTIVE COSMETIC SURGERY USING A MENTAL MODELS APPROACH
RW. Chambers UBC, Vancouver, BC, Canada.

Purpose of Study: Risk communication and effective knowledge transfer between doctor and patient is an integral part of best practice in medicine. Specifically relevant to the field of surgery is the informing of patients about potential risks and complications, both general and procedure specific, when obtaining informed consent. We propose to examine the current system of knowledge translation and exchange regarding risk existing between plastic surgeons and patients. This study will focus specifically on the area of cosmetic surgery, mainly based on the principle that the procedures are elective and as such assessment of personal risk and potential complications should have the greatest bearing on patients’ decision making.

Methods Used: We propose to use a mental models approach to elicit from 10 plastic surgeons what methods they use to inform potential patients about surgical risk and complications. Information gathered in these open ended interviews will then be used to construct a mental model of current knowledge and preferred methods of patient education. Using this construct, a second set of questions will be generated to probe former recipients of elective cosmetic procedures. Data gathered in this stage will focus on patients current knowledge
level regarding risk, how they were educated during pre-operative consultations, and if they feel there is potentially a better system that could be in place. Finally, these two models will be compared. This will help to determine if there are any potential gaps within the current system of knowledge transfer and informed consent and if so in what specific areas.

**Summary of Results:** This study is currently still underway. The first stage of data acquisition, that of interviewing 10 plastic surgeons, has been completed. Preliminary data analysis indicates that surgeons see themselves as the best source of information regarding risk and use various in-office methods of education, including but not limited to diagrams, pamphlets, and repeat visits with patients to convey information regarding potential surgical and post surgical complications.

**Conclusions:** We are currently constructing the 1st mental model based on surgeon interviews and in the recruitment phase of the second portion of the study, that of interviewing former patients. As yet no definitive conclusions have been reached.

**Session: Student Session XI – Surgery**

**VIDEO PRODUCTION AS A LEARNING TOOL FOR SURGICAL EDUCATION**

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**Purpose of Study:** A video on robotic prostatectomy was produced by undergraduate medical students participating in the “Lights, Camera, Surgery” summer project organized by the Office of Pediatric Surgical Evaluation and Innovation (OPSEI) The purpose of the video was to create a visual resource to educate both student and patient audiences on patient experiences and major surgical techniques of the procedure.

**Methods Used:** Students collected video data from a pre-operative patient interview, as well as footage from the operating room documenting patient preparation, robot setup, and laparoscopic instrument placement. Data from the surgical robot, which provided high definition endoscopic views of the procedure, was also used. This recording allows an understanding of how the surgeon approaches the surgical procedure, how adequate optics of the surgical field are chosen, and how anatomical landmarks are identified. The footage was then consolidated using commercially available video editing software, ensuring the availability of the anatomical details relevant for the operation to be relayed to audiences watching the videos for didactical purposes. The resulting synthesized footage was narrated by the operating surgeon and made into an educational video.

**Summary of Results:** The video was uploaded and stored within the DiagnosisX server and embedded within a student-authored online PBL case on prostate cancer, which allows for 24-hour access through a password protected website.

**Conclusions:** Video production has offered an invaluable learning experience for the students involved with the project, allowing for an early exposure to the field of surgery and development of mentorship relationships with surgeons in the community. Students learned and captured both the exposure to the field of surgery and development of mentorship relationships with surgeons in the community. Students learned and captured both the

**Session: Student Session XI – Surgery**

**FIRST METATARSOPHALANGEAL HEMIARTHROPLASTY FOR GRADE 3 AND 4 HALLUX RIGIDUS: A PROSPECTIVE EVALUATION OF FUNCTIONAL AND SYMPTOMATIC IMPROVEMENT**

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**Purpose of Study:** There is a paucity of objective information in the literature about 1st metatarsalphalangeal (MTP) hemiarthroplasty. The authors hypothesize that it is a good treatment option for severe hallux rigidus with early improvement in function and symptoms.

**Methods Used:** Patients that met the inclusion criteria were offered arthrodesis or 1st MTP hemiarthroplasty. Hemiarthroplasty patients were evaluated pre and post-operatively with AOFAS forefoot score, visual analogue pain score, range of motion (ROM) measurements and radiographs. Patients were contacted after 24 months to determine functional status.

**Summary of Results:** 22 elective 1st MTP hemiarthroplasties were performed on 20 patients. Average ROM improved by 15 degrees. Visual analogue pain scores improved from 5 to 2.5 at 6 weeks post-operative. Painless ambulation occurred after 6 weeks, with maximum improvement by 6 months. After 24 months, 2 patients had pain at the surgical site interfering with function leading to an unsatisfactory result. There were 8 complications with 2 revisions.

**Conclusions:** First MTP hemiarthroplasty for severe hallux rigidus is a predictable and reliable procedure, and should be considered as an alternative to fusion in patients wishing to maintain a functional range of motion.

**Session: Student Session XI - Surgery**

**500 CORRELATING ADJUSTED LIP PROPORTIONS AND FACIAL ATTRACTIVENESS**

NA. Popenko, L. Mainis, Z. Devcic, K. Karimi, BJ. Wong UC Irvine, Laguna Beach, CA.

**Purpose of Study:** Traditionally, facial beauty is defined and quantitatively measured by correlating discrete anthropometric measurements with subjective facial attractiveness scores, identifying parameters that create the “ideal” facial archetype. This study pioneers a computer-based approach that progressively modifies facial features along a continuum to determine the effects of changing lip proportion on facial attractiveness. The objectives of this study were to: 1) develop a continuum of synthetic images with modified lip proportions; 2) determine the ideal lip adjustments based on attractiveness ratings; and 3) identify the significance of lip proportion in determining facial attractiveness.

**Methods Used:** Using a facial alteration program, lip proportions in ten female portraits were scaled up and down in continuous increments of 25%, altering the lip size from -100% to 100% of the original. All of the modified and original portraits were posted for web-based facial attractiveness rating.

**Summary of Results:** These facial portraits with the highest and lowest attractiveness scores prior to changing the lip proportions, did not vary their attractiveness scores significantly after changing lip proportion in either direction.
Conclusions: Enhancing the proportion of the lips is most likely to improve the attractiveness of an attractive face. There is less correlation for unattractive faces, as other characteristics and facial features may reduce the importance of the lip proportions.

Session: Student Session XI – Surgery
501 THE USE OF A COMPOSITE FEMORAL COMPONENT IN PRIMARY THA: A PROSPECTIVE, RANDOMIZED CONTROLLED, CLINICAL, RADIOGRAPHIC AND DXA COMPARATIVE STUDY
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Purpose of Study: Composite materials for primary total hip arthroplasty (THA) are designed to parallel the modulus of elasticity of femoral bone but retain the strength of standard femoral components manufactured from alloy substrates.

The purpose of this study was to compare the clinical, radiographic, and DXA results of a composite femoral component for primary THA with other non-cemented femoral components.

Methods Used: The EPOCH and EPOCH 14+ (Zimmer, Warsaw, IN) composite femoral components were studied in conjunction with the VerSys Fiber Metal Taper,Fiber Metal Mid coat and Beaded Fullcoat femoral components (Zimmer, Warsaw, IN). All patients, 53 per arm plus additional 15 in EPOCH 14+, were randomized into one of five component groups and followed prospectively for five years. All patients were assessed clinically using the Harris Hip Score (HHS), SF-36 and WOMAC questionnaires at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years.

DXA was used to determine changes in peri-prosthetic BMD at 6 months, 1 year, 3 years, and 5 years. All DXA scans were analyzed by an independent reviewer using Gruen Zones ([I–VII] 1/3 proportional to the implant length. For all hips studied, the 6 month post-operative DXA scan was used as the baseline for subsequent follow-up DXA measurement comparisons and is reported as the percent change from baseline.

Summary of Results: There were no statistical differences in clinical assessments between groups for the HHS, SF-36, and WOMAC scores. 3 year DXA results showed slight increases in BMD for the EPOCH 14+ components, but this may be due to patient positioning and sampling errors. 5 year DXA data is still being collected.

Conclusions: The results from this prospective, randomized controlled clinical trial showed that a composite femoral component for primary THA can achieve results equal to standard alloy components of varying design. Based on these early results, the EPOCH and EPOCH 14+ femoral components for primary THA are justified for continuance of further prospective study.

Session: Student Session XI – Surgery
502 COMPLEX NEUROFIBROMAS OF THE SCALP: A CASE SERIES
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Purpose of Study: Neurofibromas of the scalp are uncommon lesions even in patients with neurofibromatosis-1 (NF1). There have only been a few isolated case reports describing scalp neurofibromas; therefore, these patients are of a particular clinical interest and worthy of a focused review with a goal to synthesizing the clinical, imaging, and operative management.

Methods Used: A retrospective chart review of patients with histologically proven neurofibromas of the scalp between 1991 to 2009 was performed. The criteria for inclusion in the study were patients who presented with a scalp mass, without other defining features of NF1, and were misdiagnosed until operative or histological findings reported the lesion to be a neurofibroma. Five patients fit the criteria for the study and their clinical information with regard to imaging, management, and outcome was documented.

Summary of Results: All five patients presented with extensive circum-scribed scalp lesions, “boggy” on clinical palpation, and initially mistakenly diagnosed as arteriovenous malformation, lipoma, dermoid, T-lymphoma or venous malformation based on physical findings and imaging. However, after surgical resection, histological findings reported the lesion to be a plexiform or diffuse neurofibroma. retrospective review of the imaging and clinical features of these cases demonstrated lesions that were circumscribed, often extending to the dermis, with no clinical findings of discolouration as typically seen with venous malformations. Although the classical “target” sign was not seen in all of those having MRI performed, absence of intra-lesional fat, with avid enhancement post-contrast administration, coupled with ultrasonographic absence of vascular channels and fluid pockets, is strongly suggestive of a unique neurofibroma of the scalp.

Conclusions: We believe that the unique clinical and radiologic features of the scalp neurofibromas in our patient series allows for a specific diagnostic pattern which may prevent their misdiagnosis. We propose that the combination of MRI and ultrasound is sufficient as imaging workup, with key clinical features being the ballottable nature of these masses, as well as lack of clinical discolouration, as commonly seen with vascular malformations extending to the skin surface.

Session: Student Session XI – Surgery
503 THE VALUE OF ANATOMIC VISUALIZATION PROVIDED BY MAGNETIC RESONANCE IMAGING IN SURGICAL PLANNING FOR CASES OF ABERRANT ANATOMY
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Case Report: A two-month old girl was referred to pediatric urology with an antenatal diagnosis on ultrasound of left hydronephrosis, which was confirmed neonatally. This showed a left duplex kidney with mild dilatation of the upper and lower pole segments and dilatation of the upper pole proximal ureter. The remainder of the history and physical examination were non-contributory.

Subsequently, mother noted continuous urinary leakage, suggesting that the upper pole moiety may insert below the bladder neck.

An MRI allowed for visualization of the duplex kidney, hydronephrove and parenchymal structure of the upper pole moiety which showed a small area of cystic dysplasia responsible for the small degree of urine production. The MRI was able to visualize the ureter associated with this moiety to be draining posterior to the bladder.

At 15-months of age, the patient underwent cystoscopy which did not reveal evidence of ectopic ureteral openings within the urethra or the bladder. Under the same anesthetic, upper pole heminephrectomy and ureterectomy were performed. After this procedure, the patient was found to be dry between trips to the bathroom and toilet training well. The most recent follow-up at 5 years of age shows a healthy child with no residual deficits.

The literature suggests that duplex kidneys with ectopic ureters may not be detected by most standard imaging modalities. Ultrasound does not allow for the same surgical planning as the distinct anatomical visualization of an MRI. Retrograde pyelography can exquisitely demonstrate the anatomy of the collecting system but in cases such as these, it can be extremely difficult to cunlate the ectopic orifice as its location is unknown and is often not visualized on cystoscopy. As the upper pole moiety typically has minimal function, CTIVP has been helpful to delineate the anatomy, but carries a significant radiation dose.

Although MRI does require sedation in infants, it avoids radiation exposure and a second anesthetic for cystoscopy and attempted retrograde pyelograms.

The surgical management of patients such as ours is benefited by the anatomical visualization provided by magnetic resonance imaging as compared with other imaging modalities.
online format. This study aimed to determine the year one student’s opinion of the online Diagnosis X cases of the Fluids, Electrolytes, Renal, and Gastrointestinal (FERGU) block within the undergraduate medical curriculum.

Methods Used: The online cases were presented to students as supplemental optional activities for weeks 3 and 4 of the FERGU block. Once the weeks were past, students were administered an open-ended survey which was completed anonymously. Qualitative analysis was performed on the data. Participation rates for the cases were determined by analyzing website usage from April 1st to June 7th 2009, timing that corresponded with the FERGU block.

Summary of Results: A total of 296 students from the three distributed sites of the undergraduate MD program were eligible to participate in the Diagnosis X survey. The study had a response rate of 24% (n = 71). A total of 46% (n = 33) of students commented positively on the cases. Specifically, 15% (n = 11) of students noted that the cases was a helpful review of block material. However 41% (n = 29) of students commented that they did not attempt the cases. Diagnosis X - MMI website data indicated that 109 students attempted at least one of these optional Diagnosis X cases.

Conclusions: The number of students utilizing Diagnosis X may be increased if the cases were made available earlier in the academic year, and through MEDICOL, the medical student home page. The majority of students who completed the cases found them to be a useful learning tool to reinforce knowledge and to lend a clinical picture to urological problems. Comments regarding the problems in content, grammatical errors, and repetitiveness could be mitigated by further peer review and revision of the cases. For many students, the Diagnosis X cases played a role in supplementing their learning in the FERGU block.

Session: Student Session XI – Surgery 505

IClicker™ Trial Study at the University of British Columbia Medical School

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Purpose of Study: In 2009 the School of Medicine employed iclicker™ technology for the first time during a first year 5 week block. Iclicker™ technology allows students to select a response with a remote device to a multiple choice survey during the lecture, as well, all students received an online open ended survey. In-class iclicker™ survey data was analyzed by a non parametric test to compare student responses between sites and the Mann Whitney U test to compare student responses between two weeks. Median responses were calculated. Qualitative analysis supports these results.

Methods Used: Medical and dental students at the three distributed sites utilized iclicker™ for the 5 weeks during the weekly case wrap up lecture. In weeks 1, 3, and 5 a multiple choice survey was administered during the lecture, as well, all students received an online open ended survey. In-class iclicker™ survey data was analyzed by a non parametric test to compare student responses between sites and the Mann Whitney U test to compare student responses between two weeks. Median responses were calculated. Qualitative analysis was carried out on the online survey data.

Summary of Results: There were no significant differences between week 1 and week 5 student responses (p > 0.05). As well, the student responses between the three sites did not significantly differ in week 1 (p > 0.05). Median student responses are seen in Figure 1. Qualitative analysis supports these results.

Conclusions: The opinion of iclicker™ remained positive throughout its trial and there is no difference in student attitude between the three sites. Iclicker™ was found to be an engaging teaching tool that improved student understanding and created focused class discussion, however iclicker™ may not be as useful in conventional week lectures. For future use technological problems should be resolved.

Session: Student Session XI – Surgery 506

Lights, Camera, Surgery: Evaluation of a Pilot Project for Medical Students to Produce Surgical Education Learning Resources

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Purpose of Study: The university has recently launched a distributed medical undergraduate program, doubling its class size in the last 4 years. This expansion has led to a necessary increase in the use of new educational resources to bridge learning at multiple sites. The application of modern technology can create valuable online resources which are accessible at all times. The Office of Pediatric Surgical Evaluation and Innovation (OPSEI) has launched a pilot project called, “Lights, Camera, Surgery” for medical students to design and produce instructional videos for teaching common surgical procedures.

Methods Used: A group of 13 medical students were given a leadership role in filming key surgical cases within the operating room setting in Pediatric Surgery. The students were mentored by faculty and by a professional videographer coach. At the end of the project, the students were surveyed using a 5-step Likert scale (strongly disagree, disagree, neutral, agree, or strongly agree). This scale was used to assess whether this pilot project allowed students to broaden access to clinical learning resources, explore careers within the surgical environment, develop skill sets necessary for creating online resources, and ignite student leadership in creating clinical learning resources.

Summary of Results: Eight of 13 surveyed students responded. All respondents indicated no previous experience filming, editing, narrating videos, or producing educational learning resources. All students reported that they agreed the overall project experience allowed them to assume a leadership role in the development of the project. All students either agreed or strongly agreed that the project allowed them to create valuable educational learning resources. When asked if the project allowed them to explore careers in surgery, 62.5% agreed and 37.5% strongly agreed. All students agreed or strongly agreed that the project allowed them to gain valuable skills in video filming.

Conclusions: A total of 21 surgical videos were developed. The pilot project “Lights, Camera, Surgery” was a worthwhile learning experience and provided students specialized skills in the production of clinical education videos. This novel approach has served as a unique way to expose students to careers in surgery and to interact with surgical mentors.
complication being arrhythmia at 44%. Although between the two time periods, the data shows no statistically significant difference (p = 0.05 and 95% C. I. includes 0) in mortality and overall complications, it is not fully indicative of the clinical differences present amongst the different eras, as there were less complications in group 2. Reoperations occurred in 12.7% of the patients at a mean interval of 15 mths (0.1–30). The main cause of re-operation was residual VSD (5.9%) and RVOTO (6.7%).

Conclusions: Repair of TOF and its variants can be performed with a low mortality but with a higher morbidity than expected when all complications are taken into account.

Session: Student Session XI – Surgery
508

COMPLIANCE OF PHACOEMULSIFICATION SYSTEMS AND THE HUMAN EYE

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Purpose of Study: The fluids of the phacoemulsification systems used in cataract surgery account for much of the success and safety of the operation. During surgery, cataract fragments occlude the instrument tip creating a vacuum in the tubing and cassette. Once an occluding fragment clears the needle tip, the potential energy stored in the tubing and cassette suddenly releases causing a fluidic surge that can be hazardous. This “occlusion break surge” would be effectively eliminated if the compliance of the phacoemulsification system was zero. Thus, the compliance of the aspiration tubing and cassettes of these systems is the major determinant of a machine’s performance. Moreover, a pressure volume curve of both the phakic and aphakic eye will provide a more complete depiction of the fluidic circuit between the phacoemulsification system and the eye.

Methods Used: The compliance of the INFINITI Vision System (Alcon Laboratories, Fort Worth, Texas), the Stallaris Vision Enhancement System (Bausch & Lomb, Rochester, New York), and the WhiteStar Signature phacoemulsification system (Abbott Medical Optics, Santa Ana, California) were measured. Also tested were older models from three manufacturers. The capacitance of each system was measured prior to compliance testing.

After each system was primed, the aspiration line was connected to an electronic pressure transducer and digital oscilloscope. Small volumes were injected and aspirated from the aspiration line to generate pressure-volume curves. Compliance testing was also done on porcine globes using a similar method.

Summary of Results: Under controlled laboratory settings, the INFINITI system with Intrepid tubing demonstrated the lowest compliance while the Legacy proved to be the most compliant. The Bausch and Lomb and AMO systems exhibited very similar pressure-volume curves. Compliance curves for the porcine globes demonstrated a steep rise in compliance after aspirating 100 microliters and a plateau at 300 microliters.

Conclusions: The lower compliance of the INFINITI Intrepid system should lessen the hazards of occlusion break surge, enhancing clinical performance and safety. Further research will involve measuring the compliance of human eyes.

Session: Student Session XI – Surgery
509

MANAGEMENT OF INTRACTABLE BLADDER NECK CONTRACTION AND URINARY INCONTINENCE: LONG TERM EVALUATION

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Purpose of Study: Urinary incontinence combined with intractable posterior urethra/ bladder neck contractures after radical prostatectomy or following radiation therapy for prostate cancer presents a very difficult management problem. Urinary incontinence is routinely managed with Artificial Urinary Sphincter (AUS); however, instrumentation required to perform multiple incisions, resections and/or dilations for treatment of recurrent bladder neck contracture is a contraindication for AUS placement. Placement of an Urolume stent across the posterior urethra/bladder neck allows it to stay open while AUS provides continence.

Methods Used: We retrospectively evaluated medical records of 12 men who underwent Urolume stent placement with subsequent implantation of the AUS between 2004 and 2008 (follow up ranging 11 to 61 months, mean 24.7 mo).

Summary of Results: 12 men with a mean age of 76 (range 67–88) underwent combined Urolume stent placement with AUS implantation.

Etiology of bladder neck contracture and incontinence was radiation therapy for prostate cancer alone in 5, radical prostatectomy alone in 4, radical prostatectomy with radiation therapy in 2, proton beam therapy in one, and radical cystoprostatectomy with orthotopic neobladder in one. Time from initial treatment to AUS/Urolume ranged from 5 months to 27 years. Number of prior incisions/dilations ranges from 3 to 18. Two patients required subsequent addition of a second Urolume for further stricture management.

Conclusions: Combination of Urolume stent and artificial urinary sphincter can be effective in management of complicated bladder neck contractures with urinary incontinence in patients suffering consequences of prostate cancer treatment. This can be accomplished with minimal morbidity and significantly less invasiveness than the alternative of urinary diversion.

Residents’ Forum
8:30 AM
Saturday, January 30, 2010

Session: Residents Forum
510

PRIMARY MYOCARDIAL DISEASE IS A CAUSE OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Purpose of Study: Myocardial disease in systemic lupus erythematosus (SLE) is usually manifested as left ventricular (LV) diastolic dysfunction (DD) and is associated with increased morbidity and mortality. LVDD is classified as impaired relaxation (type I) or decreased distensibility (type II/III). Aging and hypertension are believed to be the predominant pathogenic factors of LVDD in SLE. We sought to demonstrate that LVDD in SLE occurs independently of age and hypertension.

Methods Used: Fifty SLE patients (mean age of 38 ± 12 years) and 22 healthy volunteers matched for age, gender, and body mass index underwent clinical, laboratory, and transthoracic Doppler echocardiography (TTE) evaluations. Mitral inflow and mitral annulus tissue peak Doppler velocities were measured during rapid LV filling (E’ and atrial systole (A’)) respectively. Also LV isovolumetric relaxation time (IVRT) was measured using septal tissue Doppler imaging. Criteria for LVDD: 1) Overall LVDD = mitral E/A <1.0, septal E/E’<15, lateral E/E’<21; average E/E’≥13, septal E’/A’<0.8, lateral E’/A’<0.8, or IVRT>100msec; 2) Type I = E/A<1, septal or lateral E’/A’ ratio<0.8, or IVRT>100 msec; Type II/III = septal E/E’≥15, E’/E<12, or average E/E’≥13.

Summary of Results: Means of mitral inflow A velocities were higher, E/A ratios lower, septal and lateral E/E’ lower, E’/A’ ratios higher, and E’/A’ ratios were lower in patients as compared to controls (all p<0.01 after adjusting for heart rate (HR)). Overall and type I LVDD were more prevalent in patients as compared to controls (56% and 54% versus 18% and 18%, respectively, both p≤0.004 after adjusting for age, HR, and mean arterial blood pressure. However, Type II/III LVDD was not significantly different among groups (12% versus 0%, respectively, p<0.17).

Conclusions: Young SLE patients have a high prevalence (56%) of predominant type I LVDD independently of age, and blood pressure. Thus, immune-complex mediated inflammatory myocardial disease is a cause of LVDD in SLE. A longitudinal study is needed to determine the progression and clinical or therapeutic implications of LVDD in SLE.

Session: Residents Forum
659

MATERNAL AND NEONATAL OUTCOMES OF HOSPITAL DELIVERIES IN WESTERN NEPAL

H. Fremgen, T. Dickerson, F. Nkoy, B. Fass University of Utah, Salt Lake City, UT.

Purpose of Study: Little quantitative information exists about birth outcomes for women and children delivering in a hospital setting in rural Nepal. In order to most effectively direct maternal-child health services and resources, more information regarding birth outcomes is essential. Objectives of this study are to 1) determine the outcomes of births in one district hospital
in western Nepal, and; 2) to identify and quantify common obstetric and neonatal complications.

Methods Used: Information regarding maternal and neonatal birth outcomes over a 6 month period (July 2008 to January 2009) was abstracted from birthing records in Baglung District Hospital. Birthing records provide demographic information about the mother as well clinical information about pregnancy, labor, childbirth and postpartum course until hospital discharge. Abstracted data is described below.

Summary of Results: A total of 490 births were recorded in the study period. 54% (264/490) of infants were male. 5% of infants (24/490) were delivered by vacuum extraction and ~3% (15/490) required cesarean section. Mean birth weight was 2915 grams. Retained placenta (1.4%; 7/490) was the most common maternal complication followed by postpartum hemorrhage (PPH) (~1%; 5/490), cervical tears (~1%; 4/490) and shoulder dystocia (~0.4%; 2/490). No maternal deaths were reported. Neonatal complications included preterm delivery (~13%; 65/490), postdate delivery (~9%; 42/490), and low birth weight <2500g (~10%; 51/490). Eleven neonates (2.2%) died. 5/11 were born prematurely. Of the 11 deaths, 8 were classified as stillborn and 3 as birth asphyxia.

Conclusions: Preterm/postterm birth, low birth weight, stillbirths and birth asphyxia are important contributing factors to neonatal morbidity and mortality. Compared to other studies the incidence of retained placenta and cervical tears is lower. In contrast, we found a higher rate of postdate delivery (~9%). In western Nepal, ~65% of infants were male and ~3% required cesarean section.

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MATERNAL ZINC DEFICIENCY INDUCED CHANGES IN HEPATIC IGF-1 mRNA EXPRESSION ARE NOT ACCOMPANIED BY IGF-1 DNA METHYLATION

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Purpose of Study: Perinatal dietary zinc deficiency leads to growth and development impairments. Progyny are at risk for intrauterine growth restriction, altered IGF-1 levels, and postnatal metabolic diseases. Zinc is an essential cofactor for many enzymes involved in epigenetics, like DNA methyltransferase. We have previously demonstrated that moderate maternal zinc deficiency (MZD) increases IGF-1 mRNA levels in day 21 progeny. It is unknown if these mRNA level changes are present at day zero and if the changes observed are from alterations in the epigenome. Because perinatal zinc deficiency can be observed at birth, we hypothesize that hepatic IGF-1 mRNA changes observed are from alterations in the epigenome. Furthermore, previous studies have correlated IGF-1 mRNA levels and methylation; therefore, we hypothesize that MZD day 21 pups will have hypomethylation within the IGF-1 promoter 2 region.

Methods Used: A zinc deficient diet of 7 ppm zinc was fed to dams 3 weeks before conception and throughout gestation and lactation. Control dams were fed a diet of 25 ppm zinc. Litters were culled to 7. Liver harvested day 0 or day 21. Real time RT-PCR used to determine levels of IGF-1 mRNA variants (P1, P2, 1A, 1b). DNA methylation evaluated at six CpG sites (-41 to -231bp) using bisulfite sequencing.

Summary of Results: MZD in the day 0 male offspring trended toward an increase in all hepatic IGF-1 mRNA variants (P1 108.+/-19, P2 132.+/-25, 1A 117.+/-22, 1B 155.+/-15). No similar trend observed in the MZD day 0 females. Bisulfite sequencing within the promoter 2 region of IGF-1 displayed no difference in methylation in the MZD day 21 rats compared to controls. In contrast, we found a difference in methylation in the MZD day 21 rat pups.

Conclusions: MZD in day zero rats increases hepatic IGF-1 mRNA variant expression in a gender specific manner, similar to day 21 offspring. However, the increase in IGF-1 gene expression seen in MZD day 21 progeny is not accompanied by methylation changes within the promoter 2 region of the IGF-1 gene. We speculate that IGF-1 mRNA changes observed at day 21 are influenced by postnatal factors; such as the transcription factor STAT5b, potentially via altered DNA methylation at the stat5b binding sites on IGF-1.

Session: Residents Forum

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DHA EXPOSURE REDUCES GALACTOKINASE mRNA LEVELS IN THE IUGR RAT

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Purpose of Study: Maternal and neonatal dietary DHA supplementation is believed to improve neurological outcomes in humans and rats, and subsequently this belief has been incorporated into the lay literature. We have previously demonstrated that DHA supplementation improves pulmonary outcomes in IUGR rats by functioning as a ligand for PPARα. However, concern exists that observed benefits may be mitigated by DHA stimulation of hepatic galactokinase. This concern is particularly relevant to the IUGR newborn prone to insulin resistance, as stimulation of galactokinase increases glucose-6-phosphate (G6P) levels, which may impair glucose directly by affecting glycosylation. G6P may also indirectly affect glucose homeostasis by increasing activity of 11β hydroxysteroid dehydrogenase (11HSD1), the enzyme responsible for activating paracrine levels of glucocorticoids. Despite the concern, little is known about the effect of IUGR and perinatal supplementation on galactokinase expression.

We hypothesized that perinatal DHA would decrease levels of hepatic galactokinase mRNA in the juvenile IUGR rat.

Methods Used: IUGR was induced by bilateral uterine artery ligation at day E19 in the Sprague-Dawley rat. Dams were fed a regular diet or 1% DHA from day E13 to term and through lactation to postnatal day 21 (d21). Hepatic mRNA levels for galactokinase were measured using real-time RT-PCR in male and female pups at d21.

Summary of Results: All results are expressed as IUGR as percent of control ± SEM. IUGR did not affect mRNA levels of galactokinase in male or female rats at d21. In contrast, IUGR with perinatal DHA supplementation reduced galactokinase mRNA levels in male and female rats at d21 (M 57%*, F 73%*+/−15%)

Conclusions: We conclude that IUGR does not affect hepatic galactokinase mRNA levels. In contrast, DHA supplementation decreased galactokinase levels. These latter findings are intriguing, because galactokinase production is an important enzyme controlling the flux between lipid and carbohydrate metabolism. We speculate that IUGR rats who experience perinatal supplementation will demonstrate less hepatic insulin resistance.

Session: Residents Forum

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PROXIMAL TUBULAR ACIDOSIS AND PANCREATITIS IN A 2 YEAR OLD GIRL: A CASE REPORT AND LITERATURE REVIEW

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Case Report: Autosomal recessive proximal renal tubular acidosis (pRTA) is a rare disorder associated with ocular abnormalities, short stature, dental enamel defects, pancreatitis, and basal ganglia calcification. Kidney Na+/HCO3- Cotransporter (KNBC1) has been found to play a major role in the autosomal recessive pRTA. Pancreatic Na+/HCO3- Cotransporter (pNBC1), expressed predominantly in the pancreas, is similar to KNBC1 but has a unique 5'-end.

We report a case of a 29 month old girl with persistent pRTA associated with Fanconi Syndrome, pancreatitis, short stature, and dental enamel defects. The patient also had corneal crystals at admission which disappeared a month later.

The patient is a blue-eyed, fair-skinned daughter of non-consanguineous parents with brown eyes. There is no family history of short stature, poor dentition, or renal diseases. She had normal development and growth (weight and height at fifteenth percentile for age) until 12 months of age. Extensive metabolic and genetic investigation have ruled out cystinosis, tyrosinemia, galactosemia, and Wilson’s disease. The DNA studies for SLC4A4 gene encoding for NBC1 are pending. In reviewing the literature, only a few NBC1 mutations have been identified so far, four of which (R298S, R510S, R881C, and S427L) reside in the common coding region for KNBC1 and pNBC1. The patients with R510S, R881C, and S427L mutations have pancreatitis and pRTA but the one with R298S mutation only has pRTA without pancreatitis.

The presentation of pRTA and pancreatitis in this patient could be a result of pNBC1 and KNBC1 being affected. This patient’s early diagnosis and interventions hopefully will enhance her growth and delay glaucoma formation. In addition to helping to determine prognosis, identification of NBC1 mutations will direct genetic counseling for the family regarding risk of the disease in subsequent pregnancies.
**Session: Residents Forum**

**515**

**THE IMPORTANCE OF BEHAVIORAL AND ATTENTION DISORDERS IN INDIVIDUALS WITH 8P23.1 DELETIONS**

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**Case Report:** We describe a 32-year-old woman with history of seizures, short stature and low weight (3–10th centile), ASD and VSD, and duplication of the renal collecting system. She had dysmorphic features: microcephaly, micrognathia, thick and arched eyebrows, mildly downslanting palpebral fissures, hypertelorism, a thin nasal bridge with a bulbous nasal tip and small hands and feet. She had learning disabilities especially involving math and abstract reasoning, marked motor apraxia with poor fine motor skills and dysgraphia, but her expressive language was preserved despite occasional echolalia. Behavioral problems have been a major challenge for her family throughout her entire life, and her behaviors have included attention deficit hyperactivity disorder, aggressiveness, impulsivity, hypochondriasis and an anxiety disorder. An MRI of the brain was normal. Karyotype was normal and array Comparative Genomic Hybridization (CGH) performed at Combitrax Molecular Diagnostics, revealed a de novo deletion of chromosome 8p23 extending from 7,309,013 to 12,256,860 Mb that is around 4.94 Mb in size, together with a maternally inherited, 1.3 Mb copy number gain at 8p11.23–p11.22 which contains no genes and may represent a familial polymorphism. Deletion of 8p23.1 is associated with a spectrum of anomalies that includes congenital heart malformations, congenital dia-phragmatic hernia, developmental delays and behavioral problems. This region contains the GATA4 gene that is known to play a key role in heart and possibly diaphragm development in humans. However the 8p23.1 phenotype described in the literature is very variable and interestingly, almost all the organ systems can be affected. Mental ability varies from normal to profound mental retardation. Behavioral and attention disorders and aggressive behavior have been described in 6% (10/166) of reported cases, but are underestimated in this deletion syndrome, in which clinical attention is usually directed towards the congenital malformations. Families caring for an individual with 8p23.1 deletion syndrome should be counseled about possible behavioral and attention disturbances, especially aggressive behaviors, that can occur in affected individuals.

**Session: Residents Forum**

**516**

**SLEEPINESS IN HEALTH CARE PROVIDERS: A PILOT STUDY**

T. Singh, RS. Sirohi, GP. Singh, M. Saadat San Joaquin General Hospital, French Camp, CA.

**Purpose of Study:** This study aims to document incidence of sleepiness in health care providers. According to Institute of medicine, medical errors are responsible for many thousand deaths every year in the US hospitals. Daytime sleepiness at work can lead to medical errors.

**Methods Used:** A survey questionnaire regarding excessive daytime sleepiness at work was introduced to health care providers performing different roles in a public hospital.

**Summary of Results:** A total of 55 health care providers (Women N=44 and Men N=11), age range 18 to 75, working in a hospital completed the survey. Most participants (82%) were from day time shift. Majority of respondents (62%) slept 6 to 8 hours before coming to work. Approximately same percentage (62%) used caffeine during the work hours. Significant number of respondents (71%) preferred a designated nap time during the workday. No significant difference in daytime sleepiness is noted with medical condition or took medications that would affect sleep. Physicians in number of respondents (71%) preferred a designated nap time during the workday. In all age groups men (55%) tended to be sleepier and tired than women (22%). Compared to middle age the younger and older age groups (22% Vs.5–38%) showed similar tendency of excessive daytime sleepiness as measured by Stanford sleepiness scale.

**Conclusions:** Sleepiness while providing patient care in the hospital is suggested by the use of caffeine and need for daytime nap. Physicians are notably more tired at work. Significant difference in sleepiness was noted between men and women. The results justify need for further research in this area. Proper intervention will likely prevent many medical errors and improve patient safety.

**Session: Residents Forum**

**517**

**SOMATIC SYMPTOMS AND THE ASSOCIATION BETWEEN HEPATITIS C INFECTION AND DEPRESSION IN HIV-INFECTED PATIENTS**

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**Purpose of Study:** Prior studies examining the association of depression with hepatitis C virus (HCV) infection in HIV-infected patients have provided contradictory results. We conducted this study to examine associations between HCV infection, somatic symptoms and depression in HIV-infected patients in routine clinical care.

**Methods Used:** Cross-sectional observational study of patients from the University of Washington HIV Cohort. Patients completed instruments on depression (PHQ from the PRIME-MD), anxiety, symptoms (HIV Symptoms Index), substance use (ASSIST), alcohol risk (AUDIT-C), and health-related quality of life (EuroQOL 5-D). We generated depression severity scores using item response theory. We removed somatic items (fatigue, appetite loss, sleep disturbance) from depression severity scores in secondary analyses. We used linear regression to examine the relationship between depression severity scores and HCV accounting for demographic and clinical characteristics.

**Summary of Results:** Of 764 HIV-infected patients, 160 (21%) were HCV-infected. HCV-infected patients had higher mean symptom scores than patients without HCV, 4.8 vs. 3.9 (p = 0.02), and reported more dizziness, memory problems, nausea, appetite loss, and musculoskeletal pains (p’s < 0.002–0.03). In adjusted analysis, HCV-infected patients had higher depression severity scores than patients without HCV (p = 0.01). HCV infection remained associated with depression in secondary analyses with depression severity scores that omitted somatic PHQ-9 items (p = 0.01). When somatic symptoms were included as covariates in multivariate analyses, HCV infection was no longer associated with higher depression severity scores (p = 0.09).

**Conclusions:** We found high degrees of depression in HIV-infected patients in routine clinical care, especially among those with HCV co-infection. The association between HCV infection and worse depression severity scores persisted when somatic PHQ-9 items were omitted. However, in models that also adjusted for symptoms, the association disappeared. Longitudinal studies are needed to further assess whether symptoms in part mediate the association between HCV and depression or whether the increased symptom burden is due to increased depression.

**Session: Residents Forum**

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**FOREIGN BODY REACTION: A RARE CASE OF GRANULOMATOUS MASTITIS**

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**Case Report:** Case: A 39 year old female presents with an enlarging soft breast mass for the past six months. The patient has no family history of breast or ovarian cancer, is not on birth control and has never had any implants or foreign bodies in her breast. Mammogram and ultrasound two weeks before surgery suggested a diagnosis of lipoma. Lumpectomy and excision was performed resulting in a washout of a yellow polenta-like exudate. Pathology returned bodies in her breast. Material without definitive structure were present, suggestive of a foreign body cell; no evidence of neoplastic processes. Irregular sheets of hyaline purple like material without definitive structure were present, suggestive of a foreign body reaction. The patient was assured after pathology was confirmed and discharged with annual follow-up.

**Discussion:** Granulomatous mastitis, a rare benign inflammatory breast disease that usually occurs in younger women at childbearing age, normally presents as a unilateral, firm, slightly tender breast cyst. Clinical features may imitate breast cancer and thorough pathologic review with an excisional biopsy is warranted to rule out carcinoma. Surgical intervention leads to variable results and an elevated rate of recurrence. Some studies suggest that corticosteroid therapy increases the time interval in between recurrences. Although most cases have an identifiable foreign body source, in some instances, no sources are identified.
Granulomatous process suggestive of a foreign body reaction.

SUBMITTED BUT NOT PRESENTED

Session: Submitted but not Presented
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PHYSIOLOGICAL STRAIN INDEX IN BRUCE PROTOCOL TESTS WITH ADDED HEAT STRESS: COMPARISON WITH HAZMAT, MILITARY AND FIREFIGHTING SIMULATIONS
LW. Raymond 1 Univ of North Carolina, Chapel Hill, Chapel Hill, NC and 2Carolina’s HealthCare System, Charlotte, NC.

Purpose of Study: We compared the Physiological Strain Index (PSI) from Bruce Protocol treadmill electrocardiography (BPTE), with and without thermally restrictive suits, versus PSI values induced by Hazmat and other operational exercises in which mandatory protective apparel restricts heat loss. PSI values of 3-4 and 5-6 represent mild and moderate strain, while those of 7-8 and higher reflect severe and very severe strain.

Methods Used: We measured internal body temperature before and after BPTE (ingested thermistor, tympanic infrared bolometer) plus heat discomfort in 38 subjects, first while wearing gym clothes (A) and later wearing cotton flannel sweat clothes under a vinyl oversuit plus diver’s neoprene head-gear (B). Heart rate and blood pressure were monitored continuously during BPTE. From changes in heart rate and body temperature, we calculated PSI under conditions A and B, and compared our results with those published by others, as well as our earlier results from 57 other candidates for Hazmat duty (A2, gym clothes). We also recorded perceived heat discomfort using the Young scale (4, normothermic; 8, unbearably hot).

Summary of Results: PSI values (Table) indicated that the addition of thermally restrictive clothing increased the index from moderate to severe strain (PSI 7.6, p < 0.001), greater than Hazmat and military exercises (PSI, 6.0 and 7.4, respectively) but less than firefighting simulations (8.7). PSI in conditions A and B was closely correlated with the Young Index (r = 0.42 p < 0.001).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Type of Apparel</th>
<th>Maximum Heart Rate</th>
<th>Temperature Rise, °F</th>
<th>PSI</th>
<th>Young Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, N = 38</td>
<td>Gym Clothes</td>
<td>183 ±/− 10</td>
<td>6.3 ±/− 1.0</td>
<td>6.2 ±/− 0.8</td>
<td></td>
</tr>
<tr>
<td>B, N = 38</td>
<td>Fully Encapsulating</td>
<td>182 ±/− 11</td>
<td>2.4 ±/− 1.2</td>
<td>7.6 ±/− 1.5</td>
<td>7.4 ±/− 0.9</td>
</tr>
<tr>
<td>A2, N = 57</td>
<td>Gym Clothes</td>
<td>178 ±/− 12</td>
<td>0.7 ±/− 0.8</td>
<td>5.9 ±/− 1.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Conclusions: The addition of the readily-available apparel which we used to create heat stress in our subjects during maximal Bruce treadmill tests induced greater PSI values, which were lower than those reached during simulated firefighting, but exceeded PSI from military and Hazmat exercises. This technique may be useful in the medical evaluation of candidates for Hazmat and other duties in which heat stress is expected.

Session: Submitted but not Presented
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COMPARISON OF BEDTIME INSULIN GLARGINE VERSUS TWICE-DAILY NPH AMONG INNER CITY ETHNIC MINORITY TYPE 2 DIABETIC PATIENTS UNCONTROLLED ON BEDTIME NPH AND ORAL AGENTS
SH. Hsia Charles Drew University, Los Angeles, CA.

Purpose of Study: The optimal use of long-acting insulin analogues compared to NPH among low-income, inner city ethnic minority populations remains unclear. We compared the utility of insulin glargine administered as a single bedtime injection versus the addition of a morning injection of NPH among inner city ethnic minority type 2 diabetic patients who were sub-optimally controlled on a single injection of bedtime NPH combined with oral agents.

Methods Used: Subjects with baseline hemoglobin A1c (HbA1c) levels between 7.5–12.0% despite adequate control of fasting plasma glucose were randomized to 26 weeks of open-label therapy with either twice-daily NPH or switching of their bedtime NPH to insulin glargine. After a 2-week run-in phase of self-glucose monitoring while still on their pre-study NPH regimen, subjects were randomized and underwent an 8-week dose titration phase to optimally control fasting glucose readings (for the insulin glargine group) or pre-dinner glucose readings (for the NPH group). Thereafter, subjects maintained their insulin doses for an additional 16 weeks, with dose adjustments only if needed to avoid symptomatic hypoglycemia. Nutritional counseling was reinforced throughout the study.

Summary of Results: Twenty-four subjects were randomized. Baseline characteristics were comparable between groups; mean HbA1c at baseline was 9.3 ± 1.3% overall. HbA1c improved modestly in both groups (to 8.4 ± 1.4% overall), with no significant difference between groups, even though the twice-daily NPH group had faster control of pre-supper glucose readings than the glargine group. The NPH group used significantly higher daily doses of insulin, but there was no between-group difference in weight gain, and hypoglycemic events were not greater with twice-daily NPH compared to bedtime glargine. Treatment satisfaction scores were not different between groups.

Conclusions: Among inner city, ethnic minority type 2 diabetic patients sub-optimally controlled on bedtime NPH and oral agents, these data suggest that there is no glycemic advantage to switching to insulin glargine. The addition of morning NPH achieves faster control of pre-supper glucose readings compared to switching to bedtime glargine, without increasing weight gain or hypoglycemia.

Session: Submitted but not Presented
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SYSTEMS APPROACH TO MEDICAL MALPRACTICE
JD. Waldman University of New Mexico, Albuquerque, NM.

Purpose of Study: Practicing high quality medicine closely parallels systems thinking.

Methods Used: Both stress the dependency of outcomes on interactions among parts (viz., organs) and reaffirm that fixes-which-work start with root cause analysis (etiologic diagnosis).

Summary of Results: Application of systems thinking to med-mal confirms that the tort law model for adjudication of undesirable medical outcomes is conceptually flawed.

Conclusions: Attaining the desired outcomes from med-mal would be better served using a No-Fault approach.
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